Table 4. Abnormal History and Physical Findings

Abnormality	*Number of Patients* Ropivacaine 7.5 mg/ml	Bupivacaine 5.0 mg/ml
Abnormal Physical Exam	1	4
Borderline ECG	0	2
Abnormal ECG	0	1
Other Diseases	32	27
Surgical History	22	20

[Item 8, Vol. 98, pp. 63-64]

The two study groups were similar when compared for time from start of drug injection to the start of surgery, with a median time of 78 minutes for the ropivacaine group and 86 minutes for the bupivacaine group, and for surgical duration, with a median time of 55 minutes and 55 minutes respectively. Duration of treatment administration, with a median time of 5 minutes in both groups, and time from end of surgery to discharge, with a median of 28.2 hours for ropivacaine and 28.6 hours for bupivacaine, were also comparable. These results are summarized in the following table.

Table 5 Pertinent Time Comparisons

Measured Variable	*N*	*Median*	*Minimum*	*Maximum*
Start Injection to Start Surgery (minutes)				
Ropivacaine 7.5 mg/ml	52	78		
Bupivacaine 5 mg/ml	49	86		
Duration of Surgery (minutes)				
Ropivacaine 7.5 mg/ml	52	55		
Bupivacaine 5 mg/ml	49	55		
Duration of Administration (minutes)				
Ropivacaine 7.5 mg/ml	52	5		
Bupivacaine 5 mg/ml	49	5		
Time to Discharge (hours)				
Ropivacaine 7.5 mg/ml	52	28.2		
Bupivacaine 5 mg/ml	49	28.6		

[Item 8, Vol. 98, pp. 64-67; Item 8, Vol. 100, p. 130]

7.2.8.5 Sponsor's Efficacy Results

Primary Efficacy Variable:

Nerve-Specific Time to Onset of Analgesia

Differences between the onset times to development of analgesia between the ropivacaine group and the bupivacaine group were not clinically significant for any of the tested nerves. However, the block was least effective in the axillary nerve, with only 63.5% of ropivacaine patients and 49% of bupivacaine patients achieving analgesia. There were also a significant number of block failures in the distribution of the radial nerve. All calculations presented discount patients not achieving blockade in the specified nerve. Censored values (i.e. measurements not obtained due to bandaging or surgical field interference in test site) are also not included in these measurements. With these limitations on data it was observed that the median difference between the two groups was less than 10 minutes. The following table summarizes these results.

Table 6 Analgesia Onset Time (minutes)

Nerve	*Mean*	*SD*	*Median*
Axillary			
Ropivacaine	19.9	12.2	20.0
Bupivacaine	19.6	12.7	20.0
Median			
Ropivacaine	12.7	13.0	5.0
Bupivacaine	10.3	8.6	5.0
Musculocutaneous			
Ropivacaine	16.1	12.7	15.0
Bupivacaine	13.9	11.2	7.5
Radial			
Ropivacaine	15.7	11.7	15.0
Bupivacaine	14.0	11.1	7.5
Ulnar			
Ropivacaine	13.2	9.7	7.5
Bupivacaine	12.2	10.9	5.0

[From sponsor's Table "Summary Statistics", Item 8, Vol. 100, p. 136]

Confidence intervals for the difference in medians between the two treatments, calculated with the bootstrap technique, and log-rank p-values are summarized in the following table.

Table 7 95% Confidence Intervals – Onset of Analgesia

Nerve	*Lower Bound*	*Upper Bound*	*Median Difference*	*Log-Rank p-value*
Axillary	NA	NA	-10.00	.1022
Median	0.00	2.50	0.00	.6649
M-cutaneous	-8.00	0.00	0.00	.1112
Radial	-8.00	2.00	0.00	.4122
Ulnar	-9.50	9.00	1.50	.0916

[From sponsor's Table 12, Item 8, Vol. 98, p. 81 and Item 8, Vol. 100, p. 158]

Calculation of treatment medians was also performed utilizing survival curve methodology, thus including censored values as "zero" or "infinity" as appropriate, and was consistent with the above results, as can be seen in the following table.

Table 8 Survival Curve Medians – Block Onset (minutes)

Nerve	*Median for Ropi*	*Median for Bupi*
Axillary	25.0	**
Median	15.0	15.0
M-cutaneous	15.0	15.0
Radial	5.0	5.0
Ulnar	11.25	7.0

**Could not calculate – too few observations
[Item 8, Vol. 100, p. 155]

Secondary Efficacy Variables:

Nerve-Specific Time to Onset of Anesthesia, Partial Motor Block, and Complete Motor Blockade

In each of these comparisons, it is again noted that the respective block was least effective in the distribution of the axillary nerve. In all nerves tested, patients with absence of the recorded block were excluded from statistical analysis. Censored values and failed blocks are not included in these calculations. There were no clinically significant differences in the onset times to development of anesthesia, partial motor block, and complete motor block between the ropivacaine group and the bupivacaine group for successfully blocked nerves. The following table, ordered by type of block, summarizes these results.

Table 9 Block Onset Time (minutes)

Nerve	*Anesthesia*			*Partial Motor Block*			*Complete Motor Block*		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Axillary									
Ropivacaine	24.7	14.0	20.0	22.0	12.3	25.0	27.1	9.9	25.0
Bupivacaine	26.7	20.2	30.0	20.6	15.0	15.0	29.7	22.5	35.0
Median									
Ropivacaine	22.9	12.8	25.0	11.5	9.1	5.0	23.8	12.5	25.0
Bupivacaine	19.3	11.3	17.0	12.1	10.8	5.0	22.6	12.5	25.0
M-cutaneous									
Ropivacaine	28.3	11.9	30.0	11.8	10.1	5.0	27.0	9.1	25.0
Bupivacaine	23.7	10.1	25.0	10.3	7.8	5.0	26.0	11.4	25.0
Radial									
Ropivacaine	28.9	12.7	25.0	15.6	12.1	15.0	27.2	12.4	25.0
Bupivacaine	32.5	13.1	35.0	14.4	9.2	15.0	34.4	12.4	36.8
Ulnar									
Ropivacaine	24.4	12.9	25.0	12.3	9.7	7.5	25.7	12.3	25.0
Bupivacaine	24.5	13.0	25.0	13.5	11.7	7.0	24.1	15.0	15.0

[From sponsor's Table "Summary Statistics", Item 8, Vol. 100, pp. 136-141]

Confidence intervals for the difference in the medians between treatment groups, calculated by the bootstrap method, and log-rank p-values are summarized in the following table.

Table 10 95% Confidence Intervals – Onset Anesthesia, Partial Motor Block and Complete Motor Block

Type of Block	*Lower Bound*	*Upper Bound*	*Median Difference*	*Log-Rank p-value*
Anesthesia				
Axillary	NA	NA	NA	.1950
Median	-10.00	10.00	0.00	.0013
M-cutaneous	NA	NA	-8.00	.1096
Radial	NA	NA	-5.00	.5263
Ulnar	-26.00	0.00	-14.00	.0406
Partial Motor				
Axillary	-30.00	-10.00	-10.00	.0636
Median	-10.00	10.00	0.00	.1476
M-cutaneous	-9.50	8.00	0.00	.1900
Radial	-2.50	10.00	0.00	.2542
Ulnar	-9.50	2.50	0.00	.0280
Complete Motor				
Axillary	NA	NA	NA	.1939
Median	-20.00	10.00	-10.00	.0101
M-cutaneous	NA	NA	-10.00	.0839
Radial	NA	NA	-10.00	.1749
Ulnar	-10.00	10.00	-10.00	.0117

[From sponsor's Tables 12 & 13, Item 8, Vol. 98, pp. 81-82 and Item 8, Vol. 100, pp. 158-159]

Calculation of treatment medians was also performed utilizing survival curve methodology, including censored values as "zero" or "infinity" as appropriate, and was consistent with the above results. These results are displayed in the following table.

Table 11 Survival Curve Medians – Block Onset (minutes)

Block	*Median for Ropi*	*Median for Bupi*
Anesthesia		
Axillary	**	**
Median	35.0	**
M-cutaneous	35.0	**
Radial	25.0	25.000
Ulnar	25.0	45.000
Partial Motor		
Axillary	25.0	45.0
Median	15.0	15.0
M-cutaneous	5.8	7.0
Radial	5.0	5.0
Ulnar	8.3	15.0
Complete Motor		
Axillary	25.0	35.0
Median	35.0	**
M-cutaneous	35.0	**
Radial	35.0	**
Ulnar	35.0	**

**Could not calculate – too few observations
[Item 8, Vol. 100, pp. 155-156]

Nerve-Specific Duration of Sensory and Motor Blockade

There was no clinically significant difference in the duration of blockade, or time of disappearance minus time of onset, between the ropivacaine group and the bupivacaine group for any of the tested nerves. Again it is noted that the block was least effective in the axillary nerve and that there were also a significant number of block failures in the distribution of the radial nerve. All calculations presented discount patients not achieving blockade in the specified nerve or censored for unobtainable measurements. The results for nerve-specific block duration are summarized in the following table.

Table 12 Block Duration (hours)

Nerve	*Analgesia*			*Anesthesia*			*Partial Motor Block*			*Complete Motor Block*		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Axillary												
Ropi	7.5	5.4	6.7	3.6	2.7	2.4	7.7	5.4	6.9	5.2	4.3	2.6
Bupi	9.0	7.9	5.5	5.8	5.6	2.6	7.8	6.3	6.3	3.7	3.2	2.6
Median												
Ropi	13.0	3.8	13.2	9.5	3.9	10.8	12.1	4.1	12.8	8.4	3.8	8.9
Bupi	14.3	6.3	14.4	9.5	5.0	9.6	13.1	6.4	13.7	8.3	5.2	8.5
M-cutan												
Ropi	11.9	4.0	11.5	8.4	3.8	8.4	11.7	4.4	11.5	8.4	4.1	8.6
Bupi	10.8	6.7	10.6	8.6	5.3	6.6	11.7	5.0	11.4	6.8	4.9	4.6
Radial												
Ropi	12.0	4.2	11.4	8.4	4.5	8.6	11.8	3.9	11.4	8.5	4.5	8.6
Bupi	12.3	7.1	12.5	9.2	6.0	9.7	12.0	6.1	13.1	8.5	5.9	8.3
Ulnar												
Ropi	13.2	4.1	12.8	10.2	3.5	10.8	13.3	4.6	13.6	8.6	3.8	9.1
Bupi	15.7	7.7	15.1	12.0	6.6	12.6	14.5	6.8	14.4	10.7	7.4	10.8

[From sponsor's Table "Summary Statistics", Item 8, Vol. 100, pp. 136-141]

Confidence intervals for the difference in the medians between treatment groups, calculated by the bootstrap method, and log-rank p-values and are summarized in the table below:

Table 13 95% Confidence Intervals – Duration Analgesia, Anesthesia, Partial Motor Block and Complete Motor Block

Type of Block	*Lower Bound*	*Upper Bound*	*Median Difference*	*Log-Rank p-value*
Analgesia				
Axillary	-3.33	3.00	0.17	.4041
Median	-3.20	2.00	-1.00	.3247
M-cutaneous	-1.10	4.70	1.30	.7842
Radial	-3.68	2.52	-0.75	.0562
Ulnar	-3.47	2.93	-1.60	.0369
Anesthesia				
Axillary	NA	NA	NA	.2566
Median	-4.16	2.56	1.83	.4521
M-cutaneous	-2.34	4.25	3.67	.7612
Radial	-2.08	6.19	4.42	.6848
Ulnar	-4.26	3.62	0.17	.1635
Partial Motor				
Axillary	-3.19	4.04	1.20	.8812
Median	-2.67	1.64	-1.30	.2263
M-cutaneous	-2.93	2.90	0.10	.8642
Radial	-5.84	2.11	-1.60	.0511
Ulnar	-1.75	2.59	-0.70	.1305
Complete Motor				
Axillary	NA	NA	NA	.4445
Median	-0.89	5.44	3.60	.1638
M-cutaneous	-2.44	4.16	3.70	.3050
Radial	-4.53	3.67	4.40	.9962
Ulnar	-1.97	5.93	0.20	.3610

[From sponsor's Tables 12 & 13, Item 8, Vol. 98, pp. 81-82 and Item 8, Vol. 100, pp. 158-159]

Calculation of treatment medians was also performed utilizing survival curve methodology, including censored values as "zero" or "infinity" as appropriate, and was consistent with the above results. These results are displayed in the following table.

