Secondary Efficacy Variables are:

1. Duration of pain relief following each top-up dose.
2. Time to pain relief following each dose of study drug.
3. Time normalised area under the Visual Analogue Scale, VAS) pain score *vs.* time curve (AUC) for all assessments following each dose of study drug using the linear trapezoidal rule *i.e.*, area divided by total assessment. In the cases where VAS scores were not recorded but the patient recorded 'unaware' or 'aware but not painful' on the verbal rating scale, the missing VAS scores was to be taken as zero. All other missing VAS scores were to be replaced using linear interpolation."
8. Proportion of patients recording each grade of motor block.
9. Sensory block
10. Overall quality of analgesia

"With the exception of 4. above, all secondary endpoints were to be analysed using ANOVA methods as described above for each dose of study drug separately ('per-protocol' population only)."

"The distribution of patients recording each grade of motor block following each dose of study drug was to be compared between treatments using a Mantel-Haenszel Test stratifying for parity."

"In addition to the formal statistical analysis, VAS measurements recorded following each dose of study drug were to be summarised and illustrated graphically by treatment group. An additional summary and illustration of VAS scores, excluding those assessments where Entonox was used, was to be provided by treatment group."

"The spread of sensory block following each dose of study drug was to be tabulated by treatment for the left side only. No formal statistical analysis of the spread of block was to be performed."

.em 8, Vol. 1.58, p. 046 - 048]

PROTOCOL AMENDMENT:

Amendment 1 dated 5/15/96, Amendment 2 dated 10/8/96 and Amendment 3 dated 8/1/97 made the following changes:

A. Exclusion Criteria
- Include patients who have had a previous cesarean, have insulin-dependent diabetes, and any patients who the investigator believes to be unsuitable.

B. Study Procedures
- An aseptic preparation will be applied before the epidural is sited.
- The maximum number of injections a patient can have is 8, i.e., 7 'top-up injections'

C. Study Measurements
- The verbal rating scale and visual analog scale will also be administered before the first epidural injection and before every 'top-up'.
- The extent of motor and sensory block will be measured at 5, 15, 30 and 60 minutes following the first epidural injection, unless the first 'top-up' injection is administered. Once the first 'top-up' is given, the block will be assessed at 15 minutes post 'top-up' and then at 30 minute intervals until a further 'top-up' is given.
- The investigator will give an overall assessment of the quality of the block 30 minutes after the first epidural injection and then 30 minutes after each 'top-up'.

D. Randomization and Blinding
- The randomization will be stratified by parity. Each center will be assigned at least one block for each parity status.

E. Population for Analysis
- Broaden the scope of patients excluded from analysis by using the wording, "patients with technical failure" instead of describing certain possible

F. Epidural Anesthesia Procedure
- Deleted the specific use of a blunted 27 gauge dental needle for the sensory block assessment. (Appendix 1)
- Specified the end of injection as Time 0. (Appendix 1)
- Modified the definition of hypotension from, "a fall greater than 30% of baseline systolic pressure or below 100 mmHg systolic, to, "a fall greater than 30% of baseline systolic pressure"

G. Efficacy Analysis

- "For the purposes of analysis, a contraction recorded whilst a patient was asleep will be assigned a score of 2=unaware on the verbal rating scale and 0=no pain on the visual analog scale."
- "Patients that do not record a score of 1 or 2 on the verbal rating scale will be assigned a duration of 0 minutes for the primary efficacy endpoint..."
- "If a considerable number of patients complete the study whilst still recording pain relief then a further analysis will be performed using a log rank test with such patients providing censored observations."

H. Study Conclusion

- A completer must: (1) receive the first 'top-up' injection, (2) deliver without receiving excluded medication, or (3) receive all eight injections, without receiving excluded medication, before moving on to a standard regime.
- A patient is withdrawn if: (1) the first 'top-up' is not received, (2) administration of medication excluded by the protocol prior to delivery or prior to all 8 injections being administered, (3) Cesarean section, (4) withdrawal of consent, (5) technical failure, or (5) protocol violation

[Item 8, Vol. 1.58, p. 292]

Additionally, the amendments call for changes in administrative concerning the recording of data.

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 169 patients randomized, all 169 (100%) received study medication and were considered to be evaluable for the safety analyses. See sponsor's table 3.2.1 below. Seven patients (Patient #'s 0021, 0040, 0041, 0066, 0105, 0116, 0223) were considered to be technical failures and, therefore, were not eligible for the intent-to-treat population.

Of the 162 patients who received the study drug and were eligible for the Intent-to-Treat population, 25 patients (8 levobupivacaine and 17 bupivacaine) were excluded from the 'per-protocol' population due to the following:

(1) Received opioids in the 4 hours preceding the first injection – Patient #'s 0089, 0213, 0220 – 3 patients
(2) Received non-study medication before the onset of pain relief for the first study drug - Patient # 0228 - 1 patient.
(3) Received first 'top-up' injection before recording 2 painful contractions – Patient #'s 0002, 0003, 0004, 0005, 0006, 0015, 0026, 0030, 0032, 0034, 0056, 0133, 0201, 0202, 0203, 0210, 0211, 9223 - 18 patients
(4) Patient did not record a painful contraction prior before their first injection – Patient #'s 0001, 0207, 0231 – 3 patients

A total of 137 patients (68 levobupivacaine, 69 bupivacaine) were eligible for the 'per-protocol' population. Of those patients eligible for the per-protocol population, a total of 30 patients did not achieve pain relief and therefore were not eligible for the analysis of the primary measure of efficacy.

Table 27. Analysis of Safety Population

TABLE 3.2.1

Populations for Analysis
Patients in Each Population
Summary Statistics: Safety Population

Centre/Treatment		Safety		Intent-to-Treat				Per-Protocol			
		YES		YES		NO		YES		NO	
		N	%	N	%	N	%	N	%	N	%
001	0.25% LEVOBUPIVACAINE	23	100.0	23	100.0	0	0	18	78.3	5	21.7
	0.25% BUPIVACAINE	24	100.0	24	100.0	0	0	15	62.5	9	37.5
	ALL	47	100.0	47	100.0	0	0	33	70.2	14	29.8
002	0.25% LEVOBUPIVACAINE	35	100.0	31	88.6	4	11.4	29	82.9	6	17.1
	0.25% BUPIVACAINE	38	100.0	38	100.0	0	0	32	84.2	6	15.8
	ALL	73	100.0	69	94.5	4	5.5	61	83.6	12	16.4
004	0.25% LEVOBUPIVACAINE	24	100.0	22	91.7	2	8.3	21	87.5	3	12.5
	0.25% BUPIVACAINE	25	100.0	24	96.0	1	4.0	22	88.0	3	12.0
	ALL	49	100.0	46	93.9	3	6.1	43	87.8	6	12.2
ALL	0.25% LEVOBUPIVACAINE	82	100.0	76	92.7	6	7.3	68	82.9	14	17.1
	0.25% BUPIVACAINE	87	100.0	86	98.9	1	1.1	69	79.3	18	20.7
	ALL	169	100.0	162	95.9	7	4.1	137	81.1	32	18.9

[Sponsor's Table 3.2.1, "Populations for Analysis", Item 8, Vol. 1.58, p. 103]

Table 28. Patients Excluded from Efficacy Evaluable Population

Populations for Analysis
Reason for Exclusion from Intent-to-Treat and Per-Protocol Population
By Treatment and Centre
Summary Statistics: Safety Population

		0.25% LEVOBUPIVACAINE				0.25% BUPIVACAINE				ALL PATIENTS			
		001	002	004	ALL	001	002	004	ALL	001	002	004	ALL
ALL PATIENTS	N	23	35	24	82	24	38	25	87	47	73	49	169
	%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
TECH FAILURE (i)	N	0	4	2	6	0	0	1	1	0	4	3	7
	%	0	11.4	8.3	7.3	0	0	4.0	1.1	0	5.5	6.1	4.1
VALID FOR INTENT-TO-TREAT	N	23	31	22	76	24	38	24	86	47	69	46	162
	%	100.0	88.6	91.7	92.7	100.0	100.0	96.0	98.9	100.0	94.5	93.9	95.9
OPIOIDS (ii)	N	1	0	1	2	1	1	0	2	2	1	1	4
	%	4.3	0	4.2	2.4	4.2	2.6	0	2.3	4.3	1.4	2.0	2.4
<2 PAINFUL CONTRACTIONS (iii)	N	3	2	0	5	6	5	2	13	9	7	2	18
	%	13.0	5.7	0	6.1	25.0	13.2	8.0	14.9	19.1	9.6	4.1	10.7
NO PAINFUL CONTRACTIONS (iv)	N	1	0	0	1	2	0	0	2	3	0	0	3
	%	4.3	0	0	1.2	8.3	0	0	2.3	6.4	0	0	1.8
VALID FOR PER-PROTOCOL	N	18	29	21	68	15	32	22	69	33	61	43	137
	%	78.3	82.9	87.5	82.9	62.5	84.2	88.0	79.3	70.2	83.6	87.8	81.1

(i) Technical failure – excluded from Intent-to-Treat population - (Patient #'s 0021, 0040, 0041, 0066, 0105, 0116, and 0223).
(ii) Patient received opioid 4 hours preceding epidural injection - Patient # 's 0089, 0213, and 0220.
(iii) Patient where the first top-up was not given before 2 consecutive painful contractions - Patient #'s 0002, 0003, 0004, 0005, 0006, 0015, 0026, 0030, 0032, 0034, 0056, 0133, 0201, 0202, 0203, 0210, 0211, 9223.
(iv) Patient with no painful contractions prior to the first injection - Patient #'s 0001, 0207, 0231.

[taken from Sponsor's Table 3.2.2, "Populations for Analysis", Item 8, Vol. 1.58, p. 104]

Table 29. Patient Disposition

	0.25% Levobupivacaine	0.25% Bupivacaine
Total Patients Randomized	82	87
Patients Evaluable for Safety	82 (100%)	87(100%)
Patients Not Eligible for Intent - to-Treat :		
Technical Failure	6	1
Patients Eligible for ITT	76 (92.7%)	86 (98.8%)
Population Excluded from the Per-Protocol Population:		
Received Opioid 4 Hours Pre-Epidural	2	2
No Painful Contractions Prior to First Injection	1	2
First Top-up Given Before 2 Consecutive Contractions	5	13
Population Eligible for Per-Protocol Population	68 (83%)	69 (79.3%)
Patients Who Did Not Achieve Pain Relief	20	10
Population Eligible for the Analysis of the Primary Measure of Efficacy	48 (59%)	59 (68%)

[Note: (1) The primary analysis population for efficacy in this study was the 'per-protocol' population who achieved pain relief. A total of 30 patients eligible for the per-protocol population did not achieve pain relief (20 levobupivacaine and 10 bupivacaine) and therefore were not evaluable for efficacy. (2) Patients who received study medication but who were considered technical failures, (e.g., unblocked/ missed segments, etc.) were not eligible for the Intent-to-Treat population.

ıtient specific protocol violations are summarized for individual patients in the table below.

Table 30. Patient - Specific Protocol Violations

PROTOCOL VIOLATION	TREATMENT	PATIENT NUMBERS (CENTER)
Received Opioid 4 Hours Pre- Epidural	Levobupivacaine	0220 (4)
	Bupivacaine	0089(1), 0213(2)
No Painful Contractions Prior to First Injection	Levobupivacaine	0001(1)
	Bupivacaine	0207(1), 0231(1)
First Top-up Given Before 2 Consecutive Contractions	Levobupivacaine	0004(1), 0015(1), 0030(2), 0203(1), 0211(2),
	Bupivacaine	0002(1), 0003(1), 0005(1), 0006(1), 0026(2), 0032(2), 0034(2), 0056(4), 0133(2), 0201(1), 0202(1), 0210(2), 9223(4)
Technical Failure	Levobupivacaine	0021(2), 0040(2), 0041(4), 0066(2), 0105(2), 0116(4),
	Bupivacaine	0223(4)

(1) Center 1; (2) Center 2; (4) Center 4.

