Efficacy Endpoints:

Primary efficacy endpoint – There was 53.3% patients required rescue medication during the two-hour period after the surgery in the Levobupivacaine group, compared with 71.9% in the placebo group and 71% in the Lignocaine group. The relative risk (estimated by the statistical reviewer) for rescue medication of Levobupivacaine versus placebo was 0.742 with a 95% Mantel Haenszel confidence interval = (0.502, 1.096). The relative risk was not significantly different from 1 (p=0.189). The relative risk of Levobupivacaine versus Lignocaine was 0.752 with a 95% Confidence interval = (0.505, 1.118). The relative risk was not significantly different from 1 (p=0.192). The sponsor reported the results of analysis of difference in proportions in NDA. The results were consistent with the reviewer's estimates, though the p-values were reported larger in here using Fisher's exact test. Consistent results were found using the "per-protocol" population.

Table IV.6.2 Patients required rescue medication within 2 hours of surgery (based on NDA Tables 7.1, pp.88, vol.144)

Number of Patients	Treatment			Total
	Total			
	0.75% Levobupivacaine	2% Lignocaine with Adrenaline	Placebo	
Required rescue medication N (%)	16 (53.3%)	22 (71.0%)	23 (71.9%)	61 (65.6%)
Relative risk	Levobupivacaine/Placebo = 0.742 95% CI = (0.502, 1.096), p=0.189* Levobupivacaine/Lignocaine = 0.752 95% CI = (0.505, 1.118), p=0.192			

*: Fisher's exact test

Secondary Endpoints:

Time to first requirement of rescue medication - the curve of time to first requirement of rescue medication of each treatment groups was analyzed using Kaplan-Meier method and shown in NDA Figures 2.1 to 2.5. The mean time to rescue medication was the longest for the Levobupivacaine group (257.6 minutes) which was almost 3 times of the mean time for the placebo group (93.3 minutes) and for the Lignocaine group (85.9 minutes). The survival time was compared between Levobupivacaine and either placebo or Lignocaine was done using the log rank test. Neither of the pairwise comparisons were found to be statistically significant (p=0.045 for Levobupivacaine versus placebo, and p=0.062 for Levobupivacaine versus Lignocaine).

Table IV.6.3 Time to first requirement of rescue medication (based on NDA Table 8.1, pp.90, vol.144)

Number of Patients	Treatment			Total
	0.75% Levobupivacaine	2% Lignocaine with Adrenaline	Placebo	
Mean±SD	257.6±538.5	85.9±94.0	93.3±112.4	143.9±323.7
Median	87.5	55.0	45.0	55.0
Difference in survival time	Levobupivacaine vs. Placebo p* = 0.062 Levobupivacaine vs. Lignocaine p = 0.045			

*: Log rank test

Proportion of patients required rescue medication within 48 hours of surgery – There were 96.7% patients in the Levobupivacaine group required rescue medication, compared with 100% in each of the other groups. The difference was not statistically significant (p=0.48 for Levobupivacaine versus placebo and p=0.049 for Levobupivacaine versus Lignocaine).

Maximum pain score recorded within 2 hours of surgery – There was no treatment difference

when analyzed using ANOVA model including terms for extraction type, gender, treatment and extraction type by treatment interaction (p=0.14). In pairwise comparisons, there was no difference between Levobupivacaine and either placebo (p=0.05) or Lignocaine (p=0.24) (NDA Table 9.1.1, page 92, vol. 144).

Time to maximum VAS pain score over the two hour period after surgery - There was no treatment difference when using a generalized Wilcoxon test including terms for extraction type, gender, treatment and extraction type by treatment interaction (p=0.59 between Levobupivacaine and placebo, p=0.15 between Levobupivacaine and Lignocaine). However, there was significant extraction type by treatment interaction (p=0.019) which was contributed by effect of the extraction type in placebo and in Lignocaine groups. Such difference was not found in the Levobupivacaine group (NDA Table 9.1.2, page 93, vol.144).

VAS pain score recorded 8 hours after surgery – The data were analyzed with an ANOVA model with terms for extraction type, gender, and treatment and extraction type by treatment interaction. There were no statistically significant factors except the extraction type-by-treatment interaction was statistically significant (p=0.013) which was contributed by effect of the extraction type in placebo and in Lignocaine groups. In pairwise comparisons, there was no difference between Levobupivacaine and either placebo (p=0.077) or Lignocaine (p=0.71) (NDA Table 9.1.3, page 94, vol. 144).

VAS pain score recorded 24 hours after surgery - The data were analyzed with an ANOVA model with terms for extraction type, gender, treatment, and extraction type by treatment interaction. There were no statistically significant factors except the extraction type-by-treatment interaction was statistically significant (p=0.011) which was contributed by effect of the extraction type in placebo and in Lignocaine groups. In pairwise comparisons, there was no difference between Levobupivacaine and either placebo (p=0.012) or Lignocaine (p=0.85) (NDA Table 9.1.4, page 95, vol. 144).

Proportion of patients complaining of disturbed sleep due to pain at 10 a.m. on the morning following surgery – Seventy percent of patients for the Levobupivacaine group made complain, compared with 46.9% in placebo group and 77.6% in Lignocaine group. The difference between the Levobupivacaine group and either the placebo or the Lignocaine group was not statistically significant (p=0.12 for Levobupivacaine versus placebo, p=0.64 for Levobupivacaine versus Lignocaine).

Proportion of patients whose sensory block wore off within 2 hours after surgery – There were 6.7% of patients in the Levobupivacaine group, compared with 84.4% in placebo group and 3,2% in the Lignocaine group. The difference between the Levobupivacaine and the placebo groups was statistically significant (p<0.001) using Fisher's exact test. The difference between the Levobupivacaine and the Lignocaine groups was not statistically significant (p=0.54).

Safety Analysis:
The number of patients reported adverse events were similar in the 3 treatment groups 19 (63.3%), 20 (64.5%) and 18 (56.3%) for Levobupivacaine, Lignocaine and placebo group respectively. Six severe events were reported with 3 for the Levobupivacaine group, 2 for the Lignocaine group and 1 for the placebo group. Fourteen events were drug-related (2 for

Levobupivacaine group, 7 for Lignocaine group and 5 for placebo group).

A total of 45 adverse events were reported for the Levobupivacaine group, compared with 46 events for the Lignocaine group and 45 for the placebo group. The distribution for the body system was similar across the 3 treatments. The most frequent events were body as a whole, central and peripheral nervous system disorders, gastrointestinal system disorders, and respiratory system disorders. There was lower percentage of events at the application site for the Levobupivacaine group (3.3%), compared with Lignocaine group (22.6%) and placebo group (15.6%).

Table IV.6.5 Adverse events (based on Tables 12.1, page 104, vol. 144)

Event	Treatment		
	0.75% Levobupivacaine	2% Lignocaine + Adrenaline	Placebo
Number of patients with adverse event	19 (63.3%)	20 (64.5%)	18 (56.3%)
Number of patients with severe adverse events	3 (10.0%)	2 (6.5%)	1 (3.1%)
Number of patients with drug related adverse events	2 (6.7%)	7 (22.6%)	5 (15.6%)
Number of patients with serious adverse events	0	0	0

IV.6.e. The Reviewer's Comments and Conclusions

Primary efficacy endpoint - The primary goal of this study as stated in the protocol was to show that patients treated with Levobupivacaine had lower proportion of patients requiring rescue medication than placebo group or patients treated with Lignocaine with adrenaline. Although the proportion was lower (53.6% in the Levopubivacaine group vs. 73.3% in the Lignocaine group and 74.2% in the placebo group), the difference was not statistically significant. The result was similar when analyzed using the 'per-protocol' population.

Secondary efficacy endpoints – It was suggested that Levobupivacaine had longer time to the first request of rescue medication, lower proportion of patients required rescue medication within 48 hours after surgery than the other two groups. But, other than "proportion of patients whose sensory block wore off within 2 hours", there was no statistically significance difference between the Levobupivacaine group and either placebo or Lignocaine group in any of the other 7 secondary efficacy endpoints analyzed. The proportion of patients whose sensory block wore off within 2 hours after surgery was significantly lower in the Levobupivacaine group (6.7%) than in the placebo group (84.4%). It was tested to be statistically significant using the Fisher's exact test. The difference between the Levobupivacaine group and the Lignocaine group was not significant.

The adverse events were experienced by 63.3%, 64.5% and 56.3% of patients in the Levobupivacaine, Lignocaine group and placebo group respectively. The number of patients reporting adverse events which were study drug related were 6.6%, 22.6% and 15.6% for the Levobupivacaine, Lignocaine and placebo groups respectively.

V. Pediatric Studies

There was only one phase III randomized double blind, parallel group study, Study CS-007 designed for the efficacy and safety assessment of 0.5% Levobupivacaine when given as an ilioinguinal-iliohypogastric (IIIH) nerve block for post-operative pain control in pediatric patients following hernia repair surgery. The control group received no block. The Levobupivacaine group had 20 patients and the no-block group had 18 patients.

This study was designed for the primary purpose of assessing the efficacy of 0.50% Levobupivacaine as an ilionguinal-iliohypogastric nerve block for post-operative pain control in pediatric patients following hernia repair surgery. The efficacy of the treatment would be confirmed by comparing the treatment with no-block treatment. Statistically, the study was designed to test the null hypothesis that

H_0: E (difference in the proportion of patients needed rescue medication in two groups) = 0

The efficacy of Levobupivacaine treatment would be established when the null hypothesis was rejected with a significantly lower proportion in the Levobupivacaine group than the no-block group.

This study provided potential results on the treatment efficacy but short of confirming it. The detail conclusions of the study are given in section V.1.f.

V.1 Study CS-007

V.1.a. Study Design: This was a randomized, double-blind, single center, parallel group study designed to assess the efficacy and safety of Levobupivacaine when given as an ilioinguinal-iliohypogastric (IIIH) nerve block for post-operative pain control in pediatric patients following hernia repair surgery. The control group received no block.

The key analgesic efficacy determination was the proportion of patients needing rescue analgesia in the two-hour post-operative period. The secondary objectives were:

1. To assess the analgesia produced by Levobupivacaine, using the Children's Hospital of the Eastern Pain Scale (CHEOPS) score at various time points and an overall assessment of the quality of the block.
2. To assess the time to first use of the rescue medication.
3. To assess the overall quality of the block.
4. To evaluate the safety profile of 0.5% Levobupivacaine in the study patients.

The schedule for the patient assessment of efficacy and safety was given in Table V.1.1.

Table V.1.1 Schedule of Assessments (Based on Table 1 of NDA, page 29, vol.146)

	Pre-Study	Pre-Surgery	Surgery	Post-Surgery
Medical History and Informed Consent	x			
Physical Examination	x			
Cardiovascular Monitoring (Vital Signs)	x		X	Every 30 minutes during the 2-hour observation Period
Study Medication			x	
Pain Assessment				Time 0, every 5 minutes for 30 minutes, then every 15 minutes in the rest of the 2-hour observation period
Over Assessment: Quality of the Block				x
Adverse Events	x	x	x	x

V.1.b Study Population:

Patient included should fulfill the following inclusion and exclusion criteria.

Inclusion criteria:

1. Patients aged between 6 months and 12 years of age.
2. Patients of the ASA Class I-II.
3. Patients scheduled to undergo unilateral or bilateral herniorrhaphy, and in whom IIH nerve block for post-operative pain was appropriate.
4. Patients whose parent(s) or guardian(s) provided written informed consent.

