"Time from onset of sensory block (i.e. when the analgesia to pinprick was detected) to the complete return of sensory touch (i.e. the end of the sensory block was recorded as the time when painful sensation had returned in all dermatomes).

It was revised upon the request of the sponsor and after the study blind was broken as follow,

"Time from onset of sensory block until complete return of sensory touch, irrespective of whether or not a general anaesthetic was given".

Secondary efficacy endpoints included, time to onset of sensory block, time to onset of and duration of motor block, overall assessment of the quality of block (0=failure, 1=unsatisfactory or partial block, both were considered "treatment failure, 2=complete block, considered as a "treatment success").

Upon the request of the sponsor and after the study blind was broken, the following endpoints were also analyzed for the "intent-to-treat" population,

Maximum height and time to maximum height of sensory block
Time to onset and duration of block at selected dermatomes
Time to onset and duration of each grade of motor block.

Tolerability endpoints –
Analyses were done for vital signs, ECGs, adverse events and clinical laboratory parameters.

II.1.d. Population for Analysis:
The "intent-to-treat" population was defined as all randomized patients excluding, patients who did not receive any of the randomized anaesthetic or patients who during the administration procedure suffered an incidental intravascular injection or subarachnoid injection resulting in immediate withdrawal from the study.

All patients included in "intent-to-treat" population excluding those who received a non-protocolled anaesthetic formed the "per-protocol" population.

Primary efficacy variable was analyzed using the 'intent-to-treat' population. All other endpoints were analyzed using the "per-protocol" population.

II.1.e. Efficacy analysis:
Methods:
The confirmatory efficacy analysis:
The mean of the primary efficacy endpoint was compared among the three treatments using ANOVA and multiple comparison with Bonferomi-Holm adjustment for multiple comparison.

Sample size – The sample size was determined to be 30 evaluable patients per group. With this sample size, the study would have 80% power to reject the null hypothesis based on a 2-sided t-test approach at 5% type error rate when the true difference is 45 minute or more.

The secondary efficacy response variables:
Percentage of patients attained relief was compared among the three treatments using either chi-square test or logistic regression analysis.

Means of all other secondary endpoints were compared among the three treatments using ANOVA.

No multiple endpoint adjustment was used in the analysis of the secondary efficacy endpoints.

Results:
Subject disposition and withdrawals – The number of subjects recruited and randomized in each center and treatment group is given in Table II.1.1

Table II.1.1 Patients disposition (based on Tables 1, 2, L.1.1, and L.1.2 of NDA, page 030, 031, 354, 355, vol. 117)

Status	Treatment			Total
	0.5% Levobupivacaine	0.75% Levobupivacaine	0.5% Bupivacaine	
Recruited	32	33	31	96
Center #1	16	16	16	32
Center #2	5	6	5	33
Center #3	11	11	10	31
Intent-to-treat Population	29	30	29	88
Failure of technique	0	2	0	2
Not meet inclusion criteria	0	1	1	2
Withdrew consent	1	0	0	1
Operation postponed	2	0	1	3
Efficacy Analysis Population	27	30	27	84
Received general anaesthetic (before onset of sensory block)	2	0	2	
Per-protocol Population	27	26	28	81
Received non-study Anaesthetic	2	4	0	6
Technique failure	0	0	1	1

Demographic and Baseline Characteristics:
The demographic and baseline characteristics were summarized for all enrolled patients. Of the total 96 patients, 35 (36.5%) male and 61 (63.5% female), of mean age 47.39 years old were recruited. The mean height and weight of the whole study were 166.68 cm and 72.28 kg respectively.

The similar mean age, gender proportion, mean height and weight were found in the "intent-to-treat", "per-protocol" and "efficacy analysis" population. There was no outstanding difference among the three treatment groups.

There was no outstanding distribution difference among the three treatment groups in medical history, and concomitant mediations.

Primary Efficacy Endpoint (Intent-to-treat Population):
The number of patients did not attain a sensory block on their left side were 4(14%), 2(7%) and 1(3%) for 0.5% Levobupivacaine, 0.75% Levobupivacaine and 0.5% Bupivacaine respectively. For the right side of the body the numbers were 2(7%), 1(3%) and 2(7%) for 0.5% Levobupivacaine, 0.75% Levobupivacaine and 0.5% Bupivacaine respectively. The differences

in the number of patients failed to attain sensory block were not statistically significant.

The mean duration time (protocol defined) were estimated based on data of the patients who attained sensory block. There was no significant difference in mean duration in either left or right side sensory block among the three treatment groups (see Table II.1.2). There was no treatment-by-center interaction.

There was statistically significant treatment effect when analyzed using the revised duration time in both left (p=0.008) and right (p=0.002) side sensory blocks. 0.75% Levobupivacaine group had significantly longer duration than the 0,5% Bupivacaine in both left and right side blocks.

Secondary Efficacy Endpoints:
Duration of sensory block (per-protocol population) –
The sponsor as part of the analysis of the secondary efficacy endpoints also analyzed duration of sensory using the per-protocol population. The number of patients failed to attain sensory block was not different among the three treatment groups.

Mean duration of the sensory block was estimated based on the data of all patients who attained sensory block.

The mean duration of sensory block at the left side was significantly longer in the 0.75% Levobupivacaine (399.2 min) than either the 0.5% Levobupivacaine (335.5 min)(p=0.006) or 0.5% Bupivacaine (287.7 min) (p=0.025). The mean duration of sensory block at the right side was significantly longer in the 0.75% Levobupivacaine (410.2 min) than either the 0.5% Levobupivacaine (324.8 min)(p=0.004) or 0.5% Bupivacaine (288.2 min) (p=0.022). There was no significant treatment-by-center interaction.

Duration of motor block (Intent-to-Treat Population) –
Patients treated with 0.5% Levobupivacaine had lower percentage (52%/left side, 45%/right side) attaining motor block than patients treated with 0.75% Levobupivacaine (77%/left side, 73%/right side) or 0.5% Bupivacaine (66%/left side, 69%/right side). The differences were not statistically significant.

Duration of motor block and time to onset of motor block were analyzed using only the patients attained motor block. There was no significant difference in the mean duration of right side motor block or time to onset of right side motor block among the three treatment groups. However, the 0.75% Levobupivacaine group had significantly longer duration of left side motor block than 0.5% Levobupivacaine group (p=0.014). There was no statistically significant difference between Both Levobupivacaine group and the Bupivacaine group. There was no significant difference in mean time to onset of left side motor block among the three groups.

Duration of motor block (Per-Protocol Population) –
Patients treated with 0.5% Levobupivacaine had lower percentage (14 (52%)/left side, 12(45%/right side) attaining motor block than patients treated with 0.75% Levobupivacaine (22 (85%)/left side, 20 (77%)/right side) or 0.5% Bupivacaine (18 (64%)/left side, 20 (71%)/right side). The differences was statistically significant (p=0.039/left side, p=0.029/right side).

Duration of motor block and time to onset of motor block were analyzed using only the patients attained motor block. There was longer duration of motor block on left side of the body in the 0.75% Levobupivacaine patients (231.3 min) than the 0.5% Levobupivacaine patients (142.8 min). The difference was statistically significant (p=0.010). There was no statistically significant difference in mean duration of motor block of the right side of body between the three groups.

Time to onset of motor block –
There was no significant difference in time to onset of motor block of either left side or right side of the body between the three treatment groups.

Table II.1.2 The mean values and the 95% confidence intervals of difference of means of the efficacy endpoints (modified from NDA Tables M1.1.1.1 to M1.2.6.2, pp.425-450, Vol. 117)

Endpoint	Treatment						ANOVA p-value Treatment Effect	
	0.5% Levobupivacaine		0.75% Levobupivacaine		0.5% Bupivacaine			
	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side	Left	Right
Intent-to-Treat Population								
Sensory Block								
Duration	323.5	304.5	359.3	359.8	280.5	280.7	0.23	0.21
Revised Duration	377.4	368.7	459.7	471.0	344.8	337.2	0.008	0.002
Time to Onset	7.8	8.0	6.4	7.0	6.7	6.1	0.22	0.26
# of Patients	25	27	28	29	28	27		
Motor Block								
Duration	135.6	171.0	222.1	207.5	161.5	168.7	0.04	0.54
Revised duration	185.3	204.8	255.9	255.0	191.6	185.0	0.045	0.097
Time to Onset	24.7	25.9	27.2	31.4	16.8	17.5	0.45	0.61
# of Patients	15	13	23	22	19	20	0.133*	0.053
Per-Protocol Population								
Sensory Block								
Duration	335.5	324.8	399.2	410.2	287.7	288.2	0.019	0.011
Revised Duration	374.5	371.8	451.0	459.1	337.7	335.3	0.013	0.009
Time to Onset	8.0	7.4	6.2	6.5	6.7	6.2	0.16	0.42
# of Patients	24	25	25	25	27	26		
Motor Block								
Duration	142.6	182.2	231.3	225,7	166.3	168.7	0.029	0.37
Revised duration	181.8	202.3	256.4	251.5	191.4	185.0	0.073	0.14
Time to Onset	26.1	27.7	27.3	33.5	16.9	17.5	0.45	0.35
# of Patients	14	12	22	20	18	20		

*chi-square test

Overall assessment of block –
The percentage of failure, and unsatisfactory block was given in Table II.1.3. The percentage of treatment failure (failure and unsatisfactory block) was not statistically different among the three treatment groups when the data were analyzed using the logistic regression.

Table II.1.3 Overall Assessment of Block (modified from NDA Tables XI, Tables M1.3.2, vol. 117)

Assessment of Block	Treatment		
	0.5% Levobupivacaine	0.75% Levobupivacaine	0.5% Bupivacaine
Number (%)			
Failure	3 (10)	2 (7)	0 (0)
Unsatisfactory Block	8 (28)	5 (17)	7 (24)
Complete Block	18 (62)	25 (77)	22 (76)

There was no evidence of any significant difference among the three groups in maximum height of sensory block, time to maximum sensory block, time to onset and duration of block at various dermatomal levels, and time to onset and duration of each grade of motor block.

Safety Evaluation:
There were no serious adverse events associated with this study. There were 18 patient (62%) in the 0.5% Levobupivacaine group had at least one adverse event compared with 21 patients (70%) in the 0.75% Levobupivacaine and 19 patients (66%) in the Bupivacaine group. There were a total of 38 adverse events reported in the 0.5% Levobupivacaine group compared with 48 in the 0.75% Levobupivacaine group and 31 in the 0.5% Bupivacaine group. The three groups had very similar adverse event profiles with the most frequent events being general disorders (3 (10%) patients in the 0.5% Levobupivacaine group, 7(23%) patients in the 0.75% Levobupivacaine group and 3 (10%) in the 0.5% Bupivacaine group). The most frequent events were gastrointestinal system disorders (5(17%) patients in the 0.5% Levobupivacaine group, 7(23%) patients in the 0.75% Levobupivacaine group and 3 (10%) in the 0.5% Bupivacaine group, cardiovascular system disorders (6(21%) patients in the 0.5% Levobupivacaine group, 6(20%) patients in the 0.75% Levobupivacaine group and 7 (24%) patients in the 0.5% Bupivacaine group), and urinary system disorders (10(34%) patients in the 0.5% Levobupivacaine group, 11(37%) in the 0.75% Levobupivacaine group and 6 (21%) patients in the 0.5% Bupivacaine group. Eleven of the events were study drug related in the 0.5% Levobupivacaine group, 15 events in the 0.75% Levobupivacaine group and 16 events in the 0.5% Bupivacaine group.

There were 4 patients had hypotension treated in the 0.5% Levobupivacaine group, 7 in the 0.75% Levobupivacaine group and 8 in the 0.5% Bupivacaine group. There was no evidence of difference in vital signs, ECGs, clinical chemistry and hematology between the two groups.

II.1.f. Reviewer's Comments and Conclusions

Primary efficacy endpoint -

1. The primary efficacy measure of duration of sensory block was longer for the 0.75% Levobupivacaine than the 0.5% Levobupivacaine and 0.5% Bupivacaine groups in the analysis using the "intent-to-treat" population as proposed in the protocol. But the difference was not statistically significant. In another words, this study provided no statistically decisive evidence of either a dose response relationship in Levobupivacaine, or equivalence between the Levobupivacaine and Bupivacaine treatments.
2. In "per-protocol" population, however, the difference was statistically significant in either side of the body.
3. For the revised definition, in both "intent-to-treat" population and "per-protocol" population, the 0.75% Levobupivacaine had a longer mean duration than the 0.5% Bupivacaine group for either left or right side block. However, the revised duration was defined upon the request of the sponsor after the blind was broken and should be interpreted with caution.