Table 14 Survival Curve Medians – Block Duration (hours)

Block	*Median for Ropi*	*Median for Bupi*
Analgesia		
Axillary	2.2	2.000
Median	11.4	11.4500
M-cutaneous	11.4	6.9167
Radial	13.2	14.4167
Ulnar	12.8	14.4167
Anesthesia		
Axillary	0.0	0.0
Median	7.8	2.6
M-cutaneous	6.6	2.6
Radial	9.9	8.4
Ulnar	9.8	8.9167
Partial Motor		
Axillary	4.6	3.2
Median	11.3	12.9
M-cutaneous	11.5	11.3
Radial	12.8	13.4
Ulnar	13.6	14.3
Complete Motor		
Axillary	0.0	0.0
Median	6.6	4.4
M-cutaneous	6.6	2.6
Radial	8.5	4.6
Ulnar	9.0	6.6

[Item 8, Vol. 100, pp. 155-156]

Nerve-Specific Time to Regression of Sensory and Motor Blockade

The time to regression for each specific block, or onset time plus individual duration, was similar between the two study groups. This data is a summation of the two prior measurements and was not separately tabulated.

Time to First Postoperative Analgesic Request

A total of 41 patients in the ropivacaine group and 35 patients in the bupivacaine group requested postoperative analgesics. The median time to first request was 12.5 and 13.5 hours in the ropivacaine and bupivacaine groups respectively. Since the 95% confidence interval for the time to first request ranges from –3.0 to 2.4 hours no conclusion can be made about the increased efficacy of either drug with this measurement. These results are summarized in the following table.

Table 15 First Analgesic Request (hours)

Treatment	*N*	*Median*	*Minimum*	*Maximum*
Ropivacaine 7.5 mg/mL	41	12.50		
Bupivacaine 5.0 mg/mL	34	13.54		

[Item 8, Vol. 100, p. 130]

Quality of Analgesia and Muscle Relaxation

Both surgeon and investigator evaluated the quality of analgesia and muscle relaxation at the end of the surgical procedure. The differences between the treatment groups are all statistically significant in favor of ropivacaine. These results are summarized in the following table.

Table 16 Quality of Analgesia and Muscle Relaxation

	Ropi 7.5mg/ml (n=52)	Bupi 5mg/ml (n=49)	
ANALGESIA, BY INVESTIGATOR			p=0,0002
Excellent	39	21	
Satisfactory	11	18	
Unsatisfactory	2	10	
MUSCLE RELAXATION, BY INVESTIGATOR			p=0,0004
Excellent	42	24	
Satisfactory	9	17	
Unsatisfactory	1	8	
Excellent	38	27	
Satisfactory	9	14	
Unsatisfactory	2	8	
Unassessed	3	-	
MUSCLE RELAXATION, BY SURGEON			p=0,0002
Excellent	39	25	
Satisfactory	10	17	
Unsatisfactory	-	7	
Unassessed	3	-	

[From sponsor's Table 18, Item 8, Vol. 98, p. 86]

Tourniquet Pain

A tourniquet was used during the surgical procedure in all patients. Nine patients in the ropivacaine group experienced pain with a median onset of 2.3 hours, as did twelve patients in the bupivacaine group with a median onset of 1.8 hours. The following table summarizes these results.

Table 17 Onset Time of Tourniquet Pain (hours)

Treatment	*N*	*Median*	*Minimum*	*Maximum*
Ropivacaine 7.5mg/mL	9	2.33		
Bupivacaine 5.0 mg/mL	12	1.79		

[Item 8, Vol. 98, p. 130]

Amount of Concomitant Fentanyl, Midazolam, and Propofol:

The overall use of sedative and analgesic medications was similar between the two study groups. These results are summarized in the following table.

Table 18 Use of Concomitant Medications (Fentanyl µg/h, Midazolam mg/h, Propofol mg/h)

Therapy	DOSE	Treatment	N	MEDIAN	MIN	MAX
Fentanyl	0 - 100	ROPI 7.5	7	36.5		
		BUPI 5.0	5	70.6		
Fentanyl	>100 - 200	ROPI 7.5	2	132.2		
		BUPI 5.0	3	152.5		
Midazolam	0 - 5	ROPI 7.5	1	0.6		
		BUPI 5.0	1	0.9		
Propofol	0 - 100	ROPI 7.5	1	32.7		
Propofol	> 200	ROPI 7.5	1	840.0		
		BUPI 5.0	2	303.3		

[From sponsor's Table 18, Item 8, Vol. 98, p. 86]

7.2.8.6 Reviewer's Efficacy Discussion

In this study the efficacy comparison of ropivacaine and bupivacaine was primarily analyzed using an endpoint of analgesia onset after an axillary brachial plexus blockade. Analysis of the results does not support a conclusion that either study drug is more effective in producing analgesia in this nerve plexus.

Secondary efficacy variables, including duration of analgesia, onset and duration of anesthesia and motor blockade, use of concomitant sedative or analgesic medication, and time to first request of analgesics, were analyzed and these results also do not support a finding that one study drug is clinically more effective than the other.

Analysis of the quality of analgesia and motor blockade, as rated by investigator and surgeon, did demonstrate a statistically significant preference for ropivacaine over bupivacaine. This analysis included data from 34 patients who were considered to be "insignificant" protocol violations. However, 5 of these patients, all in the bupivacaine group, had protocol violations that could have made a difference in the ultimate quality of block established. Four patients received less than 40 mL of bupivacaine for their block and one patient had a block that failed and subsequently received a second block. A repeat analysis of the quality data, excluding these five patients, was performed. Ropivacaine again demonstrated a statistically significant advantage over bupivacaine when quality was the measured variable. These results are summarized in the following table.

Table 19 Quality of Anesthesia (Re-Analysis)

	Investigator Analysis		*Reviewer Analysis*	
Rating	Ropivacaine (n=52)	Bupivacaine (n=49)	Ropivacaine (n=52)	Bupivacaine (n=44)
Analgesia, Investigator				
Excellent	39	21	39	20
Satis	11	18	11	16
Unsatis	2	10	2	8
Musc Relax, Investigator				
Excellent	42	24	42	24
Satis	9	17	9	13
Unsatis	1	8	1	7
Analgesia, Surgeon				
Excellent	38	27	38	26
Satis	9	14	9	11
Unsatis	2	8	2	6
Unassessed	3	--	3	--
Musc. Relax, Surgeon				
Excellent	39	25	39	24
Satis	10	17	10	14
Unsatis	--	7	--	6
Unassessed	3	--	3	--

[From sponsor's Table 18, Item 8, Vol. 98, p. 86]

Because of the inherent inability to achieve adequate blockade of several brachial plexus nerves (most notably the axillary nerve but to some extent the radial nerve) with the axillary brachial plexus block technique, much of the data from these nerves was unattainable and could not be entered into the efficacy analysis. Of interest, analysis of the data demonstrates no significant increase in failure rate with either bupivacaine or ropivacaine when attempting to achieve successful blockade in these nerves.

In this study it must be noted that the sponsor chose to compare the efficacy of two different dosages of the study agents, 7.5 mg/ml of ropivacaine and 5 mg/ml of bupivacaine. Any differences that might occur in the measured variables, whether or not they are statistically significant, may be biased by dosage effect and thus may not reliably be used to support a finding of increased efficacy with equal concentrations of the tested agent.

When measuring all efficacy variables other than quality of anesthesia, this study supports the conclusion that neither ropivacaine 7.5 mg/ml nor bupivacaine 5 mg/ml is more or less effective than the other. However, when quality of anesthesia is the measured efficacy variable, this study supports the finding that ropivacaine 7.5mg/mL is more effective than bupivacaine 5.0 mg/mL when used for an axillary brachial plexus block.

7.2.8.7 Reviewer's Efficacy Summary

Brachial Plexus Block

Studies P11, P12

There were two studies comparing the efficacy of ropivacaine 7.5 mg/mL to bupivacaine 5 mg/mL for surgery on the arm or hand under brachial plexus blockade. Both studies were of a randomized, double-blind, parallel-group design. Study P11 was conducted on 106 patients (98 in APT group) at 5 centers, utilizing a perivascular subclavian technique, and Study P12 was conducted on 104 patients (101 in APT group) at 5 centers, utilizing an axillary technique.

Both studies analyzed a primary efficacy variable of analgesia onset time in the five nerves of the brachial plexus. Neither study demonstrated a clinically or statistically significant difference in the analysis of results between the two treatment groups.

Numerous secondary efficacy variables, including duration of analgesia, onset and duration of anesthesia and motor blockade, use of concomitant sedative/analgesic medication, and time to first request of analgesia were assessed in the two studies. No clinically or statistically significant differences were found between the two treatment groups when these efficacy variables were analyzed.

Analysis of the remaining secondary efficacy variable, quality of analgesia and muscle relaxation as judged by the investigator and the surgeon, did demonstrate a statistically significant difference in favor of ropivacaine 7.5 mg/mL. This statistically significant difference was found only in Study P12 and was not duplicated in the analysis for Study P11. The results from these two studies are tabulated below.

Table 1 Quality of Analgesia and Muscle Relaxation

	Study P11			*Study P12*		
Assessment	*Ropivacaine 7.5 mg/mL (n=49)*	*Bupivacaine 5 mg/mL (n=49)*	*p-value*	*Ropivacaine 7.5 mg/mL (n=52)*	*Bupivacaine 5 mg/mL (n=49)*	*p-value*
Analgesia						
Excellent	33	26		39	21	
Satisfactory	2	6	0.20	11	18	.0002
Unsatisfactory	14	17		2	10	
Muscle Relaxation						
Excellent	35	30		42	24	
Satisfactory	2	4	0.51	9	17	.0004
Unsatisfactory	12	14		1	8	
Unassessed	0	1				

[Item 8, Vol. 96, p. 67; Item 8, Vol. 98, p. 86]

Study P12 did include 5 patients in this analysis that could have potentially biased the results in favor of the ropivacaine group. All 5 patients, who were in the bupivacaine group, had significant protocol violations that could have led to a decreased block efficacy. However, a repeat analysis by the reviewer of this efficacy variable, removing the data from these patients, again demonstrated a statistically significant difference in favor of ropivacaine.

Study P11 analyzed the results of a subclavian perivascular brachial plexus block and an adequate amount of data was collected from all 5 nerves in the plexus. However, Study P12 analyzed the results of an axillary brachial plexus block and, as expected with this type of block, much of the data for axillary and radial nerve blockade was unavailable due to insufficient block effect. Of interest, when the failure data for Study P12 was analyzed, there was no significant difference in failure rate with ropivacaine 7.5 mg/mL or bupivacaine 5 mg mL.

It should be noted that in both Study P11 and Study P12, the sponsor chose to compare the efficacy of similar volumes but two different dosages of the study agents, 7.5 mg/ml of ropivacaine and 5 mg/ml of bupivacaine. Any differences that might occur in the measured variables, whether or not they are statistically significant, may be biased by dosage effect and thus may not reliably be used to support a finding of increased efficacy with equal concentrations of the tested agent. The following table lists the volumes and dosages of ropivacaine and bupivacaine used in each of the studies.

Table 2 Volume (mL) and Dosage (mg) of Study Drugs

Study Drug	***Study P11***		***Study P12***	
	Volume (mL)	*Dose (mg)*	*Volume (mL)*	*Dose (mg)*
Ropivacaine 7.5 mg/mL	30	225	40	300
Bupivacaine 5 mg/mL	30	150	40	200

In summary, when measuring all efficacy variables other than quality of anesthesia, these studies support the conclusion that neither ropivacaine 7.5 mg/ml nor bupivacaine 5 mg/ml is more or less effective than the other. However, when quality of anesthesia is the measured efficacy variable, one of the two studies (P12) supports the finding that ropivacaine 7.5 mg/mL is more effective than bupivacaine 5.0 mg/mL when used for an axillary brachial plexus block in the above dosages.