Exclusion criteria:

1. Patients with a known allergy or hypersensitivity to amide local anesthetics, morphine, NSAIDs, acetaminophen, atropine, or metoclopramide.
2. Patients with a known history or presence of severe renal, hepatic, respiratory, or cardiac disease.
3. Patients with neurological, neuromuscular, or psychiatric disorders.
4. Patients without Informed consent written by the parent(s) or guardian(s).
5. Patients who had a history of seizure disorder.
6. Patients who had a blood clotting disorders or blood dyscrasias.
7. Patients who had received an investigation drug or vaccine in the last 28 days.
8. Patients with a history of current findings of any medical or surgical condition or treatment with medication that might have obscured; in the opinion of the investigator, the evaluation of the study drugs or in any other way jeopardized patient safety in the study. This included severe chronic or terminal diseases that may have interfered with the absorption, metabolism, elimination, or desired effect of the study drug.

V.1.c. Efficacy and Safety Endpoints:

Primary efficacy endpoint was the proportion of patients needed rescue medications. The need of rescue medication was defined as the patient had a CHEOPS score equal to or greater than 10, in the 2-hour post-operative observation period.

The secondary endpoints included the CHEOPS scores at various time points, the overall assessment of the quality of the block, the use of morphine and ketorolac, and time to first use of rescue medication.

The safety variables included the vital signs (included heart rate, systolic and diastolic arterial) change from baseline and adverse events.

V.1.d. 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 drugs and patients who did not have any efficacy evaluation after the randomized treatment. 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.

V.1.e. Efficacy and safety analysis:
Methods:
The confirmatory efficacy analysis:
Primary measure - Patient needing rescue analgesia, was determined by a CHEOPS score equal to or greater than 10, in the two-hour post-operative observation period. The primary endpoint, the proportion of the patients needed rescue analgesia was compared between the two groups by using a two-sided Fisher's Exact test or chi-square test, as appropriate.

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

H_0: E (difference in the proportion of patients needed rescue medication in two groups) = 0
H_a: E (difference in the proportion of patients needed rescue medication in two groups) $\neq$ 0

Secondary efficacy endpoints - The CHEOPS scores recorded at each time point, area under the curve minus baseline (AUCMB), and the overall assessment of the quality of the block were analyzed by a one-way ANOVA with treatment as the factor. If needed, a transformation, logistic regression, or non-parametric statistic was used. The usage of morphine and ketorolac, were analyzed using a Fisher's exact test. A survival analysis using the Kaplan-Meier approach was used to analyze time to first use of rescue medication.

Two additional computation of measurement relate to the area under the curve minus baseline (AUCMB), normalized by time, were made in the NDA submission. Let X_0 be the baseline AUCMB, m = the final CHEOPS observation at rescue or final observation if no rescue needed, $X_1, \ldots, X_m$ be the m CHEOPS values at the i^{th} CHEOPS observation, t_0 =0, time of Band-Aid placement, and t_i the time at the i-th CHEOPS observation. The final sum, CHEPOS AUCMB to rescue was defined as follows,

$$\text{CHEOPS AUCMB to rescue} = [\Sigma_{i=1 \text{ to } m} (X_i+X_{i-1})(t_i - t_{i-1})/(t_m - t_0)] - X_0$$

Let M be the final observation in the 2-hour observation, then the CHEOPS AUCBM to end was defined as,

$$\text{CHEOPS AUCMB to end} = [\Sigma_{i=1 \text{ to } M} (X_i+X_{i-1})(t_i - t_{i-1})/(t_m - t_0)] - X_0$$

Safety analysis - Vital sign changes from baseline was analyzed using a Fisher's Exact Test.

Sample size - the sample size is determined based on the primary efficacy endpoint, the proportion of patients requiring rescue analgesia within two hours after the block. The sample

size of 40 evaluable patients per each group had 80% of power to detect a difference of 50% between the two groups with the background proportion of 80% in the group received no block. The statistical test used was a chi-square test with continuity correction with a 0.05 types I error rate.

Results:
The number of subject disposition and withdrawals are given in Table V.1.1.

Table V.1.1 Patient Disposition and Withdrawal Chart (Based on NDA Table 1, Appendix 7, page 259, vol. 146)

Status	Treatment		Total
	0.50% Levobupivacaine	No Block	
Randomized	15 Unilateral 5 Bilateral	13 Unilateral 5 Bilateral	38
Withdrawal prior to receiving randomized treatment	0	1 Unilateral 2 Bilateral	3
ITT Population	20	15	35
Safety Population	20	15	35
Non-protocol evaluable	0	2	2
Per-protocol population	20 (100%)	13 (72.2%)	33

Treatment allocation – Thirty-eight patients enrolled and randomized into the two treatment groups with 20 in 0.5% Levobupivacaine group and 18 in no-block group. Three patients in the no-block group withdrew before dosing; the thirty-five patients received study drugs formed the "safety " population and the "intent-to-treat " population. They were 2 patients in the no block group discontinued their study drug based on the investigator's judgement. They were excluded from the "per-protocol " population.

Demographic data:
The demographic characteristic details were given in NDA Table 2 (page 37, vol. 146). Seventeen (85%) patients in the Levobupivacaine group were male and 14 (93.3%) in the no-block group were male. Eighty-five percent of the Levobupivacaine group and 93.3% of the no-block group were Caucasians. The average age was 5.67 yr in the Levobupivacaine group and 6.21 yr in the no block group. The average height was 109.82 cm in Levobupivacaine group and 115.96 cm in the no-block group. The average weight was 23.01 kg in the Levobupivacaine group and 24.14kg in the no-block group.

Physical examinations showed normal findings for the majority of patients in each group.

Efficacy Endpoints:
The study was designed to test for the superiority of Levobupivacaine over no-block treatment for post-operative pain control with primary efficacy endpoint the proportion of patients received at least one relief medication. Efficacy endpoint analysis presented in this review was carried out using the "intent-to-treat" population.

Primary efficacy endpoint –
The Levobupivacaine group had a lower proportion, 45%, of patients than the no-block group (73.3%) received at least one relief medication. The difference –28.3% was not statistically significant using the chi-square test (p=0.167)(Table V.1.2). Similar results were shown in

analysis using "per-protocol" population.

Table V.1.2 Proportion of patients requiring rescue medication (intent-to-treat population) (based on NDA Table 3, page 39, vol 146)

Endpoint	Treatment		Diff, (95% CI) p-value
	0.50% Levobupivacaine	No Block	
Received at least one rescue medication N(%)	9 (45)	11(73.3)	-0.283 (-0.0623, 0.623) p=0.167
Received no rescue medication	11 (55)	4 (26.7)	
Number of dose received			
One dose	5 (55.6)	4 (36.4)	
two dose	3 (33.3)	5 (45.5)	
three dose	1 (11.1)	1 (9.1)	
>three dose	0 (0.0)	1 (9.1)	

Secondary efficacy endpoints

CHOEPS - The mean increase in the CHEOPS pain score from baseline ignoring the usage of rescue analgesia were significantly lower in the Levobupivacaine group than the no-block group at 15 minutes (p=0.04), 25 minutes (p=0.011), and 30 minutes (p=0.0160) following the time of Band-Aid placement. The mean CHOEPS score was lower in the Levobupivacaine group than the no-block group at 15 minutes (p=0.042), 25 minute (p=0.031), 30 minutes (p=0.006), 45 minutes (p=0.016), 60 minutes (p=0.024), and 120 minutes (p=0.027) after the time of Band-Aid placement before the rescue medication (Table V.1.4). The average CHEOPS AUCMB to the end of study was lower in the Levobupivacaine group (0.427) than the no-block group (0.946). The difference was statistically significant (p=0.03). The average CHOEPS AUCMB to the rescue medication was also lower in the Levobupivacaine group (0.537) than the no-block group (01.221). The difference was statistically significant with p=0.013.

Table V.1.3 CHOEPS change from baseline over time (based on NDA Tables 7.1, page 272-276, vol.146)

CHEOPS Score	Time in minutes											
	5	10	15	20	25	30	45	60	75	90	105	120
0.5% Levobupivacaine												
N	15	20	15	20	20	20	20	20	20	20	20	20
Mean	0.0	0.4	0.3	0.8	0.6	0.7	1.0	0.2	0.7	0.2	0.2	-0.4
No Block												
N	10	14	11	15	15	15	15	15	15	15	15	15
Mean	0.0	0.6	1.3	1.1	2.1	2.0	1.7	1.1	0.5	0.5	0.3	0.1
Diff	0.0	-0.3	-1.0	-0.3	-1.5	-1.3	-0.7	-0.9	0.2	-0.3	-0.1	-0.4
p-value*	NE	0.45	0.04	0.52	0.011	0.016	0.282	0.096	0.726	0.40	0.763	0.273

*: ANOVA treatment effect.

Table V.1.4 CHOEPS scores at or before rescue medication (NDA Tables 5, page 40-41, vol.146)

CHEOPS Score	Time in minutes											
	5	10	15	20	25	30	45	60	75	90	105	120
0.5% Levo- N	15	20	20	20	20	20	20	20	20	20	20	20
Mean	0	0.4	0.3	0.8	1.0	1.1	1.6	1.6	2.3	1.8	1.8	1.7
No Block N	10	14	14	15	15	15	15	15	15	15	15	15
Mean	0	0.6	1.3	1.6	2.5	2.9	3.5	3.5	3.3	3.4	3.4	3.5
Diff	0	-0.3	-1.0	-0.9	-1.5	-1.8	-1.9	-1.9	-1.0	-1.6	-1.6	-1.9
p-value*	NE	0.45	0.04	0.131	0.03	0.006	0.016	0.024	0.215	0.05	0.063	0.027

*: ANOVA treatment effect.

Table V.1.5 CHOEPS AUCMB (based on NDA Tables 7.3 and 7.4, page 283-284, vol.146)

CHOEPS	Treatment		Diff, (95% CI) p-value*
	0.50% Levobupivacaine	No Block	
AUCMB to rescue N, Mean±SD	20, 0.537±0.691	15, 1.221±0.844	-0.7 (-1.2, -0.2) p=0.013
AUCMB to end of study N, Mean±SD	20, 0.427±0.635	15, 0.946±0.715	-0.5 (-1.0, -0.1) p=0.030

*: ANOVA treatment effect

Volume of rescue analgesia – The proportion of patients received morphine was lower in Levobupivacaine group (45.0%) than the no-block group (73.3%). The difference (-23.3%) was not statistically significant (p=0.167, 95% CI=(-62.3%, 6.2%)). The amount of morphine received was also lower in the Levobupivacaine group (1.97 mL) than the no-block group (2.29 mL). One child in the no-block group received also ketolorac.

Time to first request for rescue medication – Among those patients who received rescue medications (45% in Levobupivacaine and 73.3% in no-block group), the time to first request of rescue medication was significantly longer in the Levobupivacaine group (118 min) than the no-block group (31 min) with p=0.041 (NDA Table 6.3, page 270, vol. 146).

Overall quality of block – The average score was higher in Levobupivacaine group (2.1 in a 4 point rating scale) than the no-block group (1.4). The difference (0.7) was not statistically significant (p=0.064. ANOVA)

Safety analysis -
Adverse events – Nineteen of 20 patients (95.0%) in the Levobupivacaine group and 13 of 15 patients (86.7%) in the no block group experienced one or more adverse event during the course of the study. The most frequent (i.e. at least 10% patients experienced) events were fever, pain, nausea, vomiting, and urinary retention. Sixteen of 20 patients (80%) in the Levobupivacaine group and 12 of 15 patients (80%) with no-block treatment that reported at least one adverse event considered to be related to the study drug.