Secondary efficacy endpoints –

1. In the analysis of secondary efficacy endpoints, there was lower percentage of patients treated with 0.5% Levobupivacaine attained sensory block and motor block in either side

of the body. The difference was not significant in the "intent-to-treat" population, but was statistically significant in the "per- protocol" population. Duration of motor block was longer in the patients treated with 0.75% Levobupivacaine than with either the 0.5% Levobupivacaine or the 0.5% Bupivacaine in either side of the body and in both "intent-to-treat" and "per-protocol" population. The difference was statistically significant in both the "intent-to-treat" and in "per-protocol" population for the left side of the body.

2. There was no significant difference among the three treatments in other secondary efficacy endpoints.

Safety evaluation - There was no statistical evidence of difference in the frequency and profile of adverse events. There was no evidence of any difference between the three groups in vital signs, clinical chemistry, hematology and ECGs.

II.2 Study CS-005

II.2.a. Study Objectives: The primary objectives of the study was to demonstrate that 0.75% Levobupivacaine and 0.75% Bupivacaine was equally effective with regard to onset of sensory block adequate to carry out surgery.

The secondary objectives of this study were:
To compare the abdominal wall relaxation produced by epidural Levobupivacaine and Bupivacaine, using a rectos abdominal muscle (RAM) assessment.

To compare the duration of sensory and motor blocks between the treatment groups.

To determine the time to T10 level, time to median maximum upper level, time to maximum upper level, time to two-level regression, time to T10 regression, and time to complete regression.

To evaluate the relative safety profiles of 0.75% Levobupivacaine and 0.75% Bupivacaine.

To determine the pharmacokinetics of Levobupivacaine and Bupivacaine following doses of 0.75% Levobupivacaine and 0.75% Bupivacaine.

II.2.b. Study Design: This was a randomized, double blind, parallel group (0.75% Levobupivacaine and 0.75% Bupivacaine) study conducted in a single center in the United Kingdom.

II.2.c. Efficacy Endpoints:
Primary measure was the time to onset of sensory block protocol adequate for surgery.

The secondary efficacy endpoints included, time to T10 regression, time to complete regression, time to onset and offset of motor block, maximum upper level, time to maximum upper level, time to onset of two-level regression, abdominal wall relaxation using the RAM score, patients pain rating at each of the three time points, overall assessment at the end of the study.

See NDA Table 1 on page 30, vol. 120 for the patients evaluation schedule chart.

II.2.d. Population for Analysis:

The "intent-to-treat" population was defined as all randomized patients excluding, patients who did not receive any of the randomized anaesthetic or patients who during the administration procedure suffered an incidental intravascular injection or subarachnoid injection resulting in immediate withdrawal from the study.

All patients included in "intent-to-treat" population excluding those who received an anaesthetic that was not specified in the protocol formed the "per-protocol" population.

Efficacy variables were analyzed using the 'intent-to-treat' population. Analysis using "per-protocol" population was presented also for the key variables.

II.2.e. Efficacy analysis:

Methods:

The confirmatory efficacy analysis:

The primary efficacy endpoint was tested to show whether the true difference in time to onset of sensory block protocol adequate to carry out surgery is not greater than a pre-defined 'equivalence limit', D_0. The statistical hypotheses to be tested are

H_0: E (mean difference in time to onset of anesthesia between the two groups) $\geq D_0$

H_0: E (mean difference in time to onset of anesthesia between the two groups) $< D_0$

The equivalence limit, D_0 was pre-specified as 7.58 minutes by the sponsor. It was selected by the sponsor based on a previous Bupivacaine study that the mean time to onset of anesthesia was 17 minutes.

Sample size – The sample size is determined to be 30 evaluable patients per group. With this sample size, the study would have 80% power to reject the null hypothesis based on a 2-sided t-test approach at 5% type error rate.

The secondary efficacy response variables:

They were time to T10 regression, time to complete regression, time to onset of motor block, time to offset of motor block, time to maximum upper level, time to onset of two-level regression, the abdominal wall relaxation using the RAM score, patient pain ratings, and overall assessment. Time to onset or offset in the secondary response variables was analyzed using a product-limit survival analysis.

No multiple endpoint adjustment was used in the analysis of the secondary efficacy endpoints.

Safety Analysis:

The primary safety parameters were vital signs, ECGs, QT and QRS intervals, adverse events and clinical laboratory parameters.

Results:

Subject disposition and withdrawals – The number of subjects recruited and randomized in

each center and treatment group was given in Table II.2.1

Demographic and Baseline Characteristics:
A total of 56 patients, 24 (43%) male and 32 (57%) female received study drugs. The male/female ratio was the same in both treatment groups (3:4). Of the 56 participants, 95% were Caucasians; the only three non-Caucasian participants (1 black and 2 others) were in Levobupivacaine group. There was no difference in mean age between the two groups (53.0 in Levobupivacaine and 52.0 in Bupivacaine group. There was no evidence of distribution difference between the two groups in weight, height, physical examination and concomitant medication.

Table II.2.1 Patients disposition (based on Tables 2 of NDA, page 039, vol. 120)

Status	Treatment		Total n (%)
	0.5% Levobupivacaine n (%)	0.5% Bupivacaine n (%)	
Randomized	29 (100)	28 (100)	57 (100)
Withdrew prior to Anesthesia (did not receive study drug)	1 (3.4)	0 (0)	1 (1.8)
Received study drug (Safety Population)	28 (96.6)	28 (100.0)	56 (98.2)
Received study drug (ITT Population)	28 (96.6)	28 (100.0)	56 (98.2)
Per-protocol Population	28 (96.6)	27(96.4)	55(96.5)
Non-evaluable	0 (0)	1 (3.6)	1 (1.8)
Discontinued	1 (3.4)	0 (0)	1 (1.8)
Completed	28 (96.6)	28 (100.0)	56 (98.2)

Primary Efficacy Endpoint (Intent-to-treat Population):
The mean time to onset of sensory block was 13.6 minutes and 14.0 minutes for the Levobupivacaine and Bupivacaine patients respectively using the "intent-to-treat" population. The difference (d=-0.4 min) was not statistically significant with 95% confidence interval (calculated by the statistical reviewer) of true difference being (-4.71, 3.91). The 95% confidence interval was between the sponsor pre-specified equivalence limits of –7.58 and 7.58.

Similar results were shown in analysis using the "per-protocol" population.

Table II.2.2 Time to onset of sensory block (based on NDA Tables 6 and 7, page 43, vol. 120)

Population	Levobupivacaine	Bupivacaine	Diff. in mean (95% CI) p-value of t-test
Intent-to-treat, mean±S.D.	13.6±5.6	14.0±9.9	-0.4, (-4.71, 3.91), 0.782
Per-protocol, mean±S.D.	13.6±5.6	12.4±5.6	1.2, (-1.83, 4.23), 0.399

Secondary Efficacy Endpoints:
Time to maximum upper level sensory block – The mean time to maximum upper level sensory block was 24.3 min for the Levobupivacaine group and 26.5 min for the Bupivacaine group. The difference was –2.2 min, which was not statistically significant using the t-test. The 95% confidence interval (as calculated by statistical reviewer) was (-8.3, 4.0). There was no testing for equivalence.

Maximum upper level of sensory block – The mean maximum upper level sensory block was 13.3 for Levobupivacaine group and 13.5 for Bupivacaine group. The difference was estimated as –0.3 with a 95% confidence interval being (-1.7, 1.2). The difference was not statistically significant using a t-test. There was no equivalence assessment.

Time to offset of sensory block – The mean value of the time to offset of sensory block was 375 min for Levobupivacaine group and 340.1 min for Bupivacaine group. The difference was estimated as 35.0 min with a 95% confidence interval being (-14.6, 84.6). The difference was not statistically significant using a t-test. There was no equivalence assessment.

Time to complete regression – The mean value of the time to complete regression was 550.6 min for Levobupivacaine group and 505.9 min for Bupivacaine group. The difference was estimated as 44.6 min with a 95% confidence interval being (1.9, 87.4). The difference was statistically significant using a t-test (p=0.016). There was no equivalence assessment.

Time to two levels bilateral regression – The mean value was 300.8 min for Levobupivacaine group and 292.7 min for Bupivacaine group. The difference was estimated as 8.1 min with a 95% confidence interval being (-40.6, 56.9). The difference was not statistically significant using a t-test. There was no equivalence assessment.

Duration of sensory block – The mean was 361.6 min for Levobupivacaine group and 327.7 min for Bupivacaine group. The difference was estimated as 33.8 min with a 95% confidence interval being (-16.5, 84.1). The difference was not statistically significant using a t-test. There was no equivalence assessment.

Duration of motor block – Four (14%) patients in the Levobupivacaine group and 20 (71%) patients in the Bupivacaine group experienced motor block prior to surgery. The difference was statistically significant. Due to the large difference in the proportion of patients achieved motor block prior to surgery; there was no statistical comparison of time to onset of motor block prior to surgery. There were 2 patients in the Levobupivacaine group and one in the Bupivacaine group did not achieved motor block during treatment. There was no analysis of time to onset of motor block (prior or post to surgery) reported in NDA. The duration of motor block was defined by the sponsor as the time from the injection to offset of motor block. The analysis was done excluding the three patients who did not achieve motor block. The mean of duration was 355.4 min for Levobupivacaine group and 375.7 min for Bupivacaine group. The difference was estimated as –20.3 min with a 95% confidence interval being (-70.9, 30.4). The difference was not statistically significant using a t-test. Duration of motor block and time to offset of motor block were the same according to the sponsor's definition. There was no equivalence assessment.

Abdominal muscle relaxation – The pre-surgery RAM score at 30 minute was lower with Levobupivacaine (mean=3.4) compared with Bupivacaine (mean=3.8). The mean difference was 0.4 points and the 95% CI was (-0.9, 0.0]. The difference was not statistically significant.

Overall assessments – Of overall assessment of muscle relaxation by anesthesiologist, the mean score was 2.3 for Levobupivacaine group and 2.2 for Bupivacaine group. The difference was estimated as 0.1 with a 95% confidence interval being (-0.3, 0.6). The difference was not statistically significant using a t-test. Of the assessment by surgeon, the mean was 2.3 for Levobupivacaine group and 2.0 for Bupivacaine group. The difference was estimated to be 0.4 with a 95% confidence interval being (0.0, 0.8). The difference was not statistically significant using a t-test. Overall assessment of block quality assessed by the investigator had 4 scores

(0=poor, 1=fair, 2=good, 3=excellent). The mean sores were 2.5 for the Levobupivacaine group compared with 2.3 for the Bupivacaine group. The difference between the two group was not statistically significant with p=0.241(2-sided t-test). No other overall assessment was analyzed or reported in NDA. There was no equivalence assessment.

Patient assessment of pain (after surgery) – The mean score was 0.2 for Levobupivacaine group and 0.6 for Bupivacaine group. The difference was estimated to be –0.4 with a 95% confidence interval being (-0.8, 0.0). The difference was not statistically significant using a t-test (0.072). There was no equivalence assessment specified in the protocol.

Table II.2.3 - Mean of the secondary efficacy variable (based on NDA Tables 8 to 13, pp.44-47, vol. 120)

Variable	Levobupivacaine Men±S.D	Bupivacaine Men±S.D	Diff. in mean (95% CI), p-value of t-test
Time to Maximum Upper Level	24.3±9.4	26.5±13.	-2.2, (-8.3, 4.0), 0.642
Maximum Upper Level (Bilateral)	13.3±2.1	13.5±3.1	-0.3, (-1.7, 1.2), 0.729
Time to Offset of Sensory Block	375.0±87.8	340.1±95.5	35.0, (-14.6, 84.6), 0.216
Time to Complete regression	550.6±87.6	505.9±71.1	44.6, (1.9, 87.4), 0.016
Time to Two Level Bilateral Regression	300.8±81.4	292.7±99.6	8.1, (-40.6, 56.9), 0.917
Duration of Sensory Block	361.6±89.7	327.7±96.2	33.8, (-16.5, 84.1), 0.183
Duration of Motor Block	355.4±83.4	375.7±99.2	-20.3, (-70.9, 30.4), 0.311
Overall Assessment of Muscle Relaxation (Anesthesiologist)	2.3±0.67	2.2±0.90	-0.1, (-0.3, 0.6), 0.505
Overall Assessment of Muscle Relaxation (Surgeon)	2.3±0.67	2.0±0.79	0.4, (-0.0, 0.8), 0.074
Overall assessment of block quality (investigator)	2.5±0.58	2.3±0.76	0.2, (-0.1, 0.6), 0.241

Safety Assessment:

All patients receiving the study drug experienced at least one adverse event. There were 24 (86%) Levobupivacaine patients and 26 (93%) Bupivacaine patients who reported moderate to severe adverse events. The relative risk was 0.92 with 95% confidence interval being (0.77, 1.11). The relative risk was not statistically significantly different from 1. However, for severe adverse events only, there were 8 patients in the Levobupivacaine group compared with 2 patients in the Bupivacaine group. The Levo/Bupi relative risk was 4 with a 95% confidence interval being (1.08, 14.82). The Levo/Bupi relative risk was significantly greater than 1 with p-value = 0.031. The severe events were abdomen enlarged, fever, pain, abdominal pain, anxiety, post-operative pain pruritus and urinary system.