Patricia Hartwell, MD, MBA

7.2.9 STUDY 91RO47 (M04)

Brief Synopsis of Study – "Ropivacaine 7.5 mg/ml in epidural anesthesia for Caesarian section"

Brief Synopsis of Study – "Ropivacaine 7.5 mg/ml in epidural anesthesia for Caesarian section"

This study was an open label study of the efficacy of epidural ropivacaine 75% when used for caesarian section. Measures of efficacy were onset and duration of analgesia, sensory blockade measured at various dermatomal levels by pinprick, quality of analgesia as assessed by both the investigator and the patient, onset and duration of motor blockade rated according to a modified Bromage scale, and quality of motor blockade as assessed by the surgeon.

38 patients were enrolled in the study. All but one patient received the protocol dose of 20 cc .75% ropivacaine (150 mg) to establish an epidural block. Seven of these patients were excluded from sensory efficacy analysis (6 due to technical failure, 1 due to a protocol violation). Of the remaining 31 patients, 26 had sensory blocks adequate for surgery. The median onset of sensory block from S3 and T6 varied between 5 and 22.5 minutes and the median duration varied between 3.4 and 4.5 hours depending on the dermatomal level. These results are summarized in the table below.

Table 1 Sensory Block (Medians)

Onset (minutes)	T6	15
	T10	10
	L1	5
	L5	15
	S3	22.5
Duration (hours)	T6	3.4
	T10	4.4
	L1	4.3
	L5	4.5
	S3	4.1

[Item 8, Vol. 103, p. 2]

Of the 31 patients, only 11 patients had a motor block of Level 3. The onset of blockade from levels 1 through 3 was between 17.5 and 26.3 minutes and the duration was between 1.6 and 2.2 hours. These results are summarized in the tables below.

Table 2 Degree of Motor Blockade

Degree	0	1/31
	1	30/31
	2	16/31
	3	11/31

[Item 8, Vol. 103, p. 2]

Table 3 Motor Block (Medians)

Onset (minutes)	degree 1 (hip)	17.5
	2 (knee)	26.5
	3 (ankle)	25
Duration (hours)	degree 1 (hip)	2.2
	2 (knee)	1.7
	3 (ankle)	1.6

[Item 8, vol. 103, pp. 2-3]

The quality of anesthesia as judged by both the investigator and the patient at the end of the surgical procedure was "satisfactory" in 25 of the 26 patients. The quality of muscle relaxation as judged by the surgeon was satisfactory in 27 patients.

In summary, this open-label study provided information on onset and duration of sensory and motor blockade at various dermatomal levels after epidural administration of 150 mg ropivacaine for caesarian section.

7.2.10 STUDY 94RO80 (M08)

Title:

An Open Study Using 150 mg, 187.5 mg and 225 mg of Ropivacaine 7.5 mg/mL in Epidural Anesthesia for Caesarean Delivery – A Clinical and Pharmacokinetic Evaluation

Objectives:

"The objective of this study is to investigate the efficacy, tolerability and pharmacokinetics of epidural administration of 150 mg, 187.5 mg and 225 mg ropivacaine 7.5 mg/ml when used for Caesarian delivery."
[Item 8, Vol. 80, p. 114]

Study in Brief:

This study was a single center, open, non-randomized, rising dose trial with three consecutive groups of patients, each containing 8 women, scheduled for elective Caesarian delivery. The first group of 8 received a single epidural dose of 150 mg ropivacaine. The second group of 8 received a single epidural dose of 187.5 mg ropivacaine. Clinical efficacy, pharmacokinetic, and safety data were collected and analyzed. The third group of 8, scheduled to receive a single epidural dose of 225 mg ropivacaine was not entered into the trial after the results from the first two groups were analyzed. All doses were delivered epidurally by a "single-shot" technique, utilizing a motorized syringe to deliver the prescribed dose over a 5 minute period.

The following efficacy variables were recorded and analyzed:
- Quality of analgesia and abdominal muscle relaxation (primary)
- Pain during surgery (primary)
- Maximum upper spread of sensory block and time to onset at maximum dermatome
- Maximum degree of motor block and regression of motor block
- Discomfort during surgery

Safety variables were also recorded and analyzed:
- Maternal heart rate, blood pressure, oxygen saturation
- Fetal hear rate
- Apgar score, Neurologic and Adaptive Capacity Score
- Birthweight
- Incidence, severity and type of adverse event
- Blood gases

Pharmacokinetic evaluation consisted of determination of total and free plasma concentrations of ropivacaine, characterization of systemic absorption, t ½, and plasma clearance.
Discussion of Results and Reviewer's Analysis

The investigators found that both doses of ropivacaine (150 mg and 187.5 mg) worked well from an efficacy point of view. The incidence of pain during the procedure, the quality of surgical anesthesia, and the amount of muscle relaxation were comparable between the two groups. However, the upper dermatomal spread of the 187.5 mg dose of ropivacaine was much higher than that achieved with the 150 mg dose.

Although these results do provide some valuable information about efficacy of ropivacaine at the two tested dosages, they should be translated to clinical practice with caution. The method of injection of the study drug, via a motorized syringe over a period of 5 minutes in a "single shot" technique does not mirror typical practice for the administration of epidural anesthesia in an elective Caesarian section. Typically, the epidural injection is administered over a period of time, with intermittent aspiration for blood or cerebral spinal fluid, allowing for the gradual onset and establishment of a surgical anesthetic level at minimum doses. By utilizing a rapid, single-dose injection method, inappropriately high levels may be obtained, leading to an increased rate of complications. Misleading conclusions may then be drawn about the required dosage for surgical anesthesia.

This study was an open-label non-randomized non-comparative pilot study on a total of 16 patients designed to establish the dose of ropivacaine to be used in comparative studies. As such, the efficacy and safety information obtained from the analysis can be used for its original intent, to establish dosing guidelines for subsequent comparative studies, and may also be helpful in contributing to the final efficacy and safety profile of the drug.

7.2.11 STUDY 95RO89 (M09)

7.2.11.1 Protocol Synopsis

Title:

Epidural anesthesia for Cesarean section: A double-blind comparison between 7.5 mg/ml ropivacaine and 5.0 mg/ml bupivacaine

Objectives:

"The objective of the study is to evaluate the efficacy and tolerability of ropivacaine 7.5 mg/ml and bupivacaine 5 mg/ml used for Cesarean section. Evaluation will be understood as the estimation of treatment differences with respect to efficacy and tolerability variables."
[Item 8, Vol. 82, p. 144]

Study Design:

This study is a multi-center, randomized, double-blind, parallel group design. One hundred sixteen women scheduled for elective Caesarian section are to be enrolled at two centers (one center will consist of two sites making a total of three sites). The subjects will be randomized to receive epidural anesthesia with 20-25 ml of ropivacaine 7.5 mg/ml or 20-30 ml of bupivacaine 5 mg/ml (200 mg). Patients will have an equal probability of receiving the two drugs.

Patients eligible for the study will be women scheduled for elective cesarean section, ASA classes I & II, with full-term (≥36 and ≤41 weeks gestational age) singleton fetuses. They will be ≥18 years of age, ≥145 cm. tall, and ≤110 kg in weight, with an estimated fetal weight ≥2500 g. Patients will be excluded if they have a known history of allergy, sensitivity or reaction to amide local anesthetics, a contraindication to epidural anesthesia as judged by the investigator, have received any sedatives, hypnotics or narcotics within the preceding 12 hours, have suspected alcohol, drug or medication abuse, have a suspected inability to comply with the study procedures, or have pre-eclampsia as defined by the existence of two of the following findings: hypertension, proteinuria and edema.

Figure 1. Study Schemata (Final Design Incorporating Protocol Amendments)

Study Design	Actions	Induction of anesthesia								During surgery	After surgery							At discharge	After surgery
		Minutes									Hours								
	before surgery	-3	0	5	10	15	25	30	40		0	2	4	6	8	12	24		weeks 3-4
Medical history																			
Physical examination																			
Preanesthetic infusion																			
Test dose, lidocaine 3 ml																			
Ropi/bupi 20 ml (150 mg)																			
Add. doses ropi/bupi 5 ml																			
Add. dose saline/bupi 5 ml																			
Maternal body temperature																			
Pain during surgery																			
Quality of analgesia																			
Quality of muscle relaxation																			
Sensory block											1.								
Motor block												2.							
Maternal BP, PR and SpO2						3.													
Fetal heart rate						4.													
Fetal body temperature																			
Adverse events																			
Apgar scores											5.								
NACS scores																			

1. Every 30 minutes after surgery until the return of normal sensation
2. 30 minutes after the end of surgery and then every 30 minutes until the return of normal motor function
3. 5, 10, 15, 20, 30, 40, 50, and 60 minutes after the end of injection of the main dose and then every 15 minutes up to 3 hours
4. Intermittently before the injection of anesthesia until preparation for surgery
5. 1 and 5 minutes after delivery

[From sponsor's Figure 1, Item 8, Vol. 82, p. 21]

Pre-operatively, patients will be assessed for inclusion or exclusion to the study, informed consent will be given, and a history and physical exam will be obtained. Pre-anesthetic baseline measurements will include pulse, blood pressure, oxygen saturation, and temperature. At least 15 ml/kg of a crystalloid solution will be administered IV prior to the injection of any epidural medication.

After infiltration of the skin with a local anesthetic other than bupivacaine or ropivacaine, an epidural catheter will be placed, preferably at the L3-L4 interspace, utilizing standard technique (sitting or LLD position, 16-18 g Touhy, loss of resistance technique, catheter placement through needle). A test dose of 3 mL lidocaine 10 mg/ml with 5 μg/ml epinephrine will be injected and a 3-minute period will elapse for adverse event monitoring. Twenty ml of the study drug, either ropivacaine 7.5 mg/mL or bupivacaine 5 mg/mL, will then be injected incrementally over a 5 minute period.

Surgery will begin when a sensory block is confirmed at T6, using a blunt needle, and adequate surgical anesthesia, measured by forceps pinch in the incisional area, is achieved. Two additional top-up doses may be used to achieve this level, administered 10 minutes after the initial dose and 10 minutes after the first top-up dose. The first top-up dose will be 5 ml of bupivacaine 5 mg/mL or 5 mL of ropivacaine 7.5 mg/mL, depending on the randomized group. The second dose will be 5 ml of bupivacaine 5 mg/mL for the bupivacaine group or 5 ml of saline for the ropivacaine group. If adequate anesthesia has not been obtained 40 minutes after administration of the initial dose, the patient may receive additional analgesics or anesthetics at the investigator's discretion.
Sensory block will be determined bilaterally using a 27G needle every 5 minutes until start of surgery, will again be determined 30 minutes after surgery, and will be monitored until return of normal sensation. Maximum upper spread of sensory block, time to T6 level, and time to maximum level will be recorded. Pain will be assessed at time of incision, delivery, closure of peritoneum, and last suture and rated according to a numerical scale from 0 (no pain) to 100 (worst pain ever). Motor block will be determined bilaterally utilizing a modified Bromage scale from 0 (full flexion) to 3 (no flexion hips, knees, ankles) starting 30 minutes after surgery ends and every 30 minutes until return of function. Maternal and fetal hemodynamic measurements will be recorded throughout the study. Neonatal assessments by Apgar score and NACS will be performed at the appropriate post-natal time periods. Laboratory assessments and monitoring for adverse events will be performed for safety analyses.

7.2.11.2 Statistical Analysis

According to the original protocol, the single primary efficacy variable is "pain at delivery". Statistical analysis of this parameter will include descriptive statistics and graphs for each treatment group. Group differences will be discerned using Hodges-Lehmann point estimates and 95% confidence intervals based on a stratified Wilcoxon (mid) rank sum test adjusted for centers and sites.
[Item 8, Vol. 82, pp. 162-163]

Secondary efficacy variables are as follows:

- Pain at skin incision, closure of peritoneum, and last suture
- Quality of anesthesia (analgesia and abdominal wall muscle relaxation
- Maximum upper spread of sensory block
- Time to onset of maximum sensory block
- Time to onset of T6 sensory level
- Time to complete regression of sensory block
- Maximum degree of motor block at 30 minutes post-surgery or later
- Time to complete regression of motor block.