Vital signs – There was no evidence of difference between the two treatment groups in vital sign change from baseline.

V.1.f. The Reviewer's Comments and Conclusions
This study was designed for the primary purpose of assessing the efficacy of 0.50% Levobupivacaine as an ilionguinal-iliohypogastric nerve block for post-operative pain control in pediatric patients following hernia repair surgery. The efficacy of the treatment would be confirmed by comparing the treatment with no-block treatment. Statistically, the study was designed to test the null hypothesis that

H_0: E (difference in the proportion of patients needed rescue medication in two groups) = 0

The efficacy of Levobupivacaine treatment would be established when the null hypothesis was rejected with a significantly lower proportion in the Levobupivacaine group than the no-block group.

In primary endpoint: Although the Levobupivacaine patients had a 28.3% lower proportion

than the no-block group in patients needed rescue medication, the evidence was not strong enough to reject the above null hypothesis (p=0.167) in the "intent-to-treat" population.

Secondary endpoints:

The results of the analysis of the supportive secondary efficacy endpoints were as follow,

1. The 0.50% Levobupivacaine group had a significantly higher average value than the no-block group in area under the curve of the "Children's Hospital of Eastern Pain Scale minus baseline" vs. time till either the rescue (p=0.013) or till the end of the study (p=0.030). The difference was at 15 minutes, 25 minutes, and 30 minutes after the Band-Aid placement.
2. Among the patients received rescue medications, the Levobupivacaine group had a statistically significantly longer average time than the no-block group till the first request for rescue medication (p=. 041).
3. The mean overall quality of block was higher for the Levobupivacaine than the no-block treatment groups. The difference was of borderline statistical significance (p=0.064).

Safety assessments:

There was 95.0% of the Levobupivacaine patients and 86.7% of no-block patients had at least one adverse event during the course of the study. The most frequent (i.e. at least 10% patients experienced) events were fever, pain, nausea, vomiting, and urinary retention. There were eighty percent of the patients in each of the Levobupivacaine groups or the no block group had at least one adverse event considered to be related to the study drug. There was no evidence of difference between the two treatment groups in vital sign change from baseline.

VI. Efficacy Summary of Phase III Studies

All seventeen trials were designed as double blind, randomized, 2 or 3 arms parallel well controlled studies. In most of the indications, placebo-controlled trial would be impracticable or unethical. In these cases, Levobupivacaine was appropriately compared with a standard drug, Bupivacaine. In some studies, additional evidence of efficacy emerged from the dose response to Bupivacaine. In an active controlled study, the effectiveness of Levobupivacaine might be shown in superiority, in equivalence or in non-inferiority to the active control drug. Since the values of the equivalence or non-inferiority limits were not always well recognized. When it was failed to demonstrate superiority in a study, the difference and confidence limits would be presented and the decision for equivalence would be relied on medical review.

For obstetric indications:

Four trials (Studies 030632, CS-001, 030276 and 030433) were obstetric trial for the drug used as extradural anesthesia in patients undergoing elective cesarean section or laboring.

1. Epidural administration in cesarean section- Two trials showed equivalence (with limits pre-specified by the investigators) of the 0.5% Levobupivacaine to Bupivacaine of the same dose in terms of "time to onset of sensory block" according to the sponsor's pre-specified equivalence limits. In fact, in Study 030632 and Study CS-001, a difference of more than 6.7 minutes was ruled out.

2. Epidural administration during labor – Study 030276 and Study 030433 were designed to study the effect of Levobupivacaine epidural injection for labor pain control was failed by comparing with Bupivacaine. In Study 030276, the primary equivalence comparison of 0.25% Levobupivacaine and Bupivacaine in terms of "duration pain relief following surgery" failed to satisfy the pre-specified limit. In fact, Levobupivacaine was shown inferior to Bupivacaine in two aspects of the primary endpoints. It had a significantly shorter median duration of pain relief than Bupivacaine (43 min Levo vs. 53 min Bup with p=0.005). In addition, it was shown that comparing to the 0.25% Bupivacaine group, patients treated with 0.25% Levobupivacaine had significantly lower proportion of patients experienced pain relief (73.3% Levo vs. 86.9% Bup with p=0.018). The effectiveness of Levobupivacaine was also measured primary by the minimum local analgesic concentration (MLAC) in Study 030433. It failed to show equivalence between Levobupivacaine and Bupivacaine according to the limits pre-specified by the sponsor. The Levo/Bupi relative potency was estimated to be 0.98 with wide confidence limits (0.58, 1.38).

In general, 0.5% Levobupivacaine had similar characteristics as of 0.5 Bupivacaine for epidural administration in cesarean section. The efficacy of 0.25% Levobupivacaine was shown in terms of significantly larger proportion of patients achieved protocol proper block. But among those who achieved proper block, Levobupivacaine provided shorter duration than Bupivacaine. The Levo/Bupi relative potency was estimated at 0.98 but can't ruled out a ratio as small as 0.58 or as large as 1.38.

For central block indications:

There were two central block trials (Studies 006175 and CS-005) for the drug to be used as epidural analgesia in patients undergoing elective surgery. The effectiveness of 0.75% Levobupivacaine was demonstrated in Study CS-005, through the equivalence (i.e. less than

7.58 minutes in difference) in mean time to onset of sensory block, to Bupivacaine of the same dose. However, the superiority of 0.75% Levobupivacaine to 0.5% Levobupivacaine or 0.5% Bupivacaine was not clear. As shown in Study 006175, a potential trend from 0.5% Bupivacaine to 0.5% Levobupivacaine to 0.75% Levobupivacaine in duration of sensory block was observed on both left and right side of the body. The difference was not statistically significant between 0.75% Levobupivacaine and 0.5% Levobupivacaine or 0.5% Bupivacaine when comparisons were made among the patients who had been given general anesthetic. The differences were statistically significant at both left and right sides of the body when the comparisons were made among patients irrespective to whether to whom a general anesthetic was given. However, the second definition was revised upon the request of the sponsor after the blind was broken.

For central block pain management:
There were four central block pain management studies (Study 030475, CS-004, CS-006, Study 30742) for the drug to be used in epidural injection as post-operative pain control following surgery. Because of the different type of surgery, different standard drugs were used as active controls in the studies. In addition, each of the study was a 3-arm trial, which including Levobupivacaine, standard drug and the combination treatment of Levobupivacaine and the standard drug.

The dose response relationship was shown in post-operative pain control following orthopedic surgery with 0.25%, 0.125% and 0.0625% Levobupivacaine in Study 30475. It was shown that 0.25% Levobupivacaine was superior than either 0.125% or 0.0625% Levobupivacaine in proportion of patients requesting analgesia ($p=0.04$ for 0.25% vs. 0.125%, $p=0.001$ for 0.25% vs. 0.0625%), in survival time to the first request ($p<0.001$ for 0.25% vs. either 0.125% or 0.0625%). Although 0.125% Levobupivacaine had fewer patients requested analgesia and had longer time to the first request than 0.0625% Levobupivacaine, the differences were not statistically significant.

The effectiveness of the combination treatment over its components was demonstrated in 0.125% Levobupivacaine plus 0.125% Fentanyl in pain control following orthopedic surgery in Study CS006 through the comparison of time to the first request of rescue analgesia ($p=0.007$ comb vs. Levo alone, $p=0.006$ comb vs. Fentanyl alone). There was no significant difference between Levobupivacaine alone and Fentanyl alone.

The effectiveness was also shown in 0.125% Levobupivacaine plus 50 $\mu g.h^{-1}$ clonidine in pain control following hip replacement in Study 30742 through the comparison of total morphine administered ($p<0.001$ comb vs. Levo alone, $p=0.004$ comb vs. clonidine alone). The 0.125% Levo alone group had a non-significant higher dose than the clonidine alone group ($p=0.022$ compared with the adjusted type I error rate of 0.017).

A trend for effectiveness of the combination of 0.25% Levobupivacaine plus 0.25% morphine over its components in pain control following abdominal surgery was shown in Study CS004. It was shown that the proportion of patients requested rescue analgesia was the lowest in the combination group (47.5% vs. 95.2% vs. 72.7% for comb. vs. Levo vs. morphine). It was also shown that the combination group had the longest time to first request for rescue analgesia (962.4 min vs. 255.6 min vs. 656.4 min comb vs. Levo vs. morphine). The difference was

statistically significant between comb and Levobupivacaine alone (p=0.001 for proportion, p=0.001 for time) and between Levobupivacaine alone and morphine alone (p=0.001 time).

For peripheral block use: Six studies (Studies 030428, 030721, 006154, 030543, 030737and 030700) were peripheral block studies for the drug used as infiltration analgesia in patients undergoing major elective surgery. In all studies, a regular superiority hypothesis testing design was adopted and all studies failed to clearly demonstrate the superiority of Levobupivacaine over Bupivacaine of the same dose. The confidence intervals were given in Study 030428, Study 030543, Study 030737 and Study 030700.

1. Infiltration analgesia – Infiltration analgesia effect of 0.25% Levobupivacaine was studied in patients with inquinal hernia repair in Study 030428 and Study 0340721. The two studies failed to demonstrate clear superiority of Levobupivacaine over Bupivacaine as planned. It was shown that patients treated with 0.25% Levobupivacaine had normalized area under the VAS curve similar to the patients treated with 0.25% Bupivacaine in all three positions measured. The differences were small and could be easily considered as equivalent. The results were consistent between the two studies.

2. Brachial plexus block - Dose response of 0.5% versus 0.25% Levobupivacaine for brachial plexus block in hand surgery was demonstrated in duration of sensory block in Study 006154. The higher dose group had a significantly longer mean duration than the lower dose group (1028.7 min vs. 662.4 min for 0.5% Levo vs. 0.25% Levo with p=0.004). The 0.5% Bupivacaine group had a mean duration (836.5 min) between the two Levobupivacaine groups. It ruled out a likelihood of having more than 86 minutes shorted duration in 0.5% Levobupivacaine than 0.5% Bupivacaine. On the other hand, the 0.25% Levobupivacaine group might had a duration shorter than the 0.5% Bupivacaine for up to 435 minutes.

3. Peribulbar block anesthesia - The 0.75% Levobupivacaine was compared with 0.75% Bupivacaine for peribulbar block in ophthalmic surgery in Study 030543 and Study 030737. The primary efficacy variable used in the studies was time to adequate sensory block for surgery. The effectiveness of 0.75% Levobupivacaine was demonstrated with all patients achieved adequate sensory block in both studies. It was also demonstrated in Study 030543 that the two treatment groups had the same median time with maximum difference no more than 5 minutes. However, it did not rule out a difference of up to 5 minutes. In Study 030737, the two groups had also the same median time with Levobupivacaine group took slightly longer time than the Bupivacaine group. The estimated odds ratio was 2 for longer time and could not rule out an odds ratio up to 60.

4. Dental Extraction - The 0.75% Levobupivacaine was compared with 2% lignocaine and placebo in inferior alveolar nerve block and infiltration for post-operative dental pain control. There were fewer patients in the Levobupivacaine group requested rescue medication than the other two groups (53.3% vs. 71.0% vs. 71.9% for Levo vs. lignocaine vs. placebo). Meanwhile it had also longer time to the first request for rescue medication (257.6 min vs. 85.9 min vs. 93.3 min for Levo vs. lignocaine vs. placebo). The differences were not statistically significant.