Table II.2.4 Adverse events (based on NDA Table 19, page 364, vol.120)

Variable	All Patients N (%)	Levobupivacaine N(%)	Bupivacaine N(%)	Relative risk, 95% CI p-values
All Patients	56	28	28	
With at least one event	56 (100)	28 (100)	28 (100)	1, NA
Moderate or severe events	50 (89.3)	24 (85.7)	26 (92.9)	0.92, (0.77, 1.11)*,0.388**
Serious adverse events	10 (17.9)	8 (28.6)	2 (7.1)	4.00, (1.08, 14.82), 0.031

*: Mantel-Haenszel confidence interval
**: Likelihood ratio chi-square test

Drug Related Adverse Events:

There were 23 (82.1%) Levobupivacaine patients and 17 (60.7%) Bupivacaine patients experienced adverse events that were study drug related (i.e. definitely, probably and possibly

related). The Levobupivacaine-to-Bupivacaine relative risk was 1.353 with a 95% confidence interval of (0.959, 1.909). The relative risk was not significantly different from 1 with p-value=0.073 using a likelihood ratio chi-square test. A detailed table was given in NDA Table 15 on page 50 of vol. 120. The most common adverse events were hypotension, nausea, bradyscrasia and vomiting.

Vital Signs:
Overall, patients in the Levobupivacaine treatment group experienced a greater mean decrease in systolic and in diastolic pressure than the patients in the Bupivacaine treatment group. The difference in systolic pressure was statistically significant at three of the six time points: at 30 min (p=0.049), 4 hour (p=0.021) and 5 hour (p=0.017). The difference in diastolic pressure was statistically significant at four of the six time points: at 4 hour (p=0.007), 4.5 hour (p=0.037), 5 hour (p=0.019) and 6 hour (p=0.015). There were no statistical differences between the two groups in heart rate change from baseline.

Table II.2.5. Vital Signs/change from baseline (based on NDA Table 17.2, pages 348-360, vol. 120)

Vital Sign	0.75% Levobupivacaine	0.75% Bupivacaine	Diff, 95% CI, p-value
Systolic Blood Pressure Change (n)			
30 min	-20.9 (28)	-9.7 (27)	-11.2, (-22.3, -0.0), 0.049
4 hr	-22.8 (28)	-10.6 (27)	-12.2, (-22.4, -1.9), 0.021
4.5 hr	-21.7 (26)	-12.7 (28)	-9.0, (-18.5, 0.6), 0.065
5 hr	-19.0 (26)	-7.5 (26)	-12.7, (-23.1, -2.4), 0.017
6 hr	-20.7 (28)	-11.3 (24)	-7.7, (-16.0, 0.7), 0.071
8.5 hr	-12.8 (19)	2.3 (10)	-15.1, (-31.2, 1.1), 0.066
Diastolic Blood Pressure Change (n)			
30 min	-13.3 (28)	-6.2 (27)	-7.1, (-15.0, 0.8), 0.076
4 hr	-14.4 (28)	-2.9 (27)	-11.5, (-19.7, -3.4), 0.007
4.5 hr	-11.9 (26)	-4.3 (28)	-7.6, (-14.6, 0.5), 0.037
5 hr	-11.3 (28)	-1.9 (26)	-9.4, (-17.1, -1.6), 0.019
6 hr	-13.5 (26)	-5.0 (24)	-8.4, (-15.1, -1.7), 0.015
8.5 hr	-10.8 (19)	-3.7 (10)	-7.1, (-16.3, 2.0), 0.121
Heart Rate Change (n)			
30 min	-0.9 (28)	-6.0 (27)	5.9, (-0.9, 12.7), 0.087
4 hr	-5.5 (28)	-5.4 (27)	-0.0, (-9.0, 8.9), 0.997
4.5 hr	-7.0 (26)	-7.3 (28)	0.2, (-7.5, 8.0), 0.949
5 hr	-6.6 (28)	-5.2 (26)	-1.5, (-8.7, 5.8), 0.687
6 hr	-1.7 (26)	-5.2 (23)	3.4, (-4.7, 11.5), 0.397
8.5 hr	3.9 (19)	3.0 (10)	-0.2, (-11.1, 10.7), 0.972

II.2.f. Reviewer's Comments and Conclusions
Effectiveness of 0.75% Levobupivacaine was shown based on the large number of patients taking Levobupivacaine achieved protocol adequate sensory block. This study was design to demonstrate that 0.75% Levobupivacaine and 0.75% Bupivacaine was equally effective with regard to onset of sensory block protocol adequate to carry out surgery.

Primary efficacy endpoint -

1. The primary efficacy endpoint, time to onset of sensory block, was analyzed by testing for the null hypothesis of equivalence assessment that the true difference in time to onset of sensory block was no less than 7.58 minutes. The equivalence limit 7.58 minutes was pre-specified by the sponsor based on a previous study. It would be the

medical reviewer's decision to determine whether this limit was set appropriately.

2. In order to test the equivalence hypothesis, this reviewer recalculated the 95% confidence interval of the difference and found both its upper and lower limits were bounded within the interval of (-7.58, 7.58) and rejects the null hypothesis. This evidence was shown in both "intent-to-treat" and "per-protocol" population.

Secondary endpoints –

1. There was no equivalence assessment planned or performed for the secondary endpoints. Nor was there any multiple endpoint adjustment made in the analysis of the secondary efficacy endpoints.
2. The estimated mean difference of time to complete regression was 44.6 min (95% CI = (-1.9, 87.4)) which was statistically significant (p=0.016).
3. The estimated mean difference of time to maximum upper level sensory block was –2.2 min (95% CI = (-8.3, 4.0)) which was not statistically significant.
4. The estimated mean difference of time to maximum upper level sensory block was –0.3 (95% CI = (-1.7, 1.2)) which was not statistically significant.
5. The estimated mean difference of time to offset of sensory block was 35 min (95% CI = (-14.6, 84.6)) which was not statistically significant.
6. The estimated mean difference of time to two level bilateral regression was 8.1 min (95% CI = (-40.6, 56.9)) which was no statistically significant.
7. The estimated mean difference of duration of sensory block was 33.8 min (95% CI = (-16.5, 84.1)) which was not statistically significant.
8. The proportion of patients experience motor block was significantly lower in the Levobupivacaine group than the Bupivacaine group.
9. The estimated mean difference of duration of motor block was –20.3 min (95% CI = (-70.9, 30.4)) which was not statistically significant different from 0. Excluding patients with no motor block from the analysis was likely to bias the result toward no difference.
10. The estimated difference in overall assessment of muscle relaxation was 0.1 (out of a total score 0f 4)(95% CI = (-0.3, 0.6)) evaluated by anesthesiologist and 0.4 (95% CI=(0.0, 0.8)) by surgeon. The estimated difference in overall assessment of block quality evaluated by the investigator was 0.2 (95% CI=(-0.1, 0.6)). None of the estimated differences were statistically significant.
11. The estimated mean difference of patient assessment of pain after surgery was –0.4 (95% CI = (-0.8, 0.0)) which was not statistically significant different.

Safety evaluation -

1. There was no additional risk of adverse events in patients treated with Levobupivacaine than those treated with Bupivacaine in "any event" or "moderate or severe event". But the relative risk was 4-fold for severe events (95% CI=(1,08, 14.8)). The relative risk was statistically significantly greater than 1 (p=0.031).
2. Although there was an estimated 1.35 (82.1%/60.7%) fold of experiencing study drug related adverse events than the patients treated with Bupivacaine. The ratio was not statistically significantly greater than 1.
3. However, patients treated with Levobupivacaine had greater decrease in systolic and diastolic pressure from baseline at all six time points presented. The estimated difference was statistically significantly different from 0 at three time points for systolic pressure and 5 time points for diastolic pressure.

III. Central Block Studies – Pain Management

Study #	Design	Dose	Number of treated (safety)	Age mean	Sex(M/F) Race (W,B,O)	Indication
030475	Dblind /random /parallel /3 centers	Levobupivacaine 6 mL/hr 0.25% , 6 mL/hr 0.125%, 6 mL/hr 0.25%	98 (91)	63.8 (32-80)	51/47 95, 0, 3	Post-operative pain control following orthopedic surgery/ Epidural infusion
CS 004	Dblind /random /parallel /2 centers	Levobupivacaine 4-10 mL /hr 0.25% +0.005% Morphine, 4-10 mL /hr 0.25% only, 4-10 mL/hr 0.005% Morphine	66(64)	51.6 (25-79)	35/31 50, 15, 1	Post-operative pain control following major abdominal surgery/ Epidural infusion
CS 006	Dblind /random /parallel	Levobupivacaine 4-14 mL /hr 0.125% +Fentanyl 4-14 mL/hr 0.125% Levobupivacaine 4-14 mL /hr 0.125% alone, Fentanyl 4-14 mL/hr 0.125% alone	66(65)	66.4 (24-80)	20/46 63, 1, 2	Post-operative pain control following orthopedic surgery/ Epidural infusion
030742	Dblind/random/parallel	Levobupivacaine 6 mL/hr 0.125% + Clonidine 6 mL/hr 0.125% Levobupivacaine 6 mL/hr 0.125% alone Clonidine alone	96 (90)	66.5 (40-80)	32/58 90,0,0	Post-operative pain control following hip replacement/epidural infusion

General inclusion/exclusion criteria for pain relief study population

Inclusion criteria:

1. Male, or female aged between 18 and 80.
2. ASA Class I-II.
3. Having elective orthopedic surgery for extradural anesthesia.
4. With informed consent.

Exclusion criteria:

1. Women who were pregnant or lactating mother.
2. Women of child bearing potential not using adequate contraceptive methods.
3. Patients who had a known hypersensitivity to amide anesthesia.
4. Patients who were unable or unwilling to give written informed consent to study procedure.
5. Patients who had a known history or presence of severe renal, hepatic, respiratory or cardiac disease.
6. Patients who had neurological, neuromuscular or psychiatric disorders.
7. Patients who had a history of drug or alcohol abuse within the last 6 months.
8. Patients who had a history of seizure disorder.
9. Patients who had a blood clotting disorders or blood dyscrasia.
10. Patients who had participated in a clinical trial in the last month.
11. Patients who would undergo controlled passive movement therapy during the study.

III.1 Study 030475

III.1.a. Study Design: The study was designed as a multi-center, randomized, double blind, three-limb parallel group (**Levobupivacaine -0.0625%, 0.125% and 0.25%**) study

conducted in four centers in the United Kingdom. The primary objective of the study was to compare the analgesic efficacy of the 3 different concentration of Levobupivacaine. The second objective was to compare the safety profiles of the treatment with thee different concentrations.

III.1.b. Efficacy and Safety Endpoints:
The primary measure was the time to the first request for analgesia during the 24-hour period following the start of the extradural infusion of Levobupivacaine.

The secondary endpoints included, the total dose of intravenous morphine administered in the post-operative period, the total dose of morphine/anti-emetic delivered via the PCA pump, the number of requests for analgesia, sensory block, motor block, and Visual Analogue Scale (VAS) pain score.

The schedule for assessment was given in Table III.1.1.

