protocol" population.

Table III.4.2 Total dose of morphine administered (based on NDA Table 14, page 95, vol. 132)

Variable	Levobupivacaine	Levobupivacaine + Clonidine	Clonidine
Mean±SD	36.5±23.7	13.9±17.3	22.6±12.8
Median	36	7	21
Treatment Difference:			
Pairwise Difference	Combination vs. Levo	Combined vs. Clonidine	Levo vs. Clonidine
Difference in median	-23	-12	13
95% C.I.	(-36, -9)	(-18, -3)	(2, 26)
P-value	<0.001*	0.004	0.022

*: Wilcoxon 2-sample test

Secondary Efficacy Endpoints:

Time to first request for analgesia post surgery — The median survival time to the first request of analgesia was longest for the Levobupivacaine plus Clonidine group (12.49 hrs including censored patients and 9.86 not including the censored patients). It was longer than either the Levobupivacaine group (2.85 hrs including censored patients and 2.85 not including the censored patients) or the Clonidine group (5.88 hrs including censored patients and 5.83 not including the censored patients). Kaplan-Meier survival curves of the three treatment groups were given in NDA Figure 1 (page 297, vol. 132). When the median survival time was compared using Wilcoxon two sample test, these two differences were both statistically significant (p<0.001 for Levobupivacaine plus Clonidine vs. Clonidine and p=0.005 for Levobupivacaine plus Clonidine vs. Levobupivacaine)(Table III.4.3). The difference between the Levobupivacaine group and the Clonidine group was also statistically significant (p=0.01) when comparing the p-value with the multiple comparison adjusted type I error rate.

Table III.4.3 Time to first request for analgesia in 24-hour post-operative study period (based on NDA Tables 16.1-16.2.2, page 97-99, vol. 132)

Variable		Levobupivacaine	Levobupivacaine + Clonidine	Clonidine
Mean ±SD		4.99±5.62	12.99±8.32	7.20±5.89
Survival analysis				
Censored patients	Uncensored observations	30 (100.0%)	26 (86.7%)	29 (96.7%)
	Censored observations	0	4 (13.3%)	1 (3.3%)
	Missing	0	0	0
Time (hrs) to first request Median				
(including censored patients*)		2.85	12.49	5.88
(not including censored patients)		2.85	9.86	5.83
Wilcoxon two sample test *			p-value	
Levobupivacaine vs. Levobupivacaine plus Clonidine			<0.001	
Levobupivacaine plus Clonidine vs. Clonidine			0.005	
Levobupivacaine vs. Clonidine			0.01	

*: Patients did not request analgesia was assigned with 24 hours.

Number of request for analgesia in 24-hour post-operative study period — The median number of requests was the lowest in the Levobupivacaine plus Clonidine group (9 requests) (Table III.4.4). The difference was statistically significant from the Levobupivacaine group (p<0.001) and from the Clonidine group (p=0.012) when tested using Wilcoxon two sample test. The difference was not statistically significant between the Levobupivacaine group and the Clonidine group (p=0.13).

Table III.4.4 Number of request for analgesia in 24-hour post-operative study period (based on NDA Tables 17, page 100, vol. 132)

Variable	Levobupivacaine	Levobupivacaine + Clonidine	Clonidine
Mean ±SD	68.0±56.0	28.7±41.4	45.7±46.1
Median	55	9	28
Wilcoxon two sample test *	Median Diff	95% CI	p-value
Levobupivacaine vs. Levobupivacaine plus Clonidine	30 requests	(11, 56)	<0.001
Levobupivacaine plus Clonidine vs. Clonidine	-18	(-27, -1)	0.012
Levobupivacaine vs. Clonidine	17	(-4, 40)	0.13

Motor block — The odds ratio for higher grade of motor block was estimated by the logit model. The Levo+Clonidine/Levo and the Levo+Clonidine/Clonidine odds ratios were both less than 1. None of the odds ratios was statistically significant (Table III.4.5).

Table III.4.5 Maximum grade of motor block during the post-operative period (based on NDA Tables 21.1 and 21.2, page 213-214, vol. 132)

Variable	Levobupivacaine	Levobupivacaine + Clonidine	Clonidine
Frequency N(%)			
No paralysis, full flexion of knee and ankle	5 (16.7%)	4 (13.3%)	2 (6.7%)
Inability to raise extended leg, able to move knee	4 (13.3%)	6 (20.0%)	6 (20.0%)
Inability to flex knee, able to flex ankle	7 (23.3%)	4(13.4%)	5 (16.7%)
Inability to move lower limb	14 (46.7%)	16 (53.3%)	17 (56.7%)
Treatment Difference: (logit model)			
Pairwise Comparison	Combination vs. Levo	Combined vs. Clonidine	Levo vs. Clonidine
Odds Ratio	0.894	0.749	0.819
95% C.I.	(0.347, 2.300)	(0.284, 1.975)	(0.508, 1.322)
P-value	0.82	0.56	0.41

Median VAS scores at rest and on passive movement of all assessments were shown in NDA Table 18.1 (Figure 2) and Table 18.2 (Figure 3) respectively. In general, the three treatment groups had the same pattern of median VAS scores over time. It was also shown that the Levobupivacaine plus Clonidine treatment had lowest median VAS score than either of the two other groups at all assessments between 3 to 12 hours rest and on passive movement. On the other hand, the Clonidine group had the highest median VAS at rest score at all assessments after 7 hours. The Clonidine group had also the highest median VAS on passivement score at all assessments between 7 and 11 hours and after 16 hours. The pattern was less clear when consider only assessments till the first rescue analgesia (NDA Tables 18.3 and 18.4, Figures 4 and 5). There was no formal statistical analysis or comparison stated in the protocol or presented in NDA.

The median value of the height of sensory block were shown in NDA Table 19.1 to 19.4 for the left upper dermatome, right upper dermatome, left lower dermatome and right lower dermatome. It was shown in NDA Figure 6-1 and Figure 6-2 that the combination group had consistently the highest median value of height of sensory block at the upper left and right dermatome at all assessments after 4 hours. On the other hand, the Clonidine group had the highest median value at all assessments before 4 hours at both the upper left and rights dermatome but the lowest median value at all assessments at both the upper and lower dermatome after 10 hours. There was no formal statistical analysis or comparison stated in the protocol or presented in NDA.

Safety Analysis:
Adverse events — There were 30 patients (100%) in the Levobupivacaine group, 29 patients (90.6%) in the Levobupivacaine plus Clonidine group and 28 patients (82.4%) in the Clonidine group had at least one adverse event (Table III.4.6). Most of the events were study drug related (90% in Levobupivacaine, 87.5% in the combination and 79.4% in the Clonidine group).

One patient in the combination treatment group was reported to have 'severe' and 'serious' adverse event. That patient completed the study but died 11 days after completion of study drug infusion. The cause of death was determined to be myocardial infarction by the study investigator. It was also determined as unrelated to the study drug by the study investigator.

There were 78 adverse events in the Levobupivacaine group, 64 in the Combination treatment group and 69 in the Clonidine group. Most of the events were cardiovascular disorders in general (80% in Levobupivacaine group, 88% in combination group and 77% in Clonidine group). It was followed by gastro-intestinal system disorders (56%/25%/27% for the three groups respectively), body as a whole (37%/28%/21% for the three groups respectively), urinary system disorders (3%/16%/30% for the 3 groups), metabolic and mutational disorders (10%/3%/9% for the 3 groups) and heart rate and rhythm disorders (13%/3%/3% for the 3 groups). The study investigator determined all the cardiovascular disorders as study drug related.

Table III.4.6. Adverse events (based on NDA Tables 22, page 215, vol. 132)

Variable	Levobupivacaine	Levobupivacaine + Clonidine	Clonidine
Number of patients with at least one adverse event	30 (100%)	29 (90.6%)	28 (82.4%)
Patients with severe adverse events	0 (0.0%)	1 (3.1%)	0 (0.0%)
Patients with study drug related events	27 (90.0%)	28 (87.5%)	27 (79.4%)
Patients with serious adverse events	0 (0.0%)	1 (3.1%)	0 (0.0%)
Patients who died	0 (0.0%)	1 (3.1%)	0 (0.0%)

Vital signs and physical examination — Plots of the mean supine heart rate of the three treatment groups was given in NDA Figure 8. It was shown that the mean heart rate of the Levobupivacaine plus Clonidine group and the Clonidine group followed the same pattern of a sharp drop at first hour and then maintaining a rate which was either similar or lower than the heart rate at the first hour. The mean heart rate of patients in the Levobupivacaine group increased from the assessment at 3 hours to a level that was 20 bpm higher than the heart rate at 0 hour. The heart rate remained to be higher than at the 0-hour assessment till the end of the infusion period. The plots of the mean systolic and diastolic blood pressure over time of the three treatment groups were given in Figures 9 and 10. The Levobupivacaine plus Clonidine group and the Clonidine group had the same pattern throughout the study period. The Levobupivacaine group had a higher mean pressure after 4 hours than the other two groups consistently till the end of the study. The plot of the mean saturated oxygen value against time of the three groups was given in Figure 11. The three groups had the same pattern throughout the study period.

III.4.f Reviewer's Comments and Conclusions:
The purpose of this study was to assess the efficacy and safety of 0.125% Levobupivacaine, 0.125% Levobupivacaine plus 50$\mu g.h^{-1}$ Clonidine and 50$\mu g.h^{-1}$ Clonidine alone administered

as a continuous extradural infusion for post-operative pain in patient undergoing elective hip replacement surgery. The primary efficacy measurement was the total dose of morphine delivered during the 24-hour postoperative infusion. In general this study had demonstrated the Levobupivacaine was effective when used in combination with Clonidine as a post-hip replacement epidural infusion. Comments on the comparison of the combination to either Clonidine or Levobupivacaine alone were given below.

Primary efficacy endpoint — The Levobupivacaine plus Clonidine group had significantly lower mean dose than the Levobupivacaine group ($p<0.001$, Wilcoxon 2-sample test for median) and the Clonidine group ($p=0.004$, Wilcoxon 2-sample test for median). The difference between the Levobupivacaine alone group and the Clonidine alone group was not statistically significant ($p=0.022$, Wilcoxon 2-sample test for median). For decision of statistical significance, the test p-value was compared with 0.017, the Bonferroni-Holm type error rate adjusted for multiple comparisons.

Secondary efficacy endpoints — The primary comparisons made between the three groups were on time to first request for analgesia, number of request for analgesia in 24-hour post-operative period and motor block. All statistical comparisons were made using the Wilcoxon rank sum test. Statistical significant was determined by comparing the p-value of the test to 0.017, the type I error rate adjusted for multiple comparisons using Bonferroni-Holm method. It was shown that the combination treatment had a significantly longer median survival time to the first request than either the Levobupivacaine group ($p<0.001$) or the Clonidine group ($p=0.005$). It was also shown that the Clonidine group had a significantly longer median survival time than the Levobupivacaine alone treatment ($p=0.01$).

The median number of request for analgesia was lower in the combination treatment than either the Levobupivacaine alone treatment ($p<0.001$), or the Clonidine alone treatment ($p=0.012$). The difference between the Levobupivacaine alone treatment and the Clonidine alone treatment was not statistically significant ($p=0.13$). The odds ratio for a higher grade of motor block was estimated using the logit model. It was shown that the difference between any two of the treatments was not statistically significant. There was no statistical comparison between the treatments in VAS scores or the height of sensory block.

Safety analysis — More than 80% of patients in each treatment group had at least one adverse event. The most common events were cardiovascular disorders in general, gastro-intestinal system disorders, body as a whole, urinary system disorders, metabolic and nutritional disorders and heart rate and rhythm disorders. Most of the cardiovascular events were study drug related. One patient in the combination treatment group was reported to have 'severe' and 'serious' adverse event. That patient completed the study but died 11 days after completion of study drug infusion. The cause of death was determined to be myocardial infarction by the study investigator. It was also determined as unrelated to the study drug by the study investigator. The combination treatment group and the Clonidine group had very similar patterns in all vital sign over the study time. The Levobupivacaine had group higher average supine heart rate, systolic and diastolic blood pressure consistently over all assessment after 4 hours of the injection.