As with the primary efficacy variable, the secondary variables will be analyzed using group-specific descriptive statistics and graphs, intergroup comparison with a stratified Wilcoxon (mid) rank sum test adjusted for centers and sites, and, where appropriate, point estimates and 95% confidence intervals. Patients receiving another anesthetic regimen before the end of surgery will be assigned the highest rank for pain analysis for any assessments performed after administration of the additional medication. All p-values reported will reflect two-sided tests and a p-value of <0.05 will be considered statistically significant. [Item 8, Vol. 82, p. 163-164]

7.2.11.3 Protocol Amendments

Amendment 1:

This amendment, dated 10/24/95, consists of the following changes:

- Administrative features – addition of study personnel
- Changes in labeling and accountability of drug – labeling of study drugs in Portuguese; delivery to investigator rather than hospital pharmacy
- Changes to the definition of adverse events - addition of the wording *"any new illness or disease or deterioration of existing illness or disease, any clinically relevant deterioration in laboratory assessments (e.g. hematological, biochemical, hormonal) or other clinical test (e.g. ECG, X-ray)"*; further changes include *"definition could include accidents and reasons for: changes in medication (drug and/or dose), medical/nursing/pharmacy consultation, admission to hospital, surgical operations"*
- Addition to the definition of serious adverse event - *"permanent or significant disability/incapacity, a congenital anomaly/birth defect, medical or surgical intervention to prevent permanent impairment of function or permanent damage to a body structure."* Reporting guidelines are defined as *"fulfilling these criteria must be reported as a Serious Adverse Event, irrespective of the dose of drug given, and even if it is a result of overdose, interaction of drug abuse. Cancer will always be reported as a Serious Adverse Event as well as an experience associated with an overdose. Medical or surgical intervention to prevent permanent damage to body structure does not include interventions regarded as standard treatment during anesthesiological procedure, e.g. ephedrine treatment of hypotension occurring during anesthesia."*
- Changes to procedure for adverse event reporting – from *"within 10 working days"* to *"within 4 working days"*
- Addition of *"urinalysis"* to adverse events reported for clinically relevant deterioration
- Deletion of specific laboratory assessments delineated in original protocol with change of wording to *"Laboratory assessments will be performed according to the hospital routines. Data will not be recorded in the Case Report Form."*

Amendment 2:

This amendment, dated 03/11/96, consists of the following change:

- Addition of study personnel

Amendment 3:

This amendment, dated 04/15/96, consists of the following change:

- Administrative changes to study personnel contact information

Amendment 4:

This amendment, dated 08/30/96, consists of the following change:

- Change to wording addressing administration of other therapy during study period from *"Administration of all therapy from administration of premedication until discharge from hospital" to "Administration of all therapy from administration of premedication until the end of surgery"*. Addition of the wording *"medications given due to an adverse event should always be recorded on the appropriate page in the CRF."*

Amendment 5:

This amendment, dated 09/18/96, consists of the following change:

- Addition of study personnel

Amendment 6:

This amendment, dated 11/11/96, consists of the following changes:

- Addition of third center to study
- Deletion of pre-operative and post-operative ECG requirement
- Deletion of maternal (pre-operative and post-operative) and neonatal (delivery and 24 hours post-delivery) body temperature recording requirement
- Changes to adverse event reporting requirement – from *"information will be collected...until a follow-up at 3-4 weeks after surgery"* to *"information will be collected ...until hospital discharge"*

7.2.11.4 Conduct of Study

Patient Distribution/Disposition:

Pending response from sponsor. When data available, it will be reviewed as an addendum to this supplemental NDA 20-533.

Demographics

The following tables summarize the general demographic characteristics of the two study populations. The groups were well matched with the exception of weight where the ropivacaine group had a mean weight 5.1 kg higher than the bupivacaine group.

Table 2 Age, Height, and Weight

Variable	Group	N	MEAN	STD	MIN	MAX
Age (years)	ROPI 7.5	64	30.0	5.5		
	BUPI 5.0	60	28.4	6.2		
Height (cm)	ROPI 7.5	64	158.8	6.8		
	BUPI 5.0	60	157.4	6.1		
Weight (kg)	ROPI 7.5	64	77.3	11.3		
	BUPI 5.0	60	72.2	10.5		

[From sponsor's Table 1, Item 8, Vol. 82, p. 46]

Table 3 Ethnicity, ASA Classification, Parity, and Allergy

	Ropivacaine (n=64)	Bupivacaine (n=60)
Ethnic backgr.		
CAUCASIAN	31	33
BLACK	32	27
ORIENTAL	1	-
Allergy		
NO	58	56
YES	6	4
Asa risk		
GROUP 1	46	45
GROUP 2	18	15
Parae		
PRIMI	7	8
MULTI	57	52

[From Sponsor's table, Item 8, Vol. 83, p. 10]

The two groups were similar with respect to the incidence of significant findings in medical and surgical history. On physical exam, there were more patients in the ropivacaine group (5 compared to 1) with abnormal findings, especially on cardiovascular examination (5 ropivacaine compared to 1 bupivacaine). Current and/or past major disease or condition, previous major surgery, and abnormal physical exam findings were noted and are summarized in the following table.

Table 4 Abnormal History and Physical Findings

Abnormality	*Number of Patients* Ropivacaine 7.5 mg/mL	Bupivacaine 5 mg/mL
Abnormal Physical Exam	12	5
Other Diseases	27	29
Surgical History	57	53

[Item 8, Vols. 82, pp. 46-49; Vol. 85, pp. 196-200]

The two study groups were similar when compared for median time from end of main dose to start of surgery, with a median time of 24 minutes for the ropivacaine group and 23 minutes for the bupivacaine group. The median duration of surgery was also similar between the groups, with times of 87 minutes and 82 minutes, respectively. These results are summarized in the following table.

Table 5 Pertinent Time Comparisons

Measured Variable	*N*	*Median*	*Minimum*	*Maximum*
End Main Dose to Start Surgery (minutes)				
Ropivacaine 7.5 mg/mL	63	24		
Bupivacaine 5 mg/mL	60	23		
Duration of Surgery (minutes)				
Ropivacaine 7.5 mg/mL	63	87		
Bupivacaine 5 mg/mL	60	82		

[Item 8, Vol. 82, pp. 42-46; Item 8, Vol. 85, p. 246]

The total volume (mL) of study drug received was similar between the two groups. However the total dose (mg) administered of the study drug was higher in the ropivacaine group. These results are summarized in the following table.

Table 6 Dose and Volume Comparisons

	Ropivacaine (n=64)	Bupivacaine (n=60)
Dose (mg)		
50	.	1
100	.	32
125	.	16
150	41	11
187.5	23	.
Dose (ml)		
10	.	1
20	41	32
25	12	16
30	11	11

[From Sponsor's Table 6, Item 8, Vol. 82, p. 53]

7.2.11.5 Sponsor's Efficacy Results

Primary Efficacy Variable:

Pain at Delivery

When analyzing only the observed scores, the number of patients experiencing pain scores above zero during delivery was similar between the two groups (two patients in the ropivacaine 7.5 mg/mL group and 4 patients in the bupivacaine 5 mg/mL group). When patients receiving other anesthetic modalities were added into these calculations and assigned a score of "100", there was still no statistically significant difference in NRS pain scores measured at delivery between the groups. All calculations discount patients termed "technical failures" by the investigators. The following table summarizes these results.

Table 7 Pain at Delivery

	With Observed Scores							*With "100" Scores*		
Treatment Group	*N*	*# With NRS> 0*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*	*N*	*p-value*	*Direction of Difference*
Ropivacaine 7.5 mg/mL	52	2	0.0			.45494	I > II	60	.58065	I > II
Bupivacaine 5 mg/mL	55	4	0.0					58		

[From sponsor's Table 14, Item 8, Vol. 82, p. 68 and Item 8, Vol. 83, pp. 261-270]

Secondary Efficacy Variables:

Pain at Skin Incision, Closure of Peritoneum, and Last Suture

There were no statistically significant differences in the amount of pain experienced at these recorded times between the treatment groups. It was noted that the number of patients experiencing some pain during peritoneal closure was higher in the bupivacaine group but, during skin incision, the ropivacaine group experienced more pain. When patients receiving other anesthetic modalities were added into the calculations and assigned a score of "100", there were still no statistically significant differences in NRS pain scores measured at any of the recorded times. All calculations discount patients termed "technical failures" by the investigators. The following table summarizes these results.

Table 8 Pain With Incision, Peritoneal Closure, and Last Suture

	With Observed Scores							*With "100" Scores*		
Assessment Event	*N*	*# With NRS> 0*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*	*N*	*p-value*	*Direction of Difference*
Incision										
Ropivacaine 7.5 mg/;mL	54	3	0.0			.08393	I > II	60	.08393	I > II
Bupivacaine 5 mg/mL	55	0	0.0					58		
Peritoneal Closure										
Ropivacaine 7.5 mg/;mL	50	5	0.0			.79335	I > II	58	.99541	I < II
Bupivacaine 5 mg/mL	54	10	0.0					57		
Last Suture										
Ropivacaine 7.5 mg/;mL	52	0	0.0			.23723	I > II	60	.93595	I < II
Bupivacaine 5 mg/mL	54	1	0.0					58		

[From sponsor's Table 14, Item 8, Vol. 82, p. 68 and Item 8, Vol. 83, pp. 261-270]

Quality of Analgesia and Abdominal Wall Muscle Relaxation

There was no statistically significant difference between the two treatment groups in the quality of analgesia, as judged by the investigator, or the quality of abdominal wall muscle relaxation, as judged by the surgeon. With the exception of "technical failures", all patients from the APT group were included in this analysis. Patients requiring spinal anesthesia received "unsatisfactory" analgesia ratings and muscle relaxation ratings were not taken. Patients receiving general anesthesia also received "unsatisfactory" analgesia ratings and received "satisfactory" muscle relaxation ratings. Patients requiring supplemental analgesic support received "unsatisfactory" analgesia ratings and muscle relaxation ratings consistent with their clinical situation. One patient in the bupivacaine group did not receive an analgesia assessment. Five patients in the ropivacaine group and two patients in the bupivacaine group did not receive assessments of muscle relaxation. The results for quality of analgesia and muscle relaxation for the two treatment groups are summarized in the following table.

Table 9 Quality of Analgesia and Abdominal Wall Muscle Relaxation

Measurement	*Ropivacaine 7.5 mg/mL (n=60)*	*Bupivacaine 5 mg/mL (n=58)*
Quality of Analgesia		
Not measured	0	1
Unsatisfactory	9	8
Satisfactory	7	9
Excellent	44	40
p-value	.78770	
Direction of Difference	I > II	
Quality of Muscle Relaxation		
Not measured	5	2
Unsatisfactory	1	2
Satisfactory	17	16
Excellent	37	38
p-value	.98994	
Direction of Difference	I > II	

[From sponsor's tables, Item 8, Vol. 83, pp. 279-285]

Maximum Upper Spread of Sensory Block

The maximum upper spread of sensory block varied between T12 and C4 for the ropivacaine group and T10 and T1 for the bupivacaine group and the difference between the groups was not statistically significant. Data from patients termed "technical failures" and discontinuation data (premature discontinuation due to adverse events or use of another anesthetic modality) is not included in the tabulations. The following table summarizes these results.

Table 10 Maximum Upper Spread of Sensory Block

Segmental Level	*Ropivacaine 7.5 mg/mL (n=56)*	*Bupivacaine 5 mg/mL (n=56)*
T12	1	0
T10	0	1
T8	0	1
T7	0	1
T6	5	7
T5	6	5
T4	18	17
T3	12	7
T2	9	11
T1	1	6
C6	1	0
C5	2	0
C4	1	0
p-value	.69310	
Direction of Difference	I > II	

[From sponsor's tables, Item 8, Vol. 83, pp. 230-239]

Time to Onset of Maximum Sensory Block, Onset of T6 Sensory Level, and Complete Regression of Sensory Block

There were no statistically significant differences for any of the sensory block time measurements between the two treatment groups. The median time to onset of maximum sensory block in both groups was 20 minutes and the median time to onset of T6 block in both groups was 10 minutes. The median time for regression of sensory block was 5.1 hours in the ropivacaine group and 5.0 hours in the bupivacaine group. The following table summarizes these results. Data from patients termed "technical failures" and discontinuation data (premature discontinuation due to adverse events or use of another anesthetic modality) is not included in these tabulations.

