Secondary Efficacy Variables:

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

Using observed values, there were no statistically significant differences between the treatment groups in the amount of pain experienced at skin incision, uterine exteriorization, and last suture. However, there was a statistically significant difference in favor of ropivacaine between the treatment groups in the number of patients experiencing pain during peritoneal closure (0 ropivacaine and 19% bupivacaine). When analysis incorporated the "100" (highest rank) scores, the only statistically significant difference between the treatment groups was for pain with uterine exteriorization. This difference was in favor of the bupivacaine group. Pain on skin incision, delivery, and last suture was not assessed for two patients in the ropivacaine group (technical failures). Pain on uterine exteriorization, closure of peritoneum, delivery, and last suture was not measured for one patient in the bupivacaine group (received general anesthesia shortly after incision). Due to variability in surgical technique, uterine exteriorization and peritoneal closure were not performed on all patients. The following table summarizes these results.

Table 9 Pain With Incision, Uterine Exteriorization, 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	81	0	0.0			NA	NA	81	.49452	I > II
Bupivacaine 5 mg/mL	39	0	0.0					39		
Uterine Exteriorization										
Ropivacaine 7.5 mg/;mL	75	12	0.0			.10140	I > II	75	.04743	I > II
Bupivacaine 5 mg/mL	38	2	0.0					38		
Peritoneal Closure										
Ropivacaine 7.5 mg/;mL	63	0	0.0			.00269	I > II	63	.54859	I < II
Bupivacaine 5 mg/mL	27	4	0.0					27		
Last Suture										
Ropivacaine 7.5 mg/;mL	81	0	0.0			.13529	I < II	81	.50710	I < II
Bupivacaine 5 mg/mL	38	1	0.0					38		

[From sponsor's Table 16, Item 8, Vol. 90, p. 61 and Item 8, Vol. 91, pp. 189-198]

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

There were no statistically significant differences between the treatment groups in the amount of perceived discomfort during any of the timed measurements. Analyses of both observed scores and "highest rank" scores yielded the same results. Discomfort on skin incision, delivery, and last suture was not assessed for two patients in the ropivacaine group (technical failures). Discomfort on delivery, uterine exteriorization, closure of peritoneum, and last suture was not measured for one patient in the bupivacaine group (received general anesthesia shortly after incision). Due to variability in surgical technique, uterine exteriorization and peritoneal closure were not performed on all patients. The following table summarizes these results.

Table 9 Discomfort With Incision, Delivery, Uterine Exteriorization, 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	81	1	0.0			.19893	I < II	81	.44156	I < II
Bupivacaine 5 mg/mL	39	2	0.0					39		
Delivery										
Ropivacaine 7.5 mg/;mL	81	9	0.0			.73377	I < II	81	.92125	I > II
Bupivacaine 5 mg/mL	38	5	0.0					38		
Uterine Exteriorization										
Ropivacaine 7.5 mg/;mL	75	9	0.0			.41741	I < II	75	.91472	I < II
Bupivacaine 5 mg/mL	38	7	0.0					38		
Peritoneal Closure										
Ropivacaine 7.5 mg/;mL	63	6	0.0			.40690	I < II	63	.89307	I > II
Bupivacaine 5 mg/mL	27	4	0.0					27		
Last Suture										
Ropivacaine 7.5 mg/;mL	81	1	0.0			.58034	I < II	81	.41346	I < II
Bupivacaine 5 mg/mL	38	1	0.0					38		

[Item 8, Vol. 91, pp. 190-204]

Quality of Analgesia and Abdominal Wall Muscle Relaxation

There was no statistically significant difference between the two treatment groups for the quality of analgesia. Seventy-five percent of the patients in the ropivacaine group and 69% of the patients in the bupivacaine group were judged by the investigator to have "excellent" analgesia. There was also no difference between the treatment groups in the quality of abdominal wall muscle relaxation. Ninety-four percent of the patients in the ropivacaine group and 97% of the patients in the bupivacaine group were judged by the surgeon to have "excellent" muscle relaxation. All patients from the APT group except the two patients classified as "technical failures" in the ropivacaine 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 11 Quality of Analgesia and Abdominal Wall Muscle Relaxation

Measurement	*Ropivacaine 7.5 mg/mL (n=81)*		*Bupivacaine 5 mg/mL (n=39)*
Quality of Analgesia			
Unsatisfactory	17 (21)		11 (28)
Satisfactory	3 (4)		1 (3)
Excellent	61 (75)		27 (69)
p-value		.41024	
Direction of Difference		I > II	
Quality of Muscle Relaxation			
Unsatisfactory	0		0
Satisfactory	5 (6)		1 (3)
Excellent	76 (94)		38 (97)
p-value		.39930	
Direction of Difference		I < II	

[Item 8, Vol. 91, pp. 207-211]

Of interest in the analysis of this efficacy variable was the finding of a wide disparity of analgesia ratings between the three centers. Center 2 rated only 57% of the ropivacaine patients as having "excellent" analgesia, as compared to 71% of the bupivacaine patients. They also rated 43% of the ropivacaine patients as having "unsatisfactory analgesia, as opposed to 29% of the bupivacaine patients. While this distribution was not statistically significant (p = .35446), and is not carried through to a similar finding of inadequate muscle relaxation, it does reflect the increased frequency of analgesic use during surgery by that site. These results are summarized in the following table.

Table 12 Quality of Analgesia and Abdominal Wall Muscle Relaxation

	Overall Results (%)		*Center 2 Results (%)*	
Measurement	*Ropivacaine 7.5 mg/mL (n=81)*	*Bupivacaine 5 mg/mL (n=39)*	*Ropivacaine 7.5 mg/mL (n=30)*	*Bupivacaine 5 mg/mL (n=14)*
Quality of Analgesia				
Unsatisfactory	21	28	43	29
Satisfactory	4	3	0	0
Excellent	75	69	57	71
p-value	.41024		.35446	
Direction of Difference	I > II		I < II	
Quality of Muscle Relaxation				
Unsatisfactory	0	0	0	0
Satisfactory	6	3	3	7
Excellent	94	97	97	93
p-value	.39930		.57644	
Direction of Difference	I < II		I > II	
Additional Analgesics	22	28	47	29

[Item 8, Vol. 91, pp. 207-212, 130-131]

Maximum Upper Spread of Sensory Block

The maximum upper spread of sensory block varied between T7 and T1 for the ropivacaine group and T6 and C4 for the bupivacaine group. The difference between the two groups was not statistically significant. Data from four patients in the ropivacaine group, two technical failures and two patients discontinued secondary to receiving analgesics prior to the time of measurement, is not included in the tabulations. The following table summarizes these results.

Table 13 Maximum Upper Spread of Sensory Block (% of Total)

Segmental Level	*Ropivacaine 7.5 mg/mL (n=79)*	*Bupivacaine 5 mg/mL (n=39)*
T7	1	0
T6	8	10
T5	18	10
T4	30	21
T3	22	38
T2	20	13
T1	1	3
C8	0	3
C4	0	3
p-value	.27283	
Direction of Difference	I < II	

[Item 8, Vol. 91, pp. 160-167]

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 minutes in the ropivacaine group and 27 minutes in the bupivacaine group. The median time to onset of T6 block was 15 minutes in the ropivacaine group and 15 minutes in the bupivacaine group. Data from five patients in the ropivacaine group, two technical failures and three patients discontinued secondary to receiving analgesics prior to the time of measurement, is not included in the tabulations. The following table summarizes these results.

Table 14 Sensory Block Time Measurements

Variable	*N*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*
Onset T6 (min)						
Ropivacaine 7.5 mg/mL	80	15			.65523	I < II
Bupivacaine 5 mg/mL	39	15				
Onset maximum (min)	79					
Ropivacaine 7.5 mg/mL	39	25			.93919	I > II
Bupivacaine 5 mg/mL		27				

[Item 8, Vol. 91, pp. 160-167]

Motor Block (Bromage Scores)

There is no statistically significant difference between the two treatment groups in the maximum degree of motor blockade achieved. When evaluated 30 minutes after surgery, 61% of the patients in the ropivacaine group and 50% of the patients in the bupivacaine group were found to have reached Level 3, or complete motor blockade. Data from patients who received additional analgesia or other anesthetic modalities prior to the time of measurement is not included in the tabulations. The following table summarizes these results.

Table 15 Maximum Motor Blockade (% of Total)

Degree of Blockade (Bromage Score)	*Ropivacaine 7.5 mg/mL (n=74)*	*Bupivacaine 5 mg/mL (n=32)*	*p-value*	*Direction of Difference*
0	4	3	.57069	I > II
1	16	13		
2	19	34		
3	61	50		

[Item 8, Vol. 91, pp. 213-216]

7.2.13.6 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 and discomfort at skin incision, uterine exteriorization, peritoneal closure, and last suture, maximum cephalad spread of sensory block, time to onset of sensory blockade, and maximum motor blockade, were analyzed. With one exception, these results do not support a finding that one study drug is clinically or statistically more effective than the other.

Analysis of the amount of perceived pain during peritoneal closure was rated significantly less ($p = .003$) in the ropivacaine group than in the bupivacaine group. This analysis was performed on the observed scores for each treatment group. However, when the analysis was performed using a score of "100" ("highest score" analysis) for those patients who received additional analgesia or anesthesia prior to the time of measurement, this statistical significance disappeared. Utilizing this "highest score" methodology, a statistical difference ($p = .047$) in favor of bupivacaine was found for perceived pain during uterine exteriorization.

The study was well designed and the resultant data was appropriately analyzed. 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 prior to the time of measurement. Analysis of pain and discomfort scores was performed twice, once excluding the patients referenced above and once including 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.

One area of interest in this study was the propensity of the investigational team at Center Two to use additional analgesics during the surgical procedure. Although their results were similar to those of the combined groups for most measured variables, they did have an increased number of patients (not statistically significant) who were judged by the investigators to have "unsatisfactory" analgesia. Whether this increase was a reflection of an actual increase in the amount of pain in their patient group or was a reflection of the investigator's lower threshold for treating perceived pain cannot be discerned from the data. Although not part of the study plan, it would have been interesting to compare guidelines for additional analgesic administration between the three centers.

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 analyzing observed scores of pain during peritoneal closure, 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. When analyzing observed scores of pain during uterine exteriorization, this study supports the conclusion that ropivacaine 7.5 mg/mL is less 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 statistically or clinically more or less effective than the other when used for epidural anesthesia in Caesarian section.

7.2.14 STUDY 96RO98 (M12)

7.2.14.1 ***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. 93, p. 94]

Study Design:

This study is a randomized, double-blind, parallel group design. One hundred sixteen women scheduled for elective Caesarian section are to be enrolled at one center. 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. 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 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 (Final Design Incorporating Protocol Amendments)

Study Design	Actions	Induction of anesthesia								Surgery	Hours after surgery							At discharge
	before surgery	Minutes									0	2	4	6	8	12	24	
		-5	0	5	10	15	25	30	40									
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																		
Pain/discomfort 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.									
Adverse events																		
Apgar scores											5.							
NACS scores																		

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

[From sponsor's Figure 1, Item 8, Vol. 93, 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. Approximately 10 ml/kg of a crystalloid solution will be administered IV over 10-15 minutes prior to the insertion of the epidural needle.

After infiltration of the skin with a local anesthetic, 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 5-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 in increments 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 5 mL 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.

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 verbal numerical rating scale (NRS) 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.