TABLE 2.2

Patient Withdrawal
Summary Statistics: Safety Population

Centre	0.25% LEVOBUPIVACAINE		0.25% BUPIVACAINE	
	N	%	N	%
001	13	21.7	16	25.0
002	29	48.3	29	45.3
004	18	30.0	19	29.7
ALL PATIENTS	60	100.0	64	100.0

[Sponsor's Table 2.2, Item 8, Vol. 1.58, p. 101]

Demographics

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

Table 31. Demographics - Safety Evaluable Population

	STATISTICS	0.5% LEVOBUPIVACAINE	0.5% BUPIVACAINE
Age (years)	n	82	87
	mean	27.1	27.4
	s.d.	5.42	5.0
	range	18-40	19-37
Women	%	100	100
Race:			
Caucasian	n (%)	77(94)	83 (95)
Hispanic	n (%)	2 (0.02)	0
Asian	n (%)	3 (0.03)	1 (0.01)
Other[3]	n (%)	0	3 (0.03)
Weight (kg)	n	81	84
	mean	76.67	75.63
	s.d.	13.81	12.39
Height (cm)	n	82	87
	mean	162.7	161.9
	s.d.	6.0	5.9
Gestational Age (weeks)	n	82	87
	mean	40.13	39.88
	s.d.	1.2	1.4
	range	36.9-42.3	36.0-42.1

[based on sponsor's Table 3.1 , Item 8, Vol.58, p. 367-369 and p. 058]

Patients' ages ranged from 18 to 40 with a mean age of 27 years in both treatment groups. The treatment groups were similar with respect to parity and gestational age. 81.7% of patients in the levobupivacaine group were primigravida compared to 78.2 % of the bupivacaine group. The mean gestational age for the levobupivacaine group was 40 .1 weeks and 39.8 weeks for the group.

The most common medical conditions reported were the following: pregnancy, childbirth and puerperium, injury and poisoning, and symptoms and signs and ill-defined conditions.

The overall medical histories at screening are described in the table below.

[3] Other – maltese, filipino, malaysian

Table 32. Medical History

TABLE III

Medical History at Screening (excluding surgical histories)
Summary Statistics: All Patients

ICD-9 Body System/Procedures in Medicine	Treatment			
	Levobupivacaine		Bupivacaine	
	N	%	N	%
Infectious and parasitic disease	3	3.7	4	4.6
Neoplasms	1	1.2	2	2.3
Endocrine, nutritional, metabolic, immunity	3	3.7	3	3.4
Blood and blood-forming organs	2	2.4	3	3.4
Mental disorders	3	3.7	4	4.6
Nervous system and sense organs	10	12.2	4	4.6
Circulatory system	3	3.7	2	2.3
Respiratory system	17	20.7	10	11.5
Digestive system	8	9.8	5	5.7
Genitourinary system	7	8.5	7	8.0
Pregnancy, child birth and puerperium	20	24.4	23	26.4
Skin and subcutaneous tissue	6	7.3	9	10.3
Musculoskeletal system and connective tissue	9	11.0	3	3.4
Congenital Anomalies	3	3.7	0	0
Symptoms, signs and ill-defined conditions	19	23.2	16	18.4
Injury and poisoning	17	20.7	18	20.7
Examination of special systems	1	1.2	0	0
Endoscopy	2	2.4	3	3.4
Physiological function tests	1	1.2	0	0
Motor vehicle traffic accidents	0	0	2	2.3

Note: Multiple diseases in the same body system have been counted once per patient

[Sponsor's Table III, "Medical History at Screening", Item 8, Vol. 1.58, p. 059]

Systemic hormonal preparations were the most common concomitant medications, taken by 83% of patients. 82% of patients took analgesics for labor pain and 56% of patients received antacids. See table below for the details.

Table 33. Concomitant Medications

TABLE V

Concomitant Medications Details
Summary Statistics: All Patients

	Treatment			
	Levobupivacaine		Bupivacaine	
	N	%	N	%
Alimentary tract and metabolism	46	56.1	49	56.3
Blood and blood forming organs	35	42.7	35	40.2
Cardiovascular system	2	2.4	4	4.6
Dermatologicals	1	1.2	2	2.3
Genito urinary system and sex hormones	24	29.3	22	25.3
Systemic hormonal preparations, excluding sex hormones	67	81.7	73	83.9
General antiinfectives for systemic use	27	32.9	26	29.9
Musculo-skeletal system	25	30.5	23	26.4
Central nervous system	70	85.4	68	78.2
Respiratory system	18	22.0	18	20.7
Sensory organs	2	2.4	0	0
Various	5	6.1	4	4.6
None	3	3.7	3	3.4

Note: Multiple medications in the same therapeutic class have been counted once per patient

[Sponsor's Table V, Item 8, Vol. 1.58, p.062]

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Measurement:

The primary measure of efficacy was the duration of pain relief following the first injection based upon the verbal rating scale. For the per-protocol population the duration of pain relief was defined as the time from the first painless contraction (i.e., 'unaware' or 'aware but not painful') until the time of the second successive painful contraction whether or not a 'top-up' injection was given. For the Intent-to-Treat population, the duration of pain relief was defined as the time from the first painless contraction until the next top-up injection.

1. Proportion of Patients Not Achieving Pain Relief

The sponsor reports that there, "...were a total of 29.4 % (20/68) of levobupivacaine patients that did not achieve pain relief from the first injection compared with 14.5% (10/69) of bupivacaine patients. The odds ratio (levobupivacaine/bupivacaine) was 0.40 (95% CI: 0.17, 0.96). This means that the odds of having pain relief after the first injection are estimated to be 0.40 times higher in the levobupivacaine group compared with bupivacaine. The Wald statistic for a treatment difference was statistically significant (p=0.039)."

The sponsor continues with the following conclusions, "A total of 26.7% (20/75) of levobupivacaine patients did not achieve pain relief from the first injection compared with 13.1% (11/84) of bupivacaine patients. The odds ratio (levobupivacaine/bupivacaine) was 0.37 (95% CI: 0.16, 0.84). This means that the odds of having pain relief after the first injection are estimated to be 0.37 times higher in the levobupivacaine group compared with bupivacaine. The Wald statistic for a treatment difference was statistically significant (p=0.018)."

Item 8, Vol. 1.58, p. 063-064]

a. *Excluding Patients with No Pain Relief*

The sponsor reports there to have been similar results of the analyses of the per-protocol and the Intent-to-Treat populations and therefore only discussed the results of the per-protocol population. "There was evidence of difference between centers (mean duration of pain relief being longest in Center 1 and the shortest in Center 2)", and between primigravida and multipara patients (i.e., primigravida patients recorded longer pain relief). "The median duration of pain relief following the first injection was 49 and 51 for levobupivacaine and bupivacaine, respectively. The treatment difference estimated as –4 minutes (90%CI: -13, 6). This means that on the average, the duration of pain relief is expected to be 4 minutes shorter following levobupivacaine compared with bupivacaine. As the 90% confidence interval lies within $\pm$ 20 minutes, the two treatments can be judged equivalent with respect to the duration of pain relief, in those patients achieving pain relief, following the first injection."

[Item 8, Vol. 1.58, p. 065]

b. Including Patients with No Pain Relief - – Per-Protocol Population

The results of the two analyses are similar, according to the sponsor, and therefore only the per-protocol results are presented. "The median duration of pain relief was 32 (range 0 to 129) and 45 (range 0 to 157) minutes for levobupivacaine and bupivacaine respectively. The treatment difference was estimated as –10 minutes (90% CI: -21, 0). This means that on average, the duration of pain relief is expected to be 10 minutes shorter following levobupivacaine compared with bupivacaine. As the 90% confidence interval contains zero, it cannot be ruled out that there is no difference between the two treatment groups, however as the confidence interval does not lie within the pre-defined equivalence criteria, the two treatments cannot be judged equivalent."

[Item 8, Vol. 1.58, p. 065]

Table 34. Analysis of Primary Efficacy Variable

TABLE 9.1.1

Duration of Pain Relief (min)
Statistical Analysis: Per-Protocol Population
(exc patients with no pain relief and non-evaluable injections)

TREATMENT	FIRST INJECTION					1ST TOP-UP				
	N	MEDIAN	DIFFERENCE[1]	LOWER 90% CONFIDENCE INTERVAL[2]	UPPER 90% CONFIDENCE INTERVAL[2]	N	MEDIAN	DIFFERENCE[1]	LOWER 90% CONFIDENCE INTERVAL[2]	UPPER 90% CONFIDENCE INTERVAL[2]
0.25% LEVOBUPIVACAINE	48	49				54	82			
0.25% BUPIVACAINE	59	51	-4	-13	6	50	76	-1	-15	12
SIGNIFICANCE LEVEL FROM GENERALISED WILCOXON MODEL FOR:										
TREATMENT EFFECT[3]					0.38					0.80
CENTRE EFFECT[3]					0.016					0.002
PARITY EFFECT[3]					0.013					0.080
TREATMENT x CENTRE INTERACTION					0.63					0.18

(1) Difference is defined as Levobupivacaine - Bupivacaine and calculated using non-parametric methods
(2) Non-parametric confidence intervals based on Mann-Whitney Test
(3) Significance level from model excluding treatment x centre interaction term

Note: Duration of pain relief defined as time from onset of pain relief until time of second consecutive painful contraction.
Non-evaluable injections are where a prohibited medication was given or top-up injection given afere two painful contractions

[Sponsor's Tables' 9.1.1, Item 8, Vol. 1.58, pp. 127]

Table 35. Analysis of Primary Efficacy Variable

TABLE 9.1.2

Duration of Pain Relief (min)
Statistical Analysis: Intent-to-Treat Population Excluding Patients with No Pain Relief

TREATMENT	FIRST INJECTION				
	N	MEDIAN	DIFFERENCE[1]	LOWER 90% CONFIDENCE INTERVAL[2]	UPPER 90% CONFIDENCE INTERVAL[2]
0.25% LEVOBUPIVACAINE	54	53			
0.25% BUPIVACAINE	73	58	-6	-14	2
SIGNIFICANCE LEVEL FROM GENERALISED WILCOXON MODEL FOR:					
TREATMENT EFFECT[3]					0.16
CENTRE EFFECT[3]					0.062
PARITY EFFECT[3]					0.20
TREATMENT x CENTRE INTERACTION					0.73

(1) Difference is defined as Levobupivacaine - Bupivacaine and calculated using non-parametric methods
(2) Non-parametric confidence intervals based on Mann-Whitney Test
(3) Significance level from model excluding treatment x centre interaction term

Note: Duration of pain relief defined as time from onset of pain relief until time of top-up.

Where patients had two painful contractions at end of pain relief but did not receive a top-up, duration of pain relief was taken as time from onset of pain relief until time of second consecutive painful contraction.

Where patients had one painful contractions at end of pain relief but did not receive a top-up, duration of pain relief was taken as time from onset of pain relief until time of first painful contraction.

Three patients [015 (Levobupivacaine) 133 ,9223 (Bupivacaine)] were withdrawn before the end of pain relief for the first injection and are therefore excluded from this analysis.

[Sponsor's 9.1.2, Item 8, Vol. 1.58, pp. 128]

Table 36. Analysis of Primary Efficacy Variable

TABLE 9.2.1

Duration of Pain Relief (min)
Statistical Analysis: Per-Protocol Population
(inc patients with no pain relief but exc non-evaluable injections)

TREATMENT	FIRST INJECTION					1ST TOP-UP				
	N	MEDIAN	DIFFERENCE[1]	LOWER 90% CONFIDENCE INTERVAL[2]	UPPER 90% CONFIDENCE INTERVAL[2]	N	MEDIAN	DIFFERENCE[1]	LOWER 90% CONFIDENCE INTERVAL[2]	UPPER 90% CONFIDENCE INTERVAL[2]
0.25% LEVOBUPIVACAINE	68	32				60	73			
0.25% BUPIVACAINE	69	45	-10	-21	0	52	75	-6	-21	8
SIGNIFICANCE LEVEL FROM GENERALISED WILCOXON MODEL FOR:										
TREATMENT EFFECT[3]					0.024					0.62
CENTRE EFFECT[3]					0.002					0.004
PARITY EFFECT[3]					0.002					0.068
TREATMENT x CENTRE INTERACTION					0.78					0.17

(1) Difference is defined as Levobupivacaine - Bupivacaine and calculated using non-parametric methods
(2) Non-parametric confidence intervals based on Mann-Whitney Test
(3) Significance level from model excluding treatment x centre interaction term

Note: Duration of pain relief defined as time from onset of pain relief until time of second consecutive painful contraction.
Non-evaluable injections are where a prohibited medication was given or top-up injection given afore two painful contractions
Patients with no pain relief have been included with a value of zero

Table 37. Analysis of Primary Efficacy Variable

TABLE 9.2.2

Duration of Pain Relief (min)
Statistical Analysis: Intent-to-Treat Population Including Patients with No Pain Relief

TREATMENT	FIRST INJECTION				
	N	MEDIAN	DIFFERENCE[1]	LOWER 90% CONFIDENCE INTERVAL[2]	UPPER 90% CONFIDENCE INTERVAL[2]
0.25% LEVOBUPIVACAINE	75	43			
0.25% BUPIVACAINE	84	53	-13	-23	-3
SIGNIFICANCE LEVEL FROM GENERALISED WILCOXON MODEL FOR:					
TREATMENT EFFECT[3]					0.005
CENTRE EFFECT[3]					<0.001
PARITY EFFECT[3]					0.022
TREATMENT x CENTRE INTERACTION					0.71

(1) Difference is defined as Levobupivacaine - Bupivacaine and calculated using non-parametric methods
(2) Non-parametric confidence intervals based on Mann-Whitney Test
(3) Significance level from model excluding treatment x centre interaction term

Note: Duration of pain relief defined as time from onset of pain relief until time of top-up.