Table 11 Sensory Block Time Measurements

Variable	*N*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*
Onset T6 (min)						
Ropivacaine 7.5 mg/mL	55	10.0			.85573	I < II
Bupivacaine 5 mg/mL	53	10.0				
Onset maximum (min)						
Ropivacaine 7.5 mg/mL	56	20.0			.48312	I < II
Bupivacaine 5 mg/mL	56	20.0				
Complete Regression (hr)						
Ropivacaine 7.5 mg/mL	33	5.1			.32984	I > II
Bupivacaine 5 mg/mL	31	5.0				

[From sponsor's tables, Item 8, Vol. 83, pp. 230-239]

Maximum Degree of Motor Block (Bromage Scores)

There was no statistically significant difference between the two treatment groups with regard to maximum degree of motor blockade. When evaluated 30 minutes after surgery, twenty-three patients (45%) in the ropivacaine group and 14 patients (28%) in the bupivacaine group were found to have reached Level 3, or complete motor blockade. The following table summarizes these results. Data from patients termed "technical failures" and discontinuation data (premature discontinuation due to adverse events or use of another anesthetic modality) is not included in these tabulations

Table 12 Maximum Motor Blockade

Degree of Blockade (Bromage Score)	*Ropivacaine 7.5 mg/mL (n=51)*	*Bupivacaine 5 mg/mL (n=50)*	*p-value*	*Direction of Difference*
0	7	9		
1	11	8	.45563	I > II
2	10	19		
3	23	14		

[From sponsor's tables, Item 8, Vol. 83, pp. 291-300]

Time to Complete Regression of Motor Blockade

There was no statistically significant difference between the treatment groups in duration of motor blockade. Median time for return to normal motor function was 3.7 hours in the ropivacaine and 4.1 hours in the bupivacaine group. The following table summarizes these results. Data from patients termed "technical failures" and discontinuation data (premature discontinuation due to adverse events or use of another anesthetic modality) is not included in these tabulations

Table 13 Duration of Motor Blockade (hours)

Treatment Group	*N*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*
Ropivacaine 7.5 mg/mL	44	3.7			.77329	I < II
Bupivacaine 5 mg/mL	40	4.1				

[From sponsor's tables, Item 8, Vol. 83, pp. 291-300]

7.2.11.6 Reviewer's Efficacy Discussion

In this study the efficacy comparison of ropivacaine 7.5 mg/mL and bupivacaine 5 mg/mL for Caesarian section under epidural anesthesia was primarily analyzed using an endpoint of pain at delivery. Analysis of the results does not support a conclusion that either study drug is clinically or statistically more effective in decreasing the amount of pain perceived during this stage of the surgical procedure.

Secondary efficacy variables, including pain at skin incision, peritoneal closure, and last suture, quality of anesthesia, maximum cephalad spread of sensory block, maximum motor block achieved, time to onset of sensory blockade, and duration of sensory and motor blockade, were analyzed. These results also do not support a finding that one study drug is clinically or statistically more effective than the other.

The study was well designed and the resultant data was appropriately analyzed. Statistical calculations were performed on observed data and again on data assigning a high score of "100" to measurements in patients receiving other anesthetic modalities during the course of the study. No significant differences were found between the treatment groups in either data set. "Highest" pain scores for time-related measurements and "unsatisfactory" analgesia and muscle relaxation ratings were appropriately assigned to patients receiving general or spinal anesthesia or analgesic support during the treatment period. Exclusion of technical failures from the APT group in the final statistical compilations was appropriate given the desired measured variables. Results would have been no more valid, and probably less so, if data from a non-functional epidural anesthetic was combined with data from functional anesthetics. As expected, the technical failure rate was similar between the two groups (4 in the ropivacaine group and 3 in the bupivacaine group) and is within the acceptable technical failure rate for the procedure

In this study it must be noted that the sponsor chose to compare the efficacy of two different dosages of the study agents, 7.5 mg/ml of ropivacaine and 5 mg/ml of bupivacaine. Any differences that might occur in the measured variables, whether or not they are statistically significant, may be biased by dosage effect and thus may not reliably be used to support a finding of increased efficacy with equal concentrations of the tested agent. In fact, the increased dosage of ropivacaine might well have contributed to the noted higher cephalad spread of sensory blockade in this treatment group.

When measuring all stated efficacy variables, this study supports the conclusion that neither ropivacaine 7.5 mg/ml nor bupivacaine 5 mg/ml is more or less effective than the other when used for epidural anesthesia in Caesarian section.

7.2.12 STUDY 95RO91 (M10)

7.2.12.1 ***Protocol Synopsis***

Title:

Epidural anesthesia for Cesarean section: A double-blind comparison between ropivacaine 7.5 mg/ml and bupivacaine 5.0 mg/ml

Objectives:

"The objective of the study is to evaluate the efficacy and tolerability of ropivacaine 7.5 mg/ml and bupivacaine 5 mg/ml used for Cesarean section. Evaluation will be understood as the estimation of treatment differences with respect to efficacy and tolerability variables."
[Item 8, Vol. 86, p. 158]

Study Design:

This study is a multi-center, randomized, double-blind, parallel group design. One hundred sixteen women scheduled for elective Caesarian section are to be enrolled at ten centers. The subjects will be randomized to receive epidural anesthesia with 150-187.5 mg of ropivacaine 7.5 mg/ml or 100-150 mg of bupivacaine 5 mg/ml. Patients will have an equal probability of receiving the two drugs.

Patients eligible for the study will be women scheduled for elective cesarean section, ASA classes I & II, with full-term (≥37 and ≤42 weeks gestational age) singleton fetuses. They will be ≥18 years of age, ≥150 cm. tall, and ≤110 kg in weight, with an estimated fetal weight ≥2500 g. Patients will be excluded if they have a known history of allergy, sensitivity or reaction to amide local anesthetics, a contraindication to epidural anesthesia as judged by the investigator, have received any sedatives, hypnotics or narcotics within the preceding 12 hours, have suspected alcohol, drug or medication abuse, have a suspected inability to comply with the study procedures, or have pre-eclampsia as defined by the existence of two of the following findings: hypertension, proteinuria and edema.

Figure 1. Study Schemata (Final Design Incorporating Protocol Amendments)

Study Design	Actions	Induction of anesthesia								During surgery	After surgery							At discharge	After surgery
		Minutes									Hours								Weeks
	before surgery	-3	0	5	10	15	20	30	40		0	2	4	6	8	12	24		3-4
Medical history																			
Physical examination, ECG																			
Pre-anesthetic infusion																			
Test dose, lidocaine 3 ml																			
Ropi/bupi 20 ml (150 mg)																			
Add. doses ropi/bupi 5 ml																			
Add. dose saline/bupi 5 ml																			
Laboratory assessments																			
Maternal body temperature																			
Pain during surgery																			
Quality of analgesia																			
Quality of muscle relaxation																			
Sensory block													1						
Motor block													2						
Maternal BP, PR and SpO2											3								
Fetal heart rate									4										
Fetal body temperature																			
Adverse events																			
Apgar scores																			
NACS scores																			

1. Every 30 minutes after surgery until the return of normal sensation
2. 30 minutes after the end of surgery and then every 30 minutes until the return of normal function
3. Every 15 minutes up to 3 hours
4. Intermittently until preparation for surgery

[From sponsor's Figure 1, Item 8, Vol. 86, p. 20]

Pre-operatively, patients will be assessed for inclusion or exclusion to the study, informed consent will be given, and a history and physical exam will be obtained. Pre-anesthetic baseline measurements will include pulse, blood pressure, oxygen saturation, and temperature. At least 15 ml/kg of a crystalloid solution will be administered IV prior to the injection of any epidural medication.

After infiltration of the skin with a local anesthetic other than bupivacaine or ropivacaine, an epidural catheter will be placed, preferably at the L3-L4 interspace, utilizing standard technique (sitting or LLD position, 16-18 g Touhy, loss of resistance technique, catheter placement through needle). A test dose of 3 mL lidocaine 15 mg/ml with 5 μg/ml epinephrine will be injected and a 3-minute period will elapse for adverse event monitoring. Twenty ml of the study drug, either ropivacaine 7.5 mg/mL or bupivacaine 5 mg/mL, will then be injected in increments of 4 ml every 2 minutes over a 10 minute period.

Surgery will begin when a sensory block is confirmed at T6, using a blunt needle, and adequate surgical anesthesia, measured by forceps pinch in the incisional area, is achieved. Two additional top-up doses may be used to achieve this level, administered 10 minutes after the initial dose and 10 minutes after the first top-up dose. The first top-up dose will be 5 ml of bupivacaine 5 mg/mL or 5 mL of ropivacaine 7.5 mg/mL, depending on the randomized group. The second dose will be 5 ml of bupivacaine 5 mg/mL for the bupivacaine group or 5 ml of saline for the ropivacaine group. If adequate anesthesia has not been obtained 40 minutes after administration of the initial dose, the patient may receive additional analgesics or anesthetics at the investigator's discretion.
Sensory block will be determined bilaterally using a 27G needle every 5 minutes until start of surgery, will again be determined 30 minutes after surgery, and will be monitored every 30 minutes until return of normal sensation. Maximum upper spread of sensory block, time to T6 level, and time to maximum level will be recorded. Pain will be assessed at time of incision, delivery, closure of peritoneum, and last suture and rated according to a numerical scale from 0 (no pain) to 100 (worst pain ever). Motor block will be determined bilaterally utilizing a modified Bromage scale from 0 (full flexion) to 3 (no flexion hips, knees, ankles) starting 30 minutes after surgery ends and every 30 minutes until return of function. At the end of the surgical procedure quality of analgesia, assessed by the investigator, and quality of abdominal muscle relaxation, assessed by the surgeon, will be judged according to an "excellent", "satisfactory", "unsatisfactory" scale. Maternal and fetal hemodynamic measurements will be recorded throughout the study. Neonatal assessments by Apgar score and NACS will be performed at the appropriate post-natal time periods. Laboratory assessments and monitoring for adverse events will be performed for safety analyses.

7.2.12.2 Statistical Analysis

According to the original protocol, the single primary efficacy variable is "pain at delivery". Statistical analysis of this parameter will include descriptive statistics and graphs for each treatment group. Group differences will be discerned using a stratified Wilcoxon (mid) rank sum test adjusted for centers and sites. [Item 8, Vol. 86, pp. 176-177]

Secondary efficacy variables are as follows:

- Pain at skin incision, uterine exteriorization, closure of peritoneum/fascia, and last suture/clip
- Quality of anesthesia (analgesia and abdominal wall muscle relaxation
- Maximum upper spread of sensory block
- Time to onset of maximum sensory block
- Time to onset of T6 sensory level
- Time to complete regression of sensory block
- Maximum degree of motor block at 30 minutes post-surgery or later
- Time to complete regression of motor block.

As with the primary efficacy variable, the secondary variables will be analyzed using group-specific descriptive statistics and graphs, intergroup comparison with a stratified Wilcoxon (mid) rank sum test adjusted for centers and sites, and, where appropriate, point estimates and 95% confidence intervals. Patients receiving another anesthetic regimen before the end of surgery will be assigned the highest rank for pain analysis for any assessments performed after administration of the additional medication. All p-values reported will reflect two-sided tests and a p-value of <0.05 will be considered statistically significant. [Item 8, Vol. 86, p. 177-178]

7.2.12.3 Protocol Amendments

Amendment 1:

This amendment, dated 06/01/95, consists of the following change:

- Changes in wording *"administration of all therapy from insertion of the epidural needle until discharge from hospital, must be recorded..."* to *"administration of all therapy from the administration of premedication and/or pre-anaesthetic infusion until discharge from hospital, must be recorded..."*

Amendment 2:

This amendment, dated 06/27/95, consists of the following changes:

- Change to adverse event reporting procedures from *"adverse events regarding the mother and child will be recorded during hospitalization and at a telephone follow-up..."* to *"adverse events reported by the patient upon open, standardized questioning at hospital discharge and at a telephone follow-up..."*
- Change to adverse event reporting from *"maternal body temperature above 38.5 and/or a change in body temperature..."* to *"maternal body temperature above 38.5 or a change in body temperature..."*
- Change in adverse event reporting from *"severe – incapacitating with ability to perform..."* to *"severe – incapacitating with inability to perform..."*
- Change in adverse event definition

  Old Version

  "An adverse event is any unintended unfavorable clinical sign, symptom, medical complaint or clinically relevant change in laboratory test, whether or not considered drug related.

  Note that the definition could include reasons for changes in concomitant medication and deterioration in concurrent illness or the development of clinically relevant changes in laboratory variables, ECG, Xray or other clinical test. It could also include reasons for referral to a consultant or admission to hospital (e.g. an accident, or an operation not planned previously)."

  New Version

  "An adverse event is:
  - *Any unintended, unfavorable clinical sign or symptom*
  - *Any new illness or disease or deterioration of existing illness or disease*
  - *Any clinically relevant deterioration in laboratory assessments (e.g. hematological, biochemical, hormonal) or other clinical test (e.g. ECG, Xray)*

  Whether or not considered treatment related.

  Note that the definition could include accidents and reasons for:
  - *Changes in medication (drug and/or dose)*
  - *Medical/nursing/;pharmacy consultation*
  - *Admission to hospital*
  - *Surgical operations"*
- Changes to procedure for adverse event reporting – from *"within 10 working days"* to *"within 5 working days"*

Amendment 3:

This amendment, dated 12/13/95, consists of the following changes:

- Administrative features – addition of study personnel
- Addition to the definition of serious adverse event – *"Cancer will always be reported as a Serious Adverse Event as well as any experience associated with an overdose."*
- Deletion of one center due to anticipated significant delay in start of the study

Amendment 4:

This amendment, dated 05/06/96, consists of the following change:

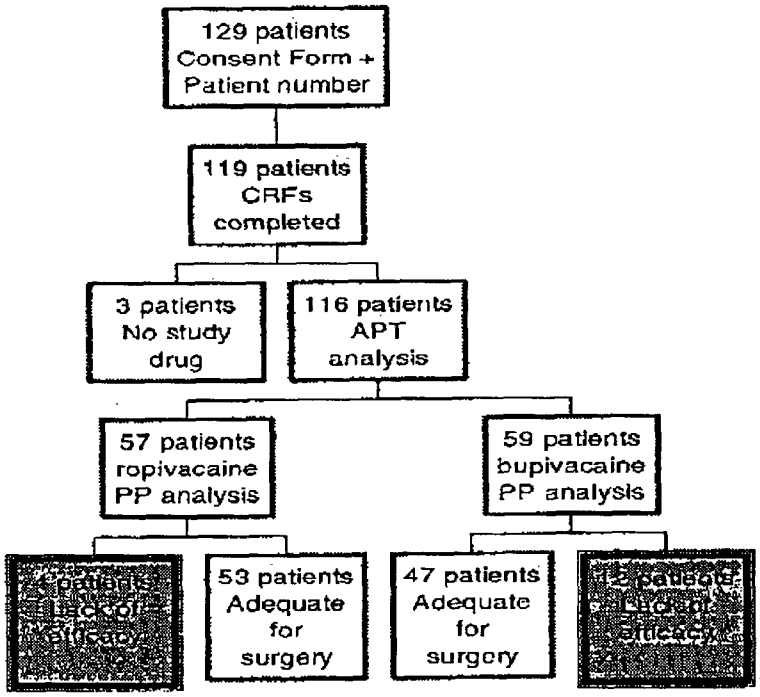
- Change of laboratory used for blood and serum analysis

7.2.12.4 Conduct of Study

Patient Distribution/Disposition:

Of the 119 patients enrolled in the study, all were randomized to receive either ropivacaine 7.5 mg/mL (59) or bupivacaine 5 mg/mL (60). Two patients in the ropivacaine group and 1 in the bupivacaine group did not receive the study drug. The APT group utilized for efficacy and safety analysis consisted of 57 ropivacaine patients and 59 bupivacaine patients. A total of 100 patients completed the study, 53 patients in the ropivacaine group and 47 patients in the bupivacaine group. Four patients in the ropivacaine group and 12 patients in the bupivacaine group were found to have a "lack of efficacy" and were given supplemental anesthetics/analgesics. Patient disposition for each treatment group is graphically represented in the following diagram.

Figure 2. Patient Disposition



[Based on Sponsor's diagram Item 8, Vol. 86, p. 46]

Six patients in the ropivacaine group and 13 patients in the bupivacaine group were prematurely discontinued from the efficacy study. The following table delineates assigned group and individual reason for discontinuation.

Table 1 Premature Discontinuation

Reason for Discontinuation	*Patient #*	*Ropivacaine 7.5 mg/mL*	*Bupivacaine 5 mg/mL*	*Included in Efficacy Studies*
No Study Drug	307, 605	X (2)		NO
No Study Drug	310		X (1)	NO
Lack of Efficacy – Analgesics	107, 301, 606, 813	X (4)		*PARTIALLY
Lack of Efficacy – Analgesics	109, 304, 317, 502, 601, 602, 804, 901, 1008		X (9)	*PARTIALLY
Lack of Efficacy – Spinal Anesth	205		X (1)	*PARTIALLY
Lack of Efficacy – Addit. Study drug	302, 303		X (2)	*PARTIALLY

* Efficacy measurements included up to time of additional analgesia/anesthesia
[Item 8, Vol. 86, pp. 53-54]

Demographics

The following tables summarize the general demographic characteristics of the two study populations. The groups were well matched in all demographic and baseline data collected.

Table 2 Age, Height, and Weight

Variable	Group	N	MEAN	STD	MIN	MAX
Age (years)	ROPI 7.5	57	30.3	5.4	19	41
	BUPI 5.0	59	31.2	5.7	18	43
Height (cm)	ROPI 7.5	56	163.0	5.8	150	182
	BUPI 5.0	59	162.0	6.7	150	175
Weight (kg)	ROPI 7.5	57	83.7	10.7	63	110
	BUPI 5.0	59	80.4	11.6	53	110

[Item 8, Vol. 87, p. 8]

Table 3 Ethnicity, ASA Classification, Parity, Gestational Age, and Allergy

	Ropivacaine (n=57)	Bupivacaine (n=59)
Ethnic background.		
CAUCASIAN	56	58
BLACK	1	.
OTHER	.	1
Allergy		
NO	36	35
YES	21	24
ASA risk		
GROUP 1	46	51
GROUP 2	11	8
Parae		
PRIMI	15	16
MULTI	42	43
Gestational age		
37	2	.
38	14	22
39	21	27
40	19	7
41	1	3

[Item 8, Vol. 86, p. 47]

The two groups were similar with respect to the incidence of significant findings in medical and surgical history. The number of patients with abnormal findings on physical exam was also similar between the two groups. Nine patients in the ropivacaine group and 6 patients in the bupivacaine group had borderline abnormal ECG's, and 2 patients in the bupivacaine group had abnormal ECG's. Current and/or past major disease or condition, abnormal ECG findings, previous major surgery, and abnormal physical exam findings were noted and are summarized in the following table.

Table 4 Abnormal History and Physical Findings

Abnormality	*Number of Patients* Ropivacaine 7.5 mg/mL	Bupivacaine 5 mg/mL
Abnormal Physical Exam	22	25
Borderline ECG	9	6
Abnormal ECG	0	2
Other Diseases	12	11
Surgical History	53	53

[Item 8, Vol. 86, pp. 47-49; Vol. 89, pp. 212-218]

The two study groups were similar when compared for median time from end of main dose to start of surgery, with a median time of 23 minutes for the ropivacaine group and 22 minutes for the bupivacaine group. The median duration of surgery was also similar between the groups, with times of 40 minutes and 42 minutes, respectively. These results are summarized in the following table.

Table 5 Pertinent Time Comparisons

Measured Variable	*N*	*Median*	*Minimum*	*Maximum*
End Main Dose to Start Surgery (minutes)				
Ropivacaine 7.5 mg/mL	57	23		
Bupivacaine 5 mg/mL	59	22		
Duration of Surgery (minutes)				
Ropivacaine 7.5 mg/mL	57	40		
Bupivacaine 5 mg/mL	59	42		

[Item 8, Vol. 86, pp. 51-55; Item 8, Vol. 89, p. 272]

The total volume (mL) of study drug received was similar between the two groups. However the total dose (mg) administered of the study drug was higher in the ropivacaine group. These results are summarized in the following table.

Table 6 Dose and Volume Comparisons

	Ropivacaine (n=57)	Bupivacaine (n=59)
Dose (mg)		
80	.	1
100	.	29
120	1	1
125	.	18
150	30	10
187.5	26	.
Dose (ml)		
16	1	1
20	30	29
24	.	1
25	17	18
30	9	10

[From Sponsor's Table 7, Item 8, Vol. 86, p. 55]

7.2.12.5 Sponsor's Efficacy Results

Primary Efficacy Variable:

Pain at Delivery

When analyzing only the observed scores, the number of patients experiencing pain scores above zero during delivery was similar between the two groups (13 patients in the ropivacaine 7.5 mg/mL group and 15 patients in the bupivacaine 5 mg/mL group). When patients receiving other anesthetic modalities (the discontinued group) were assigned a score of "100" (for highest level of pain), there was still no statistically significant difference in NRS pain scores measured at delivery between the groups. The following table summarizes these results.

Table 7 Pain at Delivery

	With Observed Scores							*With "100" Scores*		
Treatment Group	*N*	*# With NRS> 0*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*	*N*	*p-value*	*Direction of Difference*
Ropivacaine 7.5 mg/mL	57	13	0.0			45510	I < II	57	.26606	I < II
Bupivacaine 5 mg/mL	59	15	0.0					59		

[From sponsor's Table 16, Item 8, Vol. 86, p. 68 and Item 8, Vol. 87, pp. 261-271]

Secondary Efficacy Variables:

Pain at Skin Incision, Uterine Exteriorization, Closure of Peritoneum, and Last Suture

There were no statistically significant differences between the treatment groups in the amount of pain experienced at skin incision, uterine exteriorization, and peritoneal closure. However, there was a statistically significant difference between the treatment groups in the number of patients experiencing pain during last suture. This difference was present for analysis of both observed scores and the highest rank ("100") scores between the treatment groups and indicated that patients in the ropivacaine group experienced less pain than patients in the bupivacaine group. The following table summarizes these results.

Table 8 Pain With Incision, Uterine Exteriorization, Peritoneal Closure, and Last Suture

Assessment Event	With Observed Scores							With "100" Scores		
	N	*# With NRS>0*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*	*N*	*p-value*	*Direction of Difference*
Incision										
Ropivacaine 7.5 mg/;mL	57	6	0.0			.90733	I < II	57	.74252	I < II
Bupivacaine 5 mg/mL	59	6	0.0					59		
Uterine Exteriorization										
Ropivacaine 7.5 mg/;mL	23	3	0.0			.12789	I < II	19	.22605	I < II
Bupivacaine 5 mg/mL	20	6	0.0					20		
Peritoneal Closure										
Ropivacaine 7.5 mg/;mL	57	11	0.0			.76858	I < II	57	.23335	I < II
Bupivacaine 5 mg/mL	59	11	0.0					59		
Last Suture										
Ropivacaine 7.5 mg/;mL	57	2	0.0			.00575	I < II	57	.00826	I < II
Bupivacaine 5 mg/mL	59	10	0.0					59		

[From sponsor's Table 16, Item 8, Vol. 86, p. 68 and Item 8, Vol. 87, pp. 261-271]

Quality of Analgesia and Abdominal Wall Muscle Relaxation

There was a statistically significant difference between the two treatment groups for the quality of analgesia. Fifty-one patients in the ropivacaine group and 44 in the bupivacaine group were judged by the investigator to have "excellent" analgesia. However, there was no difference between the treatment groups in the quality of abdominal wall muscle relaxation as judged by the surgeon. All patients from the APT group were included in this analysis. The results for quality of analgesia and muscle relaxation for the two treatment groups are summarized in the following table.

Table 9 Quality of Analgesia and Abdominal Wall Muscle Relaxation

Measurement	*Ropivacaine 7.5 mg/mL (n=57)*	*Bupivacaine 5 mg/mL (n=59)*
Quality of Analgesia		
Unsatisfactory	4	13
Satisfactory	2	2
Excellent	51	44
p-value	.037136	
Direction of Difference	I > II	
Quality of Muscle Relaxation		
Unsatisfactory	1	1
Satisfactory	9	9
Excellent	47	49
p-value	.98337	
Direction of Difference	I < II	

[From sponsor's tables, Item 8, Vol. 87, pp. 277-280]

Maximum Upper Spread of Sensory Block

The maximum upper spread of sensory block varied between T6 and C8 for the ropivacaine group and T6 and C7 for the bupivacaine group. The difference between the two groups was not statistically significant. Data from patients discontinued from the study who received additional analgesia is not included in the tabulations. The following table summarizes these results.

Table 10 Maximum Upper Spread of Sensory Block

Segmental Level	*Ropivacaine 7.5 mg/mL (n=54)*	*Bupivacaine 5 mg/mL (n=55)*
T6	1	2
T5	7	4
T4	14	12
T3	15	15
T2	14	14
T1	2	5
C8	1	2
C7	0	1
p-value	.25030	
Direction of Difference	I < II	

[From sponsor's tables, Item 8, Vol. 87, pp. 235-242]

Time to Onset of Maximum Sensory Block, Onset of T6 Sensory Level, and Complete Regression of Sensory Block

There was no statistically significant difference between the two treatment groups for the time to onset of T6 block or maximum sensory block. The median time to onset of maximum sensory block was 25.5 minutes in the ropivacaine group and 23.0 minutes in the bupivacaine group. The median time to onset of T6 block was 10.0 minutes in the ropivacaine group and 11.0 minutes in the bupivacaine group. The investigator states (Item 8, Vol. 86, p.64) that the median time for regression of sensory block was statistically significantly longer in the ropivacaine group (6.4 hours) than in the bupivacaine group (5.5 hours). However, the presented p-value of .05317 (Item 8, Vol. 87, p. 242) does not support this statement. Data from patients discontinued from the study who received additional analgesia is not included in the tabulations. The following table summarizes these results.

Table 11 Sensory Block Time Measurements

Variable	*N*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*
Onset T6 (min)						
Ropivacaine 7.5 mg/mL	56	10.0			.89412	I > II
Bupivacaine 5 mg/mL	57	11.0				
Onset maximum (min)						
Ropivacaine 7.5 mg/mL	54	25.5			.36917	I > II
Bupivacaine 5 mg/mL	55	23.0				
Complete Regression (hr)						
Ropivacaine 7.5 mg/mL	53	6.4			.05317	I > II
Bupivacaine 5 mg/mL	45	5.5				

[From sponsor's tables, Item 8, Vol. 87, pp. 285-292]

Maximum Degree of Motor Block (Bromage Scores)

The maximum degree of motor blockade was statistically significantly higher in the ropivacaine group. When evaluated 30 minutes after surgery, 33 patients in the ropivacaine group and 19 patients in the bupivacaine group were found to have reached Level 3, or complete motor blockade. Data from patients discontinued from the study who received additional analgesia or other anesthetic modalities is not included in the tabulations. The following table summarizes these results.

Table 12 Maximum Motor Blockade

Degree of Blockade (Bromage Score)	*Ropivacaine 7.5 mg/mL (n=53)*	*Bupivacaine 5 mg/mL (n=48)*	*p-value*	*Direction of Difference*
0	3	4	.03614	I > II
1	6	8		
2	11	17		
3	33	19		

[From sponsor's tables, Item 8, Vol. 87, pp. 284-289]

Time to Complete Regression of Motor Blockade

There was no statistically significant difference between the treatment groups in duration of motor blockade. Median time for return to normal motor function was 4.3 hours in the ropivacaine group and 3.9 hours in the bupivacaine group. Data from patients discontinued from the study who received additional analgesia or other anesthetic modalities and from patients who had no motor block at any time of measurement is not included in the tabulations. The following table summarizes these results.

Table 13 Duration of Motor Blockade (hours)

Treatment Group	*N*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*
Ropivacaine 7.5 mg/mL	50	4.3			16281	I > II
Bupivacaine 5 mg/mL	44	3.9				

[From sponsor's tables, Item 8, Vol. 87, pp. 286-289]

7.2.12.6 Reviewer's Efficacy Discussion

In this study the efficacy comparison of ropivacaine 7.5 mg/mL and bupivacaine 5 mg/mL for Caesarian section under epidural anesthesia was primarily analyzed using an endpoint of pain at delivery. Analysis of the results does not support a conclusion that either study drug is clinically or statistically more effective in decreasing the amount of pain perceived during this stage of the surgical procedure.

Secondary efficacy variables, including pain at skin incision, uterine exteriorization, and peritoneal closure, maximum cephalad spread of sensory block, time to onset of sensory blockade, and duration of sensory and motor blockade, were analyzed. These results do not support a finding that one study drug is clinically or statistically more effective than the other.

However, analysis of several of the secondary efficacy variables did show a statistically significant difference between the two treatment groups. Pain with placement of last suture was rated significantly less ($p = .008$) in the ropivacaine group than in the bupivacaine group. Quality of analgesia, as judged by the investigator at the end of the surgery, was rated significantly higher ($p = .037$) in the ropivacaine group than in the bupivacaine group. And maximum motor block achieved, measured 30 minutes after surgery, was significantly greater ($p = .03614$) in the ropivacaine group than in the bupivacaine group.

The study was well designed and the resultant data was appropriately analyzed. Most of the statistical calculations for sensory and motor blockade spread and times were performed on data sets that did not include patients who had received analgesics or other anesthetic modalities during the course of the study ("discontinued" patients). However, analysis of pain scores did include these patients, with ratings of "100" for highest pain, so as not to bias the results towards effectiveness. Analysis of analgesic and motor blockade "quality" also included this patient subset. Interestingly, there were no "technical failures" reported in the total group of 116 patients, an incidence somewhat below the expected occurrence rate.

One area of confusion in this study is the statement under efficacy results that "the time to complete regression of sensory block was statistically significantly longer in the ropivacaine group" (Item 8, Vol. 86, p. 64). This statement is not supported by the p-value of .05317 generated during statistical analysis (Item 8, Vol. 87, p. 242). The "Summary of Results" in the Clinical Study Synopsis (Item 8, Vol. 86, p. 4) does not designate this efficacy variable as being one to show statistical significance and it is not mentioned in the synopsis conclusion (Item 8, Vol. 86, p. 6). It appears that the statement in the body of the report was an error that was not carried over into the final conclusions of the study.

In this study it must be noted that the sponsor chose to compare the efficacy of two different dosages of the study agents, 7.5 mg/ml of ropivacaine and 5 mg/ml of bupivacaine. Any differences that might occur in the measured variables, whether or not they are statistically significant, may be biased by dosage effect and thus may not reliably be used to support a finding of increased efficacy with equal concentrations of the tested agent.

When measuring the three efficacy variables, quality of analgesia, pain with last suture, and maximum degree of motor blockade, this study supports the conclusion that ropivacaine 7.5 mg/mL is more effective than bupivacaine 5 mg/mL in the total dosages that were given. However, when measuring all other stated efficacy variables, this study supports the conclusion that neither ropivacaine 7.5 mg/ml nor bupivacaine 5 mg/ml is more or less effective than the other when used for epidural anesthesia in Caesarian section.

7.2.13 STUDY 95RO96 (M11)

7.2.13.1 Protocol Synopsis

Title:

Evaluation of the efficacy and tolerability of ropivacaine 7.5 mg/ml and bupivacaine 5 mg/ml when used for epidural anesthesia for Caesarian section: A double-blind comparison

Objectives:

"The objective of the study is to evaluate the efficacy and tolerability of ropivacaine 7.5 mg/ml and bupivacaine 5 mg/ml used for Cesarean section. Evaluation will be understood as the estimation of treatment differences with respect to efficacy and tolerability variables." [Item 8, Vol. 90, p. 121]

Study Design:

This study is a multi-center, randomized, double-blind, parallel group design. One hundred twenty women scheduled for elective Caesarian section are to be enrolled at three centers. The subjects will be randomized to receive epidural anesthesia with 20-25 ml of ropivacaine 7.5 mg/ml or 30 ml of bupivacaine 5 mg/ml. Patients will have an equal probability of receiving the two drugs.

Patients eligible for the study will be women scheduled for elective cesarean section, ASA classes I & II, with full-term (≥36 and ≤41 weeks gestational age) singleton fetuses. They will be ≥18 years of age, ≥150 cm. tall, and ≤110 kg in weight, with an estimated fetal weight ≥2500 g. Patients will be excluded if they have a known history of allergy, sensitivity or reaction to amide local anesthetics, a contraindication to epidural anesthesia as judged by the investigator, have received any epidural analgesia, sedatives, hypnotics or narcotics within the preceding 12 hours, have suspected alcohol, drug or medication abuse, have a suspected inability to comply with the study procedures, have pre-eclampsia as defined by the existence of two of the following findings: hypertension, proteinuria and edema, or have participated in clinical studies of non-registered drugs in the preceding two weeks.

Figure 1. Study Schemata

	Actions before surgery	Induction of anesthesia Minutes										Surgery	Hours after surgery						Discharge from hospital	Weeks after surgery
		-3	0	5	10	15	20	30	40	50	60		0	2	4	5	8	24		3-4
Medical history																				
Physical examination																				
Pre-anaesthetic infusion																				
Test dose, lido 3 ml																				
Ropi/bupi 20 ml																				
Add. doses 2 x 5 ml																				
Postoptop-ups 3x8ml																				
Surgical anaesthesia																				
Pain/ discomfort during surgery																				
Quality of analgesia/ muscle relaxation																				
Sensory block				1																
Motor block													2							
Maternal BP, PR and SpO_2	3																			
Fetal HR		4																		
Adverse events	5																			
Apgar scores												6								
NACS scores																				

1. Every 5 min until the start of surgery
2. First assessment 30 min after the end of surgery
3. Continuously during anesthetic procedure and surgery, then every 30 minutes up to 5 hours
4. Monitored intermittently before the injection of anesthesia until preparation for surgery
5. AEs reported by the patient or observed by the investigational team or other person during hospitalization
6. 1 and 5 min after delivery

[From sponsor's Figure 1, Item 8, Vol. 90, p. 20]

Pre-operatively, patients will be assessed for inclusion or exclusion to the study, informed consent will be given, and a history and physical exam will be obtained. Pre-anesthetic baseline measurements will include pulse, blood pressure, oxygen saturation, and temperature. Approximately 15 ml/kg of a crystalloid solution will be administered IV prior to the injection of any epidural medication.

After infiltration of the skin with a local anesthetic other than bupivacaine or ropivacaine, an epidural catheter will be placed at any of the L2-L4 interspaces, utilizing standard technique (sitting or LLD position, 16-18 g Touhy, loss of resistance technique, catheter placement through needle). A test dose of 3 mL lidocaine 10 mg/ml with 5 μg/ml epinephrine will be injected and a 3-minute period will elapse for adverse event monitoring. Twenty ml of the study drug, either ropivacaine 7.5 mg/mL (150 mg) or bupivacaine 5 mg/mL (100 mg), will then be injected over a 5 minute period.

Surgery will begin when a sensory block is confirmed at T6 and adequate surgical anesthesia, measured by forceps pinch in the incisional area, is achieved. Two additional top-up doses may be used to achieve this level, administered 10 minutes after the initial dose and 10 minutes after the first top-up dose. The first top-up dose will be 5 ml of bupivacaine 5 mg/mL or 5 mL of ropivacaine 7.5 mg/mL, depending on the randomized group. The second dose will be 5 ml of bupivacaine 5 mg/mL for the bupivacaine group or 5 ml of saline for the ropivacaine group. Up to 25 ml of ropivacaine 7.5 mg/ml (150 or 187.5 mg) or 30 ml of bupivacaine 5 mg/ml (100, 125, 150 mg) may be administered. If adequate anesthesia has not been obtained 40 minutes after administration of the initial dose, the patient may receive additional analgesics or anesthetics at the investigator's discretion.

Following surgery a maximum of three top-up doses may be administered for pain management. These doses will be 8 ml of either ropivacaine 2 mg/ml or bupivacaine 2 mg/ml, corresponding to total doses of 48 mg of either drug.

Sensory block will be determined bilaterally using a 27G needle every 5 minutes until start of surgery. Maximum upper spread of sensory block, time to T6 level, and time to maximum level will be recorded. Pain will be assessed at time of incision, delivery, uterine exteriorization, closure of peritoneum, and last suture and rated according to a numerical scale from 0 (no pain) to 100 (worst pain ever). Discomfort will also be assessed at these times using the same scale. Motor block will be determined bilaterally utilizing a modified Bromage scale from 0 (full flexion) to 3 (no flexion hips, knees, ankles) starting 30 minutes after surgery ends and every 30 minutes until a decrease of one score is noted. At the end of the surgical procedure quality of analgesia, assessed by the investigator, and quality of abdominal muscle relaxation, assessed by the surgeon, will be judged according to an "excellent", "satisfactory", "unsatisfactory" scale. If a patient receives additional analgesics or anesthetics to complete the surgical procedure, the quality of analgesia will be recorded as "unsatisfactory". Maternal and fetal hemodynamic measurements will be recorded throughout the study. Neonatal assessments by Apgar score and NACS will be performed at the appropriate post-natal time periods. Monitoring for adverse events will be performed for safety analyses.

7.2.13.2 Statistical Analysis

According to the original protocol, the single primary efficacy variable is "pain at delivery". Statistical analysis of this parameter will include descriptive statistics and graphs for each treatment group. Group differences will be discerned using a stratified Wilcoxon (mid) rank sum test adjusted for centers and sites.
[Item 8, Vol. 90, pp. 139-140]

Secondary efficacy variables are as follows:

- Pain at skin incision, uterine exteriorization, closure of peritoneum, and last suture
- Discomfort at skin incision, delivery, uterine exteriorization, closure of peritoneum, and last suture
- Quality of anesthesia (analgesia and abdominal wall muscle relaxation
- Maximum upper spread of sensory block
- Time to onset of maximum sensory block
- Time to onset of T6 sensory level
- Maximum degree of motor block at 30 minutes post-surgery or later

As with the primary efficacy variable, the secondary variables will be analyzed using group-specific descriptive statistics and graphs, intergroup comparison with a stratified Wilcoxon (mid) rank sum test adjusted for centers and sites, and, where appropriate, point estimates and 95% confidence intervals. Patients receiving another anesthetic regimen before the end of surgery will be assigned the highest rank for pain analysis for any assessments performed after administration of the additional medication. All p-values reported will reflect two-sided tests and a p-value of <0.05 will be considered statistically significant. [Item 8, Vol. 90, p. 140-141]

Addition to statistical analysis in final Clinical Study Report:

> "Data after the time of discontinuation was not used for the efficacy variables maximum upper spread of sensory block, time to onset of maximum upper spread of sensory block and time to onset at T6, maximum degree of motor block 30 minutes after surgery or later."

7.2.13.3 Protocol Amendments

Amendment 1:

This amendment, dated 03/13/96, consists of the following changes:

- Amendments to description of treatment drug ampoules
- Changes to description of modified Bromage scale due to a typing error in original protocol
- Addition to the liability statement *"Astra's liability is covered by a liability insurance with*
- Changes to packaging, labeling, and storage criteria

Amendment 2:

This amendment, dated 05/02/96, consists of the following change:

- Change to epidural block procedure from *"one 5 ml dose 10 minutes after...a second 5 ml 10 minutes later"* to *"one 5 ml dose 15 minutes after...a second 5 ml 10 minutes later"*.

Amendment 3:

This amendment, dated 05/06/96, consists of the following change:

- Addition to procedure for adverse event reporting – *"The investigator will report serious and/or frequent adverse events directly to the Norwegian Medicines Control Authority (Statens Legemiddelkontroll) as soon as possible"*

Amendment 4:

This amendment, dated 09/02/96, consists of the following change:

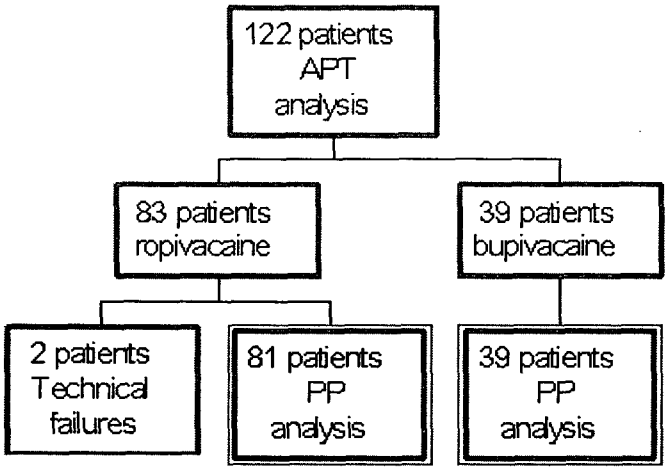
- Changes in wording *"administration of all medication (including study drugs) 2 weeks before surgery until discharge from hospital, must be recorded..."* to *"administration of all medication (including study drugs) from administration of premedication (including preanesthetic fluid) until the end of surgery must be recorded in the appropriate sections of the Case Report Form. Medications given due to an adverse event should always be recorded on the appropriate page in the CRF."*
- Changes in wording *"medication from 2 weeks before surgery until discharge from hospital"* to *"medication from administration of premedication (including preanesthetic fluid) until end of surgery"*

7.2.13.4 Conduct of Study

Patient Distribution/Disposition:

Of the 122 patients enrolled in the study, all were randomized to receive either ropivacaine 7.5 mg/mL (83) or bupivacaine 5 mg/mL (39). All 122 patients received a study drug and were part of the APT analysis group. Two patients in the ropivacaine group were termed "technical failures" and were not entered into the PP analysis group. One of these patients, #117, received 187.5 mg of ropivacaine and was subsequently given a spinal anesthetic for the surgical procedure. The other patient, #340, received 45 mg of ropivacaine and subsequently received a general anesthetic for the procedure. Patient disposition for each treatment group is graphically represented in the following diagram.

Figure 2. Patient Disposition



[Based on Sponsor's diagram Item 8, Vol. 90, p. 45]

Twenty-two patients in the ropivacaine group and 12 patients in the bupivacaine group were prematurely discontinued from the efficacy assessments. The following table delineates assigned group and individual reason for discontinuation.

Table 1 Premature Discontinuation

Reason for Discontinuation	*Patient #*	*Ropivacaine 7.5 mg/mL*	*Bupivacaine 5 mg/mL*	*Included in Efficacy Studies*
Technical Failure	117, 340	X (2)		NO
Adverse Events	101, 326	X (2)		*PARTIALLY
Lack of Efficacy – Other Epid agent	209	X (1)		*PARTIALLY
Lack of Efficacy – Other Epid agent	121		X (1)	*PARTIALLY
Lack of Efficacy – Analgesics	113, 134, 203, 206, 207, 210, 212, 215, 217, 219, 220, 223, 228, 235, 240, 309, 320	X (17)		*PARTIALLY
Lack of Efficacy – Analgesics	106, 111, 131, 208, 226, 229, 237, 316, 323, 325		X (11)	*PARTIALLY

* Efficacy measurements included up to time of additional analgesia/anesthesia
[Item 8, Vol. 90, pp. 45-53]

Demographics

The groups were well matched in all demographic and baseline data collected with the exception of an increased incidence of primiparity in the ropivacaine group. The following tables summarize the general demographic characteristics of the two study populations.

Table 2 Age, Height, and Weight

Variable	Group	N	MEAN	STD	MIN	MAX
Age (years)	ROPI 7.5	83	31.8	4.8		
	BUPI 5.0	39	32.9	4.0		
Height (cm)	ROPI 7.5	83	166.6	6.5		
	BUPI 5.0	39	165.1	5.7		
Weight (kg)	ROPI 7.5	83	78.1	12.1		
	BUPI 5.0	39	77.2	10.0		

[Item 8, Vol. 90, p. 46]

Table 3 Ethnicity, ASA Classification, Parity, Gestational Age, and Allergy

Variable	Value	Ropivacaine (n=83)	Bupivacaine (n=39)
Allergy	NO	63 (76)	30 (77)
	YES	20 (24)	9 (23)
Asa risk	GROUP 1	45 (54)	23 (59)
	GROUP 2	38 (46)	16 (41)
Ethnic background	CAUCASIAN	81 (98)	39 (100)
	ORIENTAL	1 (1)	. (.)
	OTHER	1 (1)	. (.)
Parae	PRIMI	25 (30)	5 (13)
	MULTI	58 (70)	34 (87)

(#) = Percentage of total

[Item 8, Vol. 90, p. 46]

The two groups were similar with respect to the incidence of significant findings in the medical history although the bupivacaine group had a slightly higher incidence of previous surgical procedures. The percentage of patients with abnormal findings on physical exam was slightly higher in the bupivacaine group than in the ropivacaine group. Current and/or past major disease or condition, previous major surgery, and abnormal physical exam findings were noted and are summarized in the following table.

Table 4 Abnormal History and Physical Findings

Abnormality	*Number of Patients (Percentage)* Ropivacaine 7.5 mg/mL	Bupivacaine 5 mg/mL
Abnormal Physical Exam	3 (3.6)	2 (5.1)
Other Medical Diseases	13 (15.7)	5 (12.8)
Surgical History	52 (62.7)	30 (76.9)

[Item 8, Vol. 90, p. 47; Vol. 92, pp. 156-159]

The two study groups were similar when compared for median time from end of main dose to start of surgery, with a median time of 36 minutes for the ropivacaine group and 36.5 minutes for the bupivacaine group. The median duration of surgery was also similar between the groups, with times of 35 minutes and 38 minutes, respectively. These results are summarized in the following table.

Table 5 Pertinent Time Comparisons

Measured Variable	*N*	*Median*	*Minimum*	*Maximum*
End Main Dose to Start Surgery (minutes)				
Ropivacaine 7.5 mg/mL	83	36		
Bupivacaine 5 mg/mL	38	36.5		
Duration of Surgery (minutes)				
Ropivacaine 7.5 mg/mL	83	35		
Bupivacaine 5 mg/mL	39	38		

[Item 8, Vol. 90, p. 48; Item 8, Vol. 92, p. 149]

The median volume (20 mL) of study drug used to establish the block was the same in both groups. However the median dose (mg) administered to establish the block was higher in the ropivacaine group (150 mg) than in the bupivacaine group (100 mg). These results are summarized in the following table.

Table 6 Dose and Volume Comparisons – Block Establishment

Variable	Value	Ropivacaine (n=83)	Bupivacaine (n=39)
Dose to establish block (mg)	45	1 (1)	. (.)
	100	. (.)	20 (51)
	125	. (.)	15 (38)
	150	42 (51)	4 (10)
	165	1 (1)	. (.)
	187.5	39 (47)	. (.)
Dose to establish block (ml)	6	1 (1)	. (.)
	20	42 (51)	20 (51)
	22	1 (1)	. (.)
	25	29 (35)	15 (38)
	30	10 (12)	4 (10)

[Item 8, Vol. 91, p. 16]

Table 7 Median Dose and Volume Comparisons – Block Establishment

Variable	*Media n*	*Min*	*Max*
Dose (mg)			
Ropivacaine	150		
Bupivacaine	100		
Dose (mL0			
Ropivacaine 7.5 mg/mL	20		
Bupivacaine 5 mg/mL	20		

*block classified as technical failure and remainder or study drug not injected
[Item 8, Vol. 91, p. 16]

The administration of concomitant medication for perioperative pain and discomfort was similar between the two groups. Eighteen (22%) patients in the ropivacaine group and 12 (31%) patients in the bupivacaine group received additional analgesia (fentanyl, alfentanil, chloroprocaine) before the end of the surgical procedure.

7.2.13.5 Sponsor's Efficacy Results

Primary Efficacy Variable:

Pain at Delivery

When analyzing only the observed scores, the number of patients experiencing pain scores above zero during delivery there was no statistically significant difference between the two groups (5% of patients in the ropivacaine 7.5 mg/mL group and 0 patients in the bupivacaine 5 mg/mL group). When patients receiving other anesthetic modalities (lack of efficacy) were assigned a score of "100", there was still no statistically significant difference in NRS pain scores measured at delivery between the groups. Pain at delivery was not assessed for two patients in the ropivacaine group (technical failures) and for one patient in the bupivacaine group (received general anesthesia shortly after incision). The following table summarizes these results.

Table 8 Pain at Delivery

	With Observed Scores							*With "100" Scores*		
Treatment Group	*N*	*# With NRS> 0*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*	*N*	*p-value*	*Direction of Difference*
Ropivacaine 7.5 mg/mL	81	4	0.0			.15865	I > II	81	.08146	I > II
Bupivacaine 5 mg/mL	38	0	0.0					38		

[From sponsor's Table 13, Item 8, Vol. 90, p. 60 and Item 8, Vol. 91, pp. 189-198]