7.2.14.2 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. 93, pp. 112-113]

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. 93, p. 112-113]

7.2.14.3 Protocol Amendments

Amendment 1:

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

- Change in wording from *"administration of all medication from 2 weeks before surgery until discharge from hospital is described above. Further treatment will be given at the discretion of the investigator."* to *"administration of all medication from premedication (including preanesthetic infusion) until the end of surgery must be recorded in the appropriate section of the Case Report Form. Medications given due to adverse events should always be recorded on the appropriate page in the CRF"*

Amendment 2:

This amendment, dated 09/26/96, consists of the following changes:

- Administrative changes to investigator's credential list
- Addition of wording to measurement of pain and discomfort: *"The study nurse will put her finger on the score 0, and will slowly draw the finger to the score 100. The patient is instructed to say "stop" when the score corresponds to the degree of pain or discomfort."*

7.2.14.4 Conduct of Study

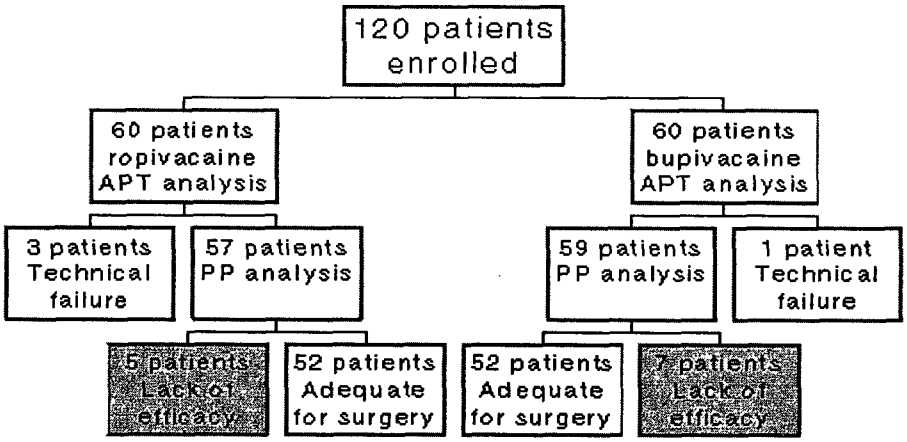
Deviation from Protocol in Final Study

The Visual Analog Scale (VAS) was used instead of the NRS for pain and discomfort ratings in patients #0101-0156. In patients #0157 and beyond, the VAS was used according to Protocol Amendment #2.

Patient Distribution/Disposition:

Of the 120 patients enrolled in the study, all were randomized to receive either ropivacaine 7.5 mg/mL (60) or bupivacaine 5 mg/mL (60). All 120 patients received a study drug and were part of the APT analysis group. Three patients in the ropivacaine group and 1 in the bupivacaine group were termed "technical failures" and were not entered into the efficacy analysis group. The three ropivacaine patients (#108, 119, 151) received doses of 187.5 mg, 150 mg, and 187.5 mg of ropivacaine and were subsequently given general anesthesia for the surgical procedure. The bupivacaine patient, #115, received 150 mg of bupivacaine and also 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. 93, p. 44]

Five patients in the ropivacaine group and 7 in the bupivacaine group were determined to have "lack of efficacy" and 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 – Gen. Anesth	108, 119, 151	X (3)		NO
Technical Failure – Gen. Anesth	115		X (1)	NO
Lack of Efficacy – Gen. Anesth	215	X (1)		*PARTIALLY
Lack of Efficacy – Analgesics	104, 117, 125, 193,	X (4)		*PARTIALLY
Lack of Efficacy – Analgesics	110, 116, 129, 137, 180, 189, 202		X (7)	*PARTIALLY

* Efficacy measurements included up to time of additional analgesia/anesthesia
[Item 8, Vol. 93, pp. 49-50, 236-289]

The total dose (mg) of study drug administered to those patients prematurely discontinued from efficacy measurements due to "lack of efficacy" is tabulated below.

Table 2 Total Dose of Study Drug - Premature Discontinuations

Study Drug (mg)	*Ropivacaine (n = 5)*	*Bupivacaine (n = 7)*
100	0	3
125	0	1
150	4	3
187.5	1	0

[Item 8, Vol. 93, p. 47]

Demographics

The groups were well matched in all demographic and baseline data collected with the exception of weight, where the ropivacaine group had a mean weight of 5.3 kg more than the bupivacaine group. The following tables summarize the general demographic characteristics of the two study populations.

Table 3 Age, Height, and Weight

Variable	Group	N	MEAN	STD	MIN	MAX
Age (years)	ROPI 7.5	60	29.7	5.4	20	48
	BUPI 5.0	60	30.8	5.2	22	45
Height (cm)	ROPI 7.5	60	154.5	4.1	146	163
	BUPI 5.0	60	154.3	5.3	145	168
Weight (kg)	ROPI 7.5	60	82.3	14.2	52	110
	BUPI 5.0	60	77.0	11.2	55	102

[Item 8, Vol. 93, p. 44]

Table 4 Ethnicity, ASA Classification, Parity, and Allergy

[Item 8, Vol. 93, p. 45]

	Ropivacaine (n=60)	Bupivacaine (n=60)
Ethnic backgr.		
CAUCASIAN	1	.
BLACK	59	60
Allergy		
NO	58	58
YES	2	2
Asa risk		
GROUP 1	57	56
GROUP 2	3	4
Parae		
PRIMI	.	3
MULTI	60	57

Patients in the ropivacaine 7.5 mg/ml group and the bupivacaine 5 mg/ml group were similar with respect to the incidence of significant findings in the medical and surgical history. The number of patients with abnormal findings on physical exam was also similar in the two groups. 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 5 Abnormal History and Physical Findings

Abnormality	*Number of Patients* Ropivacaine 7.5 mg/mL	Bupivacaine 5 mg/mL
Abnormal Physical Exam	2	4
Other Medical Diseases	9	7
Surgical History	57	56

[Item 8, Vol. 93, pp. 45-46; Vol. 95, pp. 105-108]

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 33 minutes for the ropivacaine group and 38 minutes for the bupivacaine group. The median duration of surgery was also similar between the groups, with times of 25 minutes and 24 minutes, respectively. These results are summarized in the following table.

Table 6 Pertinent Time Comparisons

Measured Variable	*N*	*Median*	*Minimum*	*Maximum*
End Main Dose to Start Surgery (minutes)				
Ropivacaine 7.5 mg/mL	60	25		
Bupivacaine 5 mg/mL	60	24		
Duration of Surgery (minutes)				
Ropivacaine 7.5 mg/mL	60	33		
Bupivacaine 5 mg/mL	60	38		

[Item 8, Vol. 93, p. 46; Item 8, Vol. 95, p. 141]

The total volume (ml) of study drug used to establish the block was similar between the two groups as depicted in the table below.

Table 7 Dose and Volume Comparisons – Block Establishment

	Ropivacaine (n=60)	Bupivacaine (n=60)
Dose (mg)		
100	.	50
125	.	5
150	53	5
187.5	7	.
Dose (ml)		
20	53	50
25	6	5
30	1	5

[Item 8, Vol. 93, p. 48]

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 tables.

Table 8 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		

[Item 8, Vol. 93, p. 48]

The administration of concomitant medication for perioperative pain and discomfort was similar between the two groups. Five patients in the ropivacaine group and 7 patients in the bupivacaine group received additional analgesia (alfentanil, nitrous oxide, opiates, pethidine, enflurane) before the end of the surgical procedure.

7.2.14.5 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 the same (11) in the two treatment groups. When patients receiving other anesthetic modalities (lack of efficacy) were assigned a score of "100" (highest on the pain scale), there was still no statistically significant difference in pain scores measured at delivery between the groups. Pain at delivery was not assessed for four patients in the ropivacaine group (3 technical failures, 1 given general anesthesia at skin incision) and for one patient in the bupivacaine group (technical failure). The following table summarizes these results.

Table 9 Pain at Delivery

Treatment Group	With Observed Scores							With "100" Scores		
	N	# With NRS> 0	Median	Min	Max	p-value	Direction of Difference	N	p-value	Direction of Difference
Ropivacaine 7.5 mg/mL	56	11	0.0			.56785	I > II	57	.42612	I > II
Bupivacaine 5 mg/mL	59	11	0.0					59		

[From sponsor's Table 14, Item 8, Vol. 93, p. 58 and Item 8, Vol. 94, pp. 100-105]

Secondary Efficacy Variables:

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

Using observed values, there were no statistically significant differences between the treatment groups in the amount of pain experienced at skin incision, uterine exteriorization, peritoneal closure, and last suture. When analysis incorporated the "highest rank" scores (patients receiving other analgesics are assigned pain score of "100" for highest pain), again there were no statistically significant differences between the treatment groups for any assessment of pain during surgery. Pain was not assessed for four patients in the ropivacaine group (3 technical failures, 1 given general anesthesia at skin incision) and for one patient in the bupivacaine group (technical failure). Pain on peritoneal closure and last suture was not assessed on one additional patient in the bupivacaine group given additional analgesia. Due to variability in surgical technique, uterine exteriorization and peritoneal closure were not performed on all patients. The following table summarizes these results.

Table 10 Pain With Incision, Uterine Exteriorization, Peritoneal Closure, and Last Suture

Table 78

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	56	1	0.0			.96058	I > II	56	.96058	I > II
Bupivacaine 5 mg/mL	59	1	0.0					59		
Uterine Exteriorization										
Ropivacaine 7.5 mg/;mL	53	7	0.0			.47193	I < II	54	.68171	I < II
Bupivacaine 5 mg/mL	50	11	0.0					51		
Peritoneal Closure										
Ropivacaine 7.5 mg/;mL	51	1	0.0			.42116	I < II	52	.29415	I < II
Bupivacaine 5 mg/mL	52	4	0.0					53		
Last Suture										
Ropivacaine 7.5 mg/;mL	56	0	0.0			.33244	I < II	57	.43072	I < II
Bupivacaine 5 mg/mL	58	3	0.0					59		

[From sponsor's Table 14, Item 8, Vol. 93, p. 58 and Item 6, vol. 94, pp. 100-105]

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

There were no statistically significant differences between the treatment groups in the amount of perceived discomfort during any of the timed measurements. Analyses of both observed scores and "highest rank" scores yielded the same results. Discomfort was not assessed for four patients in the ropivacaine group (3 technical failures, 1 given general anesthesia at skin incision) and for one patient in the bupivacaine group (technical failure). Discomfort on peritoneal closure and last suture was not assessed on one additional patient in the bupivacaine group given additional analgesia. Due to variability in surgical technique, uterine exteriorization and peritoneal closure were not performed on all patients. The following table summarizes these results.

Table 11 Discomfort With Incision, Delivery, Uterine Exteriorization, 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	56	1	0.0			.96058	I > II	56	.96058	I > II
Bupivacaine 5 mg/mL	59	1	0.0					59		
Delivery										
Ropivacaine 7.5 mg/;mL	56	15	0.0			.97786	I > II	57	.79940	I > II
Bupivacaine 5 mg/mL	59	17	0.0					59		
Uterine Exteriorization										
Ropivacaine 7.5 mg/;mL	53	6	0.0			.37664	I < II	54	.59052	I < II
Bupivacaine 5 mg/mL	50	10	0.0					51		
Peritoneal Closure										
Ropivacaine 7.5 mg/;mL	51	2	0.0			.64840	I > II	52	.41245	I < II
Bupivacaine 5 mg/mL	52	2	0.0					53		
Last Suture										
Ropivacaine 7.5 mg/;mL	56	0	0.0			.58438	I < II	57	.58617	I < II
Bupivacaine 5 mg/mL	58	2	0.0					59		

[Item 8, Vol. 94, pp. 110-111]

Quality of Analgesia and Abdominal Wall Muscle Relaxation

There was no statistically significant difference between the two treatment groups for the quality of analgesia. Forty-three patients in the ropivacaine group and 38 patients in the bupivacaine group were judged by the investigator to have "excellent" analgesia. There was also no difference between the treatment groups in the quality of abdominal wall muscle relaxation. Fifty-five patients in each treatment group were judged by the surgeon to have "excellent" muscle relaxation. All patients from the APT group except the patients classified as "technical failures" (3 in the ropivacaine group and 1 in the bupivacaine 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 12 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	5		7
Satisfactory	9		14
Excellent	43		38
p-value		.21276	
Direction of Difference		I > II	
Quality of Muscle Relaxation			
Unsatisfactory	0		0
Satisfactory	2		4
Excellent	55		55
p-value		.42849	
Direction of Difference		I > II	

[Item 8, Vol. 94, pp. 117-116]

Maximum Upper Spread of Sensory Block

The maximum upper spread of sensory block varied between T6 and C3 for the ropivacaine group and T10 and C3 for the bupivacaine group. The difference between the two groups was not statistically significant. Data from patients judged technical failures (3 in the ropivacaine group, 1 in the bupivacaine group) was not included in the analysis. The following table summarizes these results.