IV. Phase III Peripheral Block Studies

Study #	Design	Dose	# of treated (Safety)	Age mean	Sex (M/F) Race (W,B,O)	Indication
030428	Dblind/randomized/parallel/1 center	NT=Levobupivacaine up to 150 mg 0.25%, AC=Bupivacaine up to 150 mg 0.25%	33/NT 33/AC	57.4/NT 56.4/AC	66/0 66,0,0	Post-operative pain control following inquinal hernia repair/ Infiltration analgesia
030721	Dblind/randomized/parallel/1 center	NT=Levobupivacaine 150 mg 0.25%, AC=Bupivacaine 150 mg 0.25%	35/NT 34/AC	55.5/NT 61.4/AC	69/0 69,0,0	Post-operative inguinal hernia repair/infiltration anesthesia
006154	Dblind/randomized/parallel/2 centers	NT1=Levobupivacaine 4 mL/kg 0.25%, NT2=Levobupivacaine 0.4 mL/0.5% AC=Bupivacaine 0.4 mL/0.5%	26/NT1 26/NT2 24/AC	54.5	49/27 75,0,1	Brachial plexus block for elective hand surgery
030543	Dblind/randomized/parallel/1 center	NT=Levobupivacaine 37.5-112,5 mg 0.75% AC=Bupivacaine 37.5-112.5 mg 0.75%	25/NT 25/AC	73.4	23/27 43,2,5	Ophthalmic surgery/peribulbar block
030737	Dblind/randomized/parallel/1 center	NT=Levobupivacaine 37.5 mg 0.75%, AC=Bupivacaine 37.5 mg 0.75%	25/NT 25/AC	77.1	20/40 60,0,0	Peribulbar block efficacy
030700	Dblind/randomized/parallel/1 center	NT=Levobupivacaine 67.5 mg 0.75%, AC=Lidocaine 2%; PLB=Placebo	31/NT1 32/AC 32/PLB	24.7	29/64 790, 0,14	Post-operative pain control/interior alveolar nerve block and infiltration

IV.1 Study 030428

IV.1.a. Study Design: The study was designed as a single-center, randomized, double-blind, parallel group (0.25% Levobupivacaine, 0.25% Bupivacaine) study conducted in the United Kingdom. The primary objective of the study was to compare the efficacy, safety and pharmacokinetics of Levobupivacaine with Bupivacaine as infiltration anesthesia.

IV.1.b. Efficacy and Safety Endpoints:
Primary measure – The primary efficacy endpoint was the normalized area under the VAS vs. Time curve over all available assessments (i.e. the area under the curve divided by the assessment time).

The secondary efficacy endpoints included post-operative pain, time to intake of analgesic, and the total amount of analgesic medication required.

Safety assessments included, heart rate, systolic and diastolic arterial (recorded before injection of the study drug, at 10, 20 and 30 minutes after completion of the injection and then every 30 minutes until 4 hours after completion of infiltration anesthesia), continuous ECG (monitored continuously until 30 minutes after completion of surgery).

All adverse events were recorded through out the study. A schedule of all study assessments was shown in Table IV.1.1.

Table IV.1.1 Schedule of Assessments (Based on Table 2.2 of NDA, page 26, vol.135)

			Time-point (Post-completion of Injection)																				
	Pre-surgery	Surgery	minutes							Hours							Discharge	Hours					
			0	5	10	15	20	30	45	1	1.5	2.0	2.5	3.0	3.5	4.0		6	8	12	24	36	48
Pre-surgery assessment	x																						
Vital Signs	x				x		x	x		x	x	x	x	x	x	x							
Pulse Oximetry	x																						
Continuous ECG	x	x	x	x	x	x	x	x															
VAS	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 medications	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																						

IV.1.c. Population for Analysis:

Primary efficacy variable was analyzed using the 'intent-to-treat' and "per-protocol" populations. The "intent-to-treat" population was defined as all randomized patients excluding patients that did not receive any of the study drug and patients who, during the study were found to have a combined indirect/direct hernia or femoral hernia. The "per-protocol" population consisted of all patients in the "intent-to-treat" population excluding those with 'major' protocol deviations. The population for safety analysis included all patients excluding those did not received the randomized study drug.

IV.1.d. Efficacy and safety analysis:

Methods:

The confirmatory efficacy analysis:

The primary efficacy endpoint analysis was the hypothesis testing to show whether the normalized area under the VAS vs. time curve over all available assessments was smaller in Levobupivacaine treatment group than in the Bupivacaine treatment group. The area under the VAS curve for each patient was obtained using the trapezoidal rule, the area being calculated up to the last completed assessment. Supposing the VAS score for any one patient at the i^{th} assessment were labeled VAS_i, I=1,2,..., 11 for t_1, t_2, ..., t_{36}, and t_{48}, respectively, then the formula for calculating a patient's AUC was as follows:

$$AUC = \sum_{i=2 \text{ to } T}(VAS_i + VAS_{i-1})(t_i - t_{i-1})/2$$

Where T was the last completed assessment.

When the i^{th} assessment prior to withdrawal, the missing value was replaced by the following value in the formula,

$$VAS_i = VAS_{i-1} + (VAS_i + VAS_{i-1})(t_i - t_{i-1})/(t_{i+1} - t_{i-1})$$

The AUC was normalized by $AUC/(t_T - 1)$.

The statistical hypotheses for testing the primary endpoint were as follow:

H_0: E (mean difference in the normalized area under the VAS vs. time curve over all available assessments between the treatment groups) = 0
H_a: E (mean difference in the normalized area under the VAS vs. time curve over all available assessments between the treatment groups) ≠ 0

The analysis of the primary endpoint was performed for each of the three VAS score of pain relief - measured at rest, rising from the supine to the sitting position and walking.

An ANCOVA model was used with terms for treatment. The consumption of relief medication was to be considered as covariate. For the ibuprofen covariate, a normalized dose taken over all assessments was used. If a patient reported until the n^{th} assessment, the normalized value was defined as

$$[y \bullet 600/(t_n - t_{0.50})]mg$$

Where y was the total tablets taken at during the time, $t_{0.50}$ = 30 minute, the minimum time required post injection before ibuprofen was to be taken.

The sample size was determined to be 33 evaluable patients per group. The sample size was determined based on the expectation that the between patient standard deviation at 15 mm in VAS score. Using this estimate, a 0.05 type I error rate, 80% power, the sample was enough to detect any difference larger or equal to 10 mm normalized VAS score.

The secondary efficacy response variables:

i. Relief medication of ibuprofen was normalized using the above formula was analyzed using an ANOVA model.
ii. Visual analogue pain score (VAS) with the analgesia was analyzed using an ANOVA model.
iii. The distribution of the global verbal rating scale of pain experienced was analyzed using a logit model.
iv. The normalized area under VAS score for post-operative pain (at rest in the supine position, rising from the supine to sitting position and walking) vs. time curve over all assessment until the first request for relief medication was using an ANOVA model.
v. The number of relief medication taken was compared between the two treatments was normalized by the dividing by the total assessment time and compared between the 2 treatments using an ANOVA model.

Safety Analysis

Vital signs, adverse events and the continuous ECG monitoring recorded up at least 30 minutes post-injection was discussed with no formal statistical analysis.

Results:

Subject disposition and withdrawals:

Treatment allocation – Sixty-seven patients enrolled and randomized into the two treatment groups with 33 in 0.25% Levobupivacaine, 34 in 0.25% Bupivacaine groups. One patient in the Bupivacaine group was excluded before dosing because of violation of inclusion criteria. The

sixty-six patients received study drugs formed the "safety " population and the "intent-to-treat " population. They were 10 patients in each group violated the protocol as they received anesthetics or analgesics other than the medications specified in the protocol during or after surgery. The remaining forty-six patients in the two groups formed the "per-protocol" population (Table IV.1.2).

Table IV.1.2 Treatment allocation and withdrawal (based on NDA Tables 1 to 6, pp. 103-108, vol. 135)

Event	Total	Treatment	
		0.25% Levobupivacaine	0.25% Bupivacaine
Entered	67	33	34
Failed inclusion criteria	1	0	1 (2.9%)
Intent-to-treat	66	33 (100.0%)	33 (97.1%)
Per-protocol	46	23	23
Received analgesics or anesthetics unspecified in protocol	20	10	10
Safety population	66	33	33

Demographic data:

The demographic characteristic details were given in NDA Table 7 (page 89, vol. 135). All patients in the study were white males with mean age of 57.4 yr. in Levobupivacaine group and 56.4 yr. in Bupivacaine group. The average weight was 74 kg in Levobupivacaine group and 76.31kg in the Bupivacaine group. The average height was 174.5 cm in Levobupivacaine group and 176.1 cm in the Bupivacaine group. Similar results were also obtained in the "per-protocol" population.

The summary of medical and surgical history of the patients was given in NDA Table II in page 56 vol. 135. The three most frequently occurring body systems in the medical/surgical history were 'circulatory system', 'digestive system' and 'genitourinary system'. The largest difference between treatment groups was under the body system 'digestive system', where 13 (39.4%) patients in the Levobupivacaine group and 19 (57.6%) in the Bupivacaine group reported having a significant medical/surgical history.

The summary of concomitant medications before the injection was given in NDA Table 11 on page 120, vol. 135. All patients in the "intent-to-treat" population reported taken medication for 'central nervous system'.

Efficacy Endpoints:

The study was designed to test for the superiority of Levobupivacaine over Bupivacaine in pain management. It was different to the testing for no-inferiority of Levobupivacaine to Bupivacaine or equivalence of the two treatments,

The normalized dosage of relief medication (Ibuprofen) was found significant buy sponsor in ANCOVA model of all area under the VAS versus time curve. Normal assumption of the model was found invalid. Since normalized dosage of rescue medication was a continuous variable and no appropriate nonparametric model applicable. Hence, an ANCOVA model and pairwise t-test was applied to the squared-root transformed data was chosen for the analysis after the normal assumption was not rejected for the squared-root transform data.

Primary efficacy endpoint -

The confirmatory analysis was carried out using the "intent-to-treat" population. The supine VAS score was analyzed statistically through the normalized area under the supine VAS curve over time

The mean normalized area under the supine VAS curve was slightly lower in the Bupivacaine group (10.69 mm.hr) than in the Levobupivacaine group (12.51 mm.hr). As proposed in protocol, the overall treatment difference was tested using ANCOVA adjusting for the covariate, normalized dosage of relief medication of Ibuprofen. It was found not statistically significant (p=0.63). The mean normalized area under the lying to sitting VAS curve was slightly lower in the Bupivacaine group (16.46 mm.hr) than in the Levobupivacaine group (16.72 mm.hr). The difference was not statistically significant (p=0.70). The mean normalized area under the walking VAS curve was greater in the Bupivacaine group (16.95 mm.hr) than in the Levobupivacaine group (13.89 mm.hr). The difference was not statistically significant (p=0.06). The 95% confidence interval for the mean differences in squared-root transformed data was given in Table IV.1.3. The reviewer found it difficult to interpret the confidence intervals. Analysis using the "pre-protocol" resulted in non-significant differences similar to the "intent-to-treat" population except for normalized area under the walking VAS versus time curve. For the analysis using "per-protocol" population, the Levobupivacaine group had a significantly small AUC than the Bupivacaine group with p=0.019.

Table IV.1.3 Analysis of efficacy endpoints (based on NDA Tables 17, 21, and 25, page 110-129, vol. 135)

Endpoint	0.25% Levobupivacaine	0.25% Bupivacaine	Difference* (95% CI)* p-value
Normalized area under VAS vs. time curve, supine, mean±SD	12.51±15.34	10.69±9.22	-0.19 (-0.994, 0.606) 0.63
Normalized area under VAS vs. time curve, rising to sitting, mean±SD	16.72±15.99	16.46±13.90	-0.16 (-0.996 0.670) 0.70
Normalized area under VAS vs. time curve, walking mean±SD	13.89±14.86	16.95±13.85	-0.74 (-1.516, 0.044) 0.06

*: Estimated for difference of squared-root transformed AUC value.

Secondary Efficacy Endpoints:

VAS score for satisfaction with the anesthetics – The mean VAS score was 72.9mm in the Levobupivacaine group and 80.0mm in the Bupivacaine group. The difference was not statistically significant (p=0.17 with ANOVA).

Global verbal rating scale of pain experienced during surgery – Most of the patients had slight to moderate pain (84.8% in Levobupivacaine and 87.9% in Bupivacaine). A logit regression model with the proportional odds was used. The proportional odds assumption was tested and not rejected. The odds ratio for the severity was 0.505 with 95% confidence interval =(0.189, 1.3437). The odds ratio was not statistically significant (p=0.17 with Chi-square test).

Normalized dosage of relief medication – The normalized dosage was 50.44 mg/hr in Levobupivacaine group and 50.53 in the Bupivacaine group. The median difference was 0.04 mg.h. The difference was found not statistically significant with p=0.55 (ANOVA).

Time to 1st dose of relief medication – The average time to the 1st dose was 11.22 hrs (median=6.85 min) in the Levobupivacaine group and 14.67 hrs (median=7.05 min) in the

Bupivacaine group. The survival time to the first dose was compared using log rank test. The difference between the two survival curves was not statistically significant (p=0.45).
Normalized area under supine VAS for post-operative pain vs. time curve – The mean normalized AUC was 5.52 mm.hr (median=1.813 mm.hr) in Levobupivacaine group and 7.04 mm.hr (median=3.171 mm.hr) in Bupivacaine group. The two groups were no statistically significant (p=0.27) when tested using a Wilcoxon test. Similar results were found in the analysis using the "per-protocol" population.

Normalized area under resting to sitting VAS for post-operative pain vs. time curve – The mean normalized AUC was 7.12 mm.hr (median=2.31 mm.hr) for the Levobupivacaine group and 8.20 mm.hr (median=3.36 mm.hr) for the Bupivacaine group. The difference was not statistically significant (p=0.42) when tested using a Wilcoxon test.
Normalized area under walking VAS for post-operative pain vs. time curve – The normalized AUC was 6.81 mm.hr (median=2.31 mm.hr) for the Levobupivacaine group and 9.62 mm.hr (median=5.16 mm.hr) for the Bupivacaine group. The difference was not statistically significant (p=0.10) when tested using a Wilcoxon test. The analysis using the "per-protocol" population gave similar results.

Table IV.1.4 Analysis of secondary efficacy endpoints (based on NDA Tables 17.1, pp.116, vol.122)

Endpoint	0.25% Levobupivacaine	0.25% Bupivacaine	Diff (95%CI) p-value
Total dose of study drug n (%)			
< 50 ml	0 (0.0%)	1 (3.0%)	p=0.385*
50 ml	28 (84.8%)	29 (87.9%)	
> 50 ml	5 (15.2%)	3 (9.1%)	
VAS scores for satisfaction with the anesthetics mean±SD	72.±18.6	80.0±15.3	-5.8 (-14.1, 2.6) 0.17**
Global verbal rating scale of pain experienced during surgery n (%)			Odds ratio = 0.505 CI for Odds ratio
Nil	3 (9.1%)	4 (12.1%)	= (0.189, 1.347)
Slight	18 (54.5%)	22 (66.7%)	
Moderate	10 (30.3%)	7 (21.2%)	p=0.17***
Severe	2 (6.1%)	0 (0.0)	
Normalized dosage of relief medication (mg/hr), mean±SD	50.44±27.65	50.53±27.82	0.04 (-0.581, 24.82) 0.55**
Time (hrs) to 1st dose of relief medication			Relative risk = 0.333
Censored observations n (%)	2 (6.1)	6 (18.2)	(0.072, 1.533)
Uncensored observations n (%)	31 (93.9)	27 (81.8)	p=0.258***
Time (hrs) to 1st dose of relief medication Mean	11.22	14.67	p=0.45****
Normalized area under supine VAS for post-operative pain vs. time curve, mean±SD	5.52±8.87	7.04±8.75	0.021 (-2.544, 1.810) 0.27**
Normalized area under resting to sitting VAS for post-operative pain vs. time curve, mean±SD	7.13±10.26	8.20±9.91	0.0016 (-2073, 2.676) 0.42**
Normalized area under walking VAS for post-operative pain vs. time curve, mean±SD	6.81±10.275	9.618±11.803	-0.329 (-3.994, 1.813) 0.10**
Normalized number of relief medications taken, mean±SD	0.102±0.069	0.088±0.066	0.013 (-0.020, 0.047) 0.42**

*: Chi-square test for distribution difference.
**: ANOVA for treatment effect.
***:Chi-square for relative risk.
****: Log rank test.

Number of relief medication taken – The mean normalized number of medication was 0.102 meds/hr (median=0.102 meds/hr) for the Levobupivacaine group and 0.088 meds/hr (median=0.084 meds/hr) for the Bupivacaine group. The difference was not statistically significant (p=0.42) when tested using ANOVA.

Total dose of study drug – there was 84.8% in the Levobupivacaine group and 87.9% in the Bupivacaine group had 50 ml of the study drug. There was no statistically significant difference in the distribution of the dose between the two treatment groups (p=0.285 of chi-square test).

Safety analysis -
Adverse events - There were 10 patients in the Levobupivacaine group and 13 in the Bupivacaine group had adverse events. Most events had lower than 10% event rate in each group except gastrointestinal system disorder (15.2%) and platelet, bleeding and clotting disorders (12.1%) in the Bupivacaine group. Eight (24.2%) of the patients in Levobupivacaine group and 11 (33.3%) in the Bupivacaine group were considered as having drug related adverse events.

Vital signs - There were no evidence of any difference between the two groups in any vital sign change from baseline measurement.

IV.1.f. The Reviewer's Comments on Efficacy
This study was designed to evaluate the efficacy and safety of 0.25% Levobupivacaine as infiltration anesthesia. It was designed with 0.25% Bupivacaine as the active control. Statistically, the study was design to demonstrate the efficacy of Levobupivacaine through superiority testing by rejecting the following null hypothesis,

H_0: E (mean difference in the normalized area under the VAS vs. time curve over all available assessments between the treatment groups) = 0

Primary endpoint: The confirmatory analysis was carried out using the "intent-to-treat" population. The mean normalized area under the supine VAS curve was slightly lower in the Bupivacaine group (10.69 mm.hr) than in the Levobupivacaine group (12.51 mm.hr). The 95% confidence interval of the difference was (-0.994, 0.606). The difference was not statistically significant (p=0.63). The mean normalized area under the lying to sitting VAS curve vs. time was slightly lower in the Bupivacaine group (16.46 mm.hr) than in the Levobupivacaine group (16.72 mm.hr). The 95% confidence interval of difference was (-0.996, 0.670). The difference was not statistically significant (p=0.70). The mean normalized area under the supine VAS curve was slightly greater in the Bupivacaine group (16.95 mm.hr) than in the Levobupivacaine group (13.89 mm.hr). The 95% confidence interval of the difference was (-1.516, 0.044). The difference was not statistically significant (p=0.06). All the comparison was done with ANOVA and there was not adjustment for multiple endpoints used in the primary analysis. The p-values would be less significant when compared with the type I error adjusted for multiple endpoints. The evidence of this study failed to support that there was any difference in the mean normalized area under the VAS vs. time curve. However, the lack of evidence to reject the above null hypothesis was not evidence to support the claim that the Levobupivacaine treatment was equivalent to the Bupivacaine treatment as infiltration anesthesia. On the other hand, the 95% confidence intervals of three normalized areas were all bounded within the limit

of 1.6 mm.hr.

Secondary endpoints: There was no statistically significant difference between the two treatment group in total dose of study drug, VAS score for satisfaction with the anesthetics, global verbal rating scale of pain experienced during surgery, normalized dosage of relief medication over time, normalized area under the curve of either supine, lying to sitting or walking VAS for post-operative pain vs. time, and time to 1st dose of relief medication,

Safety: There were 10 patients in the Levobupivacaine group and 13 in the Bupivacaine group had adverse events. All the events had an event rate of less than 10% in each group except platelet, bleeding and clotting disorders (24.2% in Levobupivacaine and 33.3% in Bupivacaine). There was no evidence of significant difference between the two treatments. There was also no evidence of difference in vital signs monitored through the study between the two treatments.

IV.2 Study 030721

IV.2.a. Study Design: The study was designed as a single-center, randomized, double-blind, two-arm parallel group study conducted in the United Kingdom. The primary objective of the study was to compare the efficacy of 0.25% Levobupivacaine with 0.25% racemic Bupivacaine when used for infiltration anesthesia. The second objective was the comparison of the safety profiles of the two treatments

IV.2.b. Efficacy Measurements:
The efficacy measurements included

1. VAS (visual analogue scale) of post-operative pain made by patients while they were at rest in the supine position, rising from the supine to sitting position.
2. Global verbal rating of any pain experienced during surgery completed immediately following the surgery.
3. VAS of satisfaction with the anesthesia made by patients.
4. Peri-operative bleeding assessed by surgeon.
5. Time to intake of first analgesia.
6. Amount of analgesia taken.

The safety measurements included ECGs, adverse events and drug concentration measurements. The assessments were scheduled as in Table IV.2.1.

Table IV.2.1 Schedule of assessments (based on NDA Table of Schedule of assessment, page 23, vol. 137)

Assessment	Pre-surgery	Surgeryr	Timepoint (post injection)																							
			Minutes							Hours											Discharge	Hours				
			0	5	10	15	20	30	45	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6		8	12	24	36	48
Written consent	x																									
Screening assessment	x																									
Peri-surgery bleeding		X																								
ECG monitoring	x	X	x	x	x	x	x	x																		
Pulse oximetry monitoring	x	X	x	x	x	x	x	x																		x
Vital signs	x				x		x	x		x	x	x	x	x	x	x	x	x	x	x						
12-lead ECG	x	x													x											x
VAS		x								x		x		x		x		x		X						
PK Sample	x	x		x		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	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	x	x	x	x

IV.2.c. Efficacy and Safety Analysis:

Methods:

The confirmatory efficacy analysis:

The primary efficacy endpoint was the normalized area under the VAS vs. time curve observed post surgery. The normalized AUC was calculated for VAS accessed at rest in the supine position, rising from the supine to the sitting position and in walking position. The statistical null hypothesis to be tested for superiority was,

H_0: E (mean difference in normalized AUC under the VAS vs. time curve of 0.25% Levobupivacaine)

= E (mean difference in normalized AUC under the VAS vs. time curve of 0.25% Bupivacaine)

The hypothesis was tested using ANOVA. Sequential type I error rates of 0.017/ 0.025/0.05 adjusted for 3 endpoints using Bonferroni-Holm approach were used for significance testing. The sample size was determined to be 33 evaluable patients per group for the analysis of the primary endpoint. The sample size was determined based on the assumptions,

- the expectation of 15 mm between treatment difference
- 10 mm.hr of between patients standard deviation
- 5% significance level and 80% power
- 2-sided t-test

The secondary efficacy response variables:

The difference in VAS (visual analogue scale) of satisfaction with analgesia was tested using a Wilcoxon rank sum test. Global verbal rating had 4 ordinal categories (Nil, slight, moderate or severe) and was analyzed using logit model and odds ratio (Levobupivacaine /Bupivacaine) for higher rating was calculated. The normalized dosage of relief medication of the two treatments was also compared using a Wilcoxon's rank sum test because of non-normal distribution of the data. The curve of time to first relief medication was estimated using the Kaplan-Meier method. Difference between the two treatments was also analyzed using the Wilcoxon rank sum test.

Safety Analysis
The summary of the adverse events, summary of adverse event by severity of event, summary of events by relationship to the study drug and summary serious adverse events was tabulated. Data of vital sign and urinalysis were summarized and tabulated.

Population for Analysis
The 'intent-to-treat' population was defined as all randomized patients excluding the following,

- Patients who did not receive any study drug.
- Patients who during the study were found to have a combined indirect/direct hernia or femoral hernia.

The 'per-protocol' population was defined as all patients included in the 'intent-to-treat' population excluding those who received a non-protocol anesthetic.

'Safety' population was defined as all randomized patients.

Results:
Patient disposition and withdrawals:
The patient disposition chart was given in Table IV.2.2.

Table IV.2.2 Patient disposition chart (based on NDA Tables 1 to 6, page 102-107, vol. 137)

Status	Treatment	
	0.25% Levobupivacaine	0.25% Bupivacaine
Enrolled	35	34
Safety Population	35	34
Intent-to-treat population	35	34
Patient had a recurrent hernia	1	2
Patient received non-protocol analgesia	4	2
Per-protocol population	30	30

Demographic data:
All patients in the study (the safety and the intent-to-treat population) were Caucasians. The average age was 55.5 years for the Levobupivacaine group and 61.4 years for the Bupivacaine group. The Levobupicavaine group had an average weight of 79.7 kg and the Bupivacaine group had an average of 75.8 kg. The average height was 174.9 cm for the Levobupivacaine group and 177.6 cm for the Bupivacaine group.

The medical history of the patients was summarized in NDA Table 8. Twenty-seven (77.1%) patients had significant medical/surgical history in the Levobupivacaine group compared with 32 patients (94.1%) in the Bupivacaine group. The most frequent procedures were of, musculoskeletal system and connective tissues, genitourinary system, circulatory system, respiratory system, digestive system, nervous and sense system and symptoms and ill-defined conditions.

Efficacy Endpoints:
Primary efficacy endpoints –
Supine VAS scores for post-operative pain: As shown in NDA Figure 1, the peak score of the Levobupivacaine was at the 24 hours compared with the 36 hours of the Bupivacaine group. In

general, the Levobupivacaine group had slightly higher score than the Bupivacaine group between 2 and 6 hours after surgery. In the 'intent-to-treat' population, the Levobupivacaine group had lower mean AUC (7.86 mm.hr), compared with the Bupivacaine group (8.01 mm.hr). The difference was not statistically significant (p=1.00)(Table IV.2.3). Analysis using the "per-protocol" population gave similar results.

Rising VAS scores for post-operative pain: As shown in NDA Figure 3, the peak score of the Levobupivacaine was at the 24 hours compared with at the 36 hours for the Bupivacaine group. In general, the Levobupivacaine group had slightly higher score than the Bupivacaine group between 2 and 24 hours after surgery. In the 'intent-to-treat' population, the Levobupivacaine group had lower mean AUC (17.57 mm.hr), compared with the Bupivacaine group (16.12 mm.hr). The difference was not statistically significant (p=0.71)(Table IV.2.3). Analysis using the "per-protocol" population gave similar results.

Walking VAS scores for post-operative pain: As shown in NDA Figure 5, the peak score of the Levobupivacaine was at the 12 hours compared with the 36 hours of the Bupivacaine group. In general, the Levobupivacaine group had slightly higher score than the Bupivacaine group between 4 and 24 hours after surgery. In the 'intent-to-treat' population, the Levobupivacaine group had larger mean AUC (14.41 mm.hr), compared with the Bupivacaine group (12.88 mm.hr). The difference was not statistically significant (p=0.74)(Table IV.2.3). Analysis using the "per-protocol" population gave similar results.

All analysis of normalized area under the VAS versus time curve was carried out with ANCOVA model. Since the normality assumption for the normalized AUC was tested to be invalid. ANCOVA was applied to the squared root transformed data after the normal distribution assumption was verified. Sponsor estimated the 95% confidence of the mean difference of the squared root transformed data. But the interpretation of the confidence interval of difference of square rooted data was difficult.

Table IV.2.3 Normalized AUC of VAS for post-operative pain (based on Tables 12-25, pages 133-154, vol. 137)

VAS AUC	0.25% Levobupivacaine	0.25% Bupivacaine
Supine VAS AUC		
Mean ± SD	7.86±7.77	8.01±11.19
ANOVA	P = 1.00	
Rising VAS AUC		
Mean ± SD	17.57±11.68	16.12±14.81
ANOVA	P = 0.71	
Walking VAS AUC		
Mean ± SD	14.41±11.37	12.88±14.10
ANOVA	P = 0.74	

Secondary Efficacy Points:

VAS of satisfaction: The Levobupivacaine group had a slightly lower mean and median score than the Bupivacaine group (mean: 87.09 mm vs. 87.65 mm, median: 95.00 mm vs. 95.50 mm). The difference between the groups was not statistically significant (p=0.91), when tested using a Wilcoxon rank sum test (Table IV.2.4). Analysis using the "per-protocol" population gave similar results.

Global verbal rating score: There was no overall difference between the two treatments in the frequency distribution of the four categories (p=0.292 likelihood ratio test). The proportion of patients had nil or slight pain was lower in the Levobupivacaine group (91.5%) than the Bupivacaine group (79.4%). When combined the category of 'nil' and 'slight' as 'no pain' and combined 'moderate' and 'severe' as 'yes pain' group then the relative risk for pain was estimated. The Levobupivacaine-to-Bupivacaine relative risk for 'yes pain' was 0.416 which was not significantly different from 1 (p=0.188 Fisher's exact test) with 95% confidence interval being (0.117, 1.479) (Table IV.2.4). This analysis was carried out by the statistical reviewer using relative risk instead of difference in percentage as reported by the sponsor. Although the p-value of the Fisher's exact test was different from the p-value based on logit model as given by the sponsor, the results were consistent.

Normalized dosage of relief medication: There average dosage of relief medication for the Levobupivacaine group was 52.8 mg/hr (median=54.90 mg/hr), compared with 43.2 mg/hr (median=48.52 mg/hr) for the Bupivacaine group. The median difference between the treatments was 12.21 mg/hr. The two treatment was not statistically significant different when compared using a Wilcoxon rank sum test (p=0.11). A more significant p-value of 0.041 was shown in the analysis using the "per-protocol" population.

Time to first dose of relief medication: There were 5 patients in the study did not have any relief medication (1 in the Levobupivacaine group, 4 in the Bupivacaine group). The proportions of censored patients were not significantly different when tested using a likelihood ratio test (p=0.141). Including the censored patients, the Levobupivacaine group had a shorter median time to first dose of relief medication (9.33 hours) than the Bupivacaine group (10.22 hours). When tested with the log rank test for the survival time the difference between the 2 treatments was not statistically significant (p=0.385)(Table IV.2.4). Analysis using the "per-protocol" population gave similar results.

Table IV.2.4 Secondary efficacy endpoints (based on Tables 26, pages 155, vol. 137)

Endpoint	0.25% Levobupivacaine	0.25% Bupivacaine
VAS for satisfaction with the analgesia		
Median	95.00	95.50
Mean ± SD	87.09±22.41	87.65±20.40
Levobupivacaine – Bupivacaine median	Diff. = 0.00, 95% CI = (-2.00, 3.00)	
Wilconxon rank sum test	P = 0.91	
Global verbal rating of pain experienced during surgery		
Frequency N(%) Nil Slight Moderate Severe	 12 (34.3%) 20 (57.2%) 2 (5.7%) 1 (2.9%)	 14 (41.2%) 13 (38.2%) 6 (17.6%) 1 (2.9%)
Testing for distribution difference	P=0.292 (Likelihood ratio chi-square)	
Relative risk for moderate + severe (Levobupivacaine/Bupivacaine)	RR=0.416, 95% CI =(0.117, 1.479), p=0.188 (Fisher's exact test)	
Normalized dosage of relief medication		
Median	54.9	48.5
Mean ± SD	52.8±25.8	43.2±27.7
Levobupivacaine – Bupivacaine median	Diff. = 12.21, 95% CI = (-0.46, 25.26)	
Wilcoxon rank sum test	P = 0.11	

Time to 1st dose of relief medication		
Patients did not take any relief medication in the 48 hours	1 (2.9%)	4 (11.8%)
Comparison of equal proportion of censoring	P=0.141 (likelihood ratio test)	
Median (including censored patients)	9.50 hrs	9.58 hrs
Log rank test for survival time difference	P=0.385	

Safety Analysis:

There were fewer patients with adverse events and fewer adverse events for the Levobupivacaine group (25 patients with 59 events) than for the Bupivacaine group (27 patients with 83 events). There was one patient in the Levobupivacaine group had a severe adverse event. Twenty patients (58.8%) of the Levobupivacaine group had drug related adverse event and 19 (57.6%) of the Bupivacaine group had drug related adverse events. There were 3 (8.8%) patients in the Levobupivacaine group had serious adverse events and 2 patients (6.1%) in the Bupivacaine group had serious adverse events. The most frequent adverse events were body as a whole, cardiovascular system, central and peripheral nervous system and gastro-intestinal disorders (Table IV.2.5).

Table IV.2.5 Adverse events (based on NDA Tables 34 to 37, pp.164-179, vol.137)

Variable	0.25% Levobupivacaine	0.25% Bupivacaine
Number of patients with adverse events, N (%)	25 (73.5%)	27 (82.8%)
Number of patients with severe adverse events, N (%)	1 (2.9%)	0 (0.0%)
Number of patients with drug related adverse events, N (%)	20 (58.8%)	19 (57.6%)
Number of patients with serious adverse events, N (%)	3 (8.8%)	2 (6.1%)
Number of adverse events	59	83
Frequent adverse event by body system, N(%)		
Body as a whole	6 (17.1%)	6 (17.6%)
Cardiovascular	16(45.7%)	19 (55.9%)
Central & peripheral nervous system disorders	6 (17.1%)	7 (20.6%)
Gastro-intestinal system disorders	8 (22.9%)	11 (32.4%)
Possible or definite study drug related adverse event by body system,	28	33
Body as a whole	1	0
Cardiovascular disorders	16	17
Central & peripheral nervous system disorders	2	5
Gastro-intestinal system disorders	5	5
Heart rate & rhythm disorders	3	5
Myo endo pericardial	1	1
Serious adverse events	3	2
Body as a whole	1	1
Cardiovascular disorders	1	1
Central & peripheral nervous system disorders	1	0
Gastro-intestinal system disorders	0	0
Heart rate & rhythm disorders	0	0

Vital signs – The mean supine heart rates of the two groups over time were shown in NDA Figure 9. Patients of the Levobupivacaine group had heart rate returned to pre-dose value at 3 and half-hours while the patients of the Bupivacaine group remained lower than the pre-dose value until 6 hours. The mean supine systolic blood pressures over time were shown in NDA Figure 10. The systolic blood pressure remained lower than the pre-dose value in the six hours after dosing in both groups. The Levobupivacaine group maintained a slightly lower value than the Bupivacaine group during the 2 to 6 hours after dosing. The mean supine diastolic blood pressure over time was shown in NDA Figure 11. Both groups had a pressure, which was lower than its pre-dose value during the 6 hours after dosing. There was not much difference

between the two groups.

IV.2.e. The Reviewer's Comments and Conclusions

Primary efficacy analysis:

The study was designed to test against the null hypothesis that there was no difference in the normalized area under the VAS score for post-operative pain versus time curve between the Levobupivacaine and Bupivacaine group. This study failed to provide statistical evidence that the Levobupivacaine treatment was superior to the Bupivacaine treatment in post-operative analgesia. The difference could be summarized below.

The supine VAS score of the Levobupivacaine was peaked at the 24 hours post surgery compared while it peaked at the 36 hours in the Bupivacaine group. In general, the Levobupivacaine group had slightly higher score than the Bupivacaine group between 2 and 6 hours after surgery. In the 'intent-to-treat' population, the Levobupivacaine group had lower mean AUC (7.86 mm,hr), compared with the Bupivacaine group (8.01 mm.hr), but the difference was not statistically significant (ANOVA). The rising VAS scores for post-operative pain of the Levobupivacaine group was peaked at the 24 hours, while it was peaked the 36 hours in the Bupivacaine group. In general, the Levobupivacaine group had slightly higher score than the Bupivacaine group between 2 and 24 hours after surgery. In the 'intent-to-treat' population, the Levobupivacaine group had lower mean AUC (17.57 mm.hr), compared with the Bupivacaine group (16.12 mm.hr). The difference was not statistically significant (ANCOVA). The walking VAS scores for post-operative pain of the Levobupivacaine group was peaked at the 12 hours whilst it peaked at 36 hour in the Bupivacaine group. In general, the Levobupivacaine group had slightly higher score than the Bupivacaine group between 4 and 24 hours after surgery. In the 'intent-to-treat' population, the Levobupivacaine group had lower mean AUC (13.87 mm.hr), compared with the Bupivacaine group (11.72 mm.hr). The difference was not statistically significant (ANCOVA).

Secondary efficacy endpoints:

There was no statistically significant difference between the two treatments in VAS of satisfaction of analgesia, global rating score of pain during surgery, normalized dose of relief medication and time to first relief medication. The difference between the two treatments could be summarized in the following paragraph.

The Levobupivacaine group had a slightly lower mean and median VAS score of satisfaction of the surgery than the Bupivacaine group (mean: 87.09 mm vs. 87.65 mm, median: 95.00 mm vs. 95.50 mm). The difference between the groups was not more than 3 mm. There was no statistically significant overall difference between the two treatments comparing the frequency distribution of the four categories of global verbal rating score (p=0.292). The proportion of patients checked nil or slight pain in global verbal rating of pain was higher in the Levobupivacaine group (91.5%) than the Bupivacaine group (79.4%). When combined the category of 'nil' and 'slight' as 'no pain' and combined 'moderate' and 'severe' as 'yes pain' group then the relative risk for pain was estimated. The Levobupivacaine-to-Bupivacaine relative risk for 'yes pain' was 0.416 but can't rule out a possible 45% higher risk. There was higher average normalized dosage of relief medication for the Levobupivacaine group (52.8 mg/hr) than the Bupivacaine group (43.2 mg/hr). The median difference between the treatments was 12.21 mg/hr but can't rule out a possible median difference of 25 mg/hr. There

were 5 patients in the study did not have any relief medication (1 in the Levobupivacaine group, 4 in the Bupivacaine group). The proportion of patients did not require relief medication was not significantly different (likelihood ratio test). The Levobupivacaine group had a shorter median time to first dose of relief medication (9.33 hours) than the Bupivacaine group (10.22 hours).

Safety analysis:
There were fewer patients with adverse events and fewer adverse events for the Levobupivacaine group (25 patients with 59 events) than for the Bupivacaine group (27 patients with 83 events). There was one patient in the Levobupivacaine group had a severe adverse event. Twenty patients (58.8%) of the Levobupivacaine group had drug related adverse event and 19 (57.6%) of the Bupivacaine group had drug related adverse events. There were 3 (8.8%) patients in the Levobupivacaine group had serious adverse events and 2 patients (6.1%) in the Bupivacaine group had serious adverse events. The most frequent adverse events were body as a whole, cardiovascular system, central and peripheral nervous system and gastro-intestinal disorders

Supine heart rate dropped sharply once dosing started. Patients of the Levobupivacaine group had supine heart rate returned to pre-dose value at 3 and half-hours while the patients of the Bupivacaine group remained lower than the pre-dose value until 6 hours. Both systolic and diastolic blood pressures dropped sharply once the dosing started in both treatment groups. The systolic blood pressure remained lower than the pre-dose value in the six hours after dosing in both groups. The Levobupivacaine group maintained a slightly lower value than the Bupivacaine group during the 2 to 6 hours after dosing. Both groups had very similar diastolic pressure values that were lower than their pre-dose values during the 6 hours after dosing.

IV.3 Study 006154

IV.3.a. Study Design: This was a randomized, double blind, 3 limb parallel group (Levobupivacaine -0.4 ml/kg body weight of Levobupivacaine 0.25% or 0.5% and 0.4 ml/kg body weight of Bupivacaine 0.5%) study conducted in two centers in the United Kingdom.

IV.3.b. Efficacy and Safety Endpoints:
The primary efficacy measure was sensory block. Assessments were performed at 2, 5, 10, 15, 20, 25 and 30 minutes post dose and ten every 20 minutes until complete perverse of the block.

The secondary efficacy endpoints included motor block and overall assessment of the quality of the block during the operation.

Safety was measured by adverse events, hematological and clinical measurement, ECG.

IV.3.c. Population for Analysis:
The 'intent-to-treat' population was defined as all randomized patients excluding the patients who did not receive any study drug, or the patients during the administration procedure suffered an incidental intravascular puncture resulting in immediate withdrawal form the study.

The 'per-protocol' population was defined as all patients included in the 'intent-to-treat' population excluding those who received a non-protocol anesthetic.

'Safety' population was defined as all randomized patients.

IV.3.d. Efficacy analysis:

Methods:

Duration of sensory block was defined in protocol as, time from onset of sensory block to the complete return of sensory touch.

In the event of intervention, the duration was recorded as the time from onset of sensory block to the time of intervention.

The study was designed to test for the following null hypothesis,

H_0: E (duration of sensory block of 0.25% Levobupivacaine group)
= E (duration of sensory block of 0.5% Levobupivacaine group)
= E (duration of sensory block of 0.5% Bupivacaine group)

If H_0 was rejected, multiple testing for the following three null hypotheses were carried out,
H_{10}: E (difference in mean duration of sensory block between the 0.5% Levobupivacaine group and 0.5% Bupivacaine group) =0

H_{20}: E (difference in mean duration of sensory block between the 0.5% Levobupivacaine group and 0.25% Levobupivacaine group) =0

H_{30}: E (difference in mean duration of sensory block between the 0.25% Levobupivacaine group and 0.5% Bupivacaine group) =0.

A flat type I error rate of 0.017 adjusted for multiple comparison using Bonferroni-Holm approach was used.

The primary efficacy endpoint was analyzed using ANOVA with treatment, center and treatment-by-center interaction as the three factors. The pairwise comparison was done with t-test.

The sponsor also redefined the duration of sensory block after the data was the blindness was broken, as, time to onset of sensory block until complete return of sensory touch, irrespective of whether a general analgesic was given.

The secondary efficacy endpoint, duration of motor block was also redefined in the similar way after the blindness was broken.

The sample size was determined to be 25 patients per group. With this sample size, the study would have 80% power to reject the null hypothesis based if the true difference between 2 treatment was no less than 4 hours, based on a 2-sided t-test approach at 5% type error rate and a standard deviation of 5 hours (based on a previous study). On the other hand, the power was less than 0.50 if the difference was less than 2 hours.

The secondary efficacy response variables:
Duration of motor block was analyzed using the same method as for the primary endpoint. The overall assessment of quality block was a discrete variable. The variable was redefined as treatment failure if the score was 0 or 1 and as treatment success if the score was 2. It was analyzed using logistic regression.

The safety variables:
The adverse events were summarized. The vital signs (including heart rate, systolic blood pressure and diastolic blood pressure and mean arterial pressure) were compared between the treatment using ANOVA.

Results:
Subject disposition and withdrawals – The randomized, intent-to-treat, per-protocol, safety and primary efficacy analysis populations were defined in Table IV.3.1.

Table IV.3.1 Patient disposition for efficacy and safety analysis (NDA Table 1 and Tables L1.1-L1.3, pp. 30 and pages 310-312, vol. 139)

Status	Treatment			Total
	0.25% Levobupivacaine	0.5% Levobupivacaine	05% Bupivacaine	
Randomized (Safety Population)	26	26	24	76
Center #1	16	16	16	48
Center #2	10	10	8	28
Intent-to-Treat Population	25	26	23	74
Adverse reaction before dosing	1	0	0	1
Protocol violation	0	0	1	1
Pr-protocol Population	20	22	22	64
Received non-study medication	5	4	1	10

Demographic and Baseline Characteristics:
Of the "safety " population of 76 patients, 49 (64.5%) were males and 27 (35.5%) were females. The mean age was 54.42 years. The proportions of female and mean age were similar in all treatment groups. The safety population had an average height of 169.54 cm and average weight of 70.95 kg. The treatment groups were similar with respect to mean height and weight.

Patterns of medical history and concomitant medication were also similar across the treatment groups.

Primary Efficacy Endpoint:
There was 1 patient in the 0.5% Levobupivacaine group and 1 patient in the Bupivacaine group did not attain sensory block. Duration was defined in the protocol as the time from onset of sensory block until complete return of sensory block except a general anesthetic was given. In the event of intervention, duration was taken as the time from onset until intervention. The 0.5% Levobupivacaine group had the longest mean duration (1028.7 min) than either the 0.5% Bupivacaine group (836.5 min) or the 0.25% Levobupivacaine group (662.4 min). Treatment effect was shown to be statistically significant (p=0.016) in the analysis using an ANOVA model with treatment, center and treatment-by-center interaction as factors. In the pairwise

comparison using t-test, the difference between the 0.5% Levobupivacaine and the 0.25% Levobupivacaine group was statistically significant (p=0.004)(Table IV.3.2). There was no difference between any two treatments groups in mean duration using the definition revised by the sponsor after the blind was broken. There was no statistically significant difference in mean time to onset of sensory block between the treatments (Table IV.3.2).

Results from the sponsor's analysis using the "per-protocol" population were found there were no statistically significant difference between any two treatments (NDA Tables M1.2.1-M1.2.3, pages 373-375, vol 139).

The analysis was done excluding patients who did not achieve sensory block. If the two patients were to be included in the study they would be assigned a value of zero. Moderate change from the results reported in NDA would be expected. But the changes were not expected to be large enough to change the interpretations.

Table IV.3.2 Duration of sensory block (NDA Tables M1.1.1-M1.1.3, pp. 367-369, vol. 139)

Endpoint	Treatment		
	0.25% Levobupivacaine	0.5% Levobupivacaine	05% Bupivacaine
Number of patients without a sensory block	0	1 (4%)	1 (4%)
Number of patients in the following analysis	25	24	22
Duration defined in protocol			
Mean (in min)	662.4	1028.7	836.5
Least square mean (adjusted for unequal sizes)	666.9	1014.8	854.0
ANOVA p-value	Treatment effect p=0.02	Center effect p=0.90	Interaction p=0.53
Pairwise comparison	Difference	95% CI	p-value
0.5% Bupivacaine –0.25% Levobupivacaine	187.1	(-60.1, 434.4)	0.14
0.5% Bupivacaine – 0.5% Levobupivacaine	-160.7	(–407.3, 85.8)	0.20
0.5% Levobupivacaine –0.25% Levobupivacaine	347.9	(113.2, 582.5)	0.004
Duration revised by sponsor			
Mean (in min)	891.4	1039.2	895.9
Least square mean (adjusted for unequal sizes)	896.5	1027.4	912.7
ANOVA p-value	Treatment effect p=0.25	Center effect p=0.93	Interaction p=0.38
Pairwise comparison	Difference	95% CI	p-value
0.5% Bupivacaine –0.25% Levobupivacaine	16.4	(-160.9, 193.6)	0.85
0.5% Bupivacaine – 0.5% Levobupivacaine	-114.7	(–291.4, 62.0)	0.20
0.5% Levobupivacaine –0.25% Levobupivacaine	131.1	(-37.1, 299.3)	0.12
Time to onset			
Mean (in min)	6.9	5.8	8.2
Least square mean (adjusted for unequal sizes)	6.4	5.5	7.4
ANOVA p-value	Treatment effect p=0.55	Center effect p=0.01	Interaction p=0.98
Pairwise comparison	Difference	95% CI	p-value
0.5% Bupivacaine –0.25% Levobupivacaine	1.1	(-2.6, 4.7)	0.57
0.5% Bupivacaine – 0.5% Levobupivacaine	2.0	(–1.6, 5.6)	0.28
0.5% Levobupivacaine –0.25% Levobupivacaine	-0.9	(-4.4, 2.5)	0.59

Secondary Efficacy Endpoints:

Motor block - There were 2 patients in the 0.5% Levobupivacaine group and 2 patients in the Bupivacaine group did not attain motor block. All patients who did not attain motor block were excluded from the corresponding analysis. Duration was defined in the protocol as the time from onset of motor block until complete return of motor block except a general anesthetic was given. In the event of intervention, duration was taken as the time from onset until intervention. The 0.5% Levobupivacaine group had the longest mean duration (1049.7 min) than either the 0.5% Bupivacaine group (851.9min) or the 0.25% Levobupivacaine group (634.1 min). Treatment effect was shown to be statistically significant (p=0.003) in the analysis using an ANOVA model with treatment, center and treatment-by-center interaction as factors. In the pairwise comparison using t-test, the difference between the 0.5% Levobupivacaine and the 2.5% Levobupivacaine group was statistically significant (p<0.001)(Table IV.3.3). There was no difference between any two treatments groups in mean duration using the definition revised by the sponsor after the blind was broken. There was no difference in the time to onset of motor block between the treatments (Table IV.3.3).

The analysis was done excluding patients who did not achieve sensory block. If the four patients were to be included in the study they would be assigned a value of zero. Moderate change from the results reported in NDA would be expected. But the changes were not expected to be large enough to change the interpretations.

Table IV.3.3 Duration of motor block (NDA Tables M1.1.4-M1.1.6, pp. 370-372, vol. 139)

Endpoint	Treatment		
	0.25% Levobupivacaine	0.5% Levobupivacaine	05% Bupivacaine
Number of patients without a sensory block	0	2 (8%)	2 (9%)
Number of patients in the following analysis	25	23	21
Duration defined in protocol			
Mean (in min)	634.1	1049.7	851.9
Least square mean (adjusted for unequal sizes)	638.1	1037.0	895.7
ANOVA p-value	Treatment effect p=0.003	Center effect p=0.65	Interaction p=0.45
Pairwise comparison	Difference	95% CI	p-value
0.5% Bupivacaine –0.25% Levobupivacaine	257.6	(17.9, 497.4)	0.036
0.5% Bupivacaine – 0.5% Levobupivacaine	-141.3	(–382.3, 99.6)	0.25
0.5% Levobupivacaine –0.25% Levobupivacaine	399.0	(176.2, 621.8)	<0.001
Duration revised by sponsor			
Mean (in min)	846.8	1049.7	932.5
Least square mean (adjusted for unequal sizes)	848.5	1037.0	952.1
ANOVA p-value	Treatment effect p=0.082	Center effect p=0.99	Interaction p=0.55
Pairwise comparison	Difference	95% CI	p-value
0.5% Bupivacaine –0.25% Levobupivacaine	103.6	(-74.4, 281.6)	0.25
0.5% Bupivacaine – 0.5% Levobupivacaine	-84.9	(–263.8, 94.0)	0.35
0.5% Levobupivacaine –0.25% Levobupivacaine	188.5	(23.1, 353.9)	0.026

Time to onset			
Mean (in min)	8.8	5.3	6.1
Least square mean (adjusted for unequal sizes)	10.2	5.6	6.4
ANOVA p-value	Treatment effect p=0.33	Center effect p=0.09	Interaction p=0.35
Pairwise comparison	Difference	95% CI	p-value
0.5% Bupivacaine –0.25% Levobupivacaine	-3.9	(-10.8, 3.1)	0.27
0.5% Bupivacaine – 0.5% Levobupivacaine	0.7	(–6.3, 7.8)	0.84
0.5% Levobupivacaine –0.25% Levobupivacaine	-4.6	(-11.1, 1.9)	0.16

Results from the sponsor's analysis using the "per-protocol" population were found no statistically significant difference between any two groups (NDA Tables M1.2.4-M1.2.6, pages 377-379, vol 139).

Overall assessment of block – The 0.5% Levobupivacaine group had the largest proportion of patients to have satisfactory block (21 patients, 81%), compared with 17 (68%) patients for the 0.25% Levobupivacaine group and 17 (74%) patients for the Bupivacaine group. There was no significant treatment difference when analyzed using the logistic regression (p=0.62)(NDA Table M1.3.1-M1.3.2, page 379-380, vol. 139).

Time to onset and duration of sensory block at each dermatome – These variables was summarized in NDA Tables M1.4.1-M1.4.2 and Table2 M2.4.1-M2.4.3 (vol.139). There was no evidence of difference in mean time to onset or duration between the 3 treatments.

Time to onset and duration of each grade of motor block - These variables were summarized in NDA Tables M1.5.1-M1.5.2 and Tables M2.5.1 – M2.5.2 (vol.139). There was no statistically significant difference in mean time to onset between the 3 treatments. Duration of grade 1 motor block was significantly longer for the 0.5%Levobupivacaine group than the 0.25% Levobupivacaine group (1018 min vs. 835 min with p=0.015). No other statistical significant difference was found.

Number of patients responding at each dermatome – There was no evidence of any significant difference in response rates between the treatments for each grade of motor block. No other statistically significant difference was found.

Safety Analysis:

Adverse events – There were 37 patients had adverse events. Thirteen patients (52%) were of the 0.25% Levobupivacaine group, compared with 8 patients (31%) of 0,5% Levobupivacaine group and 16 patients (67%) of the Bupivacaine group. There were a total of 62 adverse events. Nineteen events were of the 0.25% Levobupivacaine group, compared with 15 events of the 0.5% Levobupivacaine group and 28 events of the Bupivacaine group. The most frequent (more than 10% in at least one group) events were central and peripheral nervous system disorders, gastro-intestinal system disorders, heart rate and rhythm disorders, metabolic and nutrition disorders, urinary system disorders, and white cell and respiratory disorders. There were 14 study drug related events. One severe adverse event in the 0.5% Levobupivacaine group.

Table IV.3.4 Adverse events (NDA Tables U1.1.1-U1.1.3, pp. 422-424, vol. 140)

Endpoint	Treatment		
	0.25% Levobupivacaine	0.5% Levobupivacaine	05% Bupivacaine
Number of patients	25	26	24
Number of patients with at least 1 adverse event	13 (52%)	8 (31%)	16 (67%)
Number of patients with drug related adverse event	3 (12%)	3 (12%)	4 (16%)
Total number of events	20	15	28
Frequent adverse event by body system			
Central & peripheral nervous system	1 (4%)	5 (20%)	2 (8%)
Gastro-intestinal system disorders	3 (12%)	2 (8%)	4 (16%)
Heart rate and rhythm disorders	2 (8%)	0 (0%)	3 (12%)
Metabolic and nutrition disorders	0 (0%)	0 (0%)	4 (16%)
Urinary system disorders	8 (32%)	3 (12%)	6 (25%)
White cell & res. disorders	2 (8%)	1 (4%)	4 (16%)
Severe adverse events	0)0%)	1 (4%)	0 (0%)
Drug related adverse events	4 (16%)	3 (12%)	7 (28%)

There was no evidence of difference or dose related trend in vital signs, ECGs, clinical chemistry, hematology and urinary analysis changes from screening.

IV.3.e. Statistical Reviewer's Comments and Conclusions

Primary efficacy analysis - There was 1 patient in the 0.5% Levobupivacaine group and 1 patient in the Bupivacaine group did not attain sensory block. The primary endpoint was duration, which was defined in the protocol as the time from onset of sensory block until complete return of sensory block except a general anesthetic was given. The 0.5% Levobupivacaine group had the longest mean duration (1028.7 min) than either the 0.5% Bupivacaine group (836.5 min) or the 0.25% Levobupivacaine group (662.4 min). In the pairwise comparison using t-test, the difference between the 0.5% Levobupivacaine and the 2.5% Levobupivacaine group was statistically significant (p=0.004). But, it was not statistically significant between either of the Levobupivacaine groups and the Bupivacaine group. The sponsor redefined duration by including patients who received general anesthesia after the blind was broken. There was no statistically significant difference between the treatment using this definition.

Secondary Efficacy Endpoints – The secondary endpoints include motor block, overall assessment of block, time to onset and duration of sensory block at each dermatome, time to onset and duration of each grade of motor block, and the number of patients responding at each dermatome. There was dose response relationship in duration of motor block. But neither of the Levobupivacaine groups showed superiority over the Bupivacaine treatment. Duration of grade 1 motor block was significantly longer for the 0.5% Levobupivacaine group than the 0.25% Levobupivacaine group (1018 min vs. 835 min with p=0.015), but not longer than the Bupivacaine group. There was no statistically significant difference between groups in overall assessment of block, time to onset and duration of sensory block at any dermatome, and number of patients responding at each dermatome.

Safety analysis –The most frequent (more than 10% in at least one group) events were central and peripheral nervous system disorders, gastro-intestinal system disorders, heart rate and rhythm disorders, metabolic and nutrition disorders, urinary system disorders, and white cell and respiratory disorders. There were 14 study drug related events. There was no evidence of

difference between the treatments in safety profiles.

IV.4 Study 030543

IV.4.a. Study Design: The study was designed as a randomized, double-blind, single center, two-arm parallel study comparing 0.75% Levobupivacaine with 0.75% racemic Bupivacaine in peribulbar block for ophthalmic anterior segment surgery. The study was conducted in the United Kingdom.

IV.4.b. Efficacy and Safety Endpoints:
The primary efficacy measure was the time to onset of block. The degree of anesthesia was measured by Akinesia score (0=Full movement, 1=almost full movement, 2=partial movement, 3=almost no movement, 4=no movement) which was recorded at the schedule time point (Table IV.4.1).

The secondary efficacy endpoints were defined as follows:

i. Total volume of study anesthetic required achieving protocol adequate block.
ii. Pre-operative analgesia using a 3 point rating scale (0=no pain, 1=some pain, 2=much pain).
iii. Post-operative analgesia using a 3-point rating scale.
iv. Operating condition using a 3 point rating scale (0=excellent, 1=satisfactory, 2=poor).

The safety analysis included the analysis of adverse events.

The schedule of assessment is given in Table IV.4.1.

Table IV.4.1 Schedule of assessment (based on NDA Table 1, vol. 141)

Assessment	Time point									
	Pre-study	Prior to perbulbar injection	Peribulbar injection	2,4,6,8,10,15, 20,25 minutes	30 min or until score of 18	Prior to surgery	Post surgery	At discharge	1st day follow-up	1 week follow-up
Written consent	x									
Screening assessment	x									
Medical history & physical exam	x									
12-lead ECG		x				x				
Akinesia score		x		x,x,x,x,x,x,x,x					x	
Analgesia score						x	x			
Surgical details							x			
Adverse events								x	x	x
Concomitant medication								x	x	x

IV.4.c. Population for Analysis:
The primary analysis population was the 'intent-to-treat' population, which was defined to include all randomized patients excluding the patients who did not receive any study drug, or whose regional block was not successful.

The following patients would be excluded from the 'per-protocol' population,

i. Patient who were not eligible for the 'intent-to-treat' population.

ii. Patient who had history of any disease or disorder likely to impact on the efficacy of the study medication.
iii. Patient who received any non-study medication, which would impact the efficacy of the study medication.
iv. Patient who had surgical complication which would impact the efficacy of the study medication.
v. Patient who did not receive appropriate eye drop prior to surgery.
vi. Patient who had peribulbar injection given less than 4 min or more than 6 min apart. Or patient who had a further peribulbar injection given after an Akinesia score of at least 18 was obtained.
vii. Patient who had surgery commenced before an Akinesia score of 18 was attained.
viii. Patient of whom when up to 2 injections were given, the volume of the first injection was not 5 ml.
ix. Patient of whom when 3 injections were given, the volume of the study drug was not 5 ml for the 1st 2 injections.

'Safety' population was defined as all randomized patients.

IV.4.d. Efficacy and safety analysis:
Methods:
The study was designed to test for the following null hypothesis,

H_0: E (time to the onset of block protocol adequate for surgery for the 0.75% Levobupivacaine group)
= E (time to the onset of block protocol adequate for surgery for the 0.75% Bupivacaine group).

Since Akinesia score was assessed only at the scheduled time point, the time to onset of protocol adequate block was not a continuous variable and was analyzed using a nonparametric Wilcxon 2-sample test.

Sample size – From a previous study, the between patient standard deviation for the primary endpoint was estimated to be 6.2 min. Using this estimate, type I error rate of 0.05, power of 0.80, the sample size of 25 patients per group was considered protocol adequate to detect a between group difference of 5 min.

The secondary efficacy response variables:
Among the secondary efficacy endpoints, the total volume of anesthetic was analyzed using a t-test; the pre-operative, post-operative analgesia and operating condition were analyzed using a logit model. The interval between achievement of suitable block until the start of surgery was considered as covariate in the model. The odds-ratio and the 95% confidence interval were also calculated.

The safety variables:
Adverse events were summarized without formal statistical analysis.

Results:

Subject disposition and withdrawals – The randomized, intent-to-treat, per-protocol, safety and primary efficacy analysis populations were defined in Table IV.4.2.

Table IV.4.2 Patient disposition for efficacy and safety analysis (NDA Table 1, page 51, vol. 141)

Status	Treatment		Total
	0.75% Levobupivacaine	0.75% Bupivacaine	
Randomized (Safety Population)	25	25	50
Dosed	25	25	50
Intent-to-Treat Population	25	25	50
Incorrect timing of injection	2	4	6
Incorrect volume of study drug	0	4	4
Pr-protocol Population	23	17	40

Demographic and Baseline Characteristics:

Of the "safety " population of 50 patients, 23 (46.0%) were males and 27 (54.0%) were females. The male/female ratio was about the same in the two treatment groups. Forty-three patients (86%) were Caucasians. There were 2 black patients, 3 Asian patients and 2 patients of other races. The mean age was 73.4 years (74.2 years for the Levobupivacaine group and 72.7 years for the Bupivacaine group). The average height was 163.7 cm (164.2 cm for the Levobupivacaine group and 163.3 cm for the Bupivacaine group). The average weight was 67.7 kg (68.3 kg for the Levobupivacaine group and 67.1 kg for the Bupivacaine group).

Patterns of medical history and concomitant medication were also similar across the treatment groups.

Primary Efficacy Endpoint:

All patents attained adequate block for the surgery. The 0.75% Levobupivacaine had slightly longer mean time to onset of adequate block than the 0.75% Bupivacaine group (12.5 min vs. 11.0 min). The two groups were not statistical different in time to onset of block when analyzed using the Wilcoxon rank sum test (p=0.42) after normal distribution assumption was rejected. The similar result was also found in the 'per-protocol' population.

Table IV.4.3 Time to adequate block for surgery (NDA Tables 8.1 to 8.2.1, page 67-68, vol. 141)

	Treatment	
	0.75% Levobupivacaine	0.75% Bupivacaine
Intent-to-treat population		
Number of patients	25	25
Mean±SD	12.5±5.6	11.0±4.4
Median	10.0	10.0
0.75% Levobupivacaine – 0.75% Bupivacaine	Difference = 0., 95% CI =(-2, 5), p=0.42	
Per-protocol population		
Number of patients	25	17
Mean±SD	11.8±5.1	10.4±4.2
Median	10.0	10.0
0.75% Levobupivacaine – 0.75% Bupivacaine	Difference = 0, 95% CI =(-2, 5), p=0.41	

Secondary efficacy endpoints –
Total volume of study drug – The mean volume was slightly greater in Levobupivacaine group (10.8 ml) than the Bupivacaine group (10.1 ml). The two groups had the same median value. The difference was not statistically significant when analyzed using the Wilcoxon rank sum test (p=0.40)(Table IV.4.4).

Pre-operative analgesia – The two groups had exactly the same number of patients in each category of pain level. Time from start of suitable block to the start of surgery was considered as a possible covariate. After tested as a covariate and found not statistical significant (p=0.80), the variable was dropped from the model. After the assumption of proportional odds for more pain was tested and not rejected, the odds ratio was estimated using a logistic regression model.

Post-operative analgesia – The two groups had almost the same number of patients in each category of the pain level. The difference was not statistically significant (p= 0.56). After tested as a covariate and found not statistical significant (p=0.16), time to the start of sensory block was dropped from the model. Since there were observations in only two categories (no pain or some pain), the odds ratio was estimated using a logistic regression model

Operation condition – Results of this endpoint was reported only in statistical Table 12. Seventeen patients (92.0%) of the Levobupivacaine group had excellent condition for surgery, compared with 14 patients (56.0%) of the Bupivacaine group. The difference was not statistically significant (p=0.46). After the assumption of proportional odds for worse grade was tested and not rejected, the odds ratio was estimated using a logistic regression model.

Table IV.4.4 Secondary efficacy endpoints (NDA Tables 9.1 to 12, page 72-76, vol. 141)

Endpoint	Treatment	
	0.75% Levobupivacaine	0.75% Bupivacaine
Total volume of study drug (intent-to-treat population)		
Mean±SD	10.9±2.6	10.1±2.7
Median	10.0	10.0
0.75% Levobupivacaine – 0.75% Bupivacaine	Difference = 0., 95% CI =(0, 2), p=0.40	
Pre-operative analgesia		
No pain Some pain Much pain	20 (80.0%) 4 (16.0%) 1 (4.0%)	20 (80.0%) 4 (18.0%) 1 (4.0%)
Levobupivacaine/Bupivacaine	Odds Ratio =1, 95% CI= (0.25, 3.98), p=1.00	
Post-operative analgesia		
No pain Some pain	23 (92.0%) 2 (8.0%)	24 (96.0%) 1 (4.0%)
Levobupivacaine/Bupivacaine	Odds Ratio =0.48, 95% CI= (0.04, 5.65), p=0.56	
Operation condition		
Excellent Satisfactory Poor	17 (68.0%) 7 (28.0%) 1 (4.0%)	14 (56.0%) 11 (44.0%) 0 (0.0%)
Levobupivacaine/Bupivacaine	Odds Ratio =1.54, 95% CI= (0.49, 4.84), p=0.46	

Safety Analysis:
Adverse events – There were 25 patients had at least one adverse event. Eleven (44%)

patients were of the 0.75% Levobupivacaine group, 14 (56%) were of the 0.75% Bupivacaine group. Total 0f 29 adverse events were reported (12 of the 0.75% Levobupivacaine group, 17 of the 0.75% Bupivacaine group). The adverse events were central and peripheral nervous system disorders (3 patients), gastro-intestinal system disorders (1 patient), cardiovascular disorders (1 patient), and vision disorders (10 in Levobupivacaine and 14 in Bupivacaine group). There were 27 study drug related adverse events. Eleven of the events were of the 0.75% Levobupivacaine group, compared with 13 of the 0.75% Bupivacaine group. There were no severe event or death.

Table IV.4.5 Adverse events (NDA Tables XIII-XIV, pp. 54-55, vol. 139)

Events	Treatment	
	0.75% Levobupivacaine	0.75% Bupivacaine
Patients with at least one adverse events N(%)	11 (44.0%)	14 (56.0%)
Number of adverse events	12	17
Most frequent adverse events (by body system)		
Central & peripheral nervous system disorders	1 (4.0%)	2 (8.0%)
Gastro-intestinal system disorders	1 (4.0%)	0 (0.0%)
Cardiovascular disorders	0 (0.0%)	1 (4.0%)
Vision disorders	10 (40.0%)	14 (56.0%)
Patients with severe adverse events	0	0
Patients with drug related adverse events	11 (44.0%)	13 (52.0%)
Number of drug-related adverse events	4	7

IV.4.e The Reviewer's Comments and Conclusions

Effectiveness of Levobupivacaine was shown by the fact that all patients attained adequate block for the surgery.

Primary efficacy endpoint - For the comparison to Bupivacaine, in the primary efficacy analysis of time to onset of adequate sensory block, the 0.75% Levobupivacaine group had slightly longer mean time to onset of adequate block than the 0.75% Bupivacaine group (12.5 min vs. 11.0 min) but the difference was not statistically significant.

Secondary efficacy endpoints - In the analysis of the secondary efficacy endpoints, the Levobupivacaine group had slightly larger total volume of study drug (10.8 ml) than the Bupivacaine group (10.1 ml), the difference was not statistically significant (p=0.40 using Wilcoxon rank sum test). The two treatment groups had also the same frequency distribution of pain level with the pre-operative analgesia. The two groups had almost identical distribution of pain level with the post-operative analgesia. The Levobupivacaine group had better operation condition than the Bupivacaine group. But the difference was not significant.

Safety analysis - There were 25 patients had at least one adverse event. Eleven (44%) patients were of the 0.75% Levobupivacaine group and 14 (56%) were of the 0.75% Bupivacaine group. The adverse events were central and peripheral nervous system disorders (3 patients), gastro-intestinal system disorders (1 patient), cardiovascular disorders (1 patient), and vision disorders (10 in Levobupivacaine and 14 in Bupivacaine group). There were 27 study drug related adverse events. There was no evidence of difference between the two treatments.

IV.5 Study 030737

IV.5.a. Study Design: The study was designed as a single-center, randomized, double-blind, two-arm parallel group study conducted in the United Kingdom. The primary objective of the study was to compare the peribulbar block efficacy of 0.75% Levobupivacaine with 0.75% Bupivacaine. The second objective was the comparison of the safety profiles of the two treatments

IV.5.b. Efficacy and Safety Endpoints:
The primary endpoint was the time anesthesia suitable for surgery.

The secondary Endpoints included,
1. The volume of study anesthetic required achieving adequate block.
2. Pre-operative analgesia.
3. Post-operative analgesia.
4. Analgesia at discharge.
5. Operating conditions.
6. Time from completion of the first injection to first requirement for post-operative analgesia.

The patient assessment schedule was given in Table IV.5.1.

Table IV.5.1 Schedule of Assessments (Based on NDA Table 1)

Assessment	Time-point														
	Pre-study	Peribulbar injection		Minutes						Surgery		At discharge	Follow up	
		Prior	at	2,4,6,8	10	15	20,25	30	240	Prior	Post		Next day	Next week
Written consent	x													
Screening assessment	x													
Medical history & physical exam	x													
ECG monitoring	—	—	—	—	—	—	—	—	—	—	—			
Pulse oximetry monitoring	—	—	—	—	—	—	—	—	—	—	—			
Non-invasive arterial pressure monitoring	—	—	—	—	—	—	—	—	—	—	—			
12-lead ECG		x				x			x					
Akinesia Score		x		x	x	x	x	x				x	x	
Analgesia Score										x	x	x		
PK blood sample		x	x		x	x		x^						
Adverse events												x	x	x
Surgical details											x			
Concomitant medication	x											x	x	x

^: Also at 45 min, 1hr and 2hr, and at 4, 6, 8, 10 and 12 hr if possible.

IV.5.c. Efficacy and Safety Analysis:
Methods:
The confirmatory efficacy analysis:
The primary efficacy endpoint was tested to show whether there was difference in mean time to onset of block suitable for surgery between the two treatment groups. The statistical hypotheses for testing the primary endpoint between the two treatments were as follow:

H_0: E (mean difference in time to onset of block suitable for surgery between the two treatments) = 0 minutes
H_a: E (mean difference in time to onset of block suitable for surgery between the two

treatments) ≠ 0 minutes

Since the Akinesia assessments were made only at set times following dosing and the time to onset would take only a few discrete value. Two analyses were considered.
1). Compared mean times using t-test with the standard error and the least square means estimated from ANOVA with treatment factor.
2). Considered the time as an ordinal variable and compared the two treatments using odds ratio for longer time category with logit model, when the normal assumption failed to hold up. The logit model was testing for the odds ratio for higher level of pain. Correspondingly, the null hypothesis for testing is

H_0: E (Odds ratio for shorter time in the Levobupivacaine treatment to the Bupivacaine treatment) =1
H_a: E (Odds ratio for shorter time in the Levobupivacaine treatment to the Bupivacaine treatment) >1

The logit model assumed proportional odds ratio across all categories of the responses. The validity of the assumption was tested using the score test statistics for goodness of fit. A nonparametric model was to be used if the assumption was clearly not satisfied.

The sample size was determined to be 25 evaluable patients per group for the analysis of the primary endpoint. The sample size was determined based on the expectation of 5 minutes difference with an assumed standard deviation to be 6.2 min. The sample size was sufficient with 80% power and 0.05 type I error rate for a 2-sided t-test.

The secondary efficacy response variables:
The volume of study anesthetic required to achieve adequate block was analyzed in an identical way to the primary endpoint with ANOVA. The pre-operative and post-operative analgesia, analgesia at discharge and operating conditions were analyzed using a logit model for testing the odds ratio for higher level of pain or less satisfactory condition (in operating condition). The validity of the proportional odds ratio across all levels of the response variable was tested and alternate nonparametric test was use when the assumption failed. The sponsor using Kaplan-Meier-survival curves presented the time from completion of the first injection to first requirement for post-operative analgesia. Comparison of the two treatments was performed using a Wilcoxon 2-sample test.

Safety Analysis
The summary of the adverse events, summary of adverse event by severity of event, summary of events by relationship to the study drug and summary serious adverse events was tabulated.

Results:
Subject disposition and withdrawals:
There were 30 patients enrolled in each treatment group. All thirty patients were randomized, received study drug and completed the study. The "safety", "intent-to-treat" and "per-protocol" populations were identical.

Demographic data:

The male/female ratio was about 1:2 in each treatment group in the study. All patients were Caucasians. The mean age was 76.6 years of the Levobupivacaine group and 77.6 years of the Bupivacaine group. The Levobupicavaine group had an average weight of 74.1 kg and the Bupivacaine group had an average of 65.40 kg. The medical history of the patients was summarized in NDA Table II.

Efficacy Endpoints:

Primary efficacy endpoint (Time to satisfactory block) – All patients in both treatment group achieved satisfactory block. Time to satisfactory (adequate) block took only values of 2, 4 and 6 minutes. There were 19 patients (63.6%) in the Levobupivacaine group took the minimum value of 2 minutes compared with 23 patients (76.7%) in the Bupivacaine group. The difference of the two groups was estimated by the odd ratio to shorter time category. The assumption of a common odds ratio across the time categories was not rejected with p=0.46, using a Score test. The common odds ratio was estimated using a logistic model.. The Levo/Bupi odds ratio was 0.51 with the 95% confidence interval being (0.16, 1.56). The odds ratio was not statistically significantly different from 1 (p=0.24).

Table IV.5.2 Time to satisfactory block (based on NDA Tables 6.1-6.2, pp.75-76, vol.142)

Time to Satisfactory Block	0.75% Levobupivacaine	0.75% Bupivacaine
2 minute N (%)	19 (63.3%)	23 (76.7%)
4 minute N (%)	10 (33.3%)	7 (23.3%)
6 minute N (%)	1 (3.3%)	0 (0)
All patients	30	30
Mean	2.8	2.5
Median	2.0	2.0
Score Test for Proportional Odds p=	0.46	
Odds Ratio for shorter time - Levo-/Bupi (95% CI)	0.51 (0.16, 1.56)	
Significant Test for Treatment difference	p=0.24	

Secondary Efficacy Points:

Total volume of study drug - The total volume of study drug was equal to 5 ml for all patients.

Pre-operative analgesia - There were exactly the same proportion of patients had pain with the pre-operative analgesia in each group. The possible covariate, time from achievement of suitable block until start of surgery was dropped as covariate after tested to be no significant association with this endpoint (p=0.46). The assumption of proportion odds was tested and not rejected. A logistic regression model was use for the odds ratio estimation.

Post-operative analgesia - There was one patient in the Bupivacaine group and no patient in the Levobupivacaine group had pain. The treatment difference was not statistically significant. Analgesia at discharge - There was one patient in each group had pain at discharge. The possible covariate, time from achievement of suitable block until start of surgery was dropped as covariate after tested to be no significant association with this endpoint (p=0.25). The assumption of proportion odds was tested and not rejected. A logistic regression model was use for the odds ratio estimation.

Operating condition - Ten percent of patients in the Levobupivacaine group had poor operating condition compared with no patient in the Bupivacaine group. The odds ratio for better condition was 0.58 with a 95% confidence interval (0.11, 3.06). The odds ratio was not

significantly different from 1 (p=0.52) using Wald statistic. The possible covariate, time from achievement of suitable block until start of surgery was included as covariate after tested to be significantly associated with this endpoint (p=0.03). The assumption of proportion odds was tested and not rejected. A logistic regression model was use for the odds ratio estimation.

Time from completion of first injection to first post-operative analgesia - The Levobupivacaine group had loner survival time to first post-operative analgesia than the Bupivacaine group as shown in the Kaplan-Meier curves in NDA Figure 2 (page 99, vol. 142). The difference was not statistically significant (p=0.63, Wilcoxon test).

The sponsor in NDA also provided two additional analyses.

Proportion of patients requiring post-operative analgesia - There were 6 patients (20.0%) in the Levobupivacaine group and 5 patients (16.7%) in the Bupivacaine group required post-operative analgesia. The difference was not statistically significant.

General regression of block - there were 28 patients (93.3%) in the Levobupivacaine group and 30 patients (100.0%) in the Bupivacaine group had general regression of block

Table IV.5.3 Analysis of secondary efficacy endpoints (based on NDA Tables 7, pp.80, vol.142)

Variable	0.75% Levobupivacaine	0.75% Bupivacaine
Total Volume of Study drug, Mean ± SD	5.0±0.0	5.0±0.0
Pre-operative analgesia, N (%) with pain	7 (23.3%)	7 (23.3%)
Post-operative Analgesia, N (%) with pain	0 (0.0%)	1 (3.3%)
Analgesia at Discharge, N (%) with pain	1 (3.3%)	1 (3.3%)
Operating Condition, N (%) Excellent Satisfactory Poor	 26 (86.7%) 1 (3.3%) 3 (10.0)	 27 (90.0%) 3 (10.0%) 0 (0.0%)
Odds Ratio for better condition (Levobupivacaine/Bupivacaine) 95% CI Significant test p-value	0.58 (0.11, 3.06) 0.52	
Patients requiring post operative analgesia	6 (20.0%)	5 (16.7%)
General regression of block, N (%) yes	28 (93.3%)	30 (100.0%)

Safety analysis -

There were 12 patients in the Levobupivacaine group had at least one adverse event. None of the event was severe. Nine of the patients had possible or definite study drug related events. Two patients had serious adverse events. In the Bupivacaine group, 10 patients had at least one adverse event. None of them had severe adverse event. Seven of the patients had study drug related events. None had serious adverse event. The most frequent adverse events in both Levobupivacaine and Bupivacaine groups were application site disorder (13.3% in Levobupivacaine and 16.7% in Bupivacaine) and vision disorders (23.3% in Levobupivacaine and 16.7% in Bupivacaine group). There were 9 possible or definitely study drug related events in the Levobupivacaine group and 7 in the Bupivacaine group. These events were either application site disorders or vision disorders. The Levobupivacaine patients experienced all 3 serious adverse events. The events were 1 central and peripheral nervous system disorders, 1 urinary system disorders and 1 vision disorders.

Table IV.5.4 Adverse events (based on NDA Tables 14.1 to 14.5.2, pp.87-98, vol.142)

Variable	0.75% Levobupivacaine	0.75% Bupivacaine
Number of patients with adverse events, N (%)	12 (40.0%)	10 (33.3%)
Number of patients with severe adverse events, N (%)	0 (0.0%)	0 (0.0%)
Number of patients with drug related adverse events, N (%)	9 (30.0%)	7 (23.3%)
Number of patients with serious adverse events, N (%)	2 (6.7%)	0 (0.0%)
Adverse event by body system, N(%)		
Application site disorder	4 (13.3%)	5 (16.7%)
Central & peripheral nervous system disorders	1 (3.3%)	1 (3.3%)
Musculo-skeletal system disorders	1 (3.3%)	0 (0.0%)
Urinary system disorders	1 (3.3%)	0 (0.0%)
Vision disorders	7 (23.3%)	5 (16.7%)
Possible or definite study drug-related adverse event by body system, N(%)		
Application site disorder	4 (13.3%)	5 (16.7%)
Central & peripheral nervous system disorders	0 (0.0%)	0 (0.0%)
Musculo-skeletal system disorders	0 (0.0%)	0 (0.0%)
Urinary system disorders	0 (0.0%)	0 (0.0%)
Vision disorders	5 (16.7%)	2 (6.7%)
Serious adverse event by body system, N(%)		
Application site disorder	0 (0.0%)	0 (0.0%)
Central & peripheral nervous system disorders	1 (3.3%)	0 (0.0%)
Musculo-skeletal system disorders	0 (0.0%)	0 (0.0%)
Urinary system disorders	1 (3.3%)	0 (0.0%)
Vision disorders	1 (3.3%)	0 (0.0%)

IV.5.e. The Reviewer's Comments and Conclusions

Primary efficacy endpoint - The primary goal of the study was to show that patients treated with Levobupivacaine had shorter time to satisfactory block than the patients treated with Bupivacaine by at least 5 minutes. However, as a result, the mean time to satisfactory block was shorter for the patients treated with Bupivacaine (mean=2.5 minutes) than the patients treated with Levobupivacaine (mean=2.8 minutes). The odds ratio for shorter time to satisfactory block of Levobupivacaine to Bupivacaine was 0.51. It had a lower 95% limit of 0.16. The odds ratio was not significantly different from 1.

Secondary endpoints - There were no statistically significant difference in total volume of study drug, post-operative analgesia, analgesia at discharge, operating condition, proportion of patients requiring post-operative analgesia, and general regression of block.

There was no difference in the profile of adverse events of the two treatments.

IV.6 Study 030700

IV.6.a. Study Design: The study was designed as a single-center, randomized, double-blind, three-arm parallel group study conducted in the United Kingdom. The primary objective of the study was to compare the efficacy of 0.75% Levobupivacaine with 2% Lignocaine (with Adrenaline) and placebo as post-operative pain relief in patients who underwent unilateral or bilateral impacted mandibular 3rd molar extractions. The second objective was the comparison of the safety of the study medications.

IV.6.b. Efficacy and Safety Endpoints:

The primary endpoint was the proportion of patients requiring rescue analgesia within 2 hours

after the completion of surgery.
The secondary Endpoints included,

1. The VAS scale after 10 min, 1 and 2 hours from the completion of surgery, and at time of first requirement of rescue medication.
2. Time to the 1st requirement of analgesia.
3. The proportion of patients requiring rescue analgesia over a period of 48 hours.
4. The maximum pain score recorded on the VAS over the 2-hour period, post surgery.
5. The time at which the maximum pain score was documented.
6. The proportion of patients whose sensory block wore off within 2 hours post surgery.
7. The pain score as recorded on VAS at 8 hours post completion of surgery.
8. The proportion of patients complaining of disturbed sleep due to pain at 10 a.m. on the morning following surgery.
9. The pain score as recorded on VAS at 24-hour post completion of surgery.
10. Time to offset of block.
11. Time to all rescue medication.

The safety measurements included adverse events.

IV.6.c. Efficacy and Safety Analysis:
Methods:
All tests for a difference between the study medications were performed at the 5% significance level with a two-sided test. The significance level pairwise comparison of Levobupivacaine vs. Lignocaine with adrenaline and Levobupivacaine vs. placebo was

The confirmatory efficacy analysis:
The primary analysis was testing for the following hypotheses

H_0: E (proportion of patients requiring rescue analgesia in the Levobupivacaine treatment group)
=E (proportion of the patients requiring rescue analgesia in the Lignocaine group)
=E (proportion of patients requiring rescue analgesia in the placebo treatment group)

H_a: E (proportion of patients requiring rescue analgesia in the Levobupivacaine treatment group)
≠E (proportion of the patients requiring rescue analgesia in the Lignocaine group)

Or E (proportion of patients requiring rescue analgesia in the Levobupivacaine treatment group)
≠ E (proportion of patients requiring rescue analgesia in the placebo treatment group)

Since the primary test was carried out with 2 pairwise comparisons, the type I error rate was adjusted to be 0.025 for the larger difference and 0.05 for the smaller difference using the Bonferroni-Holm approach. The relative risk of Levobupivacaine to either placebo or Lignocaine was tested using the Mantel-Haenszel statistic.

Sample size – it was expected that 10% of patients receiving Levobupivacaine will require rescue analgesia within 2 hours of surgery. Using this estimate, α =0.025, power=80%, the

proposed sample size of 30 patients per group eligible for the 'intent-to-treat' population was expected to be adequate to detect a difference of 35%.

The secondary efficacy response variables

The mean VAS scale and the maximum pain score were analyzed using t-test. The analysis of the proportions was carried out using Mantel-Haenszel statistic and Fisher'e Exact test. Survival analysis of the time variables in the secondary endpoints was carried out using Kaplan-Meier method. Pairwise comparison of time was carried out using log-rank test.

Safety Analysis

The summary of the adverse events, summary of adverse event by severity of event, summary of events by relationship to the study drug and summary serious adverse events was tabulated.

Results:

Subject disposition and withdrawals:

There were 95 patients (31 in 0.75% Levobupivacaine, 32 in 2% Lignocaine and 32 in placebo group) enrolled in the study. Two patients were excluded from 'safety' population and 'intent-to-treat' population because of protocol violation before receiving study medication. Two additional patients were excluded from the 'per-protocol' population because of complicated surgery (Table IV. 6.1).

Table IV.6.1 Patient disposition chart (based on Tables 3.1-3.3, page 68-71, vol. 144)

Number of Patients	Treatment			Total
	0.75% Levobupivacaine	2% Lignocaine with Adrenaline	Placebo	
Enrolled	31	32	32	95
Didn't receive study drug	1	1	0	2
Safety population	30	31	32	93
Intent-to-treat population	30	31	32	93
Complicated surgery	2	1	1	4
Per-protocol population	28	30	31	89

Demographic data:

The male/female ratio was about 1:2 in the study but it varied across the treatment group. It was 17:15 in placebo group, 8:22 in Levobupivacaine group and 4:27 in Lignocaine group. The average height was similar (168.4 cm in placebo, 164.4 cm in Levobupivacaine group and 164.5 cm in Lignocaine group). The average weight was greatest in placebo (67.06 kg), followed by Levobupivacaine group (65.17 kg) and Lignocaine group (64.31 kg). There were 26 Caucasian patients in the placebo and in Levobupivacaine groups, compared with 24 in the Lignocaine group. The rest of the patients were Asians.

About half of the patients in each group did not have a medical history or had concomitant disease in each group. The most common diseases reported in all three groups were respiratory system diseases (26.7% in the Levobupivacaine, 29% in the Lignocaine group and 25% in the placebo). There were slightly more patients who had musculoskeletal system diseases in the Levobupivacaine group (10.0%) than the other two groups (3.2% in the Lignocaine group, and 0% in placebo). Patients had the same pattern of concomitant medications across the three groups.