For Pediatric use: One study (Study CS-007) was a pediatric study for the drug used as post-operative pain control in pediatric patients following hernia repair surgery. The potential efficacy was shown in treatment of 0.50% Levobupivacaine. The primary result of the study showed that 28.3% fewer patients treated with .50% Levobupivacaine received at least one rescue medication than the group of patients treated with no block. The difference was not statistically significant.

A brief description of the studies and the primary endpoints was given in Table VI.1. Details of each study on secondary endpoints and safety analysis were given in Sections I-VI.

Table VI.1 Phase III clinical trials reviewed in this document with primary efficacy analysis and results

Study	Treatments	Protocol			Results
		Sample size	Primary efficacy variable	Null hypothesis tested	
Obstetric Studies					
030632	NT=0.5% Levobupivacaine 150mg AC= 0.5% Bupivacaine 150mg Elective cesarean cessation/epidural injection	31pts/NT 33pts/AC α=10%, 1-β=99% 2-sided	V= Time to onset of sensory block adequate for surgery	H_0 : |E(V(NT) –V(AC))| >10 min* *: 10 min was set by the sponsor	1. No significant difference in proportion of patients failed to achieve protocol proper block 2. Equivalence (rejected H_0)
CS 001	NT= 0.5% Levobupivacaine 150 mg AC= 0.5% Bupivacaine 150mg Elective cesarean cessation/ epidural injection	32pts/NT 30pts/AC α=0.5%, 1-β=80% one-sided	V= Time to onset of sensory block adequate for surgery	H_0 : |E(V(NT) –V(AC))| >7.26 min* *: 7.26 min was set by the sponsor	1. No significant difference in proportion of patients failed to achieve protocol proper block 2. Equivalence (rejected H_0)
030276	NT= 0.25% Levobupivacaine up to 200 mg AC= 0.25% Bupivacaine - 200mg Pain control for labor/epidural injection	76pts/NT 86pts/AC α=0.5%, 1-β=90% 2-sided	V= Duration of pain relief following the surgery	H_0 : |E(V(NT) –V(AC))| >20 min* *: 20 min was set by the sponsor	1. Significantly lower proportion of patients who failed to achieve protocol proper block in NT. 2. Significantly lower in NT. 3. Not equivalence (did not reject H_0)
030433	NT= Levobupivacaine (variable dose) AC= Bupivacaine (variable dose)	37pts/NT 36pts/AC α=0.5%, 1-β=90% 2-sided	V= Minimum local analgesia concentration	H_0 : |E(V(NT) –V(AC))| >0.017%* *: 0.017% was set by the sponsor	1. Not equivalence (did not reject H_0) 2. Relative potency =0.98

Central Block Studies					
006175	NT1= 0.5% Levobupivacaine 75mg NT2=0.75% Levobupivacaine 112.5mg AC= 0.5% Bupivacaine 75mg Lower limb surgery /epidural injection	29pts/NT1 30pts/NT2 29pts/AC α=0.5%, 1-β=90% 2-sided	V= Duration of sensory block	Planned to reject one of the following: H_{10} : |E(V(NT1) –V(AC))| =0 H_{20} : |E(V(NT2) –V(AC))| =0 H_{30} : |E(V(NT1) –V(NT2)| =0 Sequential multiple comparison type I error rate = 0.017/0.025/0.05	1. No statistically significant difference in proportions of patients who failed to attained sensory block. 2. Did not reject any one of the null hypotheses.
CS 005	NT= Levobupivacaine -150 mg 0.75% AC= Bupivacaine 150mg 0.75% Major abdominal pain surgery/epidural injection	29pts/NT 28pts/AC α=0.5%, 1-β=80% 2-sided	V= Time to onset of sensory block	H_0 : |E(V(NT) –V(AC))| ≥7.58 The limits was set by the sponsor	1. Equivalence by rejecting H_0.
Central Block Pain Management Studies					
030475	NT1=Levobupivacaine 0.25% 6 mL /hr NT2=Levobupivacaine 0.125% 6 mL/hr AC= Levobupivacaine 0.0625%, 6 mL/hr Post-operative pain control following orthopedic surgery/epidural injection	32pts/NT1 27pts/NT2 32pts/AC α=0.5%, 1-β=80% 2-sided	V= Time to request for first analgesia	Planned to reject one of the following: H_{10} : |E(V(NT1) –V(AC))| =0 H_{20} : |E(V(NT2) –V(AC))| =0 H_{30} : |E(V(NT1) –V(NT2)| =0 Sequential multiple comparison type I error rate = 0.017/0.025/0.05 ANOVA & Cox regression	1. Significantly lower proportion of patients who did not request analgesia in 0.25% Levobupivacaine group 2. Significantly longer mean time to request for first analgesia (i.e. rejected H_{10} and H_{30}). 3. No statistically significant difference in time to first request for analgesia between 0.125% and 0.0625% Levobupivacaine groups.
CS 004	NT1=Levobupivacaine 0.25% 6 mL /hr +0.25% morphine 6 ml/hr NT2=Levobupivacaine 0.25% 6 mL/hr AC= Morphine 0.25%, 6 mL/hr Post-operative pain control following major abdominal surgery/epidural injection	21pts/NT1 21pts/NT2 22pts/AC α=0.5%, 1-β=80% 2-sided	V= Time to request for first analgesia	H_{10} : |E(V(NT1) –V(AC))| =0 Supportive tests: H_{20} : |E(V(NT2) –V(AC))| =0 H_{30} : |E(V(NT1) –V(NT2)| =0 Sequential multiple comparison type I error rate = 0.017 for the supportive tests Wilcoxon test	1. The average value of V was ranked as V(NT1) ≤V(AC)≤V(NT2) 2. No significant difference in proportion of patients who did not request analgesia between the NT1 and AC. 3. Did not reject H_{10} :EV(NT1)=E(AC) 4. Significantly lower proportion of patients who did not request analgesia between NT1 and NT2. 5. Rejected H_{20} and H_{30}
CS 006	NT1=Levobupivacaine 4-14 mL /hr 0.125% +Fentanyl 4-14 mL/hr 0.125% NT2=Levobupivacaine 4-14 mL /hr 0.125% alone, AC= Fentanyl 4-14 mL/hr 0.125% alone Post-operative pain control following orthopedic surgery/epidural infusion	21pts/NT1 22pts/NT2 22pts/AC α=0.5%, 1-β=80% 2-sided	V= Time to request for first rescue medication	Needed to reject both H_{10} : |E(V(NT1) –V(AC))| =0 And H_{20} : |E(V(NT1) –V(NT2)| =0 No multiple comparison adjustment needed ANOVA & Wilcoxon 2-sample test	1 No significant difference in proportion of patients who did not request analgesia between the NT1 and AC or NT1 and NT2. 2 Rejected both H_{20} and H_{10}.

30742	NT1= Levobupivacaine 6mL /hr 0.125% +50 $\mu g.h^{-1}$ Clonidine NT2= Levobupivacaine 6 mL/hr 0.125% alone AC=6 mL/hr 50 $\mu g.h^{-1}$ Clonidine alone Post-operative pain control following hip replacement /epidural infusion	30pts/NT1 30pts/NT2 30pts/AC α=0.5%, 1-β=80% 2-sided	V= Total dose of morphine delivered during the 24-hour post-operative infusion	Needed to test H_{10} : |E(V(NT1) –V(AC))| =0 H_{20} : |E(V(NT1) –V(NT2)| =0 H_{30} : |E(V(NT2) –V(AC)| =0 Multiple comparison adjusted type I error rate of 0.017 was used Wilcoxon 2-sample test	1. Rejected both H_{10} and H_{20}.
Peripheral Block Studies					
030428	Levobupivacaine up to 150 mg 0.25%, Bupivacaine up to 150 mg 0.25% Post-operative pain control following inquinal hernia repair/ Infiltration analgesia	33pts/NT 33 pts/AC α=0.5%, 1-β=80% 2-sided	V1, V2, V3= Normalized area under the supine lying, lying to sitting, walking VAS vs. time curve	Needed to test H_{10} : |E(V1(NT)–V1(AC)| =0 H_{20} : |E(V2(NT) –V2(AC)| =0 H_{30} : |E(V3(NT) –V3(AC)| =0 Multiple comparison adjusted type I error rate of 0.017 was used Wilcoxon 2-sample test	1. Did not rejected either one of the null hypotheses 2. For V1: The 95% CI =(-0.994, 0.606) 3. For V2: The 95% CI =(-0.996, 0.670) 4. For V3: The 95% CI =(-1.516, 0.044).
030721	Levobupivacaine 150 mg 0.25%, Bupivacaine 150 mg 0.25% Post-operative inguinal hernia repair/infiltration anesthesia	35pts/NT 34 pts/AC α=0.5%, 1-β=80% 2-sided	V1, V2, V3= Normalized area under the supine lying, lying to sitting, walking VAS vs. time curve	Needed to test H_{10} : |E(V1(NT)–V1(AC)| =0 H_{20} : |E(V2(NT) –V2(AC)| =0 H_{30} : |E(V3(NT) –V3(AC)| =0 Multiple comparison adjusted type I error rate of 0.017/0.025/0.05 was used ANOVA & t-test	1. Did not rejected either one of the null hypotheses 2. For V1: p=1.00 3. For V2: p=0.71 4. For V3: p=0.77.
006154	Levobupivacaine 4 mL/kg 0.25%, 0.4 mL/0.5% Bupivacaine 0.4 mL/0.5% Brachial plexus block for elective had surgery	26pts/NT1 26 pts/NT2 24 pts/AC α=0.5%, 1-β=80% 2-sided	V = duration of sensory block	Needed to test H_{10} : |E(V(NT1)–V(AC)| =0 H_{20} : |E(V(NT2) –V(AC)| =0 H_{30} : |E(V(NT1) –V(NT2)| =0 Multiple comparison adjusted type I error rate of 0.017 was used ANOVA and pairwise t-test	1. Did not rejected H_{10} (p=0.14) 2. Did not rejected H_{20} (p=0.20) 3. Did not rejected H_{30} (p=0.004)
030543	Levobupivacaine 37.5-112,5 mg 0.75% Bupivacaine 37.5-112.5 mg 0.75% Ophthalmic surgery/peribulbar block	25pts/NT 25pts/AC α=0.5%, 1-β=80% 2-sided	V= Time to adequate sensory block for surgery (non-normal ordinal data)	Needed to test H_0 : |E(V(NT)–V(AC)| =0 Wilcoxon rank sum test	1. Did not rejected the null hypothesis 2. Median diff =0.0, the 95% CI =(-2, 5)
030737	Levobupivacaine 37.5 mg 0.75%, Bupivacaine 37.5 mg 0.75% peribulbar block efficacy	25pts/NT 25pts/AC α=0.5%, 1-β=80% 2-sided	V= Levo-bupi odds ratio for shorter time to satisfactory block	Needed to test H_0 : |E(V)| =1	3. Did not rejected the null hypothesis 4. Odds ratio = 0.51, the 95% CI =(0.016, 1.56)

030700	Levobupivacaine 67.5 mg 0.75%, Lidocaine 2%, Placebo Post-operative pain control/interior alveolar nerve block and infiltration	31pts/NT1 32 pts/AC 32 pts/PLB α=0.5%, 1-β=80% 2-sided	V = Proportion of patients required rescue medication	Needed to test H_{10} :E(relative risk V(NT/AC))=1 H_{20} : E(relative risk V(NT/PLB))=1 Multiple comparison adjusted type I error rate of 0.025 was used Mantel Haenszel chi-square or Fisher exact test	1. Did not rejected either one of the null hypotheses 2. For NT/AC the 95% CI =(0.51, 1.12) 3. For NT/PLB, the 95% CI =(0.50, 1.10)
Pediatric Study					
CS 007	NT= Levobupivacaine 1.25 mg 0.5%, PB= no treatment Post-operative pain control following IIIH inquinal hernia	20pts/NT1 15pts/PB α=0.5%, 1-β=80% 2-sided	V= Proportion of patients who needed rescue analgesia in the two-hour post-operative observation period	Null hypothesis needed to test H_0 : |E(V(NT) –V(PB)| =0 Chi-square or Fisher Exact test	Did not reject H_0.

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VII. Summary of Safety in Phase II/III Clinical Studies

This section summarized the safety data of all phase II and III studies. The studies included in the analysis were 4 randomized double blind obstetric studies (Study 030632, CS001, 030276 and 030433) two randomized double blind central block studies (Study 006175, CS005), one open label non-randomized central block study (Study 030412), four double blind, randomized central block pain management studies (Study 030475, CS004, CS006 and 030742), six double blind randomized peripheral block studies (Study 030428, 030721, 006154, 030543, 030737 and 030700), one open labeled peripheral block study (Study CS009), and one randomized double blind pediatric study (study CS007).

VII.1 Patient disposition and termination

VII.1.1 All phase II/III studies:

As shown in Table VII.1 that except placebo group and Lidocaine plus adrenaline group, there were about 83% patients completed the study in each of the three major treatment group in all studies combined. The most common reason for termination in Levobupivacaine alone and Bupivacaine group was administration reason. The administration reason included "lost to follow-up", withdrawal of consent", "protocol violation", and "other". Within the administrative reasons, the most common category was "other", which resulted in 9.7% of the patients of the terminated patients. The sponsor pointed out the large percentage was contributed from Study 030276. Investigator of Study 030276 categorized all premature discontinuation as "other".

There was a large proportion of patients (10.2%) in the Levobupivacaine plus other combination treatment group withdraw due to inadequate pain control, compared with 2.8% for Levobupivacaine alone and 0 for Bupivacaine group. The difference was reflective of the study designs of post-operative pain control. Contrast to the fact that all Levobupivacaine plus other combination treatments were evaluated in the post-operative pain control studies, Bupivacaine was not evaluated in these studies. No clinical or meaningful statistical differences were observed in this analysis.

Table VII.1 Patient disposition and termination (NDA Tables 2- 6, page 33-39, vol.147)

Patient status	Levo N=702	Bupi N=391	Levo + Other N=147	Placebo N=47	Lidocaine + adrenaline N=31
All Phase II/III Studies					
Patients dosed	702	391	147	47	31
Patients completed	589 (83.9%)	322 (82.4%)	122 (83.0%)	47 (100.0%)	31 (100.0%)
Patients who terminated	113 (16.1%)	69 (17.6%)	25 (17.0%)	0	0
Reasons for termination					
Inadequate block	10 (2.8%)	2 (0.5%)	0	0	0
Inadequate pain control	20 (2.8%)	0	15 (10.2%)	0	0
Patient withdrawn	2 (0.3%)	0	1 (0.7%)	0	0
Adverse Event	4 (0.6%)	2 (0.5%)	2 (1.4%)	0	0
Administrative reason	70 (10.0%)	65 (16.6%)	7 (4.8%)	0	0
Obstetric Studies					
Patients dosed	184 (100.0%)	188 (100.0%)			
Patients completed	116 (63.0%)	120 (63.8%)			
Patients who terminated	68 (37.0%)	68 (36.2%)			
Reasons for termination					
Inadequate block	6 (3.3%)	2 (1.1%)			
Inadequate pain control	2 (1.1%)	0			
Patient withdrawal	0	0			
Adverse Event	0	1 (0.5%)			
Administrative reason	60 (32.6%)	65 (34.5%)			
Central Block Studies					
Patients dosed	109 (100.0%)	57 (100.0%)			
Patients completed	105 (96.3%)	57 (100.0%)			
Patients who terminated	4 (3.7%)	0			
Reasons for termination					
Inadequate block	0	0			
Inadequate pain control	0	0			
Patient withdrawal	0	0			
Adverse Event	0	0			
Administrative reason	4 (3.7%)	0			
Post-surgery Pain Management Studies					
Patients dosed	179 (100.0%)		147 (100.0%)		
Patients completed	140 (78.2%)		122 (83.0%)		
Patients who terminated	39 (21.8%)		25 (17.0%)		
Reasons for termination					
Inadequate block	14 (7.8%)		0		
Inadequate pain control	18 (10.1%)		15 (10.2%)		
Patient withdrawal	2 (1.1%)		1 (0.7%)		
Adverse Event	4 (2.2%)		2 (1.4%)		
Administrative reason	4 (2.2%)		7 (4.8%)		
Peripheral Block Studies					
Patients dosed	210 (100.0%)	146 (100.0%)		32 (100.0%)	31 (100.0%)
Patients completed	208 (99.0%)	145 (99.3%)		32 (100.0%)	31 (100.0%)
Patients who terminated	2 (1.0%)	1 (0.7%)		0	0
Reasons for termination					
Inadequate block	0	0		0	0
Inadequate pain control	0	0		0	0
Patient withdrawal	0	0		0	0
Adverse Event	0	1 (0.7%)		0	0
Administrative reason	2 (1.0%)	0		0	0

VII.1.2 Obstetric studies:

Bupivacaine and Levobupivacaine were the only treatments investigated in obstetric studies. The proportion of patients completed the study was about 63% in both treatments. As stated earlier, the large percentage of category "other" as reason of termination was reflective of the

categorizing by the investigator of Study 030276.

VII.1.3 Central block studies:
The completion rate was high in both Levobupivacaine and Bupivacaine groups. In central block studies, there was 3.7% of the Levobupivacaine patients failed to complete the study, compared with no patients for the Bupivacaine group.

VII.1.4 Post-surgery pain management
There were 78.2% completed the study for the Levobupivacaine group and 83.0% for the combination group. The difference was not statistically significant (p=0.28 chi-square test). There were 7.8% patients had inadequate block for the Levobupivacaine group compared with none for the combination treatment group. The difference was statistically significant either as proportion of all patients in the treatment (p<0.001, chi-square test) or as proportion of the patients didn't complete the study (p<0.001, chi-square test).

VII.1.5 Peripheral block studies
There were very few patients did not completed the study in peripheral block studies (1.0% for Levobupivacaine, 0.7% for Bupivacaine, 0.0% for placebo and 0.0% for Lidocaine plus adrenaline).

VII.1.6 Pediatric studies
There were no patients who did not complete the study.

VII.1.7 0.75% Levobupivacaine studies
In this section the proportion of patients didn't complete the study in studies with highest dose of Levobupivacaine being 0.75% was analyzed. In table VII.2, Bupivacaine represented the total number of patients in the selected studies. There were 11.7% patients didn't complete the study for the Levobupivacaine group.

The proportion was slightly higher than 9.8%, the proportion of all patients in this subset. This proportion was also higher than the rate for all patients other than the Levobupivacaine alone group in this subset (7.76%). The difference was not statistically significant (p=0.088 chi-square test). The Levobupivacaine-to-other relative risk for early termination was 1.51 with 95% confidence interval (0.941, 2.406).

However, this proportion was lower than the proportion of earlier termination for all groups other than the Levobupivacaine group (15.26%), or the proportion for all patients in the no-Levobupivacaine groups (14.71%). None of the comparisons was statistically significant.

In addition, the Levo group defined in this subset represented all Levobupivacaine alone patients including those treated with doses lower than 0.75%. Hence, there was no clear and direct evidence to show that 0.75% Levobupivacaine would be safer than Bupivacaine in safety risk in terms of early termination.

Table VII.2 Patient disposition in 0.75% Levobupivacaine studies (NDA Table 8, vol. 148)

Patient status	Levo	Bupi	Levo + Other	Placebo	Lidocaine + adrenaline	Total
Patients dosed	351	112	147	32	31	673
Patients completed	310 (88.3%)	112 (100.0%)	122 (83.0%)	32 (100.0%)	31(100.0%)	606 (90.2%)
Patients who terminated	42 (11.7%)	0 (0.0%)	25 (17.0%)	0	0	66 (9.8%)
Reasons for termination						
Inadequate block	14 (4.0%)	0	0	0	0	14 (2.1%)
Inadequate pain control	18 (5.1%)	0	15 (10.2%)	0	0	33 (4.9%)
Patient withdrawn	2 (0.6%)	0	1 (0.7%)	0	0	3 (0.4%)
Adverse Event	4 (1.1%)	0	2 (1.4%)	0	0	6 (0.9%)
Administrative reason	6 (1.7%)	0	7 (4.8%)	0	0	13 (1.9%)

VII.2 Extent of expcsure

The mean doses of Levobupivacaine, Bupivacaine and Levobupivacaine plus other treatments were given in Table VII.3 by type of administration, and indication. In general the mean and standard deviation was similar between Levobupivacaine and Bupivacaine in all type of administration and indication except for Bolus injection for central block studies. The Bupivacaine group had higher dosage than Levobupivacaine (113.68 mg vs. 92.96 mg). The dosage was also comparable between Levobupivacaine alone and Levobupivacaine plus other in all type of injection and indication except in Bolus injection for post-surgery pain. The mean was much higher in the combination treatment than the Levobupivacaine alone (137.50 vs. 108.44).

Table VII.3 Dosage (mg) Levobupivacaine (NDA Tables 9- 18, vol.147)

Studies Mean ± SD (N)	Levobupivacaine	Levobupivacaine + Other	Bupivacaine
All Phase II/III Studies	97.79 ± 48.88 (702) 10.0 –300.0*	137.50 ± 37.75 (147) 75.0 – 375.0	99.95 ± 47.58 (391) 10.0 –202.5
Administered by Infusion	210.44 ±111.68 (164) 20.4 – 573.5	202.76 ± 88.96 (72) 1.9 – 486.0	
Bolus Injection : Obstetric	94.37 ± 53.34 (184) 10.0 – 200.0		92.88 ± 51.84 (188) 10.0 – 200.0
Bolus Injection: Central Block	92.96 ± 48.53 (109) 15.0 – 202.5		113.68 ± 40.85 (57) 75.0 – 202.5
Bolus Injection: Post-surgery Pain	108.44 ± 35.99 (179) 60.0 – 270.0	137.50 ± 37.75 (147) 75.0 –375.0	
Infusion: Post-surgery Pain	210.44 ± 111.68 (164) 20.4 – 573.5	202.76 ± 88.96 (72) 1.9 –486.0	
Bolus Injection: Peripheral Block	100.46 ± 51.44 (210) 33.8 – 300.0		103.69 ± 42.72 (146) 37.5 – 196.0
Bupivacaine-controlled phase II/III	100.96 ± 45.95 (445) 10.0 –202.5		99.95 ± 47.58 (391) 10.0 – 202.5

*: Range

VII.3 Adverse events

Table VII.4 presented the summary of adverse events in all phase IIII/III studies. In general, the incidence rates for Levobupivacaine were similar to that for the Bupivacaine. The high percentage of adverse events was due to the fact that the patients treated with Levobupivacaine plus other drug(s) were in the studies for post-surgery pain management. The patients were often sicker and weaker.