Table 13 Maximum Upper Spread of Sensory Block

Segmental Level	*Ropivacaine 7.5 mg/mL (n=57)*	*Bupivacaine 5 mg/mL (n=59)*
T10	0	1
T8	0	1
T6	1	1
T5	1	9
T4	20	17
T3	11	10
T2	6	9
T1	4	0
C6	6	1
C5	3	4
C4	2	2
C3	3	4
p-value	.10359	
Direction of Difference	I > II	

[Item 8, Vol. 94, pp. 75-167]

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 15 minutes for both groups. The median time to onset of T6 block was 4 minutes in the ropivacaine group and 5 minutes in the bupivacaine group. Data from patients judged technical failures (3 in the ropivacaine group, 1 in the bupivacaine group) was not included in the analysis. The following table summarizes these results.

Table 14 Sensory Block Time Measurements

Variable	*N*	*Median*	*Min*	*Max*	*p-value*	*Direction of Difference*
Onset T6 (min)						
Ropivacaine 7.5 mg/mL	57	4			.85185	I < II
Bupivacaine 5 mg/mL	59	5				
Onset maximum (min)						
Ropivacaine 7.5 mg/mL	57	15			.22564	I < II
Bupivacaine 5 mg/mL	57	15				

[Item 8, Vol. 94, pp. 76-78]

Maximum Degree of Motor Block (Bromage Scores)

There was no statistically significant difference between the two treatment groups in the maximum degree of motor blockade achieved. When evaluated 30 minutes after surgery, 26 of the patients in the ropivacaine group and 15 of the patients in the bupivacaine group were found to have reached Level 3, or complete motor blockade. Data from 8 ropivacaine patients (3 technical failures, 5 discontinued after receiving additional analgesia prior to measurement) and 8 bupivacaine patients (1 technical failure, 7 discontinued after receiving additional analgesia prior to measurement) is not included in the tabulations. The following table summarizes these results.

Table 15 Maximum Motor Blockade

Degree of Blockade (Bromage Score)	*Ropivacaine 7.5 mg/mL (n=52)*	*Bupivacaine 5 mg/mL (n=52)*	*p-value*	*Direction of Difference*
0	8	9		
1	9	15	.07241	I > II
2	9	13		
3	26	15		

[Item 8, Vol. 94, pp. 120-121]

7.2.14.6 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 and discomfort at skin incision, uterine exteriorization, peritoneal closure, and last suture, maximum cephalad spread of sensory block, time to onset of sensory blockade, maximum motor blockade, and quality of anesthesia were analyzed. These results 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 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 prior to the time of measurement. Analysis of pain and discomfort scores was performed twice, once excluding the patients referenced above and once including 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.

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

Reviewer's Efficacy Summary

Epidural Block for Caesarian Section

Open-Label Studies M04, M08

There were two open-label studies of ropivacaine 7.5 mg/mL for epidural block in elective caesarian section, one utilizing two different dosages of the study drug (M08) and one utilizing a single dose of the study drug (M04). Study M04 was conducted on 38 patients, 37 of whom received 20 cc of ropivacaine 7.5 mg/mL (150 mg). Study M08 was conducted on 16 patients, 8 of whom received 20 cc of ropivacaine 7.5 mg/mL (150 mg) and 8 of whom received 25 cc of the same drug. Both studies evaluated the quality of anesthesia, onset of maximum sensory level, and degree and duration of motor blockade. Study M08 also evaluated pain and discomfort during surgery. Comparable results from the two studies are presented in the following table.

Table 1 Study Variable Comparisons

Variable	*Study M04*	*Study M08*	
Ropivacaine Dose	150 mg (n=37)	150 mg (n=8)	187.5 mg (n=8)
Maximum Sensory Level	T3	T2	C7
Quality of Analgesia (Satisfactory or greater)	84%	88%	88%
Quality of Muscle Relaxation (Satisfactory or greater)	87%	100%	100%
Motor Block (Bromage Scale)			
0	3%		
1	42%	12.5%	0
2	19.5%	25%	12.5%
3	35.5%	62.5%	87.5%
Median Time to Motor Block Regression (hours)	2.2	3.3	4.6

Ratings of quality of analgesia and muscle relaxation were comparable in both studies and there was no discernable difference with the higher 187.5 mg dose. Ratings of motor blockade were quite different between the two studies, with only 35.5% of patients in Study M04 reaching a Bromage Level 3 and 62.5% of patients in the comparable-dose group from Study M08 reaching the same level. 87.5% of patients in the higher dose group (187.5 mg) of Study M08 reached this level. Median time to motor block regression was also different in the two studies, with 2.2 hours for Study M04, 3.3 hours for the comparable dose in Study M08 and 4.6 hours for the higher dose in Study M08.

In summary, these two studies provided information on onset, duration, and quality of sensory and motor blockade after epidural administration of ropivacaine 7.5 mg/mL that could be used to establish dosing guidelines for subsequent comparative studies.

Patricia Hartwell, MD, MBA

Reviewer's Efficacy Summary

Epidural Block for Caesarian Section

Comparative Studies M09, M10, M11, M12

There were four studies comparing the efficacy of ropivacaine 7.5 mg/mL to bupivacaine 5 mg/mL for elective caesarian section under epidural blockade. All studies were of a randomized, double-blind, parallel-group design. Study M09 was conducted on 124 patients at 3 centers, Study M10 was conducted on 116 patients at 8 centers, Study M11 was conducted on 122 patients at 3 centers, and Study M12 was conducted on 120 patients at a single center. In all studies analysis of pain and discomfort was performed on two data sets, one utilizing "observed" scores and one utilizing "100" scores (highest pain/discomfort score assigned if additional analgesia/anesthesia given prior to measurement).

All studies analyzed a primary efficacy variable of pain on delivery. None of the studies demonstrated a clinically or statistically significant difference in the analysis of results from this variable between the two treatment groups. The percentage of patients in each treatment group with an NRS > 0 (numerical rating scale) is shown for each study in the following table.

Table 1 – Study Comparisons: Pain on Delivery (NRS > 0)

Study	*Ropivacaine 7.5 mg/mL*	*Bupivacaine 5 mg/mL*
M09	4%	7%
M10	23%	25%
M11	5%	0
M12	20%	19%

Numerous secondary efficacy variables, including pain and discomfort at various times during the surgical procedure, maximum spread and time to onset of sensory block, maximum motor block, and quality of anesthesia were assessed in the four studies. Several statistically significant differences between the treatment groups were noted; however, none of the statistical differences were seen in more than one study. The statistically significant differences that were seen are summarized in the following table.

Table 2 Study Comparisons: Secondary Efficacy Variables

Study Variable	*Ropivacaine 7.5 mg/mL*	*Bupivacaine 5 mg/mL*	*p-value*
M10			
Pain with Last Suture (Observed & "100" scores)	3.5%	17%	.006
Quality of Analgesia "Satisfactory" or greater)	93%	78%	.037
Maximum Motor Blockade (Bromage Score 3)	62%	40%	.036
M11			
Pain with Peritoneal Closure (Observed)	0	15%	.003

The median dose and volume required to establish epidural blockade was similar across all four studies. The median dose of ropivacaine was 150 mg (20 mL) and the median dose of bupivacaine was 100 mg (20 mL) for all studies. Minimum and maximum dosages were also similar. It appears from these results that there may be little difference between the two study drugs when assessing required dosage. The following table illustrates these results.

Table 3 Study Comparisons: Median Dose and Volume

Variable	*Median*	*Minimum*	*Maximum*
M09			
Dose (mg)			
Ropivacaine	150		
Bupivacaine	100		
Volume (mL)			
Ropivacaine 7.5 mg/mL	20		
Bupivacaine 5 mg/mL	20		
M10			
Dose (mg)			
Ropivacaine	150		
Bupivacaine	100		
Volume (mL)			
Ropivacaine 7.5 mg/mL	20		
Bupivacaine 5 mg/mL	20		
M11			
Dose (mg)			
Ropivacaine	150		
Bupivacaine	100		
Volume (mL)			
Ropivacaine 7.5 mg/mL	20		
Bupivacaine 5 mg/mL	20		
M12			
Dose (mg)			
Ropivacaine	150		
Bupivacaine	100		
Volume (mL)			
Ropivacaine 7.5 mg/mL	20		
Bupivacaine 5 mg/mL	20		

With the exception of the results previously mentioned for M10, the studies as a whole showed little difference between the treatment groups in quality of anesthesia. These results are presented in the following table.

Table 4 Study Comparisons: Quality of Anesthesia (% "Satisfactory or Greater)

Variable	*Ropivacaine 7.5 mg/mL*	*Bupivacaine 5 mg/mL*
M09		
Quality of Analgesia	85%	85%
Quality of Muscle Relaxation	90%	93%
M10		
Quality of Analgesia	93%	78%
Quality of Muscle Relaxation	98%	98%
M11		
Quality of Analgesia	79%	72%
Quality of Muscle Relaxation	100%	100%
M12		
Quality of Analgesia	91%	88%
Quality of Muscle Relaxation	100%	100%

There was little difference among the studies in the maximum upper spread of the sensory block or the time to onset of a T6 block. There was no statistical difference shown for these two variables between the two study drugs. These results are summarized in the following table.

Table 5 Study Comparisons: Maximum Sensory Block, Time to T6

Variable	*Ropivacaine 7.5 mg/mL*	*Bupivacaine 5 mg/mL*
M09		
Maximum Upper Sensory Block (Median)	T4	T4
Time to T6 Block (minutes)	10	10
M10		
Maximum Upper Spread of Sensory Block (Median)	T3	T3
Time to T6 Block (minutes)	10	11
M11		
Maximum Upper Spread of Sensory Block (Median)	T4	T3
Time to T6 Block (minutes)	15	15
M12		
Maximum Upper Spread of Sensory Block (Median)	T3	T3
Time to T6 Block (minutes)	4	5

With the exception of the results previously mentioned for Study M10, the percentage of patients achieving maximum motor blockade (Bromage Score 3) was similar in all studies and between the two treatment groups. These results are summarized below.

Table 6 Study Comparisons: Maximum Motor Blockade (% of Total)

Study	*Ropivacaine 7.5 mg/mL*	*Bupivacaine 5 mg/mL*	*p-value*
M09	45%	28%	.456
M10	63%	40%	.036
M11	61%	50%	.571
M12	50%	29%	.072

These studies were all well designed and the resultant data was appropriately analyzed. 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 prior to the time of measurement. Analysis of pain and discomfort scores was performed twice, once excluding the patients referenced above and once including 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. Exclusion of technical failures from the analysis was appropriate given the desired measure variables. Results would have been no more valid, and possibly less so, if data from a non-functional epidural anesthetic was combined with data from functional blocks.

It should be noted that in all of the studies, 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.

In summary, when considering these studies as a whole and measuring all stated efficacy variables, analysis of the results supports the conclusion that neither ropivacaine 7.5 mg/ml nor bupivacaine 5 mg/ml is more or less effective than the other for caesarian section epidural anesthesia.

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Patricia Hartwell, MD, MBA

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(Monica L. Roberts, M.D., in support of)

Supportive Clinical Trials

I. Postoperative Pain Management Trials

7.2.15 STUDY # 94RO83-01 (I32)

7.2.15.1 Protocol Synopsis:

Title: "72-h Continuous Epidural Infusion with 20 and 30 mg/h ropivacaine 2 and 3 mg/ml for Postoperative Pain Relief following Major Orthopaedic Surgery – a Pharmacokinetic and Clinical Evaluation"

Primary Objective: "To estimate the plasma concentration- time profile of ropivacaine based on both total and free concentrations when infused epidurally for 72 h and to compare the pharmacokinetic variables obtained for two groups, using two different infusion rates."

Secondary Objective:

- "To determine the change in the plasma concentrations of alpha-1-acid glycoprotein (AAG) with time.
- To estimate the urinary excretion of unchanged ropivacaine
- To assess the plasma levels and the urinary excretion of the major metabolites 3-OH-ropivacaine (3-OH-R), N-depropylated ropivacaine (PPX) and 2-OH-methyl ropivacaine
- To exploratively estimate clinical efficacy and tolerability"

[Item 8, Vol. 36, p. 18]

Study Design:

The study was double-blind and randomized with two parallel treatment arms. Twenty-nine patients scheduled for total knee or hip replacement surgery using a combination of epidural block with ropivacaine and light general anesthesia were enrolled. Prior to surgery, patients received an epidural bolus dose of 75 mg ropivacaine (15ml, patients #1-5) or 50 mg (10 ml, patients # 6-40) followed by their randomized epidural infusion of 20 or 30 mg/h ropivacaine for 72 hours.

Group I	20 mg/h ropivacaine (0.2%)
Group II	30 mg/h ropivacaine (0.3%)

Eligible patients were American Society of Anesthesiologists physical status I -III males or females (adequately protected against pregnancy) between 18 and 80 years of age, with normal laboratory findings and body weight of 50 –110 kg. Patients had not participated in any clinical study with an investigational drug within 3 months prior to the start of the study, had no symptoms of a clinically significant illness and were not drug or alcohol abusers.

Preoperatively, patients received oral temazepam (10-20 mg) or i.m. midazolam. All patients were preloaded with consisted of ≥ 500 ml of crystalloid. Low dose heparin, warfarin, or other anticoagulant could be administered, according to hospital routine. Indomethacin could also be given rectally on the day of surgery.

Epidural anesthesia was performed in accordance with the current standard of care. Lidocaine 5 mg was used for skin infiltration. A 16G epidural needle was inserted between L2-L4 followed by a 3 ml test dose lidocaine (1% with 5 μg/ml of epinephrine) for ≤ 1 minute. A bolus dose of 75 mg ropivacaine (15ml, patients #1-5) or 50 mg (10 ml, patients # 6-40) was given followed within 3 minutes by the randomized epidural infusion of 20 or 30 mg/h ropivacaine for 72 hours.

Group I	20 mg/h ropivacaine (0.2%)
Group II	30 mg/h ropivacaine (0.3%)

The induction of general anesthesia was performed 20 minutes after the start of the infusion using thiopental, pancuronium or succinylcholine and fentanyl (≤ 200 ug). Anesthesia was maintained with isoflurane, nitrous oxide/oxygen or air/oxygen and fentanyl 50 ug (given as needed). Neostigmine with atropine or glycopyrrolate was administered for reversal of muscle relaxation.

Fentanyl 50 ug was administered if the patient exhibited signs of inadequate anesthesia, as defined as follows:

- Systolic blood pressure increased to more than 15 mmHg above normal for that patient
- Heart rate increase to above 90 beats/min in the absence of hypovolemia
- Autonomic signs, e.g., lacrimation, flushing, sweating
- Somatic responses, e.g., swallowing, coughing, eye opening or bodily movements

If the postoperative degree of motor block exceeded one (according to the Bromage scale) or if the sensory block exceeded T4, the infusion rate could be reduced by 2 ml/h. If there was a further increase in the upper level of loss of sensation to temperature or the intensity of motor block 2h after a decrease in the infusion rate, the infusion was again reduced by 2 ml/h. If the upper level of loss of sensation to temperature or the intensity of motor block remained unchanged after another 2 h, i.e., 4 h after a decrease in the infusion rate, the infusion was reduced 1 ml/h every 2 h until the upper level of loss was below T4 or the intensity of motor block was ≤1. The infusion rate could be increased again up to the maximum of 10 ml/h at the discretion of the investigator.

If the upper level of sensory block had not reached T12 within 20 minutes after the start of the infusion, the general anesthesia commenced and the patient was considered to be a drop-out.

Postoperatively, a patient-controlled analgesia morphine device was instituted. The amount of morphine requested/consumed was calculated as well as, the visual analog scale, level of sensory block (temperature perception changes) and the degree of motor block.

Peripheral venous blood samples for analyses of total and free plasma concentrations or ropivacaine and major metabolites, 2-OH-ropivacaine PPX, (N-depropylated ropivacaine) and 2-OH-methyl ropivacaine were taken during the infusion period and during 6 h post-infusion. Urine was collected at 12-h intervals to estimate the urinary excretion of unchanged ropivacaine and the major metabolites.

7.2.15.2 Sponsor's Efficacy Results:

Amount of Analgesic Requested/Administered by PCA

"Five of the 24 patients who received an epidural infusion of ropivacaine for 72 h did not require any PCA morphine. These were patients No.5 and 32 in the 2 mg/ml group and patients No.4, 11 and 24 in the 3 mg/ml group. The length of the day-1 interval varied between 14.8 h to 19.5 h depending on the end of surgery, with no major difference between the two groups.

The median morphine consumption during the three treatment days in the lower dose group was 7 mg (range 0-49 mg), 6 mg (range 0-62 mg) and 2 mg (range 0-28 mg) and in the higher group 7 mg (range 0-37 mg), 9 mg (range 0-28 mg) and 2 mg (range 0-21 mg).

The median number of PCA attempts during the three treatment days were 9, 7 and 3 (2 mg/ml) and 9, 13 and 3 (3 mg/ml)."

Pain Scores at Rest - Visual Analogue Scale (VAS)

"The pain scores (VAS) at rest were to be assessed in the morning (8:00), at noon (12:00) and in the evening (20:00) postoperatively during the treatment period. Depending on the time of the start of the epidural administration of ropivacaine and the duration of surgery, the running assessment times (related to the time of the start of ropivacaine treatment time zero) differ."

Table 79. Median VAS pain scores at Rest by Treatment Group

Table 17 Median pain scores (VAS) at rest together with the range at the morning and evening assessments during the epidural infusion of ropivacaine 2 and 3 mg/ml. Day of surgery is day 1.

		VAS scores	
		Ropivacaine 2 mg/ml	**Ropivacaine 3 mg/ml**
Day 1	evening	23 (0-70)	0 (0-35)
Day 2	morning	20 (0-50)	5 (0-65)
	evening	0 (0-25)	8 (0-28)
Day 3	morning	0 (0-15)	0 (0-25)
	evening	0 (0-28)	0 (0-31)
Day 4	morning	0 (0-53)	0 (0-10)

[Sponsor's Table 17. Item 8, Vol. 36, p. 103]

Spread of Sensory Block

The spread of sensory block was to be assessed, as determined by assessing temperature perception changes using an ice cube, in the morning (8:00), at noon (12:00) and in the evening (20:00) postoperatively during the treatment period. Depending on the time of the start of the epidural administration of ropivacaine and the duration of surgery, the running assessment times (related to the time of the start of ropivacaine treatment time zero) differ.

The highest individual spread, T3, was determined in patient No.24 after about 4 h of epidural infusion of 3 mg/ml ropivacaine.

The median upper spread after about 4 h of infusion (noon on the day of surgery) was T8 and T5 after infusion with 2 and 3 mg/ml, respectively. The following morning the median upper spread had decreased to L1 for both treatment groups. In the 2 mg/ml group the median upper spread decreased to L2.

The median lower spread was S2 after about 4 h of infusion at rates of both 2 and 3 mg/ml. When using the lower infusion rate, the median lower spread increased to S1-L5 at the time of the end of infusion (72 h), but remained at S2 in the 3 mg/ml group during the whole treatment period."
[Item 8, Vol. 36, p. 103]

Motor Block

"Motor block was to be assessed in the morning (8:00), at noon (12:00) and in the evening (20:00) postoperatively during the treatment period. Depending on the time of the start of the epidural administration of ropivacaine and the duration of surgery, the running assessment times (related to the time of the start of ropivacaine treatment = time zero) differ.

The frequency of patients with different degrees of motor block (modified Bromage scale) at different target times during the 72-h infusion are shown in Figure 18. The incidence and the degree of motor block decreased during the infusion period in both treatment groups. Two patients in the 2 mg/ml group had Bromage degree 3 at noon on the surgery day (about 4 h of infusion) compared to five patients in the 3 mg/ml group. After 72-h of infusion Bromage degree 0 was determined in eight patients who received 2 mg/ml and in six of the 3 mg/ml patients. There was a slight tendency towards a lower degree of motor block in patients treated with ropivacaine 2 mg/ml compared to patients treated with ropivacaine 3 mg/ml."

[Item 8, Vol. 36, p. 104]

7.2.15.3 Reviewer's Efficacy Discussion

In this supportive clinical trial, both the 2 mg/ml and 3-mg/ml dosage forms of ropivacaine have been demonstrated to be efficacious when administered as an epidural infusion for the treatment of post-orthopedic surgery pain.

The results of the efficacy variable, "median VAS pain scores at rest" showed complete pain relief at 72 hour for both the 2 mg/ml and 3 mg/ml treatment groups. This finding lends credence to the efficacy of a 72-hour ropivacaine infusion for the treatment of pain associated with total knee replacement.

The pharmacokinetic reviewer, Dr. Shinja Kim, will present the pharmacokinetic analysis.

7.2.16 STUDY # 94RO84 (O9)

7.2.16.1 Protocol Synopsis:

Title: "Continuous 72 Hour Epidural Infusion of Ropivacaine for Pain Management After Orthopaedic Surgery –A Pharmacokinetic and Clinical Evaluation."

Primary Objective: "To obtain information on the efficacy, tolerability an pharmacokinetics of ropivacaine during 72 hour epidural infusion after major orthopedic surgery.

[Item 8, Vol. 101, p. 23]

Study Design:

This supportive study was performed in an open uncontrolled fashion and involved 11 patients scheduled for major orthopedic surgery under ropivacaine epidural block followed by a continuous infusion of the same.

Eligible patients were American Society of Anesthesiologists physical status I -III males or females (adequately protected against pregnancy) between 18 and 75 years of age, with normal laboratory findings and body weight of 50 –110 kg. Patients had not participated in any clinical study with an investigational drug within 2 weeks prior to the start of the study, had no allergies to study drugs or symptoms of a clinically significant illness and were not drug or alcohol abusers.

Preoperatively, patients received oral temazepam or heparin at the discretion of the investigator. Prior to induction of the epidural block patients received crystalloids (10 ml/kg

Epidural block was performed as follows: 16-18 gauge needle was inserted at the appropriate interspace followed by catheter placement and testing with a 3 ml test dose lidocaine (1.5 % with 5 µg/ml of epinephrine). Five minutes later, if there were no signs of intravascular or intrathecal administration, 15-20 ml of 10 mg/ml ropivacaine. Surgery started when adequate block was achieved.

If adequate block was not achieved 30 minutes after the start of the main dose additional 5-10 ml or ropivacaine 10 mg/ml could be injected. If after an additional 30 minutes, there was inadequate sensory block, the patients was withdrawn.

The epidural infusion was to begin at 6 ml/hour of ropivacaine 2 mg/ml and continue for 72 hours. Whenever the pain score at rest exceeded 30 mm (VAS score), the infusion rate was increased to 8 ml/hour A further 2 ml/hour increase in the infusion rate to a maximum of 10 ml/hour could be made. With every increase in infusion rate, a 6 ml top-up was administered.

Assessments started two hours after the end of surgery and proceeded at specified intervals (please schedule of events below). Assessments of wound pain at rest, and on mobilization/physiotherapy, sensory and motor block, as well as return of bowel function were made at regularly scheduled intervals.

Rescue medication included 3-5 mg bolus doses of morphine i.m. at the request of the patient and at the discretion of the investigator.

The 5 –10 ml of peripheral venous blood samples for assay of ropivacaine were taken at regular intervals (see schematic below)

Table 80. Schedule of Events

Study Design 94Ro84	Actions before surgery	Induction of anaesthesia Minutes 0-5	5-10	~	-35	Surgery	72 hours postoperatively hours 0-2	72	7-14 days	3-6 weeks
Physical examination										
Medical history										
Premedication										
Preanesthetic infusion										
Test dose 3 ml										
Main dose 15-20 ml										
Additional doses 5-10 ml										
Additional doses 5 ml										
Cont. infusion 6-10 ml/h										
Top-up 6 ml (12 mg)										
Morph. i.m. upon request										
Pharmacokinetic assessments										
Urine sampling										
Pain assessments										
Motor/Sensory block										
Blood pressure/Pulse rate										
Peripheral oxygen										
Body temperature										
ECG										
Laboratory assessments										
Adverse Events open/active Q										
Adverse Events										by phone

Fig. 1. Study Design 1. If no sensory block achieved 30 minutes after the start of injection of the main dose.
2. At the discretion of the investigator. 3. At every increase of infusion rate, at the discretion of the investigator. 4. Before injection of the epidural test dose
5. At the end of surgery and immediately before start of the infusion 6. Values will be recorded before test dose and thereafter at 5, 10, 15, 20, 30, 45, and 60 min and then every 30 min until end of surgery.

[Item 8, Vol. 101, p. 25]

7.2.16.2 Sponsor's Efficacy Results:

"The median pain scores (VAS) at rest were overall low varying between 0 and 10 mm during the first 24 hours, between 3 and 5 mm during the 24 to 48 hour period and the median was less than 1 mm during the last interval 48 to 72 hours after surgery. Seven patients out of the 11 requested morphine during the first 24 hours following surgery , 6 of the 7 requesting morphine during the 24 to 48 hour period and 3 of them requesting morphine during the 48 to 72 hour period. The frequency of motor blockade decreased during the 72 hour study period."

The main efficacy results are summarized in the sponsor's table below.

Table 81. Main Efficacy Data

Efficacy		Ropi (n=11)
Pain scores (VAS mm) at rest	0-24 hours	11.50
expressed as AUCM	0-48 hours	11.10
	0-72 hours	8.19
Pain scores (VAS mm) at rest,	2 hours	0
median	24 hours	1.7
Values carried backward and forward to	48 hours	3.8
target time	72 hours	0
Morphine consumption (mg)	0-24 hours	5.00 (n=7)
median for patients receiving	24-48 hours	5.25 (n=6)
morphine	48-72 hours	5.00 (n=3)
Sensory Block Pin-Prick		
Upper Spread	2 hours	T8
median	24 hours	T10/T11
Values carried backward and forward to	48 hours	T11
target time	72 hours	T12
Lower Spread	2 hours	S2
median	24 hours	S2
Values carried backward and forward to	48 hours	S1/L5
target time	72 hours	L4/L5
Motor Block		
	2 hours	n
Bromage Score - number of patients	0	5/11
Values carried backward and forward to	1	2/11
target time	2	2/11
	3	2/11
	24 hours	
	0	7/10
	1	3/10
	2	0/10
	3	0/10

cont'd.

[Item 8, Vol. 101, p. 6]

Table 82. Main Efficacy Data (continued)

cont'd.

Efficacy		Ropi (n=11)
Motor Block	48 hours	
	0	8/10
Bromage Score - number of patients	1	2/10
Values carried backward and forward to	2	0/10
target time	3	0/10
	72 hours	
	0	7/8
	1	0/8
	2	1/8
	3	0/8

7.2.16.3 Reviewer's Efficacy Discussion

This supportive uncontrolled clinical trial involved eleven patients. Apparently, patients experienced some level of effective block in order to perform surgery; however, no definitive conclusions about the efficacy of the product can be made based upon a trial that is not adequate (N=11) or well controlled.

II. Infiltration Nerve Block Studies

A series of four infiltration nerve block studies were performed evaluating ropivacaine when administered postoperatively to patients immediately following inguinal hernia repair. None of these studies were submitted in support of any indication however. Therefore, the data submitted will be reviewed primarily for its contribution to the safety database.

Studies in Brief

A. Study CF-ROP-0001 (Q12)

Title: "Wound infiltration following inguinal hernia repair for postoperative pain relief: A Double blind Comparison Between Ropivacaine 7.5 Mg/ml and Placebo"

"The primary objective of this study was to assess the analgesic effects of wound infiltration with ropivacaine 300mg after inguinal hernia repair. 77 adult inpatients scheduled for primary unilateral hernia repair under general anesthesia were randomized in this multicenter, double-blind, controlled trial, to receive postoperative local infiltration with 40 ml ropivacaine 7.5 mg/ml (300 mg) or placebo. At the end of surgery, 40 ml of the study drug was infiltrated : 2 ml in the region of the ilioinguinal nerve, 6 ml around the neck of the hernia sac, 12 ml into the muscular layers and 20 ml into the subcutis and cutis.

Assessments of wound pain at rest, coughing and mobilization were carried out 2,3,4,5,6,8,10,12 and 24 hours after the end of infiltration using a visual analogue scale (VAS). Additional analgesics consisted of Pro-Dafalgan® (propacetamol) i.v. (8g/24 hours maximum) and/or Dafalgan® Codeine (paracetamol 500 mg + codeine 30 mg) p.o. (6 tablets/24 hours maximum) at the request of the patient during the first 24 hours postoperatively. A five- item questionnaire was used to evaluate how much the patient was bothered by difficulty in concentrating, difficulty in urinating, pain when moving around, poor appetite and nausea 2,4,6,8,10,12 and 24 hours after the end of infiltration. The time when patients were fit for discharge was evaluated using certain criteria (vital signs, activity and mental status, pain, nausea, vomiting, surgical bleeding, intake and output) 2,4,6,8,10,12 and 24 hours after the end of infiltration.

"A statistically significantly lower area under the curve divided by time (AUCM) for postoperative pain scores upon mobilization and coughing was found in the ropivacaine group compared to the placebo group at all time intervals, 0-4, 0-8, 0- 12 and 0-24 hours. At rest, this significant difference was noted until 12 hours. The mean times to the first request postoperatively for additional analgesics were 7.70 hours in the ropivacaine group, and 1.78 hours in the placebo group. This difference was statistically significant. The consumption of propacetamol and acetaminophen codeine was comparable in both groups, although 4 patients in the ropivacaine group and 13 patients in the placebo group had to take other analgesics due to insufficient pain relief. The median time when patients were fit for discharge occurred significantly earlier in the ropivacaine group (10 h) compared to the placebo group (24 h). The evolution of scores for postoperative recovery was similar in both groups regarding difficulty in concentrating, in urinating, poor appetite and nausea. Pain when moving around was found to bother more patients in the placebo group during the first few hours postoperatively."

In conclusion, infiltration with 300 mg ropivacaine (40 ml of 7.5 mg/ml) provides good analgesia if infiltrated after repair of an inguinal hernia."

[Item 8, vol. 104, p.14]

B. ***Study SP-ROA-0003 (Q09)***

Title: "Field block/ infiltration for pain management after inguinal hernia repair: A double-blind comparison between ropivacaine and bupivacaine."

The primary objective of the present study was to demonstrate improved clinical efficacy (pain upon mobilization) of ropivacaine compared to that of bupivacaine when used for field block/infiltration for pain management after primary inguinal hernia repair performed under general anesthesia. Four centers participated in this double-blind study, in which the patients were randomized to receive perioperative infiltration with either 300 mg of ropivacaine (40 ml of 7.5 mg/ml) or 100 mg of bupivacaine (40 ml of 2.5 mg/ml).

It was planned to include 140 patients. 148 patients were actually enrolled, of whom four (two in each treatment group) did not receive any study drug. A total of 144 Caucasians (73 vs. 71 patients in each group), ASA I-III, aged 21-69 years, were included in the analyses of safety and efficacy data. The hernia repair was performed as a modified Shouldice hernioplasty. Post-operatively the patients were given supplementary analgesics on demand. Citodon â (paracetamol + codeine phosphate) tablets or suppositories were to be given in the first place, followed by morphine in case of insufficient pain relief. During the first 24 hours after the start of infiltration assessments of wound pain on mobilization, on coughing and at rest as well as an evaluation of the patients' ability to perform day-to-day activities were made. The two groups were similar with regard to demographics, baseline characteristics and duration of surgery.

"The median pain scores (VAS, visual analogue scale) on mobilization, on coughing and at rest during the first 24 hours were overall low and of the same magnitude in both groups. The median pain scores on mobilization in the interval 0-24 hours varied between 13.7 and 24.7 mm in the ropivacaine group and between 17.1 and 24.1 in the bupivacaine group. On coughing, the median score varied in the range 15.2-20.4 mm in the ropivacaine group and 19.4-25.2 mm in the bupivacaine group.

The median pain scores at rest varied in the range 5.0-12.4 mm in the ropivacaine and 5.0-14.5 mm in the bupivacaine group.

Comparisons of the pain scores on mobilization, on coughing and at rest for the intervals 0-4, 4-8, 8-12, 0-12 hours and VAS at 24 hours, did not show any statistically significant differences between the treatment groups, as measured by the area under the curve divided by time (AUCM) for the pain score. 49% of the patients in the ropivacaine group and 39% in the bupivacaine group experienced wound pain during the night following surgery.

There was no statistically significant treatment difference regarding the variable "time from the start of infiltration to the first administration of complementary analgesics" or the variable "total dose of Citodon or of morphine in the first 24 hours after infiltration". The median Citodon consumption per patient during the first 24 hours after infiltration was 5 Citodon tablets/suppositories in the ropivacaine group and 4 in the bupivacaine group.

In the period 0-24 hours after the start of infiltration the ability to move around, eat, concentrate and urinate was similar in both treatment groups.

In conclusion, infiltration with 300 mg ropivacaine (40 ml of 7.5 mg/ml) or 100 mg bupivacaine (40 ml of 2.5 mg/ml) provides good analgesia after open repair of inguinal hernia."

[Item 8, vol. 104, p.91-92]

C. Study SP-ROA-0004 (Q10)

Title: "Infiltration for Pain Management After Inguinal Hernia Repair: A Double-Blind Comparison Between Ropivacaine and Bupivacaine."

The primary objective of the present study was to demonstrate improved clinical efficacy (pain on mobilisation) of ropivacaine compared to that of bupivacaine when used for field block/infiltration for pain management after primary inguinal hernia repair performed under general anesthesia. There were seven centres participating in this double-blind study, in which the patients were randomized to receive perioperative infiltration with either 300 mg of ropivacaine (40 ml of 7.5 mg/ml) or 100 mg of bupivacaine (40 ml of 2.5 mg/ml).

It was planned to include 140 patients. One hundred and fifty-five male patients were actually enrolled, of whom two (one in each treatment group) did not receive any study drug. A total of 153 Caucasians (76 vs. 77 patients in each group), physical status ASA I-III, aged 19-74 years, were included in the analyses of safety and efficacy data.

Inguinal hernia repair was performed using a Trabucco/Lichtenstein tension free technique. Postoperatively the patients were given supplementary analgesics upon request. Toradol i.m. injections were administered in the first place followed by morphine i.m. in case of insufficient effect.

Assessments of wound pain on mobilization, on coughing and at rest were made ten times during the first 24 hours after injection of study drug as well as evaluations of the patients' ability to perform day-to-day activities.

The two groups were similar with regard to demographics, baseline characteristics and duration of surgery.

"The median pain scores, measured with a Visual Analogue Scale (VAS), on mobilization, on coughing and at rest during the first 24 hours were overall low in both groups. A statistically significant difference between the treatment groups, in favor of ropivacaine, was found for the area under the curve mean (AUCM) of the pain score for wound pain on mobilization in the interval 0-4 hours (AUCM4) after injection of study drug. Statistically significant treatment differences in favor of ropivacaine were in addition found for AUCM4 for wound pain on coughing and AUCM8-12 for wound pain at rest.

The median pain scores (VAS, visual analogue scale) on mobilization, on coughing and at rest during the first 24 hours were overall low and of the same magnitude in both groups. The median pain scores on mobilization in the interval 0-24 hours varied between 13.7 and 24.7 mm in the ropivacaine group and between 17.1 and 24.1 in the bupivacaine group. On coughing, the median score varied in the range 15.2-20.4 mm in the ropivacaine group and 19.4-25.2 mm in the bupivacaine group.