Table III.1.1 Schedule of Assessments

Assessment	Time-point								
	Pre -study	15, 30 min*	1h, 2h, 3h, 4h,	6 h	8h, 10h,	12h, 18h, 24h	Post-surgery	Post Extradural Injection	Follow up
Visual Analogue Scale (VAS)			x, x, x, x	x	x, x	x, x, x			
Sensory Block		x, x	x, x, x, x	x	x, x	x, x. x			
Motor Block			x, x, x	x	x, x	x, x, x			
Laboratory Analysis	x							x	
Vital Signs	x			x		x, x, x			
12-lead ECG	x								
Adverse Events							x	x	x
Concomitant Medication	x						x	x	x
Screening Assessment	x								

*: After the pre-operative extradural injection.
Safety monitoring including heart rate, systolic and diastolic arterial pressure, sensory and motor block were monitored during surgery and a 5-lead ECG was performed at the appropriate time during the surgery.

Safety Assessment -
The safety assessments included, surgical procedure (i.e. the duration of surgery, problems during surgery, volume of blood loss and the volume of any blood transfused), safety monitoring (i.e. heart rate, arterial pressure, sensory block and motor block taken during the surgery. A 5-lead ECG was recorded at an appropriate time during surgery), hematology and biochemistry, and adverse events

III.1.c. Population for Analysis: Primary efficacy variable was analyzed using the 'intent-to-treat" and the "per-protocol" populations. The "intent-to-treat" population was defined to include all randomized patients except patients that did not receive any of the study drugs and patients who, during the administration procedure, suffered intravenous or subarachnoid injection resulting in immediate withdrawal from the study. The "per-protocol" population consisted of all patients in the "intent-to-treat" population excluding those with protocol deviations. The population for safety analysis included all patients excluding those who did not receive the

randomized study drug.

III.1.d. Efficacy analysis:

Methods:

The confirmatory efficacy analysis:

The primary efficacy endpoint was tested to show whether there was difference in mean time to request for the first analgesia between the three treatment groups. The statistical hypotheses for testing the primary endpoint were as follow:

H_0: E (mean difference in time to request for analgesia among the three groups) = 0
H_a: E (mean difference in time to request for analgesia among the three groups) ≠ 0

Once the null hypothesis was rejected, Multiple comparisons between the three treatments were carried out using the t-test with type I error rate adjusted with Bonferroni-Holm method. It ended up with a significance level of 1.7% for the greatest difference between treatments, 2.5% for the second greatest difference and 5% level for the smallest difference).

Accommodating the censored data (i.e. patients not requesting the analgesia during the 24-hour period), a secondary analysis using Cox's proportional hazard regression model was also carried out.

The sample size was determined to be 30 patients per group. The sample size was determined based on the expectation of between patient variation of time to the first request for rescue analgesia. Using this estimate, a 0.017 type I error rate (adjusted multiple comparison type I error rate), 80% power, it was necessary to have at least 21 evaluable patients per group in order to detect a difference of 120 minutes between any of the two treatment groups. Adjusting for potential loss rate of 30%, the proposed recruiting sample size was 30 patients per group.

The secondary efficacy response endpoints analyzed included, normalized dose of morphine administered, visual analogue pain score (VAS), height of sensory block, and motor block.

Tolerability analysis included vital signs and adverse events.

Results:

Subject disposition and withdrawals:

Treatment allocation - One hundred and five patients enrolled and randomized into the three dose groups with 36 in 0.0625%, 33 in 0.125% and 36 in 0.25% Levobupivacaine groups. Eighty-eight of them completed the study with 29 in 0.0625%, 27 in 0.125% and 32 in 0.025% Levobupivacaine groups respectively. The reasons of the withdrawal were given in Table II.2.2. Excluding the patients who did not received any study medication, the number of patients in the safety analysis was 91 (32 in 0.0625% Levobupivacaine, 27 in 0.125% Levobupivacaine and 32 in 0.25% Levobupivacaine). The "intent-to-treat" population included all patients in the safety population except those who did not receive the extradural infusion. The number was 98 (34 in 0.0625% Levobupivacaine, 29 in 0.125% Levobupivacaine and 35 in 0.25% Levobupivacaine). The "per-protocol" population included all patients in the "intent-to-treat" population except those who had time window violations or who received NSAIDs or other analgesics during the window of the infusion. The "per-protocol" population was 76 (28 in 0.0625% Levobupivacaine,

21 in 0.125% Levobupivacaine and 27 in 0.25% Levobupivacaine)(See Table III.2.2).

Table III.1.2 Treatment allocation and withdrawal (based on NDA Tables 1 and 2, pp. 85-86, vol. 122)

Event	Total	Treatment		
		0.0625% Levobupivacaine	0.125% Levobupivacaine	0.25% Levobupivacaine
Entered				
Center 1	10	4	2	4
Center 2	40	15	14	11
Center 3	55	17	17	21
Total	105	36	33	36
Safety population	98	34	29	35
Intent-to-treat	91	32	27	32
Per-protocol	76	28	21	27
Earlier Withdrawals				
Withdrawal of Consent	1	0	1	0
Technical Failure	2	1	1	0
Adverse Event	3	2	1	0
Insufficient Block	6	3	0	3
Other	5	1	3	1
Total Withdrawal	17	7	6	4
Completion	88	29	27	32

Demographic data:

The male/female ratio was about 1:1 in the study. There was no evidence of male/female ratio difference among the three groups. The mean age was 62.3 years in 0.0625% Levobupivacaine, 63.5 years in 0.125% Levobupivacaine and 65.7 years in 0.25% Levobupivacaine groups. All patients were white except 2 Asians in the 0.0625% Levobupivacaine and 1 black in 0.125% Levobupivacaine groups. There were no evidence of difference in mean weight, height, medical history and physical examinations among the three groups.

Efficacy Endpoints:

With three dose treatment groups, multiple comparisons were used in the pairwise comparisons. In order to adjust for the potential inflation of the overall type I error rate, a Bonferroni-Holm adjustment was used.

Primary efficacy endpoint - Time to first request for rescue analgesia was analyzed using two methods. In the first analysis, time to first request for analgesia was considered as survival time. For patients who didn't made request during the 24-hour duration, their times were considered as censored. A Cox regression was used to compare the survival curves (time to first request for rescue analgesia) of two treatment groups accommodating the censored data under the assumption that the ratio of the hazard rates of the two dose treatments group was a constant over time. When the proportion hazard assumption failed in the comparison of 0.0625% and 0.125% Levobupivacaine groups, Wilcoxon two sample test was used instead. In the second analysis, any patient who did not make any request during the 24 hour was given 24 hours as the time to first request for analgesia. An ANONA model was used to compare the mean time to first request for analgesia under this setting.

Based on the statistical reviewer's analysis, the number of patients who did not require any

relief analgesia in the 0.25% Levobupivacaine treatment group was 15 (46.9%), compared with 3 patients (11.9%) in the 0.125% and 1 patient (3.1%) in the 0.0625% Levobupivacaine treatment group. The difference in the proportions was significantly significant (p=0.001 Fisher's exact test). It showed in the pairwise comparisons that the relative risk of requesting analgesia was 0.548 for 0.25% Levobupivacaine vs. 0.125% Levobupivacaine with 95% CI=(0.409, 0.736); and was 0.598 for 0.25% Levobupivacaine vs. 0.0625% Levobupivacaine with a 95% CI=(0.421, 0.842). The relative risks were statistically significantly different from 1 (see Table II.2.3) with p-values less than 0.017, the Bonferroni-Holm types I error rate. There was no significant difference between 0.125% and 0.0625% Levobupivacaine treated patients.

In the comparison of mean time to first request for analgesia, patients who did not request analgesia during the 24-hour period were assigned 24 hrs for the variable. The mean time was highest in the 0.25% Levobupivacaine group at 16.66 hrs compared with 9.51 hrs in 0.125% Levobupivacaine group and 8.11 hrs in 0.0625% Levobupivacaine group. The difference was statistically significant (p<0.001) in both comparisons. The difference between 0.125% and 0.0625% Levobupivacaine groups was not statistically significant.

The time to the first request for analgesia was also analyzed using survival analysis. Assuming a ratio of hazard rate between the survival curve of 0.25% Levobupivacaine group and either 0.125% or 0.0625% Levobupivacaine group, the survival curve was compared using Cox regression model. The 0.25% Levobupivacaine group had a hazard rate ratio of 1.791 to 0.125% Levobupivacaine which was statistically significantly greater than 1 (p<0.001). The ratio to 0.0625% Levobupivacaine group was 4.181 to 0.625% Levobupivacaine. This hazard rate ratio was statistically significantly greater than 1 (p<0.001)(Table II.2.3). The survival curves of the 0.125% and 0.0625% Levobupivacaine groups were similar and was compared with a Wilcoxon test with either center or surgery type as factor. The difference of the survival curves was not statistically significant (p=0.19, adjusted for center and p=0.80 adjusted for surgery type). Analysis using the 'per-protocol' population gave similar results.

Table III.1.3. Analysis of efficacy endpoints (based on NDA Tables 13-15, pp.92-116, vol.122)

Endpoint	0.0625% Levobupivacaine	0.125% Levobupivacaine	0.25% Levobupivacaine
Number of patients requested analgesia n/N (%)	31/32 (96.9%)	24/27 (88.9%)	17/32 (53.1%)
	0.125% vs. 0.0625%	0.25% vs. 0.0625%	0.25% vs. 0.125%
Relative risk for requesting analgesia	0.918	0.548	0.598
95% C.I.	(0.798, 1.055)	(0.409, 0.736)	(0.421, 0.842)
p-value (chi-square)	0.224	0.001	0.003
(Fisher's exact)	0.323	0.00008	0.004
p-value (overall unequal proportions)	0.001 (chi-square)	0.001 (Fisher's)	
Time to first analgesia Mean±std, N	8.106±4.98, 32	9.506±6.95, 27	16.664±8.32, 32
ANOVA Pairwise Comparison	p-value*	Mean estimate of treatment difference	95% CI
0.0625% - 0.125%	0.49	-1.231 hrs	(-4.828, 2.365)
0.125% - 0.25%	<0.001	-6.888 hrs	(-10.521, -3.255)
0.0625% - 0.25%	<0.001	-8.120 hrs	(-11.587, -4.652)
Survival Data Analysis	p-value	Hazard ratio estimate	95% CI
0.0625% - 0.125% Wilcoxon Test			
Center as cross-classification factor	0.19		
Surgery type as cross-classification factor	0.80		
0.125% - 0.25% Cox Regression	<0.001	1.791	(1.296, 2.475)
0.0625% - 0.25% Cox Regression	<0.001	4.181	(2.210, 7.907)

Secondary Efficacy Points:

Normalized dose of morphine requirement –

The median normalized dose was 0.21mg for the 0.25% Levobupivacaine, which was less than the median (1.50mg) for the 0.0625% and the median (0.96mg) for the 0.125% Levobupivacaine treatment (Table III.1.4). The p-value using Wilcoxon test comparing the ranks of the normalized dose requirement was 0.003 for 0.25% Levobupivacaine versus 0.125% and less than 0.001 for 0.25% versus 0.0625% Levobupivacaine treatment group. The difference was statistically significant because the p-value was smaller than the type I error rate, 0.017 which was the adjusted type I error rate for multiple comparison using Bonferroni-Holm approach. There was no difference between the two lower dose treatments. The pairwise difference and its 95% confidence interval were given in Table III.1.4.

Normalized number of requests for analgesia –

The median normalized dose was 0.00 for the 0.25% Levobupivacaine, which was smaller than the median (1.46) for the 0.0625% and the median (1.48) for the 0.125% Levobupivacaine treatment (Table III.1.4). The p-value using Wilcoxon test comparing the ranks of the normalized dose requirement was less than 0.001 for 0.25% Levobupivacaine versus either 0.125% or 0.0625% Levobupivacaine treatment group. The difference was statistically significant because the p-value was smaller than the type I error rate, 0.017 which was the adjusted type I error rate for multiple comparison using Bonferroni-Holm approach. There was no difference between the two lower dose treatments. The pairwise difference and its 95% confidence interval were given in Table III.1.4.