Where patients had two painful contractions at end of pain relief but did not receive a top-up, duration of pain relief was taken as time from onset of pain relief until time of second consecutive painful contraction.

Where patients had one painful contractions at end of pain relief but did not receive a top-up, duration of pain relief was taken as time from onset of pain relief until time of first painful contraction.

Three patients (015 (Levobupivacaine) 133 ,9223 (Bupivacaine)) were withdrawn before the end of pain relief for the first injection and are therefore excluded from this analysis.

Patients with no pain relief have been included with a value of zero

[Sponsor's Tables 9.2.1 and 9.2.2, Item 8, Vol. 1.58 pp. 129 –130]

Table 38. Analysis of Primary Efficacy Variable

TABLE 9.3.1

Pain Relief

Duration of Pain Relief (min)

Summary Statistics: Per-Protocol Population

(Exc patients with no pain relief and non-evaluable injections)

	0.25% LEVOBUPIVACAINE		0.25% BUPIVACAINE	
	FIRST INJECTION	1ST TOP-UP	FIRST INJECTION	1ST TOP-UP
Mean	48.7	79.9	54.1	85.2
SD	29.8	43.1	33.4	39.7
Median	49	82	51	76
Min	3	3	7	22
Max	129	164	157	221
N	48	54	59	50

Table 39. Analysis of Primary Efficacy Variable

TABLE 9.3.2

Pain Relief

Duration of Pain Relief (min)

Summary Statistics: Intent-to-Treat Population

(Exc patients with no pain relief and non-evaluable injections)

	0.25% LEVOBUPIVACAINE		0.25% BUPIVACAINE	
	FIRST INJECTION	1ST TOP-UP	FIRST INJECTION	1ST TOP-UP
Mean	53.6	91.2	63.2	91.3
SD	26.7	39.5	34.6	38.4
Median	53	92	59	81
Min	5	8	9	26
Max	130	173	174	231
N	54	53	72	62

[Sponsor's Tables 9.3.1 and 9.3.2, Item 8, Vol. 1.58 pp. 131-132]

Table 40. Analysis of Primary Efficacy Variable

TABLE 9.3.3

Pain Relief
Duration of Pain Relief (min)
Summary Statistics: Per-Protocol Population
(Inc patients with no pain relief but exc non-evaluable injections)

	0.25% LEVOBUPIVACAINE		0.25% BUPIVACAINE	
	FIRST INJECTION	1ST TOP-UP	FIRST INJECTION	1ST TOP-UP
Mean	34.4	71.9	46.3	81.9
SD	33.5	47.5	36.5	42.3
Median	32	73	45	75
Min	0	0	0	0
Max	129	164	157	221
N	68	60	69	52

Table 41. Analysis of Primary Efficacy Variable

TABLE 9.3.4

Pain Relief
Duration of Pain Relief (min)
Summary Statistics: Intent-to-Treat Population
(Inc patients with no pain relief but exc non-evaluable injections)

	0.25% LEVOBUPIVACAINE		0.25% BUPIVACAINE	
	FIRST INJECTION	1ST TOP-UP	FIRST INJECTION	1ST TOP-UP
Mean	39.0	80.2	53.9	87.2
SD	33.9	47.5	40.1	42.5
Median	44	82	53	79
Min	0	0	0	0
Max	130	173	174	231
N	70	56	73	53

[Sponsor's Table 9.3.3 and 9.3.4., Item 8, Vol. 1.58, p. 133 and 134]

econdary Efficacy Measurement:

1. *Duration of Pain Relief Following the First Top-Up*

All non-evaluable injections, (i.e., those given study medication prior to two painful contractions were recorded or those which received prohibited medication) were excluded from the statistical analysis.

a. *Excluding Patients With No Pain Relief Following First Top-Up – Per-Protocol Population*

The sponsor has presented the results of the statistical analysis for the per-protocol population only, it is as follows: "The median duration of pain relief was 82 (range 3 to 164) and 76 (range 22 to 221) minutes for levobupivacaine and bupivacaine - respectively. The treatment difference was estimated as –1 minutes (90% CI: -15,12). This means that on average, the duration of pain relief is expected to be 1 minutes shorter following levobupivacaine compared with bupivacaine. As the 90% confidence interval contains zero, it cannot be ruled out that there is no difference between the two treatment groups."

b. *Including Patients With No Pain Relief Following First Top-Up – Per-Protocol Population*

The sponsor has only presented the results of the statistical analysis for the per-protocol population, it is as follows: "The median duration of pain relief was 73 (range 0 to 164) and 75 (range 0 to 221) minutes for levobupivacaine and bupivacaine respectively. The treatment difference was estimated as –6minutes (90% CI: -21,8). This means that on average, the duration of pain relief is expected to be 6 minutes shorter following levobupivacaine compared with bupivacaine. As the 90% confidence interval contains zero, it cannot be ruled out that there is no difference between the two treatment groups."

[Item 8, Vol. 1.58, p. 066 – 067]

Time to Onset of Pain Relief

The results of the statistical analysis for the per-protocol population showed that, "The median time to onset of pain relief following the first injection was 12 minutes for both the levobupivacaine and bupivacaine. The treatment difference was estimated as 0 minutes (90% CI: -2, 2). This means that on average, time to onset of pain relief is expected to be no different for levobupivacaine compare with bupivacaine.

The median time to onset of pain relief following the first top-up was 7 minutes for levobupivacaine and 6 minutes for bupivacaine. The treatment difference was estimated as 1 minute (90% CI: 0, 3). This means that on average, time to onset of pain relief is expected to 1 minute slower for levobupivacaine compared with bupivacaine. Because the 90% confidence interval includes zero, it cannot be ruled out that there is no difference in time to onset of pain relief between the two treatments."

3. Time Normalised Area under the VAS Score vs. Time Curve (AUC)

The sponsor used the following rules in the calculation of the time normalized AUC:

- Where patient was asleep or had recorded a 'painless' contraction on the verbal rating scale, all missing VAS scores were replaced as zero.
- VAS scores were not recorded when the patient started the second stage of labor, and missing VAS scores due to this were ignored.
- If the last score only was missing in error, it was ignored.
- Where all VAS scores were missing, no attempt was made to replace them.

a. First Injection

The sponsor's results of the statistical analysis for the 'per-protocol' population are as follows: "The geometric mean time normalised AUC (adjusted for baseline pain score) was 22.7 mm for levobupivacaine and 15.8 mm for bupivacaine following the first injection. The estimate of the treatment ratio (levobupivacaine/bupivacaine) was estimated as 1.44 (90% CI: 1.12, 1.85). This means that on average, time normalised AUC was 44% higher following levobupivacaine compared with bupivacaine."

b. First Top-Up

"The geometric mean time normalised AUC (adjusted for baseline pain score) was 7.3 mm for levobupivacaine and 6.6 mm for bupivacaine following the first top-up. The estimate of the treatment ratio (levobupivacaine/bupivacaine) was estimated as 1.09 (90% CI: 0.82, 1.45). This means that on average, time normalised AUC was 9% higher following levobupivacaine compared with bupivacaine."

[Item 8, Vol. 1.58, p. 068 – 070]

Table 42. Analysis of Secondary Efficacy Variable

TABLE 10.1

Time to Onset of Pain Relief (min)
Statistical Analysis: Per-Protocol Population
(exc patients with no pain relief and non-evaluable injections)

TREATMENT	FIRST INJECTION					1ST TOP-UP				
	N	MEDIAN	DIFFERENCE[1]	LOWER 90% CONFIDENCE INTERVAL[2]	UPPER 90% CONFIDENCE INTERVAL[2]	N	MEDIAN	DIFFERENCE[1]	LOWER 90% CONFIDENCE INTERVAL[2]	UPPER 90% CONFIDENCE INTERVAL[2]
0.25% LEVOBUPIVACAINE	48	12				54	7			
0.25% BUPIVACAINE	59	12	0	-2	2	50	6	1	0	3
SIGNIFICANCE LEVEL FROM GENERALISED WILCOXON MODEL FOR:										
TREATMENT EFFECT[3a]					0.91					0.14
CENTRE EFFECT[3a]					0.22					<0.001
PARITY EFFECT[3a]					0.013					0.96
TREATMENT x CENTRE INTERACTION					0.14					0.39

[1] Difference is defined as Levobupivacaine - Bupivacaine and calculated using non-parametric methods
[2] Non-parametric confidence intervals based on Mann-Whitney Test
[3a] Significance level from model excluding treatment x centre interaction term

Note: Non-evaluable injections are where a prohibited medication was given or top-up injection given afore two painful contractions

Table 43. Analysis of Secondary Efficacy Variable

TABLE 10.2

Pain Relief
Time to Pain Relief (min)
Summary Statistics: Per-Protocol Population
(Exc patients with no pain relief and non-evaluable injections)

	0.25% LEVOBUPIVACAINE		0.25% BUPIVACAINE	
	FIRST INJECTION	1ST TOP-UP	FIRST INJECTION	1ST TOP-UP
Mean	13.3	9.7	13.4	7.2
SD	7.5	7.5	8.4	3.6
Median	12	7	12	6
Min	5	1	2	2
Max	39	41	50	16
N	48	54	59	50

[Sponsor's Tables 10. 1 and 10.2, Item 8, Vol. 1.58, p137-8]

Table 44. Analysis of Secondary Efficacy Variable

TABLE 11.1

Time Normalised Area Under VAS x Time Curve (mm)
Statistical Analysis: Per-Protocol Population
(inc patients with no pain relief but exc non-evaluable injections)

TREATMENT	FIRST INJECTION					1ST TOP-UP				
	N	GEOMETRIC LSMEAN[1]	RATIO[2]	LOWER 90% CONFIDENCE INTERVAL	UPPER 90% CONFIDENCE INTERVAL	N	GEOMETRIC LSMEAN[1]	RATIO[2]	LOWER 90% CONFIDENCE INTERVAL	UPPER 90% CONFIDENCE INTERVAL
0.25% LEVOBUPIVACAINE	68	22.7				60	7.3			
0.25% BUPIVACAINE	69	15.8	1.44	1.12	1.85	52	6.6	1.09	0.82	1.45
SIGNIFICANCE LEVEL FROM ANCOVA:										
TREATMENT EFFECT[3]					0.018					0.60
CENTRE EFFECT[3]					0.094					<0.001
PARITY EFFECT[3]					0.014					0.58
TREATMENT x CENTRE INTERACTION					0.75					0.12

(1) LSMean is mean adjusted for any imbalance or covariate included in the model (ie baseline VAS)
(2) Ratio is defined as Levobupivacaine/Bupivacaine
(3) Significance level from model excluding treatment x centre interaction term

Note: VAS scale 0mm = no pain, 100mm = severe pain.

Non-evaluable injections are where a prohibited medication was given or top-up injection given afore two painful contractions

Table 45. Analysis of Secondary Efficacy Variable

TABLE 11.2

VAS Scores
Time Normalised Area Under the VAS x Time Curve (mm)
Summary Statistics: Per-Protocol Population
(inc patients with no pain relief and exc non-evaluable injections)

	0.25% LEVOBUPIVACAINE		0.25% BUPIVACAINE	
	FIRST INJECTION	1ST TOP-UP	FIRST INJECTION	1ST TOP-UP
Mean	27.18	13.54	19.64	8.99
Geometric Mean	18.46	7.00	12.41	4.79
SD	21.94	19.38	17.80	12.20
Median	23.19	8.12	13.50	5.26
Min	1.49	0.69	0.96	0.49
Max	100.00	100.00	68.44	65.99
N	68	60	69	52

[Sponsor's Tables 11. 1 and 11.2, Item 8, Vol. 1.58, p.139-140]

Proportion of Patients Recording Each Grade of Motor Block

a. First Injection

The sponsor reports that, 84% of levobupivacaine patients had no motor block following the first injection compared with 83% of bupivacaine patients. "The odds ratio (levobupivacaine/bupivacaine) was 0.95 (95% CI: 0.38, 2.33). This means that the odds of having increased motor block after the first injection are estimated to be 0.95 times higher in the levobupivacaine group compared with bupivacaine *(i.e.*, odds of having increased motor block after the first injection are estimated to be 1.06 times higher in the bupivacaine group compared with levobupivacaine). The Wald statistic for a treatment difference was not statistically significant p=0.90).

b. First Top-Up

Following the first top-up, 66% of levobupivacaine patients had no motor block compared with 63% of bupivacaine patients. The odds ratio (levobupivacaine/bupivacaine) was 0.90 (95% CI: 0.40, 2.01). This means that the odds of having increased motor block after the first top-up are estimated to be 0.90 times higher in the levobupivacaine group compared with bupivacaine *(ie:* the odds of having increased motor block after the first top-up are estimated to be 1.11 times higher in the bupivacaine group compared with levobupivacaine). The Wald statistic for a treatment difference was not statistically significant (p=0.80).

5. Sensory Block

No formal statistical analysis of sensory block was performed.

6. Overall Quality of Analgesia

No formal analysis of overall quality of analgesia recorded at 30 minutes post injection was performed. However, the sponsor has summarized the following study results: "Following the first injection, 51% of levobupivacaine patients had good analgesia, 26% had fair and 15% had poor analgesia compared with 67% good, 23% fair and 9% poor in the bupivacaine group. Eighty three percent of levobupivacaine patients had good analgesia following the first top-up compared with 88% in the bupivacaine group."

[Item 8, Vol. 1.58, p. 070-071]

REVIEWER'S EFFICACY DISCUSSION

The primary measure of efficacy was the duration of pain relief following the first injection based upon the verbal rating scale. For the Intent-to-Treat population, the duration of pain relief was defined as the time from the first painless contraction until the next top-up injection.

When evaluating the proportion of patients not achieving pain relief, the odds of having pain relief after the first injection are estimated to be 0.40 times higher in the levobupivacaine group compared with bupivacaine (p=0.039). In those patients achieving pain relief, the two treatments can be judged equivalent with respect to the duration of pain relief. The duration of pain relief is expected to be 4 minutes shorter following levobupivacaine compared with bupivacaine following the first injection.

The secondary efficacy analysis also shows that on average:

1. The time to onset of pain relief is expected to be no different for levobupivacaine compare with bupivacaine.

2. However, on average, time normalized AUC was 44% higher following levobupivacaine compared with bupivacaine. Because no data was present in the clinical section of NDA 20-997, the following excerpt from the statistical analysis of this secondary endpoint is provided: The levobupivacaine group had a significantly greater normalized area under the VAS score vs. time curve following the first injection than did the bupivacaine group - p=0.018 using ANOVA. The difference was not statistically significant after the first top-up.

3. The odds of having increased motor block after the first injection are estimated to be 0.95 times higher in the levobupivacaine group compared with bupivacaine. However, The Wald statistic for a treatment difference was not statistically significant p=0.90).

Overall, the clinical data shows that the product, 0.25% levobupivacaine, is effective when administered as an epidural infusion to obstetric patients in labor. This conclusion is based upon the clear evidence that patients experienced some level of analgesia sufficient for labor.

TUDY # 030433

PROTOCOL SYNOPSIS:

Title: "A Randomized Multicentre, Double-blind, Parallel Group Sequential Allocation Study to Determine the Minimum Effective Analgesic Concentration Levobupivacaine (S-enantiomer) Using Bupivacaine as a Control in Obstetric Patients Receiving Extradural Analgesia for Labour"

Primary Objective: "To determine the minimum local analgesic concentration (MLAC) of levobupivacaine when used in extradural analgesia."

Secondary Objective: "To evaluate the relative safety profiles of both formulations in the mother and the neonate."

[Item 8, Vol. 1.62, p. 013]

APPEARS THIS WAY
ON ORIGINAL

Study Design:

The study was designed as a randomized, single-center, double blind, 2-limb parallel group, up-down sequential allocation determination of the minimum local analgesic concentration (MLAC) of levobupivacaine versus bupivacaine when administered in the epidural space to women in labor.

Eligible patients were ASA Class I or II females between 18 and 40 years of age, of normal weight and height, at full-term normal pregnancy, i.e., ≥ 36 weeks gestational age, in cephalic presentation. Patients had a cervical dilation of ≤ 5 cm and a pre-dose visual analogue pain score of ≥ of 30 mm. They had no prior history of diabetes or other systemic illness, previous cesarean section, multiple pregnancies, opioid use in the prior 6 hours, local or general anesthesia in the preceding 24 hours, or participation in a clinical trial in the last 28 days.

Approximately 60 patients were randomized to receive levobupivacaine or bupivacaine in equal proportions. The first patient in each group received 0.07% study drug. This dose was based upon previous studies in which the MLAC of bupivacaine was estimated to be 0.065% [Note: The sponsor has provided no explanation for this dose determination]. The concentrations studied ranged from 0.05% to 0.11% for the levobupivacaine group and from 0.05% to 0.12% for the bupivacaine group.

The following algorithm was used to determine the concentration of study drug:

- Concentration for previous patient deemed to be effective – patient receives this dose reduced by 0.01%;
- Concentration for previous patient deemed to be ineffective – patient receives this dose increased by 0.01%;
- Concentration of study drug given to a previous patient deemed to be 'reject', (i.e., concentration of study drug as well as the rescue medication is ineffective) or concentration of drug given to a withdrawn patient – this patient receives the same concentration.

Following placement of the epidural catheter, 20 ml of study drug, (time 0 minutes) was injected over 5 minutes. Patients were then asked to record their pain of contractions using a 100 mm visual analogue scale (VAPS) at 5, 10, 15, 20, 25, 30, 45, 60 and 75 min after the injection or until an outcome was reached. These recordings were also taken before the epidural was administered. Further recordings were then taken at 15 min and 30 min post-rescue medication, if given.

At each time point, the use of Entonox (an equal mixture of nitrous oxide and oxygen) was also recorded. Any patient who recorded a visual analog score of ≤ 10 mm, continued to record the pain scores until the score returned to ≥ 30 mm and then was discontinued.
Please note Table 47. Schedule of Assessments below.

Table 46. Schedule of Assessments

SCHEDULE OF ASSESSMENTS - STUDY NUMBER: ICR 030433

Assessment	TIMEPOINT															
	Pre-Study	Immediately prior to Extradural	Extradural Injection	5min	10min	15min	20min	25min	30min	45min	60min	1hr 15min	15 mins post-rescue	30min post rescue	At 24 hours post-dose	Follow-up 3-7 days
Verbal Consent	X															
Written Consent									X*							
Screening Assessments	X															
Medical History & Physical Examination	X															
Visual Analogue Scale		X		X	X	X	X	X	X	X	X	X	X	X		
Assessment of Sensory Block									X					X		
Assessment of Motor Block									X ***					X		
Maternal Cardiovascular		X				X			X	X	X		X	X		
Foetal Heart Rate		X				X			X	X	X		X	X		
Adverse Events									X		X			X	X	X
Concomitant Medications	X										**X			X **		

Written consent will be obtained once the patient is comfortable.

* Concomitant medications to be recorded until 2 hours post dose or if related to an adverse event.

*** For 'effective' patients only.

NB. If an outcome of "effective" is reached, Visual Analogue Scale pain scores continue to be recorded until score returns to $\geq$30mm (until at least 30min post dose).

[Sponsor's Table, "Schedule of Assessments...", Item 8, Vol. 1.58, p 108]

four outcomes were defined:

- 'Effective' – VAPS ≤ 10 mm during contractions within 30 min of the study injection and without 'Entonox' being used;
- 'Ineffective' – VAPS > 10mm at all times during the 30 min following the study drug injection or until rescue medication was administered, whichever was soonest;
- 'Reject'- VAPS > 10mm at all times in the 30 min following the study drug injection and did not respond to rescue medication or a score of ≤ 10mm was recorded but this was associated with the use of Entonox;
- 'Withdrawal' – patient received non-study drug, failed to reach outcome, refused rescue, withdrew consent, was a protocol violator or technical failure.

If rescue medication was administered, further recordings were made 15 and 30 minutes later. Once an outcome was determined for a patient, they completed the study and were started on a standard analgesic regimen.

The extent of sensory block was determined by the 'pin-prick' method on the left and right sides after the injection and 30 min (± 10 min) after the administration of any rescue medication. Motor block was assessed for the right and left sides using the modified Bromage scale, where 0 = no paralysis and 3 = inability to move lower limb. This assessment was conducted only in patients whose outcome was determined to be 'effective', 30 min following the epidural injection. It was also taken 30 min after the administration of any rescue medication.

STATISTICAL ANALYSIS

"The primary objective of this study was to demonstrate that the 2 study drugs are equipotent with regard to pain relief, i.e., if it could be shown with some degree of statistical certainty that the true difference in minimum local analgesic concentration (MLAC) is unlikely to be greater than 25% of the MLAC for bupivacaine (i.e., 0.017%)."

"The formula of Dixon and Massey was used to derive the MLAC and the 95% confidence interval from the results of the sequential allocation. The difference between the MLAC for bupivacaine and levobupivacaine was calculated together with a 95% confidence interval for the difference. If the 95% confidence interval was contained within the 'acceptance range' of –0.017% to 0.017% bupivacaine then the 2 study drugs were to be judged as equipotent."

PROTOCOL AMENDMENT:

Amendment 1 dated 1/16/97 made the following changes:

A. Exclusion Criteria
- Include patients who have pre-eclampsia and have had a general or local anesthetic in the preceding 24 hours.

B. Inclusion Criteria
- Include a pre-dose VAS pain score of ≥ 30 mm.

C. Visual Analog Pain Score (VAPS)
- Patients will record their pain using visual analog scale immediately prior to the epidural irrespective of the number of previous contractions.

D. Assessments of Epidural Analgesia
- Entonox has been added to the list of pain treatments to be considered during the period of pain assessments, i.e., an outcome of effective means that the VAPS score was, "... ≤ 10 mm during contractions within 30 min of the study dug injection and without Entonox being used."

E. Sensory Block
- The sponsor has included a provision in the event of rescue medication administration: "...if a patient requires rescue medication, sensory block will also be measured at 30 min post-rescue (± 10minutes)."

F. Motor Block
- Assessments will only be made in "...those patients who have an outcome of effective. Those patients who require rescue medication will be assessed for motor block at 30 min post-rescue."

G. Monitoring
- All cardiovascular recordings will take place in the sitting position
  The normal range for fetal heart rate is declared as well as a descriptive term to be applied to heart rates outside of the normal range, i.e., fetal bradycardia or tachycardia

H. Adverse Events
- An additional time has been added to the schedule of follow-up evaluations, i.e., 24 hours post-dose.

I. Withdrawal
- Technical failure has been added to the list of withdrawal criteria

Additionally, the amendment call for changes in administrative issues concerning data management.

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 73 patients randomized, all 73 (100%) received study medication; however, only 60 patients were considered evaluable for efficacy. The remaining 13 patients were considered to be nonevaluable for the calculation of the minimum local analgesic concentration (MLAC). The number of unevaluable patients in each group was similar, i.e., 7 levobupivacaine patients and 6 bupivacaine patients. As this study was designed to determine the MLAC primarily, there is no intent-to-treat or per-protocol populations per say.

There was no intent-to-treat or per-protocol populations, A patient who took the same randomization number but prefixed with an 'A' replaced any patient who was withdrawn from the study. If that patient was replaced, the same number was used again but prefixed with a 'B', etc.

Table 47. Patient Disposition

TABLE II

Reasons for Withdrawal

Withdrawal Category	Reason for Withdrawal	Number of Patients	
		Levobupivacaine	Bupivacaine
Protocol violator	Weight >110 kg	0	1
	Age <18 years	0	2
	Breech Presentation	1	0
	Cervical dilation >5 cm	0	1
	Opiates administered in preceding 6 h	1	0
Failure to reach outcome	Failure to reach outcome	3	1
Other	Infusion started before outcome reached	1	0
	Incorrect rescue given	0	1
	Rescue administered with a falling VAS score	1	0
Total		7	6

[Sponsor's Table II, Item 8, Vol. 1.62, p. 034]

ere were patients who, despite being protocol violators, were not withdrawn and were considered to be evaluable. These include the following patients (Note: the sponsor's explanation for the discrepancy is seen italicized in parentheses):

- Patient A01 – weight > 110 kg (112 kg) *("Patient AO1 - should have been excluded from entering the study because she was >110kg (112kg). An upper weight limit of 110kg was set, however, this is an arbitrary figure which was selected purely for this study to standardise the population. This weight limit is not routinely used in anaesthetic practice. This patient was discussed once she had completed the study and it was agreed that because she was only 2kg above the maximum weight this would not make any difference to the absorption of the study medication and therefore she was classed as evaluable. (Patient 001 weighed 130kg and was withdrawn from the study by the investigator and replaced without discussing this with Chiroscience and Inveresk Research.")*

- Patient 012 received 0.01% levobupivacaine 1 hr outside the expiry time, Patient 014 received 0.01% levobupivacaine 1 hr 15 min outside the expiry time, and Patient 045 received 0.05% levobupivacaine 5 min outside the expiry time. *("Patients 12, 14 and 45 received expired study medication (5 min, 1 hour and 1 hour l5min outside expiry time respectively. A stability report provided by Chiroscience shows that there is no deterioration of 0.25% levobupivacaine in polypropylene syringes at 36 hours. Therefore, it was decided that these 3 patients should be included in the Minimum Local Analgesic Concentration (MLAC) calculation.")*

- Patients 008 and 056 experienced intravascular placement of the epidural catheter. *(Patients 8 and 56 had evidence of intravascular placement of the extradural catheter. However, in both cases the catheter was pulled back until clear of blood before the extradural bolus injection was given. The investigator was confident that the catheter was clear of the vein and in both cases both patients received good blocks, therefore these patients were included in the MLAC calculation.)*

- Patient 038 experienced catheter insertion at L1–L2 instead of L2-L3 or L3-L4(*"Patient 38 had the epidural catheter placed at L½ rather than L⅗ or L¾. It was agreed that this would only make a slight different to the block received (if any) and therefore the patient should be included in the MLAC calculation.")*

Table 48. Patient Disposition

	0.25% Levobupivacaine	0.25% Bupivacaine
Total Patients Randomized	37	36
Patients Evaluable for Safety	37(100%)	36(100%)
Patients Withdrawn:		
Protocol Violator	2	4
Failure to Reach Outcome	3	1
Other[1]	2	1
Evaluable Patients	30 (81%)	30 (83.3%)

[1] Other – infusion started before outcome reached; incorrect rescue given; rescue medication administered with a falling VAS score

.e sponsor has provided the following explanation of the use of the phrase, "failed to reach outcome", it is as ıollows: " 'Failed to reach an outcome' means that a patient is classed as a withdrawal because they do not fall into one of the three outcome categories defined in the protocol: 'Effective', 'Ineffective' or 'Reject'. If an outcome is not reached for a particular patient then the study drug and concentration that patient received is repeated by the next patient."

Patient specific protocol violations are summarized for individual patients in the table below.

Table 49. Patient - Specific Protocol Violations

PROTOCOL VIOLATION	TREATMENT	PATIENT NUMBERS
Protocol Violator	Levobupivacaine	003, 033
	Bupivacaine	001, 024, 042, 058
Failure to Reach Outcome	Levobupivacaine	027, 030, 044
	Bupivacaine	047
Infusion Started Before Outcome Reached	Levobupivacaine	034
	Bupivacaine	0
Rescue Administered With a Falling VAS Score	Levobupivacaine	A34
	Bupivacaine	0
Incorrect Rescue Given	Levobupivacaine	0
	Bupivacaine	051

Demographics

.ıe following table summarizes the demographic characteristics of the two treatment groups:

Table 50. Demographics - All Patients

TABLE 11.1

Demographics
Summary Statistics: All Patients

Treatment		Age (Years)	Height (cm)	Weight (kg)
LEVOBUPIVACAINE	Mean	26.92	162.81	75.93
	SD	5.07	6.39	12.25
	Min	18.0	150.0	50.0
	Max	35.0	180.0	99.0
	N	37	37	36
BUPIVACAINE	Mean	25.94	162.78	76.87
	SD	5.66	6.17	17.58
	Min	16.0	150.0	48.0
	Max	37.0	177.0	130.0
	N	36	36	36
ALL	Mean	26.44	162.79	76.40
	SD	5.35	6.24	15.05
	Min	16.0	150.0	48.0
	Max	37.0	180.0	130.0
	N	73	73	72

[Sponsor's Table 11.1 , Item 8, Vol.1.62, p. 208]

Table 51. Demographics - All Evaluable Patients

TABLE 11.2

Demographics
Summary Statistics: All Evaluable Patients

Treatment		Age (Years)	Height (cm)	Weight (kg)
LEVOBUPIVACAINE	Mean	26.80	163.03	75.43
	SD	5.05	6.67	12.48
	Min	18.0	150.0	50.0
	Max	35.0	180.0	99.0
	N	30	30	29
BUPIVACAINE	Mean	26.93	163.33	77.51
	SD	5.39	6.52	14.94
	Min	19.0	150.0	49.0
	Max	37.0	177.0	112.0
	N	30	30	30
ALL	Mean	26.87	163.18	76.49
	SD	5.18	6.54	13.71
	Min	18.0	150.0	49.0
	Max	37.0	180.0	112.0
	N	60	60	59

[Sponsor's Table 11.2 , Item 8, Vol.1.62, p. 209]

Patients' ages ranged from 16 to 37 years with a mean age of 26.4 years. The treatment groups were similar with respect to age, height and weight. The levobupivacaine group had a mean height of 162.8 cm (range 150 – 180 cm) and a mean weight of 75.9 kg (range 50 – 99 kg).

The bupivacaine group had a mean height of 162.8 cm (range 150 – 177 cm) and a mean weight of 76.9 kg (range 48 – 130 kg). The average cervical dilation for the levobupivacaine and bupivacaine groups was 2.83 cm (range 1.0 – 5.0 cm) and 3.1 cm (range 1.0 – 5.0 cm), respectively. The mean gestational age was 39.78 weeks (range 37.1 – 41.3 weeks) and 39.44 weeks (range 36.1 – 42 weeks) for the levobupivacaine and bupivacaine groups respectively. 70% of patients in the levobupivacaine group verses 53% of patients in the bupivacaine group were primigravida.

The most common medical conditions reported were "injury and poisoning", (Note: this category includes such conditions such as allergy) present in 32.95 of patients, pregnancy, childbirth and puerperium in 24.7% of patients, and respiratory system disorders in 20.5% of patients.

The overall medical histories at screening are described in the table below.

Table 52. Medical History

TABLE III

Medical History at Screening (excluding surgical histories)
Summary Statistics: All Patients

ICD-9 Body System/Procedures in Medicine	Treatment			
	Levobupivacaine		Bupivacaine	
	N	%	N	%
Infectious and parasitic disease	1	2.7	1	2.8
Endocrine, nutritional, metabolic, immunity	1	2.7	0	0
Blood and blood-forming organs	3	8.1	0	0
Mental disorders	4	10.8	2	5.6
Circulatory system	2	5.4	2	5.6
Respiratory system	6	16.2	9	25.0
Digestive system	1	2.7	3	8.3
Genitourinary system	5	13.5	6	16.7
Pregnancy, child birth and puerpenum	7	18.9	11	30.6
Skin and subcutaneous tissue	6	16.2	1	2.8
Musculoskeletal system and connective tissue	1	2.7	3	8.3
Symptoms, signs and ill-defined conditions	3	8.1	11	30.6
Injury and poisoning	13	35.1	11	30.6
Endoscopy	1	2.7	1	2.8
Chemical function tests	0	0	1	2.8

Note: Multiple diseases in the same body system have been counted once per patient

[Sponsor's Table III, "Medical History at Screening", Item 8, Vol. 1.62, p. 038]

The most common medication taken was for blood and blood forming organs, taken by 16.4% of patients, mainly for the treatment of anemia of pregnancy. The next most commonly taken medication was for the treatment of asthma and emesis, taken by 6.8% of patients. Heartburn was also a fairly common complaint with 5.5 % of patients taking medications for the alimentary tract and metabolism.

REVIEWER'S EFFICACY DISCUSSION:

The primary objective of this study was to demonstrate that the 2 study drugs are equipotent with regard to pain relief, i.e., the true difference in minimum local analgesic concentration (MLAC) is unlikely to be greater than 25% of the MLAC for bupivacaine (i.e., 0.017%). The MLAC values were estimated as 0.083% (95% CI 0.065, 0.101%) and 0.081% (95% CI 0.054, 0.109%) for levobupivacaine and bupivacaine, respectively. As the 95% confidence interval did not lie within the 'equivalence range' of $\pm$ 0.017%, the 2 study drugs were not deemed equivalent with respect to the MLAC.

Additionally, the potency of levobupivacaine relative to bupivacaine was estimated as 0.98 (95% CI 0.58, 1.38) *i.e.*, on average levobupivacaine is 2% less potent than bupivacaine.

The results of the statistical analysis of sensory and motor block were reported as percentages only without p-values to determine significance.

Of concern is the seemingly arbitrary and possibly biased judgement of protocol violations. Patients who clearly fell outside of the inclusion criteria were in some cases withdrawn and in other cases not withdrawn from analysis of MLAC.

Overall, the clinical data shows that the product, levobupivacaine, is effective when administered as an epidural infusion to obstetric patients in labor. This conclusion is based upon the clear evidence that patients experienced some level of analgesia sufficient for labor. It failed, however, to prove that the MLAC of the two drugs was equally efficacious.

STUDY # 006175

PROTOCOL SYNOPSIS:

Title: "A Randomized Multicentre, Double-blind, Parallel, Group Study to Evaluate the Dose Response, Safety and Kinetics of 15 ml of 0.5% and 0.75% Levobupivacaine (S-enantiomer) with 15 ml of 0.5% Bupivacaine (racemic mixture) in Patient Undergoing Elective Surgery Under Epidural Anaesthesia"

Primary Objective: To compare the efficacy (duration and onset of anesthesia) of two different concentrations of levobupivacaine (0.5% and 0.75%) with 0.5% racemic bupivacaine.

Secondary Objective: To determine the plasma concentration and safety profiles of 0.5% and 0.75% levobupivacaine and 0.5% bupivacaine

[Item 8, Vol. 1.63, p. 012]

Study Design:

The study is designed as a randomized, multi-center, double blind, 3-limb parallel group, study of the efficacy, safety and plasma concentration of 0.5% and 0.75% levobupivacaine and 0.5% bupivacaine administered epidurally to patients undergoing elective lower limb vascular surgery or arthroscopy. Ninety-six patients were randomized on a 1:1:1 basis.

Eligible patients underwent a brief screening phase, followed by 1:1:1 randomization to receive either 0.5% or 0.75% levobupivacaine or 0.5% bupivacaine via epidural catheter for lower limb surgery.

Group I	0.5% levobupivacaine
Group II	0.75% levobupivacaine
Group III	0.5% bupivacaine

Eligible patients were ASA Class I or II females over the age of 18 undergoing uncomplicated elective lower limb vascular surgery or arthroscopy which was considered to be appropriate for the use of epidural anesthesia. Patients were neither pregnant nor lactating, had no prior history of systemic illness, had no history of alcohol or drug abuse in previous 6 months, nor had participated in a clinical trial in the last 3 months.

On dosing day, patients received pre-medication of up to 20 mg of temazepam (orally) approximately 60 min before entering the operating room. Upon completion of the epidural procedure, a total of 15 ml of study drug was administered (time 0). Initially, a test dose of study drug was administered. If after 5 minutes, there was no evidence of intravascular or subarachnoid injection, a further 12 ml of study drug was administered in three increments of 4ml each lasting 15 seconds and with an interval of 1 minute between increments.

Additionally, sedation was provided using a propofol infusion which could be increased to induce general anesthesia in the event of an inadequate block (fentanyl co-administered as needed for pain).

Assessment of level of sensory block was measured using the blunt end of a 27 gauge needle at 2, 5, 10, 15, 20, 25, and 30 min and then every 30 min until the complete reversal of block. The time of onset of the block was defined as the time when the first analgesia to pinprick was detected. The duration of the block was defined as the time from onset of block to the complete return of painful sensation.

The investigator used the modified Bromage scale (0 = no paralysis, 1= inability to raise extended leg, 2 = inability to flex knees, 3 = inability move lower limb) to assess level of motor blockade at 2, 5, 10, 15, 20, 25 and 30 and then every 30 min until full return of motor power. An overall assessment of the quality of block was made by the anesthesiologist and surgeon during the operation using the following criteria: 0 = failure 1 = unsatisfactory block and 2 = complete block.

STATISTICAL ANALYSIS

The intent-to–treat population was defined as all randomized patients excluding those who (1) did not receive study drug (Note: 8 patients withdrew before dosing and were not included in this analysis) or (2) experienced an intravascular or subarachnoid injection of study drug (Note: no patients fell into this category). The per-protocol population was defined as all Intent-to-Treat patients excluding those who received a non-protocol anesthetic (Note: 7 patients were excluded from the per-protocol population).

The primary efficacy variable in this study was defined as the duration of block, i.e., from when the first analgesia to pinprick was detected to return of sensation in all dermatomes, using the Intent-to-Treat population. In the event of need for a general anesthetic, the duration of block was redefined as the time from onset of sensory block to the time of intervention. [Note: At the request of the sponsor, after the study blind was broken, the definition of sensory and motor block were revised as follows: ...time to onset of sensory/motor block until complete return of sensation/function *irrespective of whether or not a general anesthetic was given.*]. Any patient who did not achieve a block was excluded from the statistical analysis.

"The duration of block was analysed using analysis of variance techniques (ANOVA) with terms for treatment, centre and treatment by centre interaction. Using the error variance from the ANOVA, pairwise comparisons of the 3 treatments were made using Student's 't'-tests. To compensate for multiple comparisons, a sequentially rejective Bonferroni-Holm method was used. Estimates of treatment differences and the associated 95% confidence intervals were calculated. This analysis was performed for left and right sides separately."

The secondary efficacy response variables were analysed using ANOVA (on left and right sides separately) and are defined as follows:

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

"For the overall assessment of the quality of block, scores of 0 (failure) and 1 (unsatisfactory or partial block) were considered treatment failures and a score of 2 (complete block) as a treatment success. This derived endpoint was analysed using logistic regression."

[Item 8, Vol. 1.63, pp. 024 –028]

The following additional endpoints were statistically analysed for the "intent-to-treat" population only:

1. "Maximum height and time to maximum height of sensory block over all assessments for both sides combined. For each side separately, the height of block at each assessment was taken as the highest dermatome to achieve sensory block. Where the height differed for the left and right sides, the mean height was calculated and used in the analyses. For the purposes of analysis, scores were assigned to each dermatome as follows: score of I to dermatome C1, 2 to dermatome C2, ..., 29 to dermatome S4 and 30 to dermatome S5. The spread of the sensory block at each assessment has been illustrated graphically using treatment group medians and their respective interquartile range."

2. "Time to onset and duration of block at the following dermatomes: S5, S3, SI, L5, L2, T12, T10, T8, T6 and T4. Time to onset and time to return of sensation in each of the dermatomes (offset time) was calculated for each side separately. Where onset (or offset) times differed between sides, the mean onset (or offset) time was used in the analysis. Duration of block for each dermatome was taken as the time from the mean onset time until the mean offset time. In order for a block to be considered to have reached a dermatome, the dermatome must have been blocked on both sides for at least one assessment (not necessarily the same assessment). Time to onset and duration of sensory block have been illustrated graphically using treatment group medians and their respective interquartile range."

3. "Time to onset and duration of each grade of motor block. As with the sensory block, mean onset and offset times were used where times differed between sides. Time to onset and duration of motor block have been illustrated graphically using treatment group medians and their respective interquartile range."

"In the calculation of the above endpoints, all strictly unilateral blocks *(i.e.,* no block attained on one side) were excluded from the analyses. In the event of a general anesthetic being used before onset of block, the patient was excluded from the analyses. All the above additional endpoints were analysed using a Kniskal-Wallis non-parametric analysis of variance. Pairwise comparisons between treatments were performed using a 'Z'-test. To compensate for multiple comparisons, a sequentially rejective Bonferroni-Holm method was used. Treatment group medians have been presented together with the range and significance level of the 'Z'-tests. For the purposes of these analyses, data from all 3 centres were combined."

"In addition to these analyses, the proportion of patients responding at each grade of motor block were compared between treatment groups using a chi-squared test. Contrary to the methods outlined in the clinical protocol, for consistency with the other analyses, the data from the left and right side were combined before analysis."

[Item 8, Vol. 1.63, pp. 027-028]

PROTOCOL AMENDMENT:

Amendment 1 dated 2/23/95, Amendment 2 dated 3/24/95 and Amendment 3 dated 3/15/96 made the following changes:

A. Efficacy Analysis
- After the blinding was broken, the sponsor requested the analysis of the duration of sensory and motor block to be performed irrespective of whether or not a general anesthetic had been performed. The sponsor has added a statement regarding this change.

B. Additional Endpoints
- The sponsor has requested additional endpoints to be statistically analyzed for the Intent-to-Treat population. They are the following:
  - Maximum height and time to maximum height of sensory block over all assessments
  - Time to onset and duration of block
  - Time to onset and duration of each grade of motor block

Additionally, the amendments call for changes in administrative issues concerning data management.

APPEARS THIS WAY
ON ORIGINAL

CONDUCT OF STUDY

Patient Distribution/Disposition:

Of the 96 patients randomized, 88 (91.7%) received study medication and were considered to be evaluable for the safety analyses. No further withdrawals occurred, leaving the total population for the Intent-to-Treat analysis at 88. However, there were 7 patients eliminated from the per-protocol population, resulting in a total per-protocol analysis population of 81. Please see the sponsor's table below.

Table 55. Population Disposition

TABLE L1.1

Efficacy Evaluation Population

STUDY ENROLMENT/EVALUATION	0.5% LEVOBUPIVACAINE	0.75% LEVOBUPIVACAINE	0.5% BUPIVACAINE	TOTAL
Total Enroled	32	33	31	96
Patients withdrawn prior to dosing	3	3	2	8
Total Dosed	29	30	29	88
Patients eliminated from intent-to-treat analysis	0	0	0	0
Total evaluated for intent-to-treat analysis	29	30	29	88
Patients eliminated from the per-protocol analysis	2	4	1	7
Total evaluated for per-protocol analysis	27	26	28	81

[Sponsor's Table L1.1, "Efficacy Evaluable Population", p. 354]

Patient specific protocol violations are summarized in the table below.

Table 56. Patient-Specific Protocol Violations

TABLE L1.2

Efficacy Evaluation Populations
Patients Excluded from Per-Protocol Analysis

Patient	Treatment	Patients withdrawn prior to dosing
025	3	Did not meet inclusion criteria - no adequate contraception
056	1	Patient withdrew consent
061	2	Failed epidural - drug not given
068	2	Did not meet inclusion criteria - first degree heart block
072	3	Operation postponed for surgical reasons
085	2	Dural tap ie failed epidural technique
094	1	Operation cancelled due to intercurrent illness - hypertension
104	1	List over-ran, operation cancelled by surgeons
		Patients eliminated from the per-protocol analysis
026	1	Nitrous oxide general anaesthetic
039	2	Nitrous oxide general anaesthetic
043	3	Bupivacaine infiltration into wound
044	2	Nitrous oxide general anaesthetic
058	1	Nitrous oxide general anaesthetic
070	2	Nitrous oxide general anaesthetic
078	2	Nitrous oxide general anaesthetic

Key for Treatment
1 = 0.5% Levobupivacaine
2 = 0.75% Levobupivacaine
3 = 0.5% Bupivacaine

[Sponsor's Table L1.2, "Efficacy Evaluable Population", Item 8, Vol. 1.58, p. 355]

Table 57. Treatment Details – All Patients

TABLE L1.3

Treatment Details
Enrolment by Centre
Summary Statistics: All Patients

Centre	0.5% LEVOBUPIVACAINE		0.75% LEVOBUPIVACAINE		0.5% BUPIVACAINE		TOTAL	
	N	%	N	%	N	%	N	%
1	16	33	16	33	16	33	48	50
2	5	31	6	38	5	31	16	17
3	11	34	11	34	10	31	32	33
TOTAL	32	33	33	34	31	32	96	100

[Sponsor's Table L1.3 "Treatment Details", Item 8, Vol. 1.58, p. 356]

A number of assessments were not performed according to protocol, these include the following: nerve block, vital signs, pharmacokinetic, ECG and clinical laboratory data. These were recorded as protocol violations.

Demographics

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

Table 58. Demographics - All Patients

TABLE K1.1.1

Demographic Data
Summary Statistics: All Patients

		Treatment			
		0.5% LEVOBUPIVACAINE	0.75% LEVOBUPIVACAINE	0.5% BUPIVACAINE	All Patients
Age (Years)	Mean	47.00	46.70	48.52	47.39
	SD	14.70	13.82	15.75	14.62
	Min	20.0	24.0	19.0	19.0
	Max	75.0	76.0	80.0	80.0
	N	32	33	31	96
Height (cm)	Mean	166.19	165.12	169.42	166.86
	SD	9.79	9.68	11.18	10.28
	Min	150.0	150.0	151.0	150.0
	Max	186.0	182.0	190.0	190.0
	N	32	33	31	96
Weight (kg)	Mean	71.28	71.01	74.65	72.28
	SD	15.86	15.00	14.32	15.01
	Min	45.0	45.0	48.0	45.0
	Max	128.2	99.0	110.0	128.2
	N	32	33	31	96
MALE	N	12	9	14	35
FEMALE	N	20	24	17	61

[Sponsor's Table K1.1.1"Demographic Data", Item 8, Vol. 1.58, p.229.]

Of the 96 patients total recruited, 35 (36.5%) were male and 61(63.5%) were female with a mean age of 47.39 years (range 19-80 years, SD = 14.62).

For the 'intent-to-treat' population analysis - a total of 88 patients – there were 31(35%) males and 57 (65%) females, of mean age 47.24 years (range 19-80 years, SD = 14.44) considered. This group had a mean of 166.81 cm (SD 10.31) and a mean weight of 72.26 kg (SD = *14.75)*.The whole study group had a mean height of 166.86 cm (SD = 10.28) and a mean weight of 72.28kg (SD 15.01).

Of the twenty nine patients who received 0.5% levobupivacaine, 30 patients who received 0.75% levobupivacaine and 29 who received 0.5% bupivacaine, the 0.5% levobupivacaine group had a mean age of 46.34 years (range 20-75 years, SD = 14.70),mean height of 166.34 cm (SD 10.16) and mean weight of 72.10 kg (SD 15.28). The 0.75% levobupivacaine group had a mean age of 45.53 years (range 24-74 years, SD = 13.38), mean height of 165.20 cm (SD = 9.57) and mean weight of 70.04 kg (SD = 14.52). The 0.5% bupivacaine group had a mean age of 49.90 years (range 19-80 years, SD = 15.34), mean height of 168.93 cm (SD = 11.18) and mean weight of 74.73 kg (SD = 14.58).

Of the total of 81 patients who were considered for the 'per-protocol' population analysis, 27 (33%) were male and 54 (67%) were female and had a mean age of 47.86 years (range 19-80 years, SD = 14.52). This group had a mean height of 166.02 cm (SD = 9.76) and a mean weight of 71.47 kg (SD-13.36).

Please see the sponsor table below for the statistical analysis.

Table 59. Demographic Data – Intent-to-Treat Population

TABLE K1.1.2

Demographic Data
Summary Statistics: Intent-to-Treat Population

		Treatment			
		0.5% LEVOBUPIVACAINE	0.75% LEVOBUPIVACAINE	0.5% BUPIVACAINE	All Patients
Age (Years)	Mean	46.34	45.53	49.90	47.24
	SD	14.70	13.38	15.34	14.44
	Min	20.0	24.0	19.0	19.0
	Max	75.0	74.0	80.0	80.0
	N	29	30	29	88
Height (cm)	Mean	166.34	165.20	168.93	166.81
	SD	10.16	9.57	11.18	10.31
	Min	150.0	150.0	151.0	150.0
	Max	186.0	182.0	190.0	190.0
	N	29	30	29	88
Weight (kg)	Mean	72.10	70.04	74.73	72.26
	SD	15.28	14.52	14.58	14.75
	Min	51.0	45.0	48.0	45.0
	Max	128.2	99.0	110.0	128.2
	N	29	30	29	88
MALE	N	10	8	13	31
FEMALE	N	19	22	16	57

[Sponsor's Table K1.1.1 "Demographic Data", Item 8, Vol. 1.58, p. 230]

Medical History

"The most commonly reported medical conditions were circulatory system disorders, present in 96.9% of patients, and musculoskeletal and connective tissue disorders, present in 36.5% of patients. Varicose veins were reported by 93.8% of patients and peripheral vascular disease by 5.2% of patients. Pain, arthritis and general disorders of the knee were recorded by 16.7% of patients."

[Item 8, Vol. 1.62, p. 036]

Table 60. Medical History

Table III
Concomitant Diseases and Medical Histories (excluding surgical histories): All Patients

Concomitant diseases and previous medical histories: classified by ICD-9 groupings where possible	Number of Patients		
	0.5% Levobupivacaine	0.75% Levobupivacaine	0.5% Bupivacaine
Infectious and parasitic disease	3	0	2
Neoplasms	3	7	4
Endocrine, nutritional, metabolic and immune system	3	2	2
Blood and blood-forming organs	2	2	1
Mental disorders	6	9	3
Nervous system and sense organs	6	9	10
Circulatory system	31	33	29
Respiratory system	9	9	12
Digestive system	7	12	12
Genitourinary system	4	7	9
Pregnancy, child birth and puerperium	3	2	0
Skin and subcutaneous tissue	10	11	5
Musculoskeletal and connective tissue	11	11	13
Congenital anomalies	1	1	1
Symptoms, signs and ill-defined conditions	9	10	11
Injury and poisoning	18	13	6

Note: Multiple diseases in the same body system have been counted once per patient.

[Sponsor's Table III. "Concomitant Diseases and Medical Histories..." Item 8, Vol. 1.63, p. 034]

Concomitant Medication

The majority of patients randomized took medications prior to being recruited. Specifically, a total of 63 patients, 17 in the 0.5% levobupivacaine group, 22 in the 0.75% levobupivacaine group and 24 in the 0.5% bupivacaine group, took concomitant medication in the 3 months before screening.

Central nervous system medications represented the most commonly taken medication i.e., 20.8% of patients. These included analgesics, anxiolytics and hypnotics. Cardiovascular medications, taken by 17.7% of patients, were mainly for control of hypertension, fluid retention and anxiety. In addition, 14.6% of patients were taking oral contraceptives or hormone replacement therapy at screening.

Table 61. Concomitant Medications

TABLE V

Concomitant Medications Details
Summary Statistics: All Patients

	Treatment			
	Levobupivacaine		Bupivacaine	
	N	%	N	%
Alimentary tract and metabolism	46	56.1	49	56.3
Blood and blood forming organs	35	42.7	35	40.2
Cardiovascular system	2	2.4	4	4.6
Dermatologicals	1	1.2	2	2.3
Genito urinary system and sex hormones	24	29.3	22	25.3
Systemic hormonal preparations, excluding sex hormones	67	81.7	73	83.9
General antiinfectives for systemic use	27	32.9	26	29.9
Musculo-skeletal system	25	30.5	23	26.4
Central nervous system	70	85.4	68	78.2
Respiratory system	18	22.0	18	20.7
Sensory organs	2	2.4	0	0
Various	5	6.1	4	4.6
None	3	3.7	3	3.4

Note: Multiple medications in the same therapeutic class have been counted once per patient

[Sponsor's Table V, "Concomitant Medications", Item 8, Vol. 1.58, p. 062]

Premedication, Sedation and General Anesthesia

Premedications given included temazepam, (up to 20 mg; 77.3% of the intent -to-treat population) and in one case (Patient 034), 10 mg of metoclopramide was given in addition to the authorized 20 mg temazepam.

Protocol–driven sedation or anesthesia was given to 79.5% of the intent-to-treat population. This includes the 78.4% of patients who received propofol and the 22.7% who received fentanyl. However, nitrous oxide, enflurane, isoflurane, morphine or atracurium were given to Patients 026, 039, 044, 058, 070 and 078 who, therefore, were excluded from the per-protocol population.

Similar percentages of patients were given general anesthesia or sedation in each treatment group; 24.1% and 55.2% (respectively) in the 0.5% levobupivacaine group, 26.7% and 53.3% (respectively) in the 0.75% levobupivacaine group and 17.2% and 62.1% (respectively) in the 0.5% bupivacaine group.

All patients were given dose increments as per the protocol except for 13 patients with a 1-min discrepancy and one patient with a 4-min discrepancy.

SPONSOR'S EFFICACY RESULTS:

Primary Efficacy Measurement:

In addition to the 15 patients withdrawn (8 patients from the Intent-to-Treat population and 7 from the per-protocol population) an additional 4 randomized patients were excluded from the efficacy analysis. These patients include three patients (003, 071, and 088) who received a general anesthetic before onset of block on both sides. These patients were excluded from all statistical analyses on the unblocked side but were included in the overall assessment of block. This also applied to Patient 058 who was already excluded from the per-protocol population.

The fourth patient excluded from the efficacy analysis is Patient 074 who had a strictly unilateral block and was excluded from all the analyses requested by the Sponsor after the study blindness was broken. This also applied to Patient 070 who was already excluded from the per-protocol population.

Time to Onset and Duration of Block

Sensory Block: Intent-to-Treat Population

The sponsor reports that the, "...number (%) of patients not attaining a 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. The number (%) of patients not attaining a block on their right side were 2 (7%), 1(3%) and 2 (7%) for 0.5% levobupivacaine, 0.75% levobupivacaine and 0.5% bupivacaine respectively. All patients who did not attain a sensory block were excluded from the corresponding analysis.

There were no significant differences between the 3 treatments in terms of mean duration of sensory block or time to onset of sensory block for either left or right sides. Revised duration of sensory block (i.e, time from onset of sensory block until complete return of sensory touch, irrespective of whether or not a general anesthetic was given) was found, on average, to be significantly longer for the 0.75% levobupivacaine treated group compared with the 0.5% levobupivacaine and 0.5% bupivacaine groups. This effect was statistically significant for both the left and right sides."

[Item 8, Vol. 1.63, pp. 039-040]

Table 62. Analysis of Primary Efficacy Measurement

Table VII
Mean Duration, Revised Duration and Time to Onset of Sensory Block (min)
Intent-to-Treat Population

Sensory Block	Treatment					
	0.5% Levobupivacaine		0.75% Levobupivacaine		0.5% Bupivacaine	
	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side
Duration	323.5	304.5	359.3	359.8	280.5	280.7
Revised duration	377.4	368.7	459.7	471.0	344.8	337.2
Time to onset	7.8	8.0	6.4	7.0	6.7	6.1
Number of patients analysed	25	27	28	29	28	27

Table 63. Analysis of Secondary Efficacy Measurement

Table VIII
Mean Duration, Revised Duration and Time to Onset of Motor Block (min)
Intent-to-Treat Population

Motor Block	Treatment					
	0.5% Levobupivacaine		0.75% Levobupivacaine		0.5% Bupivacaine	
	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side
Duration	135.6	171.0	222.1	207.5	161.5	168.7
Revised duration	185.3	204.8	255.9	255.0	191.6	185.0
Time to onset	24.7	25.9	27.2	31.4	16.8	17.5
Number of patients analysed	15	13	23	22	19	20

[Sponsor's Tables 7 and 8, Item8, Vol. 1.63, p. 039-041]

Motor block: Intent-to-Treat Population

The sponsor reports the following results: "The number (%) of patients not attaining a motor block on their left side were 14 (48%), 7 (23%) and 10 (34%) for 0.5% levobupivacaine, 0.75% levobupivacaine and 0.5% bupivacaine respectively. The number (%) of patients not attaining a motor block on their right side were 16 (55%), 8 (27%) and 9 (31%) for 0.5% levobupivacaine, 0.75% levobupivacaine and 0.5% bupivacaine respectively. All patients who did not attain a motor block were excluded from the corresponding analysis."

"There were no significant differences between the 3 treatments in terms of mean revised duration of motor block or time to onset of motor block for both sides. In the case of duration of motor block, the 0.75% levobupivacaine treated group was found, on average, to have longer duration of motor block compared with 0.5% levobupivacaine. However, this effect was statistically significant for the left side only."

Sensory Block: Per-Protocol Population

According to the sponsor, "The number (%) of patients not attaining a sensory block on their left side were 3 (11%), 1(4%) and 1(4%) for 0.5% levobupivacaine, 0.75% levobupivacaine and 0.5% bupivacaine respectively. The number (%) of patients not attaining a sensory block on their right side were 2 (7%), 1(4%) and 2 (7%) for 0.5% levobupivacaine, 0.75% levobupivacaine and 0.5% bupivacaine respectively. All patients who did not attain a sensory block were excluded from the corresponding analysis.

Duration and revised duration of sensory block were found, on average, to be significantly longer in the 0.75% levobupivacaine treated patients compared with both 0.5% levobupivacaine and 0.5% bupivacaine treated groups. This effect was seen in both left and right sides. There were no significant differences between the 3 treatments in terms of mean time to onset of sensory block for both sides.

Motor Block: Per-Protocol Population

The sponsor reports that, "The number (%) of patients not attaining a motor block on their left side were 13 (48%), 4 (15%) and 10 (36%) for 0.5% levobupivacaine, 0.75% levobupivacaine and 0.5% bupivacaine respectively. The number (%) of patients not attaining a motor block on their right side were 15 (56%), 6 (23%) and 8 (29%) for 0.5% levobupivacaine, 0.75% levobupivacaine and 0.5% bupivacaine respectively. All patients who did not attain a motor block were excluded from the analysis."

"Duration of motor block was found, on average, to be significantly longer in the 0.75% levobupivacaine treated group compared with 0.5% levobupivacaine. However, this effect was statistically significant for the left side only."

'There were no significant differences between the 3 treatments in terms of revised duration and time to onset of motor block for either left or right sides.'

[Item 8, Vol. 1.63, p. 040 - 042]

Overall Assessment of Block

The sponsor reports there to have been no evidence of a statistically significant difference in the success rates between treatment for either population.

Maximum Height of Sensory Block and Time to Maximum Height

According to the sponsor, "These analysis were performed on the "intent-to-treat" population only. Patients with a unilateral block or who did not attain a block were excluded from these analyses. There was no evidence of a statistically significant difference in either maximum height of block or time to maximum height between the 3 treatments."

Time to Onset and Duration of Block at Various Dermatomal Levels

According to the sponsor, "Time to onset and duration of block were calculated for the following dermatomes only: S5, S3, S1, L5, L2, T12, T10, T8, T6 and T4. Patients who did not attain a block or who had a unilateral block were excluded from the analyses. There was no evidence of any significant differences in time to onset between the 3 treatments for any of the dermatomes considered. Duration of sensory block at S3, S1 and L5 was, on average, significantly longer for the 0.75% levobupivacaine treated group compared with 0.5% bupivacaine."

Time to Onset and Duration of Each Grade of Motor Block

According to the sponsor, "Time to onset and duration of block were calculated for each grade of motor block. For the purposes of the statistical analysis and summary tables, only patients attaining the grade of interest were considered. All unilateral blocks were excluded. Only 2 patients (both in the 0.5% levobupivacaine treated group) reached motor grade 3. As a result, the data for Grade 3 were not analysed. There was no evidence of any significant differences in either time to onset or duration of block between the 3 treatments for motor grades 1 and 2."

Number of Patients Responding at Each Grade of Motor Block

According to the sponsor, "There was no evidence of a significant difference in response rates between the 3 treatment groups for each grade of motor block."

[Item 8, Vol, 1.63, p.041-046

Table 64. Analysis of Secondary Efficacy Measurement

Table IX
Mean Duration, Revised Duration and Time to Onset of Sensory Block (min)
Per-Protocol Population

Sensory Block	Treatment					
	0.5% Levobupivacaine		0.75% Levobupivacaine		0.5% Bupivacaine	
	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side
Duration	335.5	324.8	399.2	413.2	287.7	288.2
Revised duration	374.5	371.8	451.0	459.1	337.7	335.3
Time to onset	8.0	7.4	6.2	6.5	6.7	6.2
Number of patients analysed	24	25	25	25	27	26

Table 65. Analysis of Secondary Efficacy Measurement

Table X
Mean Duration, Revised Duration and Time to Onset of Motor Block (min)
Per-Protocol Population

Motor Block	Treatment					
	0.5% Levobupivacaine		0.75% Levobupivacaine		0.5% Bupivacaine	
	Left Side	Right Side	Left Side	Right Side	Left Side	Right Side
Duration	142.6	182.2	231.5	225.7	166.3	168.7
Revised duration	181.8	202.3	256.4	251.5	191.4	185.0
Time to onset	26.1	27.7	27.3	33.5	16.9	17.5
Number of patients analysed	14	12	22	20	18	20

Table 66. Analysis of Secondary Efficacy Measurement

Table XI
Overall Assessment of Block
Intent-to-Treat Population

	Treatment					
	0.5% Levobupivacaine		0.75% Levobupivacaine		0.5% Bupivacaine	
	N	%	N	%	N	%
Failure	3	10	2	7	0	0
Unsatisfactory block	8	28	5	17	7	24
Complete block	18	62	23	77	22	76

[Sponsor's Tables 9,10 and 11, item 8, Vol. 1.63, p. 042-044]

REVIEWER'S EFFICACY DISCUSSION

The primary efficacy variable in this study was defined as the duration of block, i.e., time from onset of block until complete return of sensation/function. The definition was revised to the following: time from onset of block until complete return of sensation/ function *irrespective of whether or not a general anesthetic was given.*

The analysis of the original definition of the primary efficacy variable revealed no significant differences between the 3 treatments in terms of mean duration of sensory block or time to onset of sensory block for either left or right sides. However, upon analysis of the revised definition, duration of sensory block was found, on average, to be significantly longer for the 0.75% levobupivacaine treated group compared with the 0.5% levobupivacaine and 0.5% bupivacaine groups. This effect was statistically significant for both the left and right sides.

Of significance is the fact that all patients who did not attain a sensory block were excluded from the corresponding analysis. The elimination of this population of patients could possibly weigh in favor of positive study results if these patients were not evenly distributed between treatment groups.

However, upon discussions with the statistical reviewer for this NDA submission, there are differences which weigh in favor of levobupivacaine on the left side and bupivacaine on the right side, but these differences are small and balance out.

Overall, the clinical data shows that the product, levobupivacaine, is effective when administered as an epidural to patients for lower limb surgery. This conclusion is based upon the clear evidence that patients experienced some level of analgesia sufficient for lower limb surgery. Additionally, It has been shown to behave as expected in terms of concentration – effect, i.e., the 0.75% concentration had a longer duration of action than the 0.5% concentration.

TUDY # CS-005

PROTOCOL SYNOPSIS:

Title: "A Double-blind, Randomized Controlled Trial of 0.75% Levobupivacaine Compared to 0.75% Bupivacaine for Epidural Anaesthesia in Patients Undergoing Major Elective Abdominal Surgery"

Primary Objective: "To compare the efficacy and safety of 0.75% levobupivacaine with 0.75% bupivacaine for epidural anesthesia in patients undergoing major elective abdominal surgery"

Secondary Objective: "To compare abdominal wall relaxation produced by epidural levobupivacaine and bupivacaine, to compare the duration of sensory and motor block, and to evaluate the relative safety profiles of 0.75% levobupivacaine and 0.75% bupivacaine."

[Item 8, Vol. 1.66, p. 004]

Study Design:

The study was designed as a randomized, single-center, double blind, parallel group comparative evaluation of the efficacy and safety of 0.75% levobupivacaine and 0.75% bupivacaine when given epidurally to patients scheduled for major abdominal surgery. Patients were randomized to receive either levobupivacaine or bupivacaine using a 1:1 allocation.

Group I - 0.75% levobupivacaine
Group II - 0.75% bupivacaine

Eligible patients were ASA I - III males or females between 18 and 80 years of age, of normal weight and height, who consented to receive epidural anesthesia for major elective abdominal surgery. They had no prior history of systemic illness, drug or alcohol use in the preceding 6 months, or participation in a clinical trial in the prior month.

A total of 57 patients were randomized to receive levobupivacaine or bupivacaine in equal proportions. Prior to entry, patients underwent a brief physical and history followed by an overnight fast. Additionally, patients received midazolam (1-5 mg), antibiotics, cimetidine and a 500 ml iv solution. Additional doses of midazolam (1-10) and propofol by infusion were permitted intra-operatively for sedation.

Following placement of the epidural catheter, 20 ml of study drug (time 0 minutes) was injected. Initially, a test dose of 3ml of study drug with 15 micrograms of epinephrine was administered. If there was no evidence of intravascular or subarachnoid injection, then the remaining amount of study drug was given over 5 minutes to a total of 20 ml, according to the following schemata:

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

During surgery, patients were re-dosed once with 7 ml of study drug to (1) increase muscle relaxation, (2) to increase patient comfort, (3) in the event of a prolonged surgical procedure, or (4) at the discretion of the investigator. If a second re-dosing of study drug was needed, the patient was excluded from the efficacy analysis.

Sensory block was measured bilaterally using the blunted end of a 27-gauge dental needle at 0, 2, 5, 10, 15, 20, 25, 30, and 60 minutes post dose or until adequate block was achieved for surgery. Subsequently, sensory measurements were made every 30 minutes, if possible, until complete regression of block.

Motor block was measured in both legs at Time 0 and at 10, 20 and 30 minutes post dose, using a modified Bromage scale, (0= no paralysis, full flexion of knees and ankles - 3 = inability to move lower limbs). If the scores of the legs differed, the lower score was used. After surgery, motor block was measured in both legs every 30 minutes until a score of "0" was obtained in both legs. If the scores of the legs differed, the higher score was used.

Additionally, abdominal muscle relaxation was measured pre-surgically and at 10, 20, and 30 minutes post dose. A RAM (rectus abdominis muscle) score was assigned, as follows:

0 = able to rise to sitting position with hands behind head
1 = able to rise to sitting position only with arms extended forward
2 = only able to lift head and scapulae off bed
3 = only able to lift shoulders off bed
4 = increase in abdominal muscle felt, but no movement
5 = no muscle tension or movement

Finally, the surgeon and/or anesthesiologist rated the overall degree of muscle relaxation at the end of surgery, using a categorical scale from 0 = poor to 3 = excellent. The investigator assessed the overall quality of the sensory and motor blocks, using a categorical scale, where 0= poor and 3 = excellent. Patients assessed their level of pain during surgery, at the conclusion of surgery, and prior to leaving the recovery room, using the following scale: 0= none, 1 = mild, 2 = moderate, and 3 = severe.

Blood samples were taken from 20 patients, via a contralateral intravenous cannula, at Time 0, 15, 30, 45, 60 minutes and 2, 4, 6, 8, and 10 hours post Time 0 sufficient to measure the pharmacokinetic (PK) parameters of levobupivacaine and bupivacaine.

In addition to PK sampling, QRS complex data were also collected from these 20 patients, using ECG machines with signal-averaging capability. Tracings, collected to analyze QT dispersion, were taken pre-dosing, then at 15, 30, 45 minutes and at 1, 2 and 4 hours post Time 0. These data are the subject of a separate protocol.

Please see the table below for details of patient evaluation schedule.

Table 67. Patient Evaluation Schedule

Table 1 Patient Evaluation Schedule

Study Parameter	Pre-Study	Pre-Surgery	Surgery	Post-Surgery
History[1] and Patient Consent	X			
Physical Examination[2]	X			
12-lead ECG	X	15 min. post epidural		4 hours
Vital Signs	X		Every 30 minutes	Every 30 minutes
Study Medication		X	Possible one 7 mL[3]	
Sensory Block		Time 0, 2, 5, 10, 15, 20, 25, 30, 60 minutes and every 30 minutes until adequate block is achieved		Every 30 minutes until completely resolved
Motor Block		Time 0, 10, 20, and 30 minutes		Every 30 minutes until a score of "0" is obtained in both legs
Abdominal Muscle Relaxation (RAM)		Presurgically and at 10, 20 and 30 minutes post injection		X[4]
Cardiovascular Monitoring, continuous		Time 0 to 8 hours post injection.		
Pain Rating			X	X
Overall Assessment of Sensory and Motor Block				X
Pharmacokinetic Sampling[5]		Time 0, 15, 30, 45, 60 minutes and 2, 4, 6, 8, and 10 hours		
Signal Averaging ECG	Pre-Dose, Time 0, and post Time 0 at 15, 30, 45 minutes, then at 1 and 2 hours			
Adverse Events	X	X	X	X[6]

[1]Includes medical history and medications. [2]Includes body weight and height, and a urine pregnancy test for women of childbearing potential. [3]Redose for any of the following reasons: to increase muscle relaxation, to increase patient comfort, in the event of a prolonged surgical procedure, at the discretion of the Investigator. [4]Will be assessed by the surgeon and/or anesthesiologist. [5]Pharmacokinetics sampling will be done on the first 20 patients. [6]Within 3-7 days post-discharge to determine residual effects of the study drug.

[Sponsor's Table 1, "Patient Evaluation Schedule", Item 8, Vol. 1.66, p. 030]

STATISTICAL ANALYSIS

The primary objective of this study was to demonstrate that the 2 study drugs are equipotent with regard to onset of sensory block adequate to carry out surgery. The analysis of efficacy was performed on the Intent-to-Treat population which was defined as all randomized patients, excluding those who did not receive randomized study drug and those who, suffered an incidental intravascular subarachnoid injection, resulting in immediate withdrawal from the study.

"All comparisons were done using a two-tailed alpha level of 0.05. Except where otherwise stated, all analysis are done on the ITT population. In order to assess equivalence, a 90% confidence interval (CI) was constructed. This was to allow the use of the Schuirmam two one-sided test to assess equivalence of the different regimens. It was observed by Morikawa and Yoshida[7] that the closed testing procedure allowed for a test of significance and test of equivalence without the need to adjust for multiplicity. Although statistical inferences from the CI on the mean may not correspond to the more appropriate product-limit (Kaplan-Meier) survival analysis, the CI on the mean is presented as a descriptive statistic. In addition, in order to assess treatment difference (test of significance), a 95% CI was constructed."

"For the survival analyses, if the time was missing, then the data for that patient was to be censored as of the time of the last observation."

Analysis of Primary Parameters

The primary parameter, onset of sensory block adequate to carry out surgery, was defined as the first time the patient bilaterally experienced analgesia at T10 or above."

"For the computation of the CI and the descriptive statistics, if the time of onset of sensory block adequate to carry out surgery was missing and could not be determined from sensory block data, then the time to surgery was used. If surgery was not performed, then these data were to be treated as missing for the CI. A survival analysis, using the product-limit (Kaplan-Meier) approach with study drug as a treatment factor, was also used to analyze onset of sensory block."

"A 90% CI of the difference between levobupivacaine and bupivacaine fell entirely within [-7.58, 7.58], then the two treatments were considered equivalent with respect to time of onset of anesthesia sufficient to carry out surgery. A further analysis, using a two-sided test, was done when the CIs indicated that the difference was greater than zero in favor of levobupivacaine."