Twenty-one percent of the patients in the ropivacaine group and 31% in the bupivacaine group reported that they had experienced wound pain during the night following surgery. There was no statistically significant treatment difference regarding the time from start of injection of study drug to first administration of complementary analgesics or the total dose of Toradol the first 24 hours after infiltration.

Twenty-three patients (30%) in the ropivacaine group and 31 patients (40%) in the bupivacaine group received Toradol during this period. Thus, the median Toradol consumption per patient during the first 24 hours after infiltration was 0 mg in both groups. No patient in the study required morphine injections."

[Item 8, vol. 104, p.171-172]

In conclusion, infiltration with 300 mg ropivacaine (40 ml of 7.5 mg/ml) or 100 mg bupivacaine (40 ml of 2.5 mg/ml) provides good analgesia when used for field block/infiltration for pain management.

D. Study SP-ROA-0006 (Q11)

Title: "Field Block/Infiltration for Pain Management After Inguinal Hernia Repair: A Double Blind Comparison Between Ropivacaine and Bupivacaine"

The primary objective of the present study was to demonstrate the improved clinical efficacy (pain on mobilization) of ropivacaine compared to bupivacaine when used for field block/infiltration for pain management after primary inguinal hernia repair performed under general anesthesia.

Seven centers participated in this double-blind study, in which the patients were randomized to receive perioperative infiltration with either 300 mg ropivacaine (40 ml of 7.5 mg/ml) or 100 mg bupivacaine (40 ml of 2.5 mg/ml).

It was planned to include 140 patients; however, 151 patients were enrolled and six of these did not receive any study drug. A total of 145 Caucasians (75 and 70 patients respectively) aged 19-75 were valid for the All Patients Treated (APT) analysis of the efficacy data.

The hernia repair was performed as a Lichtenstein hernioplasty. Postoperatively the patients were given complementary analgesics on demand. Tylex capsules were administered initially followed by morphine 10 in case of insufficient effect.

Assessments of wound pain on mobilization, on coughing and at rest as well as an evaluation of the patients' ability to perform day-to-day activities were made ten times during the first 24 hours after injection of the study drug.

"The median pain scores, measured using a Visual Analogue Scale (VAS), on mobilisation, on coughing and at rest during the first 24 hours were overall low in both groups. A statistically significant difference between the treatment groups, in favor of ropivacaine, was found for the Area Under the Curve, Mean, divided by time (AUCM) of the VAS score for wound pain on mobilisation in the interval 0-12 hours after injection of study drug (primary objective).

Statistically significant treatment differences in favor of ropivacaine were also found for the following secondary efficacy variables: AUCM4, AUCM4-8 and AUCM12 for wound pain on coughing, and AUCM4 and AUCM4-8 for wound pain on mobilisation. 41% of the patients in the ropivacaine group and 34% in the bupivacaine group reported experiencing wound pain during the night following surgery. [Note: p values not provided in clinical section – Item 8].

There was no statistically significant treatment difference regarding the time from the start of injection of the study drug to the first administration of complementary analgesics or the total dose of Tylex capsules or of morphine/Cyclimorph 10 in the first 24 hours after infiltration. [Note: p values not provided in clinical section – Item 8].

The median Tylex consumption per patient during the first 24 hours after infiltration was four capsules in the ropivacaine group and five capsules in the bupivacaine group. The distribution of the ability to move around, eat, concentrate and urinate was similar in both treatment groups.

In conclusion, postoperative analgesia, by means of infiltration following open inguinal hernia repair, was efficiently established within both treatment groups. 300 mg ropivacaine (7.5 mg/ml) provides better pain relief on mobilisation and on coughing during the first twelve hours postoperatively compared to 100 mg bupivacaine (2.5 mg/ml). This study also shows that 300 mg ropivacaine can be effectively used for postoperative infiltration analgesia."

[Item 8, vol. 104, p.257-258]

7.2.16.4 Reviewer's Efficacy Discussion

Despite the apparently adequate and well controlled nature of these trials, they have not been submitted in support of any indication and therefore will primarily be reviewed based upon their contribution to the safety database (see below).

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

In total, there are twenty (20) clinical trials - 17 controlled and 3 uncontrolled - involving 1991 and 59 patients, respectively. The percentage of patients treated with ropivacaine may change upon response from sponsor to Agency request for clarification.

Anesthetic related adverse events are specific to both the anesthetic agent as well as the anesthetic technique. Therefore, to correlate with current clinical practice and to best determine the safety of increasing the concentration of and extent of exposure to ropivacaine, the review of this data is presented according to categories of anesthesia technique, i.e., lumbar epidural anesthesia for cesarean section, thoracic and lumbar epidural infusion for postoperative pain management, and brachial plexus block.

8.1.1 Deaths – All Studies

8.1.1.1 Methods

8.1.1.1.1 Sponsor's Methods

8.1.1.1.1.1 Ascertainment/Classification in Development Program

No description was provided of the sponsor's rules for including deaths for consideration in the sNDA. Available for review were case report forms, narrative summaries, and case report tabulations.

8.1.1.1.2 Sponsor's Analyses

No analyses of overall or cause specific mortality were performed/submitted.

8.1.1.2 Reviewer's Methods

8.1.1.2.1 Reviewer's Rationale for Further Analyses

8.1.1.2.2 Reviewers Analysis

The sponsor has not provided an analysis of deaths; therefore, an in depth analysis of the CRFs, narrative summaries and case report tabulations for each death was performed by this reviewer. All events surrounding each death, e.g., time and date of death, dosing, medical and surgical histories, concomitant medications, surgical intervention and complications, etc. were analyzed and tabulated. As all of the deaths occurred in the postoperative pain management trials, conclusions about dose response and causality are made with respect to this route of administration.

8.1.1.2 Results

Cesarean Section

A total of 264 patients were exposed to 0.75% ropivacaine and 218 patients to 0.5% bupivacaine via epidural anesthesia for cesarean section. In these clinical trials, there were no reports of death.

Brachial Plexus Block

A total of 119 patients were exposed to 0.75% ropivacaine and 102 patients to 0.5% bupivacaine via brachial plexus block (axillary or transarterial subclavian approach). In these clinical trials, there were no reports of death.

Infiltration Block

A total of 282 patients were exposed to 0.75% ropivacaine, 218 patients to 0.25% bupivacaine and 40 patients to placebo via either wound infiltration or field block post-inguinal hernia repair. In these clinical trials, there were no reports of death.

Postoperative Pain Management

All deaths (n=9, 1%) occurred in the post-operative pain management trials. In these trials, patients scheduled for major abdominal surgery underwent a bolus dose of ropivacaine 7.5 mg/ml followed by a continuous infusion of ropivacaine ± narcotic.

Of relevance is the commonality of the trials with respect to the following:

(1) All trials included patients with American Society of Anesthesiologists physical status of III (defined as functional impairment) to be enrolled,
(2) Many of the patients randomized were at risk for complications, e.g., advanced cancer, cardiorespiratory disease,
(3) Patients were given an anesthetic with inherent increased risk, i.e., **thoracic epidural,**
(4) The dose (**7.5 mg/ml**) and infusion rate (≤ **14 ml/hour**) of ropivacaine given was increased over that currently approved.

All deaths occurred in Studies 010, 011, and 014 and were similar in the following ways:

(1) 8/9 patients were exposed to 7.5 mg/ml ropivacaine
(2) 7/9 patients were ASA III and,
(3) all patients received high levels of anesthesia, i.e., ≥ T5 thoracic levels of anesthesia.

The presence of a narcotic did not appear to be the causative factor, as the incidence of death did not consistently increase with the addition of fentanyl or morphine, see below.

Study 011 (N=244)
1. Fifty-five percent (5/9) of total number of deaths
2. 0.2% ropivacaine alone (2 cases)
3. 0.2% ropivacaine + fentanyl 1 ug/ml (2 cases),
4. 0.2% ropivacaine + fentanyl 2 ug/ml (0 cases),
5. 0.2% ropivacaine + fentanyl 4 ug/ml (1 case)

Study 010 (N=147)
1. Thirty-three percent (3/9) of total number of deaths
2. 0.2% ropivacaine alone (1 case)
3. 0.2% ropivacaine + fentanyl 2 ug/ml (2 cases)

Study 014 (N=130)
1. Eleven percent (1/9) of total number of deaths
2. 0.2% ropivacaine alone (1 case)
3. 0.2% ropivacaine + PCA morphine (0 cases)
4. PCA morphine alone (0 cases)

Case Narratives

Below please find a brief description of the study design followed by a narrative of all corresponding deaths.

Study 011

"A Double-Blind, Randomized Study Comparing Efficacy and Safety of Epidural Ropivacaine Alone and in Combination with Fentanyl for the Management of Postoperative Pain in the First 72 Hours Following Major Abdominal Surgery"

Study Design

Briefly, randomized ASA I-III patients, between 18 and 79 years of age, scheduled for elective major abdominal surgery (e.g. partial or total gastrectomy, biliary or pancreatic surgery and colonic resection) were to receive combined general anesthesia and thoracic epidural block (ropivacaine 7.5 mg/ml) for surgery followed by 72 hours of postoperative thoracic epidural analgesia with ropivacaine 0.2% + 1, 2, or 4 ug/ml fentanyl.

Five minutes following a negative test dose, 8-15 ml of ropivacaine 7.5 mg/ml (37.5-112.5 mg) was to be injected within a 5-minute period. Induction of general anesthesia and surgery was then to be performed. The continuous epidural infusion of ropivacaine:

Group 1: ropivacaine 2 mg/ml,
Group 2: ropivacaine 2 mg/ml +1 ug/ml fentanyl,
Group 3: ropivacaine 2 mg/ml +2 ug/ml fentanyl,
Group 4: ropivacaine 2 mg/ml + 4 µg/ml fentanyl,

was to start at 5 ml/h within one hour after the induction of general anesthesia and to continue during the surgical procedure. Postoperatively, the epidural infusion was to continue for 72 h with a maximum infusion rate of 14 ml/h.

Case Narratives - Study 011

I. Patient 324 – Thoracic Epidural

A 77-year-old ASA III male with a past medical history significant for congestive heart failure, myocardial infarction, chronic obstructive airway disease, cerebrovascular accident, rheumatoid arthritis, renal impairment, gastric ulcer disease, depression and coronary artery by-pass grafts was enrolled. His preoperative vital signs were significant for an EKG finding of frequent ventricular ectopy, and mild nonspecific, lateral ST segment depression.

He was scheduled to undergo a high anterior resection of an obstructive sigmoid colon carcinoma under general anesthesia with supplemental epidural blockade using ropivacaine **7.5 mg/ml.** Postoperatively, his epidural blockade was to continue for 72 hours using ropivacaine + 4ug/ml of fentanyl at 4-14 ml/hour (Group 4).

The patient received an uncomplicated **T9/T10** epidural block with 15 ml of ropivacaine (3 ml of lidocaine was given as a test dose) followed by a continuous infusion of ropivacaine at 8 ml/hour. He underwent an uneventful high anterior resection of an obstructive sigmoid colon carcinoma with 400 ml of blood loss. In the postanesthesia care unit (PACU), despite a T1 level of anesthesia, the patient received multiple "top-ups" and increases in the rate of study drug infusion as needed for pain.

Approximately one half hour after arrival in the PACU, the patient was noted to have decreased level of consciousness, labored breathing (requiring airway support), generalized weakness and a **C8 level of anesthesia.** The patient was then given neostigmine and atropine for a presumptive diagnosis of recurarization (presumed etiology: renal impairment) and was transferred to the intensive care unit.

The rate increases and bolus dosing continued. The patient ultimately received 112.5 mg ropivacaine (15 mL x 7.5 mg/mL) as the main dose and 1047 mg of ropivacaine (2 mg/mL) mixed with 2095 μg fentanyl (4 μg/mL) as a continuous infusion. The total bolus dose received was approximately 20 ml and the final rate of infusion received was **14 ml/hour** over 14 hours postoperatively. The study treatment was discontinued 41 hours after arrival at the PACU due to the acute pulmonary edema (occurred 20 hours after arrival in the PACU).