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

Endpoint	0.0625% Levobupivacaine	0.125% Levobupivacaine	0.25% Levobupivacaine
Normalized dose of morphine requirement (mg)			
Mean±std, N	1.751± 1.323, 32	1.230± 0.930, 27	0.552±0.691, 32
Median	1.50	0.96	0.21
Pairwise Comparison (Wilcoxon test)	0.0625% -0.125%	0.125% -0.25%	0.0625% - 0.25%
Difference	0.417	0.583	0.963
95% C.I.	(-0.083, 1.087)	(0.250, 0.958)	(0.542, 1.702)
p-value	0.16	0.003	<0.001
Normalized number of morphine requirement (mg)			
Mean±std, N	2.445± 2.943, 32	2.605± 2.351, 27	0.535±0.830, 32
Median	1.46	1.48	0.00
Pairwise Comparison (Wilcoxon test)	0.0625% -0.125%	0.125% -0.25%	0.0625% - 0.25%
Difference	0.458	0.917	1.292
95% C.I.	(-0.333, 1.625)	(0.458, 2.122)	(0.625, 2.447)
p-value	0.72	<0.001	<0.001

Motor block –

The pairwise comparison of the distribution of maximum motor block grade was done using logit regression assuming a proportional odds model for the higher grade of motor block. The 0.125 Levobupivacaine group had a higher odds ratio (3.972) for higher grade of motor block than the 0.0625% Levobupivacaine group. The odds ratio was statistically significantly larger than 1 (p=0.012). The 95% confidence interval of the odds ratio was estimated to be (1.356, 11.637).

The odds ratio for the 0.25% Levobupivacaine group to the 0.0625% group was estimated to be 8.004. It was significantly larger than 1 (p<0.001) with a estimated 95% confidence interval of

(2.750, 23.291).

The odds ratio for the 0.25% Levobupivacaine group to the 0.125% Levobupivacaine was estimated to be 1.289. It was not statistically significant. The 95% confidence interval of the odds ratio was (0.799, 2.080).

Visual analogue pain scale, height of sensory block –
No formal statistical analysis was presented.

Safety Evaluation:
All adverse events –
The number of adverse events was 158 in 0.25% Levobupivacaine treatment group, compared with 149 in 0.0625%- and 131 in 0.125%- Levobupivacaine treatment groups. Patients treated with 0.25% Levobupivacaine had higher proportion with severe event (11.3%) compared with 6.9% in 0.0625%- and 8.8% in 0.125%- Levobupivacaine group. The difference was not statistically significant. There was no difference in the proportion of patients with adverse events that was related to study drug or patients with serious adverse events (Table III.1.5).

The three treatment groups had the same most commonly experienced events classified by the ICD-body system. These four adverse events were experienced by more than 30% of the patients in each group. They were "body as a whole" disorders (44.1% in 0.0625%-, 44.8% in 0.125%- and 54.3% in 0.25%- Levobupivacaine treatment); "cardiovascular disorders in general" (52.9% in 0.0625-, 62.1% in 0.125%- and 62.9% in 0.25%- Levobupivacaine treatment); "GI system disorders" (52.9% in 0.0625%-, 41.4% in 0.125%- and 60% in 0.25%- Levobupivacaine treatment); "red blood cell disorders" (44.1% in 0.0625%-, 41.4% in 0.125%- and 51.4% in 0.25%- Levobupivacaine treatment); and "urinary system disorders" (32.4% in 0.0625%-, 44.8% in 0.125%- and 40% in 0.25%- Levobupivacaine treatment). There was no statistical evidence of difference or dose response trend in the distribution of events.

Vital signs –
The 0.25% Levobupivacaine group and the 0.0625% Levobupivacaine group had similar patterns over the 24 hour of mean supine heart rate except that the rates were consistently higher in the 0.0625% Levobupivacaine treatment group. The 0.125% Levobupivacaine group have supine heart rate between the other two groups over the time but the pattern over time was different.

Supine systolic blood pressure –
Overall, the mean changes (decreases) in the 0.25% Levobupivacaine treatment group were consistently the largest among the three groups except at 6 hour point where 0.125% Levobupicaine had a larger mean change. Although without formal statistical analysis, the dose response pattern was observed.

Supine diastolic blood pressure –
Overall, the mean changes (decreases) in supine diastolic blood pressure pattern was similar to the patterns in the mean changes of supine systolic blood pressure.

Clinical safety assessment during and post-surgery –

The number of patients recorded abnormal results for continuous lead ECG, non-invasive arterial pressure, pulse oximetry, sensory and motor block throughout surgery and intra-operative 5-lead ECG were given in Table 31 in NDA. The dose response pattern was shown in abnormal results in non-invasive arterial pressure (45.5% vs. 53.6% vs. 57.6% in 0.0625%, 0.125% and 0.25% Levobupivacaine treatment respectively) and pulse oximetry (81.8% vs. 85.7% vs. 93.9% in 0.0625%, 0.125% and 0.25% Levobupivacaine treatment respectively).

Table III.1.5 Summary of adverse events (based on NDA Table 23, page 158, vol. 122)

Adverse Event	Levobupivacaine Treatment					
	0.0625% N=34		0.125% N=29		0.25% N=35	
	N	%	N	%	N	%
All Adverse Events	149		131		158	
Patients with at least one adverse event	33	97.1	28	96.6	34	97.1
Patients with severe events	3	8.8	2	6.9	4	11.4
Patients with drug related adverse events	29	85.3	24	82.8	27	77.1
Patients with serious adverse events	2	5.9	1	3.4	2	5.7
Patients who died	0		0		0	

III.1.e. The Reviewer's Comments and Conclusions

The reviewer had the following conclusions regarding to the efficacy and safety assessment of this trial. This trial was designed with three treatments with different dose of Levobupivacaine. It was designed to show efficacy and safety of the 0.25% Levobupivacaine as compared with the two lower doses. The results were summarized as follows.

Primary efficacy endpoint:

1. The proportion of patients requested analgesia was lower in 0.25% Levobupivacaine treatment group than the other two lower dose groups. The difference was statistically significant.
2. The mean time to first request for analgesia was shorter in 0.25% Levobupivacaine treatment group than the other two treatment groups as shown in ANOVA. The difference was statistically significant.
3. In survival analysis with Cox regression model, the ratio of hazard rate in requesting analgesia was shown statistically significantly smaller than 1 when 0.25% Levobupivacaine treatment group was compared with the other two groups.

Secondary efficacy endpoints:

1. Normalized dose of morphine requirement – It was shown that 0.25% Levobupivacaine treatment group required less dose of morphine than the other two treatment groups. The difference was statistically significant.
2. Normalized number of morphine requirements – It was shown that 0.25% Levobupivacaine treatment group had less number of request for analgesia than the other two treatment groups. The difference was statistically significant.
3. A dose response relationship was shown in motor block. The odds for higher grade of motor block was greater than 1 for the 0.25% and 0.125% Levobupivacaine groups when compared with either of the two Levobupivacaine groups of higher concentration. The difference was statistically significant. The odds was larger than 1 for 0.25% Levobupivacaine group when compared with the 0.125% Levobupivacaine group. But the difference was not statistically significant.

Safety Analysis:
There were positive dose response patterns shown in the number of adverse events, consistently lower supine heart rate, and lower systolic and diastolic blood pressures over the surgery, in the number of abnormal results and the number of non-invasive arterial pressure. However, no formal statistical testing was performed.

III.2 Study CS-004

III.2.a. Study Objectives: The primary objective of this study was to assess the analgesic effect of 0.25% Levobupivacaine when combined with 0.005% morphine. The efficacy of the combination treatment was to be established by showing that the combination was superior to the 0,005% morphine treatments. Comparisons between the combination treatment with the 0.25% Levobupivacaine alone or between the treatments with 0.25% Levobupivacaine alone and 0.005% morphine alone were supportive analysis.

In addition, the secondary objectives of this study was to assess the amount of rescue analgesia required in the 24-hour post-operative period, to assess motor block, pain at various time points and to evaluate the relative safety and efficacy profile of the three treatment groups.

III.2.b. Study Design: This was a randomized, double blind, three-arm, parallel group (0.25% Levobupivacaine combined with 0.005% morphine, 0.25% Levobupivacaine alone and 0.005% morphine alone) study conducted in two centers in the United Kingdom.

III.2.c. Efficacy and Safety Endpoints:
Primary measure was the time to first request for administration of rescue analgesia during the 24-hour infusion period post surgery.

The secondary efficacy endpoints were the volume of post-operative study drug and ketorolac administered during the 24-hour infusion period, sensory block (assessed at 0, 2, 5, 10, 15, 20, 25, 30, 40, 50 and 60 minutes or until an appropriate block for abdominal surgery was achieved, and at 4, 8, 12, 16, 20, 24 hours after surgery), motor block (assessed at 0, 10, 20, 30 minutes or until a score 3 in Bromage scale achieved, and every 4 hours after surgery or until a Bromage score of 0 was achieved), pain assessment using VAS (assessed at 0, 4, 8, 12, 16, 20, 24 hours), heart rate, systolic and diastolic blood pressure (assessed at 4, 8, 12, 16, 20, and 24 hours).

Safety evaluations were vital signs (assessed at every 30 minutes during surgery and every 4 hours during the 24-hour post-operative period), laboratory assessments, cardiovascular monitoring and adverse events.

The patient evaluation schedule was given in Table III.2.1.

Table III.2.1 Patient Evaluation Schedule (based on NDA Table 2, page 32 of vol. 126).

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

III.2.d. Population for Analysis:

"Intent-to-treat" population was defined to include all randomized patients except patients who did not receive any of the randomized anaesthetic or patients who during the administration procedure suffered an incidental intravascular, subarachnoid injection, or injection into cerebrospinal fluid resulting in immediate withdrawal from the study.

"Per-protocol" population was defined to include all patients defined by the criteria determined by the Medical Director or designee at Chiroscience prior to the unblinding of the study.

Efficacy variables were analyzed using the 'intent-to-treat' population. Analysis using "per-protocol" population was presented also for the key variables in NDA.

"Safety" population was defined to include all patients received the 0.75% Levobupivacaine as pre-surgical anesthesia and randomized study drugs for post-operative analgesia. Patients who did not received any of the three study drugs after surgery were included in all safety analysis as a fourth treatment group.

III.2.e. Efficacy analysis:

Methods:

<u>The confirmatory efficacy analysis</u> -

The primary efficacy analysis was to test whether the combination treatment of 0.25% Levobupivacaine with 0.005% morphine was superior to the treatment with 0.005% morphine alone. To achieve this goal, the following null hypothesis was to be tested,

> H_{10}: E (mean difference in time to first request for rescue medication between the combination treatment and morphine alone treatment) =0.

A supportive analysis with the primary efficacy endpoint was to test against the following hypothesis

H_{20}: E (mean difference in time to first request for rescue medication between the combination treatment and Levobupivacaine alone treatment) =0

H_{30}: E (mean difference in time to first request for rescue medication between the Levobupivacaine alone treatment and the morphine alone treatment) =0

Multiple comparison adjusted type I error rate of 0.017 was used in these two tests. The hypotheses were tested with survival analysis using Kaplan-Meier approach.

The sample size was determined to be 20 evaluable patients to be enrolled in each treatment group. This sample size was determined based on the assumption that the standard deviation of 2 hours and a difference of 2 hours was expected between the combination treatment and the morphine alone treatment group for the primary efficacy variable, time to first use of rescue analgesic medication. With this sample size, the study would have more than 80% power to reject the null hypothesis based on a 2-sided t-test approach at a 5% type I error rate.

The secondary efficacy response variables included, the amount of study drug administered in the 24-hour postoperative period, the amount of ketorolac administered in the 24-hour postoperative period, the post-operative motor block at six time points, the post-surgery VAS assessment at rest and when the patient coughed, and the global VAS assessment by patients and by investigators. These variables were analyzed by ANOVA with factors of treatment, center, and their interaction. No multiple comparison adjustment was applied because the primary interest was the difference between the combination treatment and the morphine alone treatment. No multiple endpoint adjustment was used in the analysis of the secondary efficacy endpoints.

The primary safety parameters including vital signs, clinical laboratory parameters were analyzed and adverse events were summarized.

Results:

Subject disposition and withdrawals – The number of subjects recruited and randomized in each center and treatment group was given in Table III.2.2. The reasons for early terminations were adverse event (1), patient request (1), investigator judgement (3), protocol violation (1), no protocol adequate sensory block (2), no control of pain (13), and other (1).

Table III.2.2 Patients disposition (based on Tables 1 of NDA, page 471, vol. 126)

Status	Treatment			Total n (%)
	Levobupivacaine/ morphine N (%)	Levobupivacaine N (%)	Morphine N (%)	
Randomized	22 (100)	23 (100)	23 (100)	68 (100)
Center 1	10	11	11	33
Center 2	12	12	12	12
Withdrew prior to Anesthesia (did not receive study drug)	1(4.5)	1 (4.3)	0	2 (2.9)
Received Levobupivacaine For Anesthesia (Safety Population)	21 (95.5)	22 (95.7)	23 (100.0)	66 (97.1)
Received study drug for Anesthesia (ITT Population)	21 (95.5)	21 (91.3)	22 (95.7)	64 (94.1)
Per-protocol Evaluable Population	21(95.5)	19(82.6)	20 (87.0)	60 (88.2)
Non-protocol Evaluable	0	2 (8.7)	2(8.7)	4(5.9)
Discontinued	2(9.1)	13 (56.5)	9(39.1)	24(35.3)
Completed	20 (90.9)	10 (43.5)	14 (60.9)	44 (64.7)

Demographic and Baseline Characteristics:

Overall there were a total of 64 patients in "intent-to-treat" population. There were overall, 34 (53.1%) male and 30 (46.9%) female received study drugs. The male/female ratio was the greatest in the combined treatment (13:8) and the smallest in Levobupivacaine alone treatment (10:11). Seventy-five percent of the patients were Caucasians. There were 23.4% blacks. The percentage of black patients was similar in all three treatment groups. The mean age of this population was 51.3 years with minimum being 25 years and maximum being 79 years. Patients received morphine alone treatment were older (mean=56.2 yrs) than the other two treatment groups (mean=48.8 yrs in combination and in morphine alone groups). Average weight of all patients was 77.9 kg. Patient's weight ranged from 47.0 kg to 107.7 kg. There was no large difference among the three treatment groups in weight.

Concomitant medications mostly administered in this study included pre-operative sedative agents, prophylactic agents for nausea, anesthetics, vasopressors and pain medication.

Primary Efficacy Endpoint (Intent-to-treat Population):

Proportion of patients requested rescue analgesia – There were 10 (of 21) patients in the combined treatment group requested rescue analgesia, compared to 16 (of 22) patients in the morphine alone treatment group and 20 (of 21) patients in the Levobupivacaine alone treatment group. The relative risk for rescue medication of the combination treatment group to the morphine alone group was 0.66 (95% CI=(0.39, 1.08)) which was not statistically significantly different from 1 with Chi-square p-value=0.062 (Table III.2.3). The sponsor in the secondary efficacy analysis reported this part of the analysis as difference in proportions.

In the survival analysis of time to first request for rescue analgesia, the patients who did not request any rescue analgesia were considered censored data. The sample mean of the three treatments were 962.4 minutes for the combination treatment, 255.6 minutes for Levobupivacaine alone group and 656.4 minutes for the morphine alone group respectively (Table III.2.3). The difference between the combination treatment group and the morphine alone group was not statistically significant with p-value=0.066 using Wilcoxon 2-sample test for median. Due to the moderately unequal group censoring, analysis might be slightly negatively biased. Analysis using the 'per-protocol' population gave similar results.

In the supportive comparisons, the p-value was compared with the Bonferroni-Holm type I error rate, 0.017 for the three comparisons for statistical significance. In the analysis of proportion of patients requested rescue analgesia, the relative risk of the combination treatment group to the Levobupivacaine alone treatment group was 0.50 (95% CI=(0.33, 0.75)) which was statistically significantly different from 1 with p-value=0.001. The relative risk between the Levobupivacaine alone group and the morphine alone group was 1.31 (95% CI=(1.002, 1.711)) which was not statistically significantly different from 1 with p-value=0.044. In the survival analysis, the Levobupivacaine alone group had a statistically significantly shorter time to the first request for rescue analgesia than the combination treatment group (p=0.001) or the morphine alone group (p=0.001).

Table III.2.3 Time to first request for rescue analgesia (based on NDA Tables 6 and 7, page 44-45, vol. 126)

Variable	Levobupivacaine + morphine	Levobupivacaine Alone	Morphine Alone
Number of patients in the group	21	21	22
Number of patients made request	10	20	16
Quintiles			
25%	353.0	60.0	86.0
50%	>1440.0*	174.0	480.5
75%	>1440.0*	255.0	>1440.0
Mean	>962.4**	>255.6**	>656.4**
Treatment Difference:			
Difference in proportion of patients requested rescue analgesia -			
Overall Difference	p-value =0.001 (likelihood ratio test)		
Pairwise Difference	Combination vs. Levo	Combined vs. morphine	Levo vs. morphine
Difference	-47.5%	-25.1%	22.5%
Relative Risk (95% CI)	0.50 (0.33, 0.75)	0.66 (0.39, 1.08)	1.31 (1.002, 1.711)
P-value	0.001***	0.062 ****	0.044***
Difference in time to request -			
Pairwise comparison p-value#	0.001	0.066	0.001

*: Censored data.. **: Include censored data (censored value=24 hrs).
: Fisher's exact test *: Likelihood ratio chi-square test
#: Wilcoxon 2-sample test.

Secondary Efficacy Endpoints:

Amount of rescue study medication – The mean amount was not differ significantly across treatments when tested with analysis of variance model (Table III.2.4). Similar result was also shown in pairwise comparisons. The rate of administration rescue analgesia was lower in the combination group than the morphine group.

Proportion of patients requested ketorolac – The proportion of patients that requested ketorolac was lower in the combination treatment group (7/21) than either the morphine alone group (14/22) or the Levobupivacaine group (18/21)(Table III.2.5). The relative risk of requesting Ketorolac in The combination treatment to the morphine alone group was 0.52 (95% CI=(0.28, 0.99)). The relative risk was significantly different from 1 (p=0.047). In other pairwise comparisons, the combination group had also a relative risk 0.39 (95% CI=(0.23, 0.67)) that was significantly lower than 1 (p=0.001) after adjusting for the multiple comparison. The relative risk of Levobupivacaine to morphine was not statistical different from 1 (p-0.092). The analysis was done as difference in proportions by the sponsor and was reviewed by the medical reviewer. The statistical reviewer calculated the odds ratio analysis.

Rate of administration of rescue medication – The rate of administration of rescue analgesia

was lower in the combination group (adjusted mean=5.0 ml/hr) than in the morphine group (5.9 ml/hr). The difference was found not to be statistically significant (p=0.109).

Amount of ketorolac administered – For that requested ketorolac, the amount administered did not differ significantly between the combination treatment group and the morphine alone group. Neither the difference was significant in the other pairwise comparisons.

Table III.2.4 Amount of rescue study medication administered in 24-hour post-operative study period (based on NDA Tables 8, page 45, vol. 126)

Variable	Levobupivacaine + morphine	Levobupivacaine Alone	Morphine Alone
Number of patients in the group	21	21	22
Mean ± SD	116.3±39.71	121.68 ±52.38	103.42±48.64
Adjusted Mean	115.28	122.11	103.42
Treatment Difference:			
ANOVA treatment effect		p=0.429*	
	Combination-Levo	Combination-morphine	Levo.-morphine
Difference (95% CI)	-6.83 (-36.26, 22.61)	11.86 (-17.22, 40.95)	18.69 (-10.62, 47.64)
Pairwise comparison p-value	0.644	0.418	0.201

*: ANOVA with treatment, center and treatment-by-center interaction as factors. The treatment-by-center interaction was not significant.

Table III.2.5. Amount of Ketorolac administered during the 24-hour post-operative study period (NDA Tables 9 and 10, page 46, and Appendix 1 Tables 8.1 to 8.2, page 529-530, vol. 126)

Variable	Levobupivacaine + morphine	Levobupivacaine Alone	Morphine Alone
Number of patients in the group	21	21	22
Number of patients made request	7	18	14
Overall Difference	p-value =0.002 (likelihood ratio test)		
Pairwise Difference	Combination vs. Levo	Combined vs. morphine	Levo vs. morphine
Difference	-52.4%	-30.3%	21.1%
Relative Risk (95% CI)	0.39 (0.23, 0.67)	0.52 (0.28, 0.99)	1.35 (0.94, 1.92)
P-value *	0.001	0.047	0.092
Mean quantity±SD	34.3±11.34	51.7±30.53	35.4±20.89
Adjusted Mean	33.8	51.6	33.5
Treatment Difference:			
Treatment effect in ANOVA	p-value =0.119**		
Pairwise Difference	Combination vs. Levo	Combined vs. morphine	Levo vs. morphine
Pairwise comparison p-value	0.064	0.984	0.132

*: Likelihood ratio Chi-square test. **: ANOVA with treatment, center and treatment-by-center interaction as factors. The treatment-by-center interaction was not-significant.

Extent of motor block – There was no evidence of difference in duration of post-surgery motor block between the combination treatment and the morphine alone treatment throughout the study. There was neither any evidence of difference among the three groups during the study (NDA Table 9, page 531-536, vol. 126).

VAS assessment – VAS assessments were obtained for both at rest and when the patient was coughing. At rest, the combination group was significantly lower than the morphine alone group at 8 hours (p=0.001)(significant after adjusting for multiple comparisons at 6 time points)(NDA Table 10.1, page 537- 542, vol. 126). While coughing, the combination group had lower VAS score than the morphine group at 4 hours and 8 hours (NDA Table 10.2, page 543-548, vol. 126). The difference had p-value lower than 0,05 at both 4 hours and 8 hours. However, after

adjusting for six comparisons made at six time points, the difference was not significant statistically.

Global assessment of pain by patient and investigator – Patients in the combination group recorded the lowest overall assessment of pain (2.35) than either the morphine group (3.56) or the Levobupivacaine group (4.43). The difference to the morphine group was not statistically significant (p=0.167)(Table III.2.6). The difference to the Levobupivacaine was statistically significant (p=0.029). Similar results were obtained in the investigator overall assessment of pain.

Table III.2.6. Overall assessment of pain at the end of the study (based on NDA Tables 10.3 and 10.4, page 549-550 in Appendix 7, vol. 126)

Variable	Levobupivacaine + morphine	Levobupivacaine Alone	Morphine Alone
Patient Overall Assessment			
Number of patients	19	15	17
Mean quantity±SD	2.35±2.19	4.43±3.39	3.56±2.05
Adjusted Mean	2.37	4.35	3.56
Treatment effect	p-value =0.084 (ANOVA*)		
Pairwise Difference Combination -.Levo	Combined -. morphine	Levo -.morphine	
Difference (95% CI)	-1.98 (-3.76, -0.21)	-1.20 (-2.91, 0.52)	0.79 (-1.08, 2.61)
P-value**	0.029	0.167	0.389
Investigator Overall Assessment			
Number of patients	20	15	17
Mean quantity±SD	1.10±1.02	3.99±3.26	2.47±1.84
Adjusted Mean	1.14	3.93	2.50
Treatment effect	p-value =0.001 (ANOVA)		
Pairwise Difference	Combination -.Levo	Combined -. Morphine	Levo -.morphine
Difference (95% CI)	-2.78 (-4.23, -1.34)	-1.36 (-2.76, 0.04)	1.43 (-0.07, 2.92)
P-value**	<0.001	0.056	0.062

*: ANOVA with treatment, center and treatment-by-center interaction as factors. The treatment-by-center interaction was not significant.

**: t-test without adjusting for multiple comparison.

Safety Analysis:

Adverse events - Every patient had at least one adverse event reported. The list of events by body system was given in Table 12 in NDA (page 49-50, vol.126). The pattern of adverse event that was considered by investigators as possibly study drug related was given in Table 13 of NDA, page 52, vol. 126). There was no evidence for difference among the three groups. A total of 18 patients withdrew from the study due to adverse event, one from the combination group, ten from the Levobupivacaine group and seven from the morphine group. The relative risk of withdrawal due to adverse events of the combination group was 0.15 (95% CI=(0.03, 0.78)) to the morphine group. The relative risk was statistically significant with p=0.03. The combination group had also significantly lower risk than the Levobupivacaine group with relative risk 0.1 (95% CI=(0.02, 0.43)). The p-value was 0.002.

Table III.2.7. Withdrew due to adverse events (based on NDA Tables 14, page 53, vol. 126)

Variable	Levobupivacaine + morphine	Levobupivacaine Alone	Morphine Alone
Number of patients	21	21	22
Number of patients withdrew	1	10	7
Treatment effect	p-value =0.008 (chi-square)		
Pairwise Difference	Combination -.Levo	Combined -. morphine	Levo -.morphine
Relative risk (95% CI)	0.1 (0.02, 0.43)	0.15 (0.03, 0.78)	1.50 (0.70, 3.18)
P-value**	0.002	0.03	0.29

Vital signs and physical examination – A total of 27 patients had a fall in blood pressure ≥ 30 % of their baseline value during the time of surgery and 8 patients had a ≥ 30% fall in the post-operative period. The incidence rate was similar across the treatment groups (NDA Table 16, page 55, vol. 126).

III.2.f Reviewer's Comments and Conclusions:
The purpose of this study was to assess the efficacy and safety of 0.25% Levobupivacaine with 0.005% morphine for control of in patients undergoing major abdominal surgery. The study was designed to show that the combination treatment was superior to the morphine alone treatment. Although a third treatment arm of 0.25% Levobupivacaine was included in the study, the primary comparison was between the combination group and the morphine group. Hence no multiple comparison adjustment was applied. However, a Bonferroni-Holm adjusted type I error rate of 0.017 was applied by the reviewer in any comparison between the combination treatment and the Levobupivacaine or between the morphine treatment and the Levobupivacaine treatment,

Primary efficacy endpoint – The additive effect of 0.25% Levobupivacaine combined with 0.005% morphine in terms of longer time to first request for rescue analgesia was suggested and in terms of smaller proportion of patients requested rescue analgesia in this study. The difference between the combination treatment and the morphine treatment was however failed to show statistical significant with borderline p-values (p=0.062 for proportion and p=0.066 for time).

Secondary efficacy endpoints – The combination treatment was shown to be superior to the morphine group in the number of patients requested ketorolac. The amount of ketorolac among the patients requested it was similar in both the combination and morphine alone groups. It showed also significant improvement than the morphine treatment in VAS assessment at rest. The combination and morphine were similar also in the measurements of improvement in VAS assessment while the patient was coughing, in duration of post-surgery motor block, in global VAS assessment by either patients or investigators. There was no type I error rate adjustment for multiple endpoints applied in any of the analysis of the secondary endpoints.

Safety analysis – There was no evidence to show difference in safety profiles of the combination treatment and the morphine alone treatment or Levobupivacaine alone treatment, except in the proportion of patients withdrew due to adverse events. There was only one withdrawal in the combination group, 10 in the Levobupivacaine alone group and 7 in the morphine only group. The difference was statistically significant.

III.3 Study CS-006

III.3.a. Study Objectives: The primary objective of this study was to assess the efficacy and safety of 0.125% Levobupivacaine combined with Fentanyl, 0.125% Levobupivacaine alone, or Fentanyl alone in the control of post-operative pain. The primary efficacy endpoint was the time to the first request for administration of PCEA in the 24-hour post-operative period.

The secondary objectives of this study were:

1. Volume of post-operative study drug administered during the 24-hour infusion period
2. Motor block
3. Assessment of pain recorded using a visual analog scale (VAS)
4. Vital signs including blood pressure and heart rate monitored prior, during and after the surgery procedure
5. Laboratory assessment
6. Cardiovascular assessment
7. Adverse events

III.3.b. Study Design: This was a randomized, double blind, three-arm, parallel group (0.125% Levobupivacaine combined with Fentanyl, 0.125% Levobupivacaine alone and Fentanyl alone) study conducted in two centers in the United Kingdom.

III.3.c. Efficacy Endpoints:
Primary measure was the time to first request for administration of PCEA in the 24-hour post-operative period.

The secondary efficacy endpoints were the volume of rescue analgesia required during the post-operative period, motor block and assessment of pain (VAS)

Patients evaluation schedule was given in NDA Table 1 on page 31, vol. 129.

III.3.d. Population for Analysis:
Sponsor defined the three populations used in this report as follows:

"Intent-to-treat" population was defined as all randomized patients excluding patients who did not receive any of the randomized anaesthetic or patients who during the administration procedure suffered an incidental intravascular, subarachnoid injection, or injection into cerebrospinal fluid resulting in immediate withdrawal from the study;

"Per-protocol" population was defined to include all patients included in "intent-to-treat" population excluding those who received an anaesthetic that was not specified in the protocol:

"Safety" population was defined to include all patients received either the 0.75% Levobupivacaine as pre-surgical anesthesia or the randomized study drugs. Patients who did not received any of the three study drugs after surgery were included in all safety analysis as a fourth treatment group.

Efficacy variables were analyzed using the 'intent-to-treat' population. Analysis using "per-protocol" population was presented also for the key variables.
III.3.e. Efficacy analysis:
Methods:
<u>The confirmatory efficacy analysis</u> -
The primary efficacy endpoint was tested to show that the combination treatment of 0.125% Levobupivacaine plus Fentanyl was superior than both Fentanyl alone treatment and 0.125% Levobupivacaine alone treatment in pain control measured by time to first request for rescue medication. To achieve the goal, the following two null hypotheses were to be rejected,

H_{10}: E (mean difference in time to first request for rescue medication between the combination and Levobupivacaine alone) =0

H_{20}: E (mean difference in time to first request for rescue medication between the combination and Fentanyl alone) =0

Due to the confounding of center and type of surgery, strata refer to the center and type of surgery combined. Therefore, there were three strata:
Site 1 – Hip patients, Site 1 – knee patients, Site 2 – Hip patients.

There were no summary statistics for center alone or type of surgery alone.

The sample size was determined to be 20 per-protocol patients to be enrolled in each treatment group. This sample size was determined based on the assumption that the standard deviation of 2 hours and the difference was 2 hours for the primary efficacy variable, time to first use of rescue medication. With this sample size, the study would have more than 80% power to reject the null hypothesis based on a 2-sided t-test approach at 5% type I error rate.

The secondary efficacy response variables:
A two-way ANOVA with treatment, strata and their interaction as 3 factors was used to analyze the secondary efficacy variables at each of the 4 time points. If appropriate, nonparametric procedure or data transformation would be used in the analysis.

No multiple endpoint adjustment was used in the analysis of the secondary efficacy endpoints.

Safety Analysis:
The primary safety parameters were vital signs, ECGs, QT and QRS intervals, adverse events and clinical laboratory parameters.

Results:
Subject disposition and withdrawals – The number of subjects recruited and randomized in each center and treatment group is given in Table III.3.1

Table III.3.1 Patients disposition (based on Tables 2 of NDA, page 041, vol. 129)

Status	Treatment			Total n (%)
	Levobupivacaine/ Fentanyl N (%)	Levobupivacaine N (%)	Fentanyl N (%)	
Randomized	22 (100)	23 (100)	23 (100)	68 (100)
Withdrew prior to Anesthesia (did not receive study drug)	0	1 (4.3)	1 (4.3)	2 (2.9)
Received Levobupivacaine for Anesthesia (Safety Population)	22 (100)	22 (95.7)	22 (95.7)	66 (97.1)
Received study drug for Anesthesia (ITT Population)	21 (95.5)	22 (95.7)	22 (95.7)	65 (97.1)
Per-protocol Evaluable Population	18 (81.8)	21 (91.3)	21 (91.3)	65 (65.6)
Non-protocol Evaluable	3 (13.6)	1 (4.3)	1 (4.3)	5 (7.4)
Discontinued	5 (22.7)	11 (47.8)	12 (52.2)	28 (41.2)
Completed	17 (77.3)	12 (52.2)	11 (47.8)	40 (58.8)

Demographic and Baseline Characteristics:

There were a total of 65 patients in the "intent-to-treat" population. There were overall, 20 (30,3%) male and 45 (69.2%) female received study drugs. The male/female ratio was the greatest in the combined treatment (9:12) and the smallest in the Fentanyl treatment (4:18). Most of the patients were Caucasian (95.4%). There rest were 1 black (combined treatment) and 2 Hispanics (all in Levobupivacaine alone treatment). The mean age of this population was 66.34 years with minimum being 24 years and maximum being 80 years. There was no large difference in means age and age distribution among the three treatments groups. Average weight of all patients was 81.33 kg. Patient's weight ranged from 50.9 kg to 110.0 kg. There was no large difference among the three treatment groups in weight.

Concomitant medications mostly administered in this study included pre-operative sedative agents, prophylactic agents for nausea, anesthetics, vasopressors and pain medication.

Primary Efficacy Endpoint (Intent-to-treat Population):
Proportion of patients requested rescue analgesia – There were 2 of 21 patients in the combined treatment group didn't require rescue analgesia (three had missing value because of withdrawal), compared to 1 of 22 patients in the Levobupivacaine alone group and none in the Fentanyl alone group (1 missing in Fentanyl group). The difference was not statistically significant (Table III.3.2)

In the analysis of time to first request for rescue analgesia, a 24-hour was assigned to the patients who did not request any rescue analgesia. The sample mean of the three treatments was 603.5 min for the combination treatment, 421.5 min for Levobupivacaine alone and 420.5 for Fentanyl alone (Table III.3.2). The combination treatment group had significantly longer mean time to first request for rescue analgesia than Levobupivacaine group (p=0.007) and Fentanyl alone group (p=0.006). The survival analysis was shown using the Kaplan-Meier approach. Comparison of mean survival time was performed using log rank test. Due to the larger number of censored patients, the combination group has the greatest negative bias than the other two treatment groups. There was no statistically significant difference between Levobupivacaine and featly treatment groups.

Table III.3.2 Time to first request for rescue analgesia (based on NDA Table 4, page 43, vol. 129)

Variable	Levobupivacaine + Fentanyl	Levobupivacaine Alone	Fentanyl Alone
Number of patients in the group	21	22	22
Number of patients didn't make request (censored)	2	1	0
Censored at last observed time (early terminated patients)	3	0	1
Quintiles			
25%	433.0	359.0	341.0
50%	535.0	448.0	416.0
75%	1000.0	495.0	479.0
Mean	603.1	421.5	420.5
Treatment Difference:			
Difference in proportion of patients requested rescue analgesia -			
Pairwise Difference	Combination vs. Levo	Combined vs. Fentanyl	Levo vs. Fentanyl
Difference	5.0%	9.5%	4.5%
P-value (Fisher's Exact)	0.386	0.126	0.355
Difference in time to request -			
Pairwise comparisOn p-value	0.007	0.006	0.679

Secondary Efficacy Endpoints:

Amount of rescue medication – It was compared across treatment groups at 6, 12, 18 and 24 hours. There was no statistically significant difference between any two of the treatment groups at any time point (Table III.3.3). There was no statistically significant treatment-by-strata interaction.

Request for femoral nerve block – The proportion of patients who requested femoral nerve block for pain control was 3 (14.3%) in the combination treatment, which was lowest compared with 4 (18.2%) in the Levobupivacaine and 5 (22.7%) in the Fentanyl treatment groups. The difference was not statistically significant (Table 7 page 46, NDA vol. 129).

Extent of motor block – The extent of post-surgery motor block was assessed at 6, 12, 18, and 24 hours post-operatively or until the patients had no lingering paralysis. Patients treated with Levobupivacaine alone had consistently higher average Bromage score than the other two treatment groups. The three groups were different significantly at 6 hour with p=0.013 (ANOVA)(Tables 9, pp.442-457, vol. 129). In the pairwise comparison at 6 hour, patients treated with Levobupivacaine and Fentanyl combination had no statistically significant difference from the patients treated with Fentanyl alone (p=0.85). The only significant pairwise comparison was between Levobupivacaine alone and Fentanyl alone of them the Levobupivacaine group had significantly higher mean score (1.1 vs. 0.2 with p=0.004). The p-value was significant with adjustment for 3 pairwise comparisons. The combination treatment had slightly higher (but not statistically significant) mean than either the Levobupivacaine alone or the Fentanyl alone group.

Post-surgery Visual Analog Scale (VAS) – It was assessed at 6, 12, 18, and 24 hours post-operatively both at rest and following movement. Patients treated with combination drugs rated their discomfort at rest significantly less than the Fentanyl group at 6 hour (p=0.022) and at 12 hour time (p=0.002). Similarly, the VAS score following movement was significantly lower in the combination group than the Fentanyl group at 6 hour (p=0.036) and 12 hour time (p=0.001). There was no significant difference among the three treatment groups at other time points (Tables 10.1 and 10.2, NDA pp.1-32, vol. 130).

Overall assessment of pain – Both patients and investigators gave an overall assessment of pain at the end of the study. Both the patients and the investigators rated the overall pain assessment significantly less in the combination group than the Fentanyl group (p=007 by patient, p=0.005 by investigators)(Tables 10.3 and 10.4 NDA pp.33-38, vol. 130).

Table III.3.3 Analysis of amount of rescue medication administered over 24 hours (based on NDA Tables 7.5, pp.398-413, vol. 129)

Variable	Levobupivacaine + Fentanyl	Levobupivacaine Alone	Fentanyl Alone
Number of patients in the group	21	22	22
Amount of rescue Study Medication			
Administered Over 24 Hours			
Amount in the 1st 6 hrs			
Mean			
Mean (adjusted least square)*	21.40	26.90	26.15
Amount in the 1st 12 hrs	21.40	26.73	26.13
Mean			
Mean (adjusted least square)	51.78	68.06	68.50
Amount in the 1st 18 hrs	51.78	68.81	68.61
Mean			
Mean (adjusted least square)	88.22	107.40	102.80
Amount in the 1st 24 hrs	88.22	106.17	103.12
Mean			
Mean (adjusted least square)	118.40	132.65	129.17
	118.40	131.80	129.41
Treatment Difference (p-value)			
At 1st 6 hrs			
Overall treatment		0.149**	
Pairwise comparisons		Difference (95% CI)	p-value
Combination vs. Levobupivacaine		-4.72 (-10.57, 1.14)	0.112
Combination vs. Fentanyl		0.61 (-5.20, 6.43)	0.833
Levobupivacaine vs. Fentanyl		-5.33 (-11.21, 0.55)	0.075
At 1st 12 hrs			
Overall treatment		0.123	
Pairwise comparisons		Difference (95% CI)	p-value
Combination vs. Levobupivacaine		-16.83 (-34.57, 0.92)	0.063
Combination vs. Fentanyl		-1.63 (-19.24, 15.99)	0.854
Levobupivacaine vs. Fentanyl		-15.20 (-33.20, 2.61)	0.093
At 1st 18 hrs			
Overall treatment		0.495	
Pairwise comparisons		Difference (95% CI)	p-value
Combination vs. Levobupivacaine		-14.90 (-45.73, 15.93)	0.337
Combination vs. Fentanyl		2.06 (-28.55, 32.67)	0.893
Levobupivacaine vs. Fentanyl		-16.95 (-47.89, 13.99))	0.277
At 1st 24 hrs			
Overall treatment		0.762	
Pairwise comparisons		Difference (95% CI)	p-value
Combination vs. Levobupivacaine		-11.01 (-49.58, 27.57)	0.570
Combination vs. Fentanyl		2.39 (-35.91, 40.69)	0.901
Levobupivacaine vs. Fentanyl		-13.40 (-52.10, 25.31)	0.491

*, **: From analysis of variance with factors of treatment, strata and their interaction

Safety Analysis:

Adverse events - Every patient had at least one adverse event reported. The list of events with at least 10% patients was given in Table 9 in NDA. The pattern of adverse event that was considered by investigators as possibly study drug related was similar in all three treatment groups (Table 10 of NDA). Twenty-five patients (4 of combination group, 10 of 0.125% Levobupivacaine alone group and 11 of Fentanyl alone group) withdrew prematurely from the study after received study drugs (Table 11 of NDA)

Vital signs and physical examination – A total of 35 patients had a fall in blood pressure ≥ 30 % of their baseline value during the time of surgery and 15 patients had a ≥ 30% fall in the post-operative period. The incidence was similar across the treatment groups (Table 13 of NDA).

III.3.f Reviewer's Comments and Conclusions:
The purpose of this study was to assess the efficacy and safety of 0.125% Levobupivacaine with Fentanyl, 0.125% Levobupivacaine alone or Fentanyl alone for control of operative pain in patients undergoing major orthopedic surgery.

Primary efficacy endpoint – The efficacy of the treatments with Levobupivacaine alone, Fentanyl alone and combination was assessed with time to first request for rescue analgesia. There was no statistical significance in the proportion of patients who did not make request in 24 hours. Patient who did not request rescue medication or with missing data due to any reasons of discontinuation of study drug was considered censored in the survival analysis at the last time in the study. The combination treatment group had longer time to the first request than the two single-drug treatment groups. The difference was statistically significant based on Kaplan Meier survival analysis. Since the patients withdrew from the study was taken as censored instead of required rescue medication, the comparison was bias in favor of the combination treatment.

Secondary efficacy endpoints – Analysis for secondary efficacy endpoint was adjusted for multiple comparison of the three treatment groups but not adjusted for multiple endpoints analyzed. Data of amount of rescue medication, request for femoral nerve block, 24 hour monitoring of extent of motor block, post-surgery VAS and the overall pain assessment at the end of study was collected and analyzed. There was no statistically significant difference in the amount of rescue medication among the three treatment groups measured at 6, 12, 18 and 24 hours post-surgery and in the proportions of patients who requested femoral nerve block. The comparisons was statistically significant between the combination treatment group and either one of the single-drug treatment group in with post-surgery VAS at 6 and 12 hours at rest and following movement and with less overall pain assessed by either patients or investigators at the end of surgery. Patients treated with Levobupivacaine alone had significantly higher motor block at 6 hour than patients received Fentanyl alone. There was no significant difference among the three groups in any of the other comparisons.

Safety analysis – The pattern of adverse event was similar in all three groups. The incidence of blood pressure decreased more than 30% from baseline was similar across the treatment groups.

III.4 Study 030742

III.4.a. Study Objectives: The primary objective of this study was to assess the analgesic effect 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 patients undergoing elective hip replacement surgery. In addition, the safety of each treatment was to be evaluated.

III.4.b. Study Design: This was designed as a randomized, double blind, three-arm, parallel group (0.125% Levobupivacaine, 0.125% Levobupivacaine plus 50 $\mu g.h^{-1}$ clonidine and 50$\mu g.h^{-1}$ clonidine alone) study conducted in a single centers in the United Kingdom.

III.4.c. Efficacy and Safety Endpoints:
Primary measure was the total dose of morphine for analgesia delivered via the PCA pump during the 24-hour infusion period

The secondary efficacy endpoints were "time to the first request for analgesia via PCA pump during the 24 hour period following the completion of the extradural injection of the study drug", "the number of requests for analgesia", "visual analogue pain scale recorded hourly by patient until 12 hours post extradural infusion", "height of sensory block (assessed hourly up to 24 hours after the extradural infusion)", and "motor block (Bromage scale assessed hourly up to 24 hours after the extradural infusion)".

Safety evaluations were vital signs (assessed continuously during surgery and hourly up to 27 hours post extradural infusion), laboratory assessments and adverse events.

III.4.d. Population for Analysis:
"Intent-to-treat" population was defined to include all randomized patients who received the complete 24-hour extradural infusion of study drug.
"Per-protocol" population was defined to include all patients in "intent-to-treat" population except those been decided to be excluded by the study director before breaking the blindness of the study.

The primary efficacy analysis was performed on an "intent-to-treat" population with confirmatory analysis with the "per-protocol" population.

"Safety" population was defined to include all patients who received randomization.

III.4.e. Efficacy analysis:
Methods:
The primary confirmatory efficacy analysis -
The primary efficacy analysis was to test if the total dose of morphine delivered during the 24-hour postoperative infusion was different among the three treatment groups. The statistical hypothesis behind the trial was as follows:

> H_{10}: E (average difference in the total dose of morphine delivered in patients receiving an infusion between the treatment groups (0.125% Levobupivacaine, 0.125% Levobupivacaine plus 50 $\mu g.h^{-1}$ clonidine and 50 $\mu g.h^{-1}$ Clonidine)) = 0
>
> H_{1a}: E (average difference in the total dose of morphine delivered in patients receiving an infusion between the treatment groups (0.125% Levobupivacaine, 0.125% Levobupivacaine plus 50 $\mu g.h^{-1}$ clonidine and 50 $\mu g.h^{-1}$ clonidine)) $\neq$ 0

Upon the rejection of H_{10}, multiple comparisons were performed to test for the difference between any two of the treatments. In order to compensate the multiple comparisons, a Bonferroni-Holm correction was used to adjust the type I error rate. The adjusted rate for the three pair comparisons was 0.017%. The data was initially analyzed with ANOVA with treatment effect. Since the normality assumption was rejected using a Shapiro-Wilks test, the

data was reanalyzed using the non-parametric Wilcoxon two sample test for pair comparisons.

The sample size was determined to be 30 patients to be enrolled in each treatment group. This sample size was determined based on the assumption that the standard deviation of 6 mg and the mean dose of morphine delivered in patients receiving 50 $\mu g.h^{-1}$ clonidine was 10.5 mg (based on a previous study). With this sample, this study had 80% power to detect a difference of more than 5.2mg (50% of the mean of 50 $\mu g.h^{-1}$ clonidine treatment) between either one of the Levobupivacaine treatment and 50 $\mu g.h^{-1}$ clonidine treatment. This was done taking into account of adjusted type I error rate (0.017).

The secondary efficacy response variables
Patients who did not request analgesia via PCA pump were considered censored. Time to the first request for analgesia via PCA pump data were analyzed using Kaplan-Meier survival curves. Since the assumption of proportion hazard was not satisfied for any two survival curves, the mean survival time was compared between groups with Wilcoxon two-sample test. The number of requests for analgesia via PCA pump was analyzed using Wilcoxon test after failed to satisfy the normal assumption for ANOVA.

Maximum grade of motor block achieved in each group was compared using pairwise comparisons in ANOVA with type I error rate adjusted with the Bonferroni-Holm method.

Visual analogue pain scale (VAS) recorded at rest and on passive movement and height of sensory block were summarized with no formal statistical analysis specified in the protocol or presented.

Safety Analysis:
The primary safety parameters including vital signs, clinical laboratory parameters were analyzed and adverse events were summarized.

Results:
Subject disposition and withdrawals — The number of subjects recruited and randomized in each center and treatment group was given in Table III.4.1. The reasons for terminations before receiving any study drug were technical failure (5), insufficient block for surgery (1) and other protocol violation (2). Three patients were excluded from the "per-protocol" population because received analgesia other than the study drugs (1) and started infusion too earlier (1).

Table III.4.1 Patients disposition (based on Tables 1 of NDA, page 72, vol. 132)

Status	Treatment			Total n (%)
	Levobupivacaine N (%)	Levobupivacaine + Clonidine N (%)	Clonidine N (%)	
Randomized	31(100)	32 (100)	35(100)	98(100)
Technical failure (did not receive study drug)	1(3.2)	0(0.0)	1(2.9)	2 (2.0)
Safety Population	30(96.8)	32 (100)	34 (97.1)	96 (98.0)
Technical failure (did not receive study drug)	0 (0.0)	2 (6.3)	1(2.9)	3 (3.1)
Insufficient block (did not receive study drug)	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.0)
Other (did not receive study drug)	0 (0.0)	0 (0.0)	2(5.7)	2 (2.0)
Intent-to-treat population	30(96.8)	30 (93.8)	30 (85.7)	90 (91.8)
Received analgesia other than the study drug	2(6.5)	0(0.0)	1(2.9)	3(3.1)
Started Infusion less than 2 hrs after extradural injection	1(3.2)	0(0.0)	0(0.0)	1(1.0)
Per-protocol Population	27(871)	30 (93.8)	29 (82.9)	89 (90.8)

Demographic and Baseline Characteristics:

Overall there were a total of 90 patients in the "intent-to-treat" population. There were slightly differences in the distribution of sex between the treatment groups. The distribution of males and females was identical in the Levobupivacaine and the Clonidine group (13 males (43.3%) and 17 females (56.7%) in each, while in the combination group the distribution was 6 males (20.2%) and 24 females (80.0%). Differences in average age, and weight between the groups were much smaller. The average age was 64.9 years in the Levobupivacaine group, 64.6 years in the combination group and 67.2 years in the Clonidine group. The average weight was 164.1 kg in the Levobupivacaine group, 160.4 kg in the combination group and 164.3 kg in the Clonidine group. All patients were Caucasians.

Medical history reported most frequently under "circulatory system", "digestive system", and "muskoskeletal system and connective tissue". The difference in the distribution of medical history among the three groups was small.

The physical examination details were given in Table 10 of NDA (page 86, vol.132). There was not much difference of distribution of abnormal body systems among the three groups.

The largest difference in percentage of concomitant medication reported at screening and continued after dosing among the three groups was the medications for central nervous system (13% in Levobupivacaine group, 7% in combination group and 23% in Clonidine group). The distribution was similar for other drugs.

Primary Efficacy Endpoint (Intent-to-treat Population):

The median of the total dose of morphine administered was the lowest for the Levobupivacaine plus Clonidine group (7 mg in 24 hours). The difference was statistically significant between the combination group and the Levobupivacaine group at -23 mg with $p < 0.001$. It was also statistically significantly lower than the Clonidine group at -12 mg with $p=0.004$. The Levobupivacaine group had a median dose larger than the Clonidine group by 13 mg. The difference was not statistically significant with $p=0.022$ when comparing with the multiple comparison adjusted p-value of 0.017 (Table III.4.2). Similar results were shown in the "per-