Table VII.4 Summary of adverse events: All phase III studies (NDA Tables 22 and 8.2, vol. 148)

Number of patients with	Levo	Bupi	Levo + Other	Placebo	Lidocaine + adrenaline
At least one adverse event	512 (72.9%)	263 (67.3%)	143 (97.3%)	31 (66.0%)	20 (64.5%)
At least one moderate or severe AE	287 (40.8%)	139 (35.5%)	89 (60.5%)	30 (63.8%)	18 (58.1%)
At least one moderate or severe and at least one possibly drug-related AE	142 (20.2%)	66 (16.9%)	68 (46.3%)	17 (36.2%)	6 (19.4%)
At least one serious AE	52 (7.4%)	36 (9.2%)	8 (5.4%)	0	0
Deaths	0	0	1 (0.7%)	0	0
Discontinuations due to AE	4 (0.4%)	2 (0.5%)	2 (1.4%)	0	0

In order to have a compare the incidence rate among similar type of patients, the rates were also calculated by the type of studies and the results were given in Table VII.5 (NDA Tables 23-27, vol. 148). It was shown that the incidence rate were similar between the Levobupivacaine and the Bupivacaine groups in the obstetric studies and peripheral studies. In patients treated for central block, the incidence rates for the Levobupivacaine group were lower than that for the Bupivacaine group. However, when restricted to studies involved with Bupivacaine group, the differences were much smaller in incidence rate between the Levobupivacaine and the Bupivacaine groups (NDA Table 28, page 63, vol. 148). When restricted to post-surgery pain management studies, the incidence rates for the Levobupivacaine plus other group had incidence rates similar to that of the Levobupivacaine group except for a higher rate of moderate, severe and possibly drug related adverse events.

Table VII.5 Summary of adverse events: Phase III studies by type of indication (NDA Tables 23 to 27, vol. 148)

Number of patients with	Levo	Bupi	Levo + Other	Placebo	Lidocaine + adrenaline
Obstetrics Studies					
At least one adverse event	144 (78.3%)	136 (72.3%)			
At least one moderate or severe AE	71 (38.6%)	80 (42.6%)			
At least one moderate or severe and at least one possibly drug-related AE	27 (14.7%)	31 (16.5%)			
At least one serious AE	26 (14.1%)	30 (16.0%)			
Deaths	0	0			
Discontinuations due to AE	0	1 (0.5%)			
Central Block Studies					
At least one adverse event	74 (67.9%)	47 (82.5%)			
At least one moderate or severe AE	47 (43.1%)	35 (61.4%)			
At least one moderate or severe and at least one possibly drug-related AE	32 (29.4%)	21 (36.8%)			
At least one serious AE	8 (7.3%)	2 (3.5%)			
Deaths	0	0			
Discontinuations due to AE	0	0			
Post-surgery Pain Management Studies					
At least one adverse event	171 (95.5%)		143 (97.3%)		
At least one moderate or severe AE	112 (62.6%)		89 (60.5%)		
At least one moderate or severe and at least one possibly drug-related AE	61 (34.1%)		68 (46.3%)		
At least one serious AE	10 (5.6%)		8 (5.4%)		
Deaths	0		1 (0.7%)		
Discontinuations due to AE	4 (2.2%)		2 (1.4%)		
Peripheral Block Studies					
At least one adverse event	104 (49.5%)	80 (54.8%)		18 (56.3%)	20 (64.5%)
At least one moderate or severe AE	43 (20.5%)	24 (16.4%)		17 (53.1%)	18 (58.1%)
At least one moderate or severe and at least one possibly drug-related AE	11 (5.2%)	14 (9.6%)		5 (15.6%)	6 (19.4%)
At least one serious AE	8 (3.8%)	4 (2.7%)		0	0
Deaths	0	0		0	0
Discontinuations due to AE	0	1 (0.7%)		0	0
Pediatric Studies					
At least one adverse event	19 (95.0%)			13 (86.7%)	
At least one moderate or severe AE	14 (70.0%)			13 (86.7%)	
At least one moderate or severe and at least one possibly drug-related AE	11 (55.0%)			12 (80.0%)	
At least one serious AE	0			0	
Deaths	0			0	
Discontinuations due to AE	0			0	

The sponsor tabulated adverse event by body system in NDA Table 30 to Table 37 (vol. 148). Of particular interest was the incidence of cardiovascular system disorder events. As shown in Table VII.6, the incidence rate was similar between the Levobupivacaine and the Bupivacaine groups in all phase II and III studies and by type of studies. The higher rate in the Levobupivacaine plus other group was due partially to the reason as described earlier,

Table VII.6 Cardiovascular disorder adverse event (NDA Tables 31, vol. 148)

Number of patients with	Levo	Bupi	Levo + Other	Placebo	Lidocaine + adrenaline
All phase II/III studies	236 (33.6%)	115 (29.4%)	117 (79.6%)	0	0
Obstetric studies	60 (32.6%)	71 (37.8%)			
Central block studies	39 (35.8%)	19 (33.3%)			
Post-surgery pain management studies	111 (62.0%)		116 (78.9%)		
Peripheral block studies	16 (7.6%)	17 (11.6%)		0	0
Pediatric studies	1 (5.0%)			0	

In order to study the adverse event safety of 0.75% Levobupivacaine, the sponsor compared the incidence rates of the 0.75% Levobupivacaine group with the rates of all Levobupivacaine groups combined, the Bupivacaine group, the Levobupivacaine plus other group and the Lidocaine + adrenaline group. The results were shown in Table VII.6 that was the NDA Table 29,vol. 148. It was shown that the 0.75a% Levobupivacaine group had higher incidence rate than that for all Levobupivacaine group, for "at least one adverse event", "at least one moderate to severe adverse event" and ""at least one moderate to severe possibly drug related adverse event". The incidence rates for the 0.75% Levobupivacaine group were comparable with that of the all Bupivacaine group.

Table VII.7 Summary of adverse events: 0.75% Levobupivacaine vs. all phase III studies (NDA Tables 29, vol. 148)

Number of patients with	Levo	Bupi	Levo + Other	Placebo	Lidocaine + adrenaline
At least one adverse event					
All phase II/III studies	512 (72.9%)	263 (67.3%)	143 (97.3%)	31 (66.0%)	20 (64.5%)
0.75% Levobupivacaine phase II/III	280 (79.8%)	71 (63.4%)	143 (97.3%)	18 (56.3%)	20 (64.5%)
At least one moderate or severe AE					
All phase II/III studies	287 (40.9%)	139 (35.5%)	89 (60.5%)	30 (63.8%)	18 (58.1%)
0.75% Levobupivacaine phase II/III	186 (53.0%)	42 (37.5%)	89 (60.5%)	17 (53.1%)	18 (58.1%)
At least one moderate or severe and at least one possibly drug-related AE					
All phase II/III studies	142 (20.2%)	66 (16.9%)	68 (46.3%)	17 (36.2%)	6 (19.4%)
0.75% Levobupivacaine phase II/III	100 (28.5%)	26 (23.2%)	68 (46.3%)	5 (15.6%)	6 (19.4%)
At least one serious AE					
All phase II/III studies	52 (7.4%)	36 (9.2%)	8 (5.4%)	0	0
0.75% Levobupivacaine phase II/III	22 (6.3%)	2 (1.8%)	8 (5.4%)	0	0
Deaths					
All phase II/III studies	0	0	1 (0.7%)	0	0
0.75% Levobupivacaine phase II/III	0	0	1 (0.7%)	0	0
Discontinuations due to AE					
All phase II/III studies	4 (0.6%)	2 (0.5%)	2 (1.4%)	0	0
0.75% Levobupivacaine phase II/III	4 (1.1%)	0	2 (1.4%)	0	0

Comparison between the incidence for group of all Levobupivacaine patients and the group of 0.75% Levobupivacaine patients by the body system was shown in Table VII.8 (NDA Table 39, vol. 148). It was clear that the incidence rate was consistently higher for the 0.75% Levobupivacaine group across all body systems. As expected, the incidence rate was lower in the 0.75% Levobupivacaine group for post-operative pain as secondary terms of adverse event.

Table VII.8 Adverse events that occurred in all Levobupivacaine treated patients and the corresponding incidence in patients who received 0.75% Levobupivacaine, phase II/III studies (NDA Tables 39, vol. 148)

Number of patients with	Levo N=702	0.75% Levo N=351
Body as a whole		
Fever	107 (15.2%)	89 (25.4%)
Pain	50 (7.1%)	30 (8.5%)
Back pain	39 (5.6%)	20 (5.7%)
Cardiovascular disorders, hypotension	213 (30.3%)	145 (41.3%)
Central and peripheral nervous systems		
Headache	42 (6.0%)	27 (7.7%)
Dizziness	49 (7.0%)	29 (8.3%)
Gastrointestinal disorders		
Nausea	122 (17.4%)	87 (24.8%)
Vomiting	79 (11.3%)	58 (16.5%)
Constipation	49 (7.0%)	38 (10.8%)
Red blood cell disorders (puritus)	109 (15.5%)	66 (18.8%)
Secondary terms (post-operative pain)	81 (11.5%)	34 (9.7%)
Urinary retention	36 (5.1%)	32 (9.1%)

VII. Conclusions

Analysis presented in this summary of patient dispositions and adverse events did not include any formal statistical testing. If there was any difference or trend would be considered a potential concern rather than a verified result.

Patient disposition: It was shown that the rate of early termination due to any reason, due to lack of efficacy or due to adverse event was comparable with Bupivacaine. The same conclusion was also being drawn in the analysis by the type of study. But, in studies for post-surgery pain management, there was higher proportion of patients terminated the study early due to inadequate block for the Levobupivacaine group than the Levobupivacaine plus other treatment group (7.8% vs. 0% with $p<0.001$).

In addressing the potential increased risk of the 0.75% Levobupivacaine, the sponsor's analysis showed that the proportion for early termination for the 0.75% Levobupivacaine was 11.7% which was higher than the overall proportion (9.8%) of all groups in studies involving the 0.75% Levobupivacaine. This was different to the statement given by sponsor on NDA vol. 148 page 40. However, this proportion was lower than the proportion (14.7%) of all non-Levobupivacaine groups combined.

Hence, there was no clear evidence to show that there was no potential increased risk for 0.75% Levobupivacaine based on proportion of early termination.

Extent of exposure: This summary analysis showed that the dosage was comparable (in mean and range) between Levobupivacaine and Bupivacaine in all phase II/III studies. Bupivacaine had a slightly higher mean dosage than Levobupivacaine in central block studies (92.96/Levo vs. 113.68/Bupi). The mean dosage was higher for the Levobupivacaine plus other treatment in all phase II/III combined analysis (97.79/Levo vs. 137.5/Levo+). This difference was reflected in the post-surgery pain control studies.

Adverse events: The rate of adverse events was comparable between Levobupivacaine and Bupivacaine in proportion of "patients to have at least one event", "patients to have at least one

moderate to severe event", "at least one moderate to severe possibly drug related event" in the analysis of all phase II/III studies and in the analysis in each type of study except the central block studies. In the central block studies, Bupivacaine had slightly more adverse events than Levobupivacaine.

The incidence rates were comparable between Levobupivacaine and Bupivacaine by body system. For example, the incidence rate of cardiovascular disorders was 33.6% for Levobupivacaine compared with 29.4% for Bupivacaine.

In order to study the risk of 0.75% Levobupivacaine in terms of adverse events, the sponsor made comparison between the studies involved with 0.75% Levobupivacaine with all phase II/III studies. The rate was consistently higher for the Levobupivacaine groups in studies involved with 0.75% Levobupivacaine than for the Bupivacaine groups of all phase II/III studies or for the Bupivacaine groups in the studies involved 0.75% Levobupivacaine as shown in Table VII.7.

When compared the adverse event rates by body system between the 0.75% Levobupivacaine and all Levobupivacaine groups, the rates were consistently higher in the 0.75% Levobupivacaine group in all body systems except post-operative pain (the secondary terms). This summarized analysis with adverse events indicated clearly that 0.75% Levobupivacaine had a potential to have higher rate of adverse events.

VIII ECG Analysis of Four Studies

VIII.1 Study design

The study was undertaken to determine any effects on QT dispersion or QRS interval as results of receiving racemic Bupivacaine or Levobupivacaine. ECGs were collected from 4 studies: 3 studies involved patients undergoing surgical procedures under regional anesthesia and one investigating intravenous administration in volunteers. The 4 studies were one phase II Study 004801 and three phase III clinical trials including CS-005, Study 030721, and Study 030632.

In Study 004801, the cardiovascular effects in 14 volunteers who received a maximum of 150 mg of Levobupivacaine and 110 mg Bupivacaine in a randomized crossover design as an intravenous infusion were recorded. QT dispersion for all 14 subjects was calculated for 4 time points (pre-dose, end of infusion, +30 min and +2 hr). In Study 030721, 60 patients who participated in a randomized double blind, parallel trial received a maximum of 60 ml of 0.25% (150 mg) Levobupivacaine or Bupivacaine as infiltration anesthesia for hernia repair. Their signal averaged ECG measurements and QT dispersion measurements were recorded at 3 time-points (pre-dose, end of surgery and +4 hr).

In Study CS005, 57 patients participated in a randomized, double blind parallel trial and received a standard dose of 20 ml of 0.75% (150 mg) Levobupivacaine or Bupivacaine a s an epidural abdominal surgery. Twenty nine of the patients in the study had their signal averaged ECG measurements recorded at 7 time points (pre-dose, 15 min, 30 min, 45 min, 1 hr, 2 hr, 4 hr). In Study 030632, 60 patients was randomized to receive a standard dose of 25-30 ml of 0.5% (125-150 mg) Levobupivacaine or Bupivacaine as an epidural for cesarean section had their ECG measurements recorded and their QT dispersion calculated at 3 time points (pre-dose, post dose and recovery).

All available 12-lead ECGs of the 4 studies were randomized, blinded before being read and QT dispersions were calculated and interpreted by an independent cardiologist.

VIII.2 Statistical Methods

Study 004801-

The primary endpoint of the study was the difference in QT dispersion from pre-dose to the maximum observed post-dose value (included end of infusion). The primary endpoint was to be analyzed using ANOVA techniques, including terms of sequence, subject within sequence, period and treatment. If the normal distribution assumption was found invalid, a corresponding nonparametric approach, comparing the difference between period 1 and period 2 for the sequence groups would be carried out using the Mann-Whitney-Wilcoxon method.

The secondary endpoints included, difference in QT dispersion from pre-dose and the +30 min, +2 hr and the end of infusion time points, and incidence of absolute QT dispersion $\geq$ 100 ms at one or more post dose time points. The differences in QT dispersion were to be analyzed using identical methods to the primary endpoint. The incidence was to be compared between the two treatments using McNemar's test.

In additional, the difference in ECG intervals from pre-dose to the ECG closest to the 5 min post end of infusion time points were analyzed using ANOVA model. Man-Whitney-Wilcoxon method would be used when the normal distribution assumption was invalid.

Study 030721, Study 030632 and CS-005 –
The primary endpoint of the study was the difference in QT dispersion from pre-dose to the maximum observed post dose value. The endpoint was analyzed using ANOVA model including a term of treatment. A Wilcoxon rank sum test would be used when the normal distribution assumption was invalid.

The secondary endpoints included:
Difference in QT dispersion between the pre-dose and each of the post dose time points.
Incidence of absolute QT dispersion ≥100 ms at one or more post dose time points;
Difference in QRS values from pre-dose to maximum observed post dose;
Difference in PR values from pre-dose to the maximum observed post dose;
Difference in QT values from pre-dose to the maximum observed post dose;
Difference in QTc values from pre-dose to the maximum observed post dose;
The secondary endpoints, apart from the incidence of QT dispersion values ≥100 ms, were to be analyzed using identical methods to the primary endpoint.

The secondary endpoints, except the incidence of QT dispersion, were to be analyzed using methods identical to the primary endpoint.

The incidence of QT dispersion was to be compared between the 2 treatments using McNemar's test.

VIII.3 Results
The results of the analysis by each study were presented completely in NDA vol.1.95. They were summarized in to Tables VIII.1 to VIII.6.

Table VIII.1 QT Dispersion Value of Study 004801 (i.e. NDA Table 1, page 089, vol. 1.95, Appendix B)

Change from pre-dose to	0.5% Levobupivacaine LSMean* (N)	0.5% Bupivacaine LSMean (N)	Difference, 95% CI, p-value**
+30 min	-4.2 ms (14)	7.9 (14)	-12.1 (-33.7, 9.6), p=0.25
+2 Hr	0.8 ms (14)	-0.4 (14)	1.2 (-13.2, 15.6), p=0.86
End	-1.5 ms (14)	2.8 (14)	-4.3 (-13.2, 15.6), p=0.67
Maximum	12.2 ms (14)	17.7 (14)	-5.4 (-21.0, 10.2), p=0.47

*: Crossover design.
**: t-test

Table VIII.2 ECG difference from pre-dose of Study 004801 (i.e. NDA Table 3, page 091, vol. 1.95, Appendix B)

ECG interval	0.5% Levobupivacaine LSMean (N)	0.5% Bupivacaine LSMean (N)	Difference, 95% CI, p-value
PR interval	0.0057 (12)	0.0052 (12)	0.0005 (-0.0064, 0.0074), p*=0.89
QRS interval	0.0026 (12)	0.0030 (12)	-0.0004 (-0.0052, 0.0044), p=0.86
QT interval	-0.0102 (12)	-0.0110 (12)	0.0008 (-0.0101, 0.0117), p=0.87
QTc interval	0.0069 (12)	0.0073 (12)	-0.0004 (-0.0135, 0.0126), p=0.94

*: ANOVA

Table VIII.3 Endpoints of Study 030721 (i.e. NDA Table 1, page 113, vol. 1.95, Appendix C)

Change from pre-dose to	0.25% Levobupivacaine	0.25% Bupivacaine	Difference, 95% CI, p-value*
QRS Duration Value			
Maximum post-dose Median (N)	3 (31)	6 (30)	-3 (-23, 4), p=0.52
QT Dispersion Value (ms)			
End of surgery, LSMean (N)	-3.0 (30)	-2.8 (31)	0.2 (-11.0, 10.5), p=0.96
+4Hr, LSMean (N)	-4.8 (30)	-4.1 (33)	-0.7 (-10.9, 9.4), p=0.89
Maximum Post-dose, LSMean (N)	2.6 (30)	3.6 (3.3)	-1.0 (-10.9, 8.9), p=0.83

Table VIII.4 QRS duration value of Study CS005 (i.e. NDA Table 1, page 150, vol. 1.95, Appendix D)

Change from pre-dose to	0.75% Levobupivacaine	0.75% Bupivacaine	Difference, 95% CI, p-value*
QRS Duration Value			
Maximum post-dose Mean (N)	4.2 (13)	4.5 (13)	-0.4 (-3.0, 2.2), p=0.76

Table VIII.5 Endpoints of Study 030632 (i.e. NDA Tables 1-5, page 165-169, vol. 1.95, Appendix E)

Change from pre-dose to	0.5% Levobupivacaine	0.5% Bupivacaine	Difference, 95% CI, p-value*
QRS Duration Value			
Maximum post-dose Median (N)	1.87 (31)	3.00 (34)	-1.13 (-4.39, 2.13), p=0.49
QT Dispersion Value (ms)			
Post-dose, Mean (N)	-3.43 (31)	-5.59 (33)	2.16 (-6.89, 11.20), p=0.64
Recovery, Mean (N)	-11.91 (12)	-1.42 (17)	-10.49 (-25.81,4.82), p=0.17
Maximum Post-dose, Mean (N)	-0.18 (31)	0.90 (33)	-1.09 (-9.25, 7.08), p=0.79
PR Interval			
Maximum Post-dose, Mean (N)	0.77 (31)	11.21 (33)	-10.44 (-18.87, -2.00), p=0.016
QT Interval			
Maximum Post-dose, Mean (N)	10.13 (31)	11.71 (34)	-1.58 (-12.35, 9.20), p=0.77
QTc Interval			
Maximum Post-dose, Mean (N)	10.94 (31)	15.35 (34)	-4.42 (-13.49, 4.66), p=0.33

*: t-test

VIII.4 Reviewer's Comments and Conclusions

The overall results of the ECG analysis of the 4 studies could be summarized as follows,

QRS duration effects (the primary endpoint):

The analysis showed that there was no statistical difference in QRS duration (i.e. the primary endpoint) in three studies between either the 0.25% (Study 030271), 0.5% (Studies 030632) or 0.75% (Study CS005) Levobupivacaine and its corresponding Bupivacaine group of the same dose. The difference (Levobupivacaine-Bupivacaine) could be between –23 and 4 for the 0.25% dose, -4.39 and 2.13 for the 0.5% dose, and -3 and 2.2 for the 0.75% dose. There was no evidence that Levobupivacaine had a QRS longer or shorter duration change from pre-dose than Bupivacaine.

The QRS interval change from pre-dose was not significantly different between 0.5% Levobupivacaine and Bupivacaine (Study 004801). The estimated difference (Levobupivacaine-Bupivacaine) was between –0.0052 and 0.0044.

There was no statistical testing reported in the NDA in order to conclude that there was no QRT duration effect (no-zero changes from pre-dose to maximum post-dose value) due to Levobupivacaine. However, changes from pre-dose was shown to be significantly different from 0 in 2 studies (p=0.047 in Study 004801, p=0.055 in Study 30721, p=0.001 in CS005 and p=0.076 in Study 30632).

QT dispersion effects (secondary endpoint):
The QT dispersion change from pre-dose to the maximum post-dose value was not statistically different between Levobupivacaine and Bupivacaine of the same dose at 0.25% dose (Study 030721), 0.5% (Study 004801 and Study 030721). The difference (Levobupivacaine – Bupivacaine) was estimated to be between –10.9 and 8.9 for the 0.25% dose, -21.0 and 10.2 for the 0.5% dose. The change from pre-dose QT interval was not statistically significant between the two treatments in Study 004801. The difference was estimated between –0.0101 and 0.00117. There was no evidence to indicate that Levobupivacaine had a change in QT dispersion from pre-dose different from Bupivacaine. There was no statistical testing reported in the NDA in order to conclude that there was no QT dispersion effect (no-zero changes from pre-dose to maximum post-dose value) due to Levobupivacaine. However, using t-test, it was shown that the changes was statistically significantly different from 0 in Study 04801 (p=0.038).

PR Interval (secondary endpoint):
The PR interval change from pre-dose to the maximum post-dose value was found to be statistically higher in Bupivacaine (Bupivacaine-Levobupivacaine=10.44, p=0.016) at dose of 0.5% (Study 030662). However, the p-value was not adjusted for the multiple comparisons made in this study. This finding was not confirmed in study 004801 with signal average ECG.

QTc interval (secondary endpoints):
The QTc interval change from pre-dose to the maximum post-dose value was not found to be significantly different between Bupivacaine and Levobupivacaine at study with dose of 0.25% (Study 030662) and 0.5% (Study 004801). The difference (Levobupivacaine-Bupivacaine) was estimated to be between –13.49 and 4.66 for 0.5% dose with 12-lead ECG (Study 030662), and between –0.0135 and 0.0126 for 0.5% dose with signal average ECG. There was no evidence to indicate that Levobupivacaine had a large or smaller change in QT dispersion from pre-dose than Bupivacaine.

IX Cardiovascular effects in Study 004801

IX.1 Study objectives and design

This was a double blind, randomized, complete crossover study of S-Bupivacaine and racemic Bupivacaine. Each subject received one dose of each formulation on 2 successive occasions by an interval of at least 7 days. The study was carried out to compare the tolerability and the pharmacokinetics of a racemic mixture of Bupivacaine with that of the S-bupivacaine alone.

The subjects recruited in this study were all healthy male subjects aged between 18 and 40 years with no clinically relevant abnormality. The details of the inclusion and exclusion criteria were referred to the NDA vol.1.48, page 14-15.

This review focused only on the cardiovascular effect of the treatments.

IX.2 The study endpoints

The primary endpoints of the study were: cardiac index, stroke index, acceleration index and ejection fraction, systolic blood pressure and diastolic blood pressure, heart rate, PR, QT and QTc, as recorded at the end of infusion.

IX.3 Statistical methods

This study was designed as an exploratory study rather than a confirmatory study even though some hypothesis testing were made. The sample size of 14 subjects was not determined through a regular statistical considerations that would involve with the power, type I error rate, the targeted difference in the primary endpoint. All 14 subjects completed the study. Because of the exploratory nature of the study, the sponsor reported the results with p-values and statistical significance without adjusting for the multiple comparisons associated with the multiple endpoints.

For each infusion session, the difference from pre-dose was calculated for each subject. Analysis of variance (ANOVA) was used to evaluate whether the "response" differed significantly between the two treatments.

IX.4 Results

Although all subjects completed the study, two subjects were stopped in each of the treatment period because of either a significant fall in cardiac index or CNS symptoms.

Vital signs :

The statistics of vital sign effects were given in Table IX.1 (NDA, vol 1.48, Tables from page 29 to page 39).

Systolic blood pressure – Systolic blood pressure increased from pre-dose in both treatments ($p=0.13$ Bupi, $p=0.20$ S-bupi). The increase was not statistically significant in either group. The increase was slightly larger in Bupivacaine group, but the difference was not statistically significant ($p=0.85$).

Diastolic blood pressure – Diastolic blood pressure increased from pre-dose in both treatments. The increase was statistically significant in both treatments ($p<0.001$ Bupi, $p=0.002$ S-bupi). The increase was slightly larger in the Bupivacaine group, but the difference was not statistically significant ($p=0.067$).

Heart rate – Heart rate increased from pre-dose in both treatments. The increase was not statistically significant (p=0.11 Bupi, p=0.20 S-bupi). The increase was slightly larger in Bupivacaine group, but the difference was not statistically significant (p=0.80).

ECG:
PR interval – PR interval increased from pre-dose in both treatments. The increase was significant in the Bupivacaine group (p=0.0012), but was not in the S-bupivacaine group (p=0.085). The increase was higher in Bupivacaine but the difference was not statistically significant (p=0.098).

QT interval – QT interval decreased in both treatments. The decrease was not statistically significant (p=0.32 Bupi, p=0.91 S-bupi). There was more decrease in the Bupivacaine group, but the difference was statistically significant (p=0.52).

QTc interval – QTc interval increased from pre-dose in both treatments. The increase was statistically significant in the Bupivacaine group (p=0.034 Bupi, p=0.068 S-bupi). The size of increase was bout the same and there was no statistical difference (p=0.78).

Cardiovascular functions:
Cardiac index – Cardiac index decreased from pre-dose in both treatments. The decreased was statistically significant in both treatments (p<0.001 for both). There was no statistically difference in the decrease between the two treatments (p=0.29).

Strokes index – Stroke index decreased from pre-dose in both treatments. The decrease was statistically significant in both treatments (p<0.001 Bupi, p=0.026 S-Bupi). There was larger decrease in the Bupivacaine group. The difference was statistically significant (p=0.002).

Acceleration index – Acceleration index decreased from pre-dose in both treatments. The decrease was statistically significant in Bupivacaine (p<0.001 Bupi, p=0.052 S-bupi). The decrease was greater in the Bupivacaine group. The difference was statistically significant (p=0.015).

Ejection fraction – Ejection fraction decreased from pre-dose in both treatments. The decrease was statistically significant in both treatments (p<0.001 Bupi, p=0.005 S-bupi). There was greater decrease in the Bupivacaine group, but the difference was not statistically significant (p=0.06).

Table IX.1 Statistics of the study endpoints (NDA Tables from page 29-39, vol. 1.48)

Treatment	Pre-dose	End of infusion	Difference	p-value (change)	P-value (treatment)	Adjusted significance
Systolic blood pressure						
Bupivacaine	115.2	123.8	8.6	0.13	0.85	NS
S-bupivacaine	119.0	125.8	6.8	0.20		
Diastolic blood pressure						
Bupivacaine	71.7	84.3	12.7	<0.001	0.067	NS
S-bupivacaine	75.3	82.6	7.3	0.002		
Heart rate						
Bupivacaine	66.8	71.2	4.4	0.11	0.80	NS
S-bupivacaine	64.3	68.2	3.9	0.20		
PR interval						
Bupivacaine	0.1648	0.1763	0.0114	0.0012	0.098	NS
S-bupivacaine	0.1651	0.1701	0.0050	0.085		
QT interval						
Bupivacaine	0.3818	0.3746	-0.0073	0.32	0.52	NS*
S-bupivacaine	0.3875	0.3868	-0.0007	0.91		
QTc interval						
Bupivacaine	0.3838	0.4060	0.0222	0.034	0.78	NS
S-bupivacaine	0.3878	0.4088	0.0211	0.068		
Cardiac index						
Bupivacaine	3.57	3.18	-0.39	<0.001	0.29	NS
S-bupivacaine	3.60	3.34	-0.26	<0.001		
Stroke index						
Bupivacaine	55.33	44.42	-10.92	<0.001	0.002	*
S-bupivacaine	52.42	49.08	-3.33	0.026		
Acceleration index						
Bupivacaine	1.36	1.18	-0.18	<0.001	0.015	NS
S-bupivacaine	1.35	1.28	-0.06	0.052		
Ejection fraction						
Bupivacaine	65.33	61.42	-3.92	<0.001	0.060	NS
S-bupivacaine	64.33	62.17	-2.17	0.005		

IX.5 Reviewer's comments and conclusions

It was shown in this phase II pharmacological study that there were significant cardiovascular effects of Bupivacaine in diastolic blood pressure, PR interval, QTc interval, cardiac index, stroke index, acceleration index and ejection fraction. Similar effects were also shown in S-bupivacaine treated subjects. However, the effects were statistically significant in diastolic blood pressure, cardiac index, stroke index, and ejection fraction. The effects were significant larger in the Bupivacaine group in stroke index and in acceleration index. However, as pointed out earlier, the significant level was not adjusted for the multiple comparisons. The results of this study suggested that S-bupivacaine had lower cardiovascular risk than Bupivacaine. However, these results were not confirmed by any confirmatory study included in this NDA.

X. Overall Conclusions

The safety and efficacy of Levobupivacaine for the various indications was summarized as follows,

Safety:
Levobupivacaine was shown to be a safe drug and in general had a similar safety profile to Bupivacaine. There was also potential evidence of less cardiovascular effect than Bupivacaine. However, the difference was observed in one phase II pharmacology study without a confirmatory study. There were some concern regarding the higher dosage of 0.75% Levobupivacaine in terms of adverse event profile.

Early termination - Based on the summary safety, special analysis and Study 004801, the reviewer would summarized the safety evidence as follows,

Levobupivacaine had a similar safety profile to Bupivacaine of the same dose in terms of dropouts and adverse events. There were a few differences that needed to be point out. Contrary to the sponsor's claims in NDA vol.148, the early termination rate for 0.75% Levobupivacaine was 11.7% which was slightly higher than the 9.8% overall rate of all treatments in the studies involving 0.75% Levobupivacaine. There was no clear evidence to show the absence of a potential increased risk for the 0.75% Levobupivacaine.

In studies for post-surgery pain management, there was a higher proportion of patients who terminated the study early due to inadequate block for the Levobupivacaine than Levobupivacaine plus other treatment.

Extent of exposure - The dosage was comparable (in mean and range) between Levobupivacaine and Bupivacaine.

Adverse events: In general, the rate of adverse events was comparable between Levobupivacaine and Bupivacaine. In the central block studies, Bupivacaine had slightly more adverse events than Levobupivacaine. The incidence rates were also comparable between Levobupivacaine and Bupivacaine by body system.

However, there was potential concern with the adverse event rate with 0.75% Levobupivacaine in the following two observations:

1. The rate was consistently higher for the 0.75% Levobupivacaine groups in studies with 0.75% Levobupivacaine than for the Bupivacaine groups of phase II/III studies or for the Bupivacaine groups in the studies with 0.75% Levobupivacaine.

2. Comparing the adverse event rates by body system between the 0.75% Levobupivacaine and all Levobupivacaine groups, the rates were consistently higher in the 0.75% Levobupivacaine group in all body systems except post-operative pain (the secondary terms).

QRS duration effects:
As shown in the special ECG analysis study, there was no statistical difference in QRS duration (i.e. the primary endpoint) in three studies between either the 0.25% (Study 030271), 0.5%

For Pediatric use: One study (Study CS-007) was a pediatric study for the drug used as post-operative pain control in pediatric patients following hernia repair surgery. The potential efficacy was shown in treatment of 0.50% Levobupivacaine. The primary result of the study showed that 28.3% fewer patients treated with .50% Levobupivacaine received at least one rescue medication than the group of patients treated with no block. The difference was not statistically significant.

1/13/99

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See my secondary review

/S/ 1/4/99

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/S/ 1/4/99

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Appendix A
Statistical Issues in Analysis with Active Control Data:

In a well controlled phase III clinical trials, efficacy of a new treatment (NT) is defined as that the mean response of the patients treated by NT is better than that of the patients treated with placebo control (PB). However, because of ethnical and practical reasons, patients participated in some trials can't be treated with placebo. Hence, an active control (AC) is used instead of a placebo control. There are two issues that should be aware of when an active control is used in a non-inferiority clinical trial without placebo control.

1. In order to show that the new treatment is significantly better than placebo, we consider the active control as a surrogate measure for the efficacy of NT over PB. In order to achieve that one needs to know what is the expected improvement due to active control treatment over a placebo. The size of the improvement is clearly a good benchmark to be used in the active control non-inferiority study. More specifically, if the expected value of (AC – PB) is no less than D_0, then one needs to show that the expected value of (NT – AC) > - D_0 in order to assure that NT is efficacious over placebo through an active control only non-inferiority trial. The critical value D_0 is often established based on the historical clinical trial data and should be agreed upon by the sponsor and the medical reviewer.

2. In a standard placebo control trial, it is a general understanding that a new treatment is considered to be efficacious if NT is shown to be statistically significantly better than the placebo treatment with a type I error rate of 0,025. The non-inferiority trial is designed to establish that NT is efficacious over the placebo through the surrogate setup. Hence efficacy of the new treatment will be established by showing that the null hypothesis H0: (NT – AC) ≤ - D_0 is rejected, using an appropriate statistical test with a type I error of 0.025.