In the ensuing six hours, respiratory fatigue, elevated pulmonary capillary wedge pressure, oliguria and finally multi-organ failure accompanied the pulmonary edema. The patient died five days postoperatively. The immediate cause of death said to be cardiac ischemia.

According to the investigator, recurarization due to renal failure was the basis for the patient's labored breathing and generalized weakness. Other plausible explanations include (1) the C8 level of anesthesia, which has a depressing effect on both the cardiac and respiratory systems, and (2) the congestive heart failure as evidenced by presence of pulmonary edema.

II. Patient 1122 – Thoracic Epidural

A 74-year-old ASA III male with a medical history significant for chronic obstructive pulmonary disease, peripheral vascular disease and bowel obstruction secondary to recurrent carcinoma of the colon was scheduled to receive a gastrojejunostomy. The patient was status post a left hemicolectomy (1992) and a right below the knee amputation (1993). His preoperative physical examination was significant for an EKG finding of inverted T waves (V5 and V6) and Q waves at V2 and V3.

He was randomized to the ropivacaine alone group and underwent an uneventful **T8-T9** epidural with ropivacaine 7.5 mg/ml followed by a continuous infusion of 2 mg/ml ropivacaine for 72 hours. The patient received a total of 60 mg ropivacaine (8 x **7.5 mg/mL**) as a main dose and a total dose of 1655 mg of ropivacaine (2 mg/mL) as a continuous infusion. No fentanyl was given. The maximum rate of infusion was 14 mg/h and **anesthesia levels as high as T3** were achieved.

Eight days postoperatively, the patient's surgical wound dehisced; surgical repair was performed the same day. Six days later the patient died. Immediate causes of death were reported to be oliguria and dyspnea, secondary to colon cancer.

This case likely demonstrates death secondary to advanced colon carcinoma; however, investigation into the case report forms revealed post- infusion left ventricular failure (treated with lasix), labored breathing and anesthesia levels as high as T3. This triad of events while occurring twelve days before the patient died which temporally weakens any argument for a drug-induced mortality but does not refute an argument for drug induced myocardial depression, which may or may not have contributed to the patients demise.

III. Patient 616 – Thoracic Epidural

A 51-year-old ASA III female with a past medical history significant for non-insulin dependent diabetes mellitus, hypertension, hepatitis A and ovarian cancer, and a past surgical history significant for cholecystectomy, and hysterectomy was scheduled for oophorectomy and salpingectomy due to metastatic ovarian adenocarcinoma. Her preoperative examination was significant for cachexia, ascites, and tachycardia (HR 100, otherwise normal ECG). She was enrolled and randomized to the ropivacaine with 1 ug fentanyl study group.

She underwent an uncomplicated **T10–T11** epidural with 75 mg of ropivacaine (10 mL x **7.5 mg/mL**) as the main dose followed by an infusion of 2 mg/mL ropivacaine (total dose of 1080 mg) mixed with 1 μg/mL fentanyl (total dose 540 μg). Her surgery consisted of an oophorectomy and salpingectomy, omentectomy, drainage of a subdiaphragmatic collection and oversewing of a liver laceration. There was a substantial amount of blood lost during this 2-hour procedure.

The 72-hour, postoperative ropivacaine epidural infusion was marked by multiple episodes of hypotension (minimum BP=77/55, baseline 115/90) for which ephedrine was given. The maximum rate of infusion reached was only 8 ml/hour, i.e., probably to avoid further episodes of hypotension and to prevent bradycardia. A diagnosis of excessive block was made only on 12/4/96 and 12/6/96; however, there was evidence of this occurring as early as 12/3/96 – within hours of the start of the infusion. These episodes prompted multiple moments when the infusion had to be turned off– this occurred as late as the third day of infusion. The **maximum level of anesthesia reached was T2** and never was lower than T5 throughout the course of her treatment.

On the eighth postoperative day, (five days after the infusion was discontinued), the patient had an episode of bradycardia (30/min) with a nonpalpable pulse (implication being concurrent hypotension), tachypnea, diaphoresis and a depressed level of consciousness. The heart rate was said to improve spontaneously and rapidly. However later that same day, the patient deteriorated, the hypotension recurred and she died.

Escherichia coli and anaerobes were cultured from her ascites. The Coroner's report was said to state that the immediate cause of death was sepsis due to feculent peritonitis.

This patient's immediate cause of death is likely due to sepsis. It is important to mention, however, that the difficulty the practitioner was having in maintaining a constant rate of infusion (i.e., an infusion rate which would not result in hypotension) is possibly due to the combination of the patient's overall poor medical condition and a high level of anesthesia.

IV. Patient 714 – Thoracic Epidural

A 59-year-old ASA III female with a medical history significant for ovarian cancer, stage C (disseminated) and chronic bowel obstruction was randomized to receive ropivacaine alone. Her physical examination was significant for a pale, thin female with a right pleural effusion and palpable liver.

She underwent a jejunocolic anastomosis and multiple gastroenterostomies. She received, via an uncomplicated T10-T11 epidural, 60 mg of ropivacaine (8 mL x **7.5 mg/mL**) as the main dose and a total dose of 1952 mg of ropivacaine (2 mg/mL) as a 72-hour continuous infusion. No fentanyl was given. The epidural infusion began intraoperatively and was increased over a 72-hour period from 8 ml/hour to 14 ml/hour. There were also multiple bolus doses given during this timeframe. The **maximum level of anesthesia reached was T2.**

Two weeks after the operation, she began to deteriorate. Secondary to disseminated cancer, it was decided to withdraw further treatment and keep her as comfortable as possible. She died 4 days later. The probable cause of death was said to be respiratory failure.

There is little evidence to support a drug-induced etiology of the patient's morbidity. It is more plausible that the patient death was secondary to her underlying pathology – metastatic ovarian carcinoma.

V. Patient 918 – Thoracic Epidural

An otherwise healthy 76-year-old male underwent an anterior resection for carcinoma of the colon with thoracic (T8-T9) epidural ropivacaine **7.5 mg/mL** (total 37.5 mg) followed by a continuous infusion of 2 mg/mL ropivacaine (total 714 mg) mixed with 1 μg/mL fentanyl (total 357 μg). The **maximum level of anesthesia reached was T2.**

The intraoperative course was significant for recurrent bradycardia and hypotension, for which atropine and aramine were given, respectively. No other intraoperative complications were reported. Postoperatively, after 24 hours of study drug infusion, despite top-up bolus doses of study drug and reaching the maximum infusion rate of 14 ml/hour, it was determined that the patient was inadequately blocked. No vital signs were recorded following removal of the epidural catheter.

Alternatively, the patient received an intercostal block with 75 mg of ropivacaine (**7.5 mg/ml**). [**Note**: intercostal nerve blocks are associated with the highest serum levels of anesthesia than any other route of administration]. One hour following this dose of ropivacaine, the patient experienced a repeat episode of hypotension and eight hours later the patient expired. The cause of death was said to be myocardial infarction with cardiogenic shock.

The clinical assessment of cardiac risk associated with anesthesia has been the subject of many debates since the early 1930's. Multiple clinical trials have been performed to determine the best predictors of postoperative cardiac events. There are certain preoperative findings which have been conclusively shown to increase a patient's risk for postoperative myocardial infarction, e.g., advanced age, coronary artery disease, prior history of myocardial infarction, arrhythmias, cardiac failure or ischemia.

Patient 918, with no preexisting risk factors, had a myocardial infarction within 72 hours of surgery and within 8 hours of dosing. This is a rare event. Possible explanations include the following: (1) undetected coronary artery disease, pulmonary or systemic hypertension, valvular disease (2) drug - induced myocardial infarction. This later question, will be the subject of this reviewers final conclusions, see Section 8.1.1.3.2 Reviewers Discussion below.

Study 010

"A Double-Blind, Randomized Study Comparing Efficacy and Safety of Epidural Ropivacaine Alone and in Combination with Fentanyl for the Management of Postoperative Pain in the First 72 Hours Following Colonic Resection"

Study Design

Briefly, randomized ASA I-III patients, age 18 to 79 years, scheduled for elective colonic resection and suitable for 72 hours of epidural analgesia postoperatively were to receive a combined general anesthesia and thoracic epidural block with ropivacaine 7.5 mg/ml.

Prior to surgery, an thoracic epidural block was to be established with 5-10 ml ropivacaine 7.5 mg/ml, followed by the induction of general anesthesia and a continuous infusion of ropivacaine 8 ml/hour :

Group 1: ropivacaine 2 mg/ml and,
Group 2: ropivacaine 2 mg/ml + 2 mg/ml fentanyl

and continuing during surgery. Postoperatively, the epidural infusion was to continue at 8 ml/h for up to 72 hour. The maximum infusion rate was to be 14 ml/h.

Case Narratives - Study 010

I. Patient 603 – Thoracic Epidural

A 51-year-old ASA III male, with history of metastatic (liver and lung) colon cancer and a recent 20-pound weight loss underwent an uncomplicated segmental transverse colon resection via a T9-T10 epidural. Preoperative vital signs were significant for tachycardia (HR-105) and hypotension (BP-95/65).

Intraoperatively, following a bolus dose of 5 ml of ropivacaine 7.5 mg/ml, an infusion of ropivacaine 2 mg/ ml at 8 ml/h was started. A top-up dose of the same medication (ropivacaine 2 mg/ ml) was given postoperatively, followed by an increase in the infusion rate to 10 ml/h. The patient completed 73.2 hours of postoperative infusion and received a total main dose of 37.5 mg of ropivacaine **7.5 mg/mL** and 1465.8 mg of ropivacaine 2 mg/mL as a continuous infusion. The **maximum level of anesthesia reached was T3.**

The patient was discharge to home in stable condition and two and a half months later he died. Due to the extensive lapse of time between dosing and death, the most plausible explanation is that this patient's death was secondary to advanced colon carcinoma.

II. Patient 316 – Thoracic Epidural

This patient was a 64-year-old ASA III female with a medical history of degenerative disc disease, hypertension, borderline thyroid function, peripheral vascular disease, hiatal hernia, and carcinoma of the sigmoid colon and a surgical history significant for an aortoiliac endarterectomy and aortobifemoral bypass graft. She underwent a low anterior resection (sigmoid colectomy) via a T9-T10 uncomplicated epidural. The patient received 37.5-mg of ropivacaine **7.5 mg/mL** as main dose and 195.4 mg of ropivacaine 2 mg/mL mixed with 195.4 µg fentanyl as a continuous infusion for 18.4 hours.

Thirteen serious adverse events were reported for this patient. The first of these events occurred postoperatively, when the patient's blood pressure was reported to be not measurable. Fluid boluses (500 mL of 5% albumin and 1000mL of normal saline) and ephedrine 10 mg x 2 was given. The blood pressure normalized, however, the urine output remained less than 20 mL/hour after discharge from PACU.

The block was noted to be T4 bilaterally during this hypotensive episode. [**Note: levels as high as T2** were obtained, however]. Consequently, the epidural was stopped for 1 hour and 20 minutes and restarted after a bolus dose at 4 mL/hour. The hypotension persisted and neither her urine output or blood pressure improved with fluid boluses.

At this time the patient also complained of feeling short of breath (RR-24). The work-up for her shortness of breath was negative for pulmonary edema (chest X-ray did not reveal evidence of fluid overload), and myocardial infarction (ECG showed no evidence of infarction). The tachypnea persisted with rates as high as 36 bpm. As confirmatory evidence of low output renal insufficiency, was the increase in creatinine from a baseline value of 70 to 144 umol/l, postoperatively (normal values are 50 – 110 umol/l).

The patient ultimately was diagnosed with septic shock and was transferred to the intensive care unit. There she was started on dopamine, a Swan-Ganz catheter was inserted and she received ventilatory support. Further work-up revealed a negative CAT scan of the abdomen for a leak in the surgical anastomosis. Nevertheless, a laparotomy was done two days later for worsening sepsis. A large hole in the rectum was found just below the anastomosis with fecal peritonitis. Hartmann resection was done. Postoperatively, the patient continued to deteriorate and ultimately developed multi-organ failure. Life support was withdrawn and the patient died.

The patient's immediate cause of death was apparently due to septic multi-organ failure secondary to leaking surgical anastomosis. However, the coinciding anesthetic events may have contributed to the patient's inability to compensate for the surgical complication.

It was clear from the hypotension and dyspnea that the T4 level of anesthesia was not well tolerated. Secondly, there were at least two organ systems that were showing signs of poor perfusion – the kidneys (oliguria) and lungs (tachypnea). This lack of adequate perfusion may have contributed to the lack of wound healing and subsequent anastomotic leak of bowel contents.

The presence of peripheral vascular disease (was has been shown to translate into coronary vascular disease), advanced carcinoma and high dose local anesthetics administration (vasodilatation), may have placed this patient at risk for decreased preload and thereby decreased end organ perfusion.

III. Patient 407

A 52 -year-old ASA III male with a history of chronic obstructive pulmonary disease and recurrent rectal cancer underwent abdominal perineal rectal resection via a T10-T11 uncomplicated epidural. The patient completed 73.5 hours of postoperative infusion and received a total main dose of 37.5 mg ropivacaine **(7.5 mg/mL)** and a total of 1492.1 mg of ropivacaine 2 mg/mL mixed with 1417.1 µg fentanyl as continuous infusion. The patient developed an unexplained high fever near the end of the epidural infusion which continued to recur postoperatively (maximum temperature of 39.2). The **maximum level of anesthesia reached was T5.**

The following day, the patient complained of generalized abdominal cramping and re-spiked a temperature. A CT scan of abdomen was performed which showed liver abscesses and pelvic abscesses. The patient was treated with antibiotics and was discharged home ten days later.

Four months later the diagnosis was changed from liver abscesses to liver metastasis and seven months postoperatively, the patient died of rectal cancer with metastases in both liver and lungs.

There is obviously no temporal relationship identifiable from the history provided between the study drug and the patient's death. Therefore it is more plausible to conclude that the patient's death was likely secondary to advanced rectal cancer and not drug induced.

If in fact, the patient did not have abscesses and the fever is unexplained, then the question remains, was the fever secondary to (1) the commonly seen postoperative hyperthermia, or (2) drug-induced fever. This second possibility was alluded to in the medical review of the original NDA safety update, where the medical reviewer stated the following: "Fever ≥ 38.5° C continues to be observed and remains a dose-dependent issue during continuous...[ropivacaine]...epidural infusions for analgesia[12] This finding is the subject of a special investigation found below in Section 8.1.2.3.5.1 "Special Safety Evaluation – Fever"

[12] NDA 20-533, "Medical Officer Safety Update Review" by Robert F. Bedford, M.D., August 4, 1996, (letter/submission date: July 16,1996)

Study 014

"A Comparison of Continuous Epidural Infusion of Ropivacaine, Epidural Ropivacaine Plus PCA Morphine and PCA Morphine Alone for the Management of Pain After Major Abdominal Surgery"

Study Design

Briefly, randomized patients, preoperatively, were to receive a lumbar or low thoracic (≤T10) epidural with a test dose of 3 ml lidocaine 2% with epinephrine (12.5 ug/ml). Five minutes later, if there were no signs of intravascular or intrathecal administration, the induction of general anesthesia was to be performed followed by surgery.

Within 30 minutes of the end of surgery (last suture) a 20-ml bolus of ropivacaine 2 mg/ml was to be administered through the epidural catheter, followed by a continuous infusion of ropivacaine 2 mg/ml at a rate of 10 ml/h. The infusion was to be stopped 24 hours after the end of surgery. The infusion was not to exceed 10 ml/h at any time during the 24 h of study treatment.

A PCA device was to be connected (Group 2 and Group 3) when the patient was sufficiently awake after surgery. The device was to be set to deliver 1.0-mg bolus doses of morphine, with a lock-out time of 5 minutes. Background infusions of morphine were not allowed.

Case Narrative - Study 014

I. Patient 616:

73 year old ASA II male with history of hypertension, obesity, duodenal ulcer, anxiety disorder, glaucoma, and cancer of the bladder underwent cystectomy on July 20, 1995. The patient received a general anesthetic intraoperatively followed by 506.3 mg of epidural (T11-L1) ropivacaine 2 mg/mL alone (Group 1) during the 24-hour postoperative period. The intraoperative course was significant for 1800 milliliters of blood loss.

The postoperative course was marked by multiple episodes of desaturation x 4 (SaO_2 – 90) treated with supplemental oxygen. The desaturation was said to improve only to recur a few hours later. A **maximal sensory block of T4** was recorded.

No comments were recorded in the case report forms to assist in the interpretation of the refractory hypoxia. However, T4 levels of sensory blockade frequently cause desaturation due to its effect on myocardial contractility and diaphragmatic excursion. These consequences are exacerbated in patients over 65 years of age.

The patient was diagnosed with paresis of the leg adductors and was treated with physiotherapy. [**Note**: No comments were recorded in the case report forms to assist in the interpretation of this finding.]

Two days postoperatively the patient suffered from bedsores on buttock and heel for which surgical excision was performed. Two weeks after surgery the patient experienced a fistula between "Bricker" (a urinary bladder constructed by using the small intestine and urinary bladder) and the sigmoid colon. Further surgery was performed. These episodes resulted in prolonged hospitalization and permanent/severe disability.

Additional surgery was performed on September 22, 1995 for treatment of the fistula, however, the patient died on October 14, 1995. The cause of death was reported to be peritonitis (perforation of sigmoid) and septic shock. No autopsy was performed.

Additionally, the patient suffered from recurring hyperthermia (T = 38.8 x 2). No comments were recorded to assist in the interpretation of this hyperthermia. Please note Section 8.1.2.3.5.1 "Special Safety Evaluation – Fever".

The patient recovered from the recurring episodes of hypoxia; therefore it is unlikely that it was the cause of death. However, one can not discount the role persistent hypoxia may have played in the inability of the patient to heal postoperatively.

Table 83. Deaths All Studies (adapted from Sponsor's Table 8-17 "Patient Deaths")

STUDY CODE	PATIENT #	DRUG	SERIOUS ADVERSE EVENT	MAXIMUM LEVEL OF ANESTHESIA OBTAINED†
7.5 mg/ml ROPIVACAINE				
010	603	Ropivacaine	Death**	T3
	316	Ropivacaine + Fentanyl 2 ug/ml	Hypotension, Dyspnea, Pulmonary Edema, Oliguria, Multi-system Organ Failure, Septic Shock , Death	T2
	407*	Ropivacaine + Fentanyl 2 ug/ml	Fever (maximum temperature of 39.2), Death**	T5
011	714	Ropivacaine	Death**	T2
	1122	Ropivacaine	Left Ventricular Failure, Dyspnea, Oliguria, Death	T3
	616	Ropivacaine + Fentanyl 1 ug/ml	Hypotension, Bradycardia, Tachypnea, Decreased Level of Consciousness, Diaphoresis, Death	T2
	918	Ropivacaine + Fentanyl 1 ug/ml	Hypotension, Bradycardia, Myocardial Infarction, Cardiogenic Shock, Death	T2
	324	Ropivacaine + Fentanyl 4 ug/ml	Pulmonary Edema, Left Ventricular Failure, Respiratory Insufficiency, Myocardial Ischemia, Oliguria, Multi-system Organ Failure, Death	C8
2 mg/ml ROPIVACAINE				
014	616	Ropivacaine	Fever, Hypoxia, Paresis, Death	T4

*Patient 407 was not included in the clinical database - died 7 months after study concluded
†T4 level of sensory block inhibits cardiac accelatory fibers
**Death due to preexisting advanced carcinoma

8.1.1.3 Discussion

8.1.1.3.1 Sponsor's Discussion

The sponsor has not provided any comments on drug-relatedness for the deaths occurring in the postoperative pain management trials.

8.1.1.3.2 *Reviewer's Discussion*

Typically abdominal surgical procedures and the postoperative pain management thereof can adequately be performed under lumbar epidural blockade with low thoracic levels of anesthesia. A thoracic epidural does provide some added level of certainty of surgical anesthesia (for the anesthesiologist) for high abdominal procedures over that provided by a lumbar epidural. However, one would caution its use in any debilitated patient, e.g., advanced carcinoma, preexisting cardiac or respiratory disease, who may or may not have the cardiorespiratory reserve necessary to compensate for its untoward effects.

Specifically, the use of highly concentrated local anesthetics, e.g., 7.5-mg/ml ropivacaine, strengthens the density of blockade as well as the consequences of that block. For example, a T4 level of anesthesia with 7.5 mg/ml local anesthetic has been shown to result in a highly dense block of sensory conduction as well as the conduction of all other fibers represented by that T4 dermatome. Most importantly of which are the cardioaccelatory fibers and those responsible for diaphragmatic excursion. The consequences of this blockade often includes the following: bradycardia, hypoxia, hypotension, arrhythmia, cardiac and respiratory insufficiency, and even cardiac arrest. The more severe side effects are typically seen with the more potent agents and in those patients least able to compensate for the early, less severe, prodromal symptoms.

In conclusion, in light of the severity and predictability of adverse events following exposure to the highly concentrated 7.5 mg/ml ropivacaine to patients with preexisting debilitating disease, the use of thoracic epidural ropivacaine at concentrations of 7.5 mg/ml should be restricted to patients who can tolerate the potential myocardial and respiratory compromise that may result.

8.1.2 Cesarean Section

8.1.2.1 Other Serious Adverse Events

There were a total of five hundred and thirty (N=535) patients evaluable for safety in the six (6) cesarean section trials conducted. Of these six trials, four were active controlled, (0.75% ropivacaine versus 0.5% bupivacaine; M9-M12) and two (M8 and M4) were uncontrolled (one of which was a dose ranging study- M8). Five of the total trials (M9-M12 and M8) were submitted in support of proposed indications.

Trials M9-M12 are double blind and randomized comparing 0.75% ropivacaine to 0.5% bupivacaine for cesarean section. All trials were identically performed – lumbar epidural administration of twenty – thirty milliliters of study drug followed by evaluations of efficacy and tolerability. The primary tolerability variable was maximum drop in maternal blood pressure.

The sponsor has pooled safety data from the controlled studies separately from that of the uncontrolled studies. The review of this data will follow the same format; however, with an additional analysis of all data combined.

Controlled Clinical Trials

There were seven total serious adverse events in the controlled clinical trials with 0.75% ropivacaine – six of which occurred in patients exposed to ropivacaine. The "related" serious adverse events were those typically seen following local anesthetic administration to parturients. The leading serious adverse events included, e.g., hypotension, fetal bradycardia, low APGAR scores, etc.

Upon review of the case narratives, in all but one case of intravascular administration of bupivacaine, the technique performed was in compliance with the standard of care and was without complications. Therefore, the preponderance of serious adverse events occurring in patients exposed to 0.75% ropivacaine (the proposed increased concentration) can not be explained by technical error and is likely the result of the increased potency of the 0.75% ropivacaine over that of the 0.5% bupivacaine.

Notably, bupivacaine 0.5% when administered intravascularly, resulted only in dizziness – demonstrating the less potent and therefore more safe concentration of bupivacaine over that of the previously available 0.75% bupivacaine concentration. Please note Appendix 8.0 for the Case Narratives of Serious Adverse Events – Cesarean Section.

Despite a disparity of patient exposure, i.e., ropivacaine-exposed patients (N=264) and bupivacaine-exposed (N=218), the incidence of serious events is still far greater in the ropivacaine exposed group of patients (ropivacaine 6/264 = 2% versus bupivacaine 1/218=0.4%).

Alternatively, a statistical argument citing the lack of significance of serious events between groups is refuted by the mere clinical severity of the events. Additionally, it is not likely that in clinical trials with small numbers of patients such as these will likely demonstrate statistical significance of serious adverse events