CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-533/S-002

MEDICAL REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel: (301) 443-3741

REVIEW and EVALUATION of CLINICAL DATA

NDA:	20-533 (SE2-S002)
SPONSOR:	ASTRA USA
DRUG:	NAROPIN (ROPIVACAINE HCL INJ.)
PROPOSED INDICATION:	SURGICAL ANESTHESIA/ PAIN CONTROL
CLINICAL REVIEWER:	MONICA L. ROBERTS, M.D.
ORIGINAL RECEIPT DATE:	SEPTEMBER 28, 1998
DATE of REVIEW:	August 11, 1999
MATERIALS RECEIVED:	EFFICACY SUPPLEMENT
PROJECT MANAGER:	SUSMITA SAMANTA, M.D.

TABLE OF CONTENTS

Introduction

The supplemental NDA safety data is herein reviewed for the product, ropivacaine (approved September 24, 1996).

The original application for Naropin (ropivacaine injection) was received by the Agency on March 31, 1995 and was approved on September 24, 1996 for the 2.0, 5.0 and 10 mg/ml concentrations. Prior to this approval, the Anesthetics and Life Support Advisory Committee was convened to discuss the cardiac toxicity of 0.75% ropivacaine for cesarean section and the need for a boxed warning advising against its usage. Astra Pharmaceuticals, LP was encouraged at that time to conduct additional trials in cesarean sections to gain approval of the 0.75% concentration, as its availability would be welcomed by the anesthesiology community.

On September 28, 1998, Astra Pharmaceuticals, LP submitted a supplemental new drug application (sNDA) containing a series of clinical trials in support of the following:

1. Increase in the dosage of ropivacaine from 5 mg/ml to 7.5 mg/ml used in:
    a) brachial plexus block,
    b) lumbar epidural for cesarean section and,
    c) thoracic epidural
2. Increase in the duration of epidural infusion for post-operative pain management from 24 to 72 hours
3. Increase in the lumbar epidural infusion rate from 6-10 ml/h to 6-14 ml/h and,
4. Increase in the thoracic epidural infusion rate from 4-8 ml/h to 6-14 ml/h.

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.

Additionally, the sponsor has submitted safety data on four (4) clinical trials investigating ropivacaine for infiltration block, which involve five hundred and nineteen (N=519) patients. This indication is not being sought, however.

Ropivacaine has demonstrated efficacy and safety in the indications sought (NDA 20-533); therefore, the approval of the requested increase in dosage, rate and duration of the product will rely more heavily on the adequacy of the safety database.

SCOPE AND DESIGN OF THE DEVELOPMENTAL PROGRAM

CLINICAL STUDIES

Description - Clinical Studies[1]

This supplemental new drug application (sNDA) contains twenty (20) clinical trials - 17 controlled and 3 uncontrolled involving 1991 and 59 patients, respectively. The pivotal clinical trials were conducted in multiple countries including, e.g., Brazil, Canada, Norway and South Africa.

The **pivotal** studies include the following:

1. Epidural Anesthesia for **Cesarean Section** (6 trials) – a total of 317 patients received **7.5 mg/ml** of ropivacaine and 218 patients received 5 mg/ml bupivacaine

2. **Brachial Plexus Block** (2 trials) - a total of 102 patients received **7.5 mg/ml** of ropivacaine and 100 patients received 5 mg/ml bupivacaine

3. **Post–Operative Pain Management** (8 trials):
   a) 72 hours continuous infusion (N=417) – 3 Trials
   b) 24 hours continuous infusion (N=278) – 3 trials
   c) 48 hours continuous infusion (N=88) – 1 Trial
   d) One trial was discontinued due to a high incidence of fever (N=11)

Additional clinical trials:

1. Infiltration Block (4 trials) – N=519

[1] Patient enumeration may change upon response from sponsor to Agency request for clarification.

Table 1. SUMMARY OF ALL STUDIES SUBMITTED[2]

STUDY	STUDY DESIGN	Number Entered (Safety)	DOSE (s) Rop.[3] Bupiv[4]	AGE Range	SEX (M,F)	OBJECTIVE
POSTOPERATIVE PAIN MANAGEMENT						
I32	Double blind, Lumbar Epidural, Post-Orthopedic Surgery; 72 H Infusion	29 (26)	Rop. 0.2% vs. Rop. 0.3 + PCA Morphine	22-80 ASA I-III	9/20	Primary Objective: 1) estimate plasma concentration –time profile of ropivacaine based on both total and free concentrations and, 2) compare pharmacokinetic variables for the two infusions. Secondary: efficacy and tolerability
012*	Double blind, randomized, Lumbar Epidural Post-Orthopedic Surgery; 24 H Infusion	54(52)	Rop. 0.2%: 8 ml/h for 24h vs. Bupiv. 0.2%: 8 ml/h for 24 hour	29-75 ASA I-III	15/37	Primary Objective: 1) compare ropivacaine 2-mg/ml and bupivacaine 2 mg/ml, administered postoperatively after total knee replacement, with regard to pain at rest and motor block.
013*	Open label, randomized, Lumbar Epidural Post-Orthopedic Surgery; 24 h Infusion	106 (96)	Rop 1% + PCA Morphine vs. Rop 1% Alone vs. PCA Morphine Alone	20-86 ASA I-III	39/57	Primary Objective: 1) determine the efficacy and tolerability of the three treatment methods. Primary outcome measure: pain at rest
010*	Double blind, Postoperative Colon Resection 72 h Thoracic Epidural Infusion	155 (147)	Rop. 7.5 mg/ml bolus →[5] a) Rop. 0.2% vs. b) Rop. 0.2% + fentanyl infusions	20-79 ASA I-III	68/83	Primary Objective 1) compare the mean infusion rate of the two treatment groups

[2] Patient enumeration may change upon response from sponsor to Agency request for clarification.
[3] Rop: Ropivacaine
[4] Bupiv: Bupivacaine
* Statistical review and evaluation by Tom Permutt
[5] →: followed by

POSTOPERATIVE PAIN MANAGEMENT(continued)						
STUDY	**STUDY DESIGN**	**Number Entered (Safety)**	**DOSE (s)**	**AGE Range**	**SEX (M,F)**	**OBJECTIVE**
014*	Open, Randomized, Lumbar Epidural Post-Abdominal Surgery, 24h Infusion	141(130)	Rop. 0.2% +PCA Morphine vs. Rop. 0.2% Alone vs. PCA Morphine Alone	26-75 ASA I-III	64/66	Primary Objective: compare the efficacy and the tolerability of three treatments for 24 hours following major abdominal surgery. Primary Efficacy Variable: pain experienced (VAS score) upon coughing.
015*	Open, Randomized, Lumbar Epidural Postoperative 48h Infusion	90(88)	Ropivacaine 0.2% → PCA Morphine vs. GA[6] → PCA Morphine	49-75 ASA I-III	44/46	Primary Objective: Compare the efficacy and the tolerability of three treatments for 24 hours following major abdominal surgery. Primary Efficacy Variable AUCM24 in mm-scale based on the VAS measurements for pain at rest.
011*	Double-blind, randomized, Post-Abdominal Surgery, 72 h Thoracic Epidural Infusion	259 (244)	Rop. 0.2% + 1 ug/ml fentanyl vs. Rop. 0.2% + 2 ug/ml fentanyl vs. Rop. 0.2% + 4 ug/ml fentanyl	21-80 ASA I-III	127/ 128	Primary: compare the mean infusion rate of the treatment groups

[6] GA: general anesthesia

OBSTETRIC STUDIES						
STUDY	**STUDY DESIGN**	**Number Entered (Safety)**	**DOSE (s)**	**AGE Range**	**SEX (M,F)**	**OBJECTIVE**
M9*	Double-blind, Epidural Cesarean Section	126(124)	Rop. 0.75%: vs. Bupiv. 0.5%	18-43	All females	Primary Objective: to evaluate the efficacy and tolerability of rop. 7.5 mg/ml and bupivacaine 5 mg/ml used for cesarean section. Primary Efficacy Variable: pain on delivery. Primary Tolerability Variable: maximum drop in maternal blood pressure.
M10*	Double-blind, Epidural Cesarean Section	119(116)	Rop. 0.75%: vs. Bupiv. 0.5%	18-43	All females	See Above
M11*	Double-blind, Epidural Cesarean Section	122(122)	Rop. 0.75%: vs. Bupiv. 0.5%	18-42	All females	See Above
M12*	Double-blind, Epidural Cesarean Section	120(120)	Rop. 0.75%: vs. Bupiv. 0.5%	20-48	All females	See Above
M8						1)

* Statistical review and evaluation performed by Tom Permutt

STUDY	STUDY DESIGN	Number Entered (Safety)	DOSE (s)	AGE Range	SEX (M,F)	OBJECTIVE
BRACHIAL PLEXUS BLOCK						
P11*	Double-blind, Random, Two Parallel Groups	104(102)	Rop. 0.75%: vs. Bupiv. 0.5%	18-75	63/41	Primary Objective: efficacy of ropivacaine 7.5 mg/mL compared with bupivacaine 5 mg/mL for subclavian perivascular brachial plexus block. Primary Measure of Efficacy: onset of analgesia.
P12*	Double-blind, Two Parallel Groups	104(100)	Rop. 0.75%: vs. Bupiv. 0.5%	19-75	63/41	See Above

UNCONTROLLED CLINICAL STUDIES						
STUDY	**STUDY DESIGN**	**Number Entered (Safety)**	**DOSE (s)**	**AGE Range**	**SEX (M,F)**	**OBJECTIVE**
M8	Open Label Epidural Cesarean Section	16(16)	Ropivacaine 0.75% 150, 187.5, 225 mg	24-40	All females	Primary Objective: investigate the efficacy, tolerability and pharmacokinetics of each dose. Primary Efficacy Variables: 2) Quality of analgesia and abdominal wall muscle relaxation. 3) Pain during surgery.
09	Open Label Lumbar Epidural, Post-orthopedic Surgery, 72 Hour	15(11)	Ropivacaine 10 mg/ml → 2 mg/ml @ 6-14 ml/hour for 72 hours	21-74	10/5	Primary: to determine the efficacy, tolerability and pharmacokinetic of ropivacaine 0.2% for 72 hours
M4	Open Label Epidural Cesarean Section	38 (37)	Ropivacaine 0.75%: 20 ml	23-44	All females	Objectives: the efficacy of 0.75% ropivacaine for C-sec.

"OTHER STUDIES"						
INFILTRATION BLOCK						
STUDY #	**STUDY DESIGN**	**Number Entered (Safety)**	**DOSE (s)**	**AGE Range**	**SEX (M,F)**	**OBJECTIVE**
Q12	Double blind, Placebo Controlled Wound Infiltration after Inguinal Hernia Repair	77(77)	Ropivacaine 7.5 mg/ml (40 ml) vs. Normal Saline (40 ml)	>18	All Males	Primary Objective: analgesic effects of wound infiltration after inguinal hernia repair under general anesthesia with ropivacaine 300mg compared to placebo. Primary Efficacy Variable: pain experienced (VAS score) upon mobilization.
Q9	Double blind Active Controlled, Field Block/ Infiltration After Inguinal Hernia Repair	148(144)	Ropivacaine 7.5 mg/ml (40 ml) vs. Bupivacaine 2.5 mg/ml (40 ml)	21-69	139/5	Primary Objective: demonstrate improved clinical efficacy of ropivacaine compared to that of bupivacaine for field block/infiltration after inguinal hernia repair. Primary Measure of Efficacy: pain (VAS score) upon mobilization.
Q10	Double blind Active Controlled, Infiltration After Inguinal Hernia Repair	155(153)	Ropivacaine 7.5 mg/ml (40 ml) vs. Bupivacaine 2.5 mg/ml (40 ml)	19-74	All Males	Primary Objective: demonstrate improved clinical efficacy of ropivacaine compared to that of bupivacaine for field block/infiltration after inguinal hernia repair. Primary Measure of Efficacy: pain (VAS score) upon mobilization

"OTHER STUDIES" (continued)						
INFILTRATION BLOCK (continued)						
STUDY #	**STUDY DESIGN**	**Number Entered (Safety)**	**DOSE (s)**	**AGE Range**	**SEX (M,F)**	**OBJECTIVE**
Q11 SP-ROA-0006	Double blind Active Controlled, Field/ Infiltration After Inguinal Hernia Repair	151(145)	Ropivacaine 7.5 mg/ml (40 ml) vs. Bupivacaine 2.5 mg/ml (40 ml)	19-75	138/7	Primary Objective: demonstrate improved clinical efficacy of ropivacaine compared to that of bupivacaine for field block/infiltration after inguinal hernia repair. Primary Measure of Efficacy: pain (VAS score) upon mobilization

1.0 Materials Utilized in Review

1.1 Material from NDA/IND

Received	9/28/98:	sNDA 20-533, includes both text and CDROM
		Case Report Forms and Tabulations (NDA 20-533, Item 12)
		Integrated Summary of Safety (NDA 20-533; Vols. 105-107)
		Pharmacology and Toxicology Review– A. Goheer, Ph.D. Clinical Pharmacology and Biopharmaceutics Review - S. Kim, Ph.D Statistical Review and Evaluation– T. Permutt, Ph.D.
Received	7/16/96	Original NDA 20-533 Medical Officer Safety Update Review, 8/4/96 Project Manager's Action Packet

1.2 Related Reviews and Consults for the sNDA

None

1.3 Other Resources

a) Akerman, Hellberg, Trossvik: Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Acta Anaesthesiol Scand 32:571, 1988
b) Barash PG, Clinical Anesthesia: Basic Principles of Pharmacology in Anesthesia Practice. Lippincott – Raven, 1997.
c) Carpenter R. and Mackey D: Local Anesthetics. Barash, P (ed.): Clinical Anesthesia, Third Edition, Chapter 17, p. 413-436.Lippincott-Raven, 1997.
d) Guildner CW: Resuscitation. Opening the airway: A comparative study of techniques for opening an airway obstructed by the tongue. JACEP 5:588, 1976
e) Redding JS, Pearson JW: Resuscitation from ventricular fibrillation (drug therapy), JAMA 203:255, 1968

2.0 Background

2.1 Indication - Surgical Anesthesia and Pain Management

2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

Bupivacaine is a long-acting local anesthetic with potentially lethal cardiac toxicity. Secondary to its tenacious affinity for sodium channels, bupivacaine conduction blockade persists throughout diastole thereby creating a more potent depressant effect on cardiac transmission than other local anesthetics. [**Note**: other local anesthetic induced cardiac sodium channel blockade dissipates before completion of diastole].

The consequence of this prolonged (≥ 2 hours) and often-unsuccessful cardiopulmonary resuscitation, is neurologic morbidity or death. This has been of particular concern to the obstetric community due to the potential mortality and morbidity of both the fetus and the mother.

Regulatory response to reports of accidental intravascular injection of 0.75% bupivacaine has been in the form of a box warning against its use. Obstetric anesthesiologists have expressed an interest in the development of an alternative local anesthetic, which possesses equal or greater potency to bupivacaine without its cardiotoxicity.

Ropivacaine, a currently available local anesthetic, was developed based upon the premise of stereospecificity of cardiac effects, with the l-isomer having equal potency but less cardiotoxicity than the d-isomer. Initial human experience indicates ropivacaine to have similar potency and duration to bupivacaine;[7] however, the risk of cardiovascular toxicity has not been completely eliminated.

2.3 Administrative History

Please see introduction above.

2.4 Proposed Labeling

Please see introduction above.

2.5 Foreign Marketing

Ropivacaine was first approved for marketing in Sweden on September 15, 1995 and since has been approved for surgical anesthesia and acute pain management in forty countries, including the United States. The 7.5 mg/ml preparation is approved in all of these forty countries except the United States and Canada, where the 5.0 mg/ml concentration is recommended, and in Australia, where the use of ropivacaine was not approved for cesarean section.

Since is release, ropivacaine has not had any changes in labeling information or marketing status. Nine additional countries are currently evaluating ropivacaine for marketing.

---

[7] Akerman, Hellberg, Trossvik: Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Acta Anaesthesiol Scand 32:571, 1988

2.6 Miscellaneous Background

No additional background information pertinent to this submission to be included.

3.0 Chemistry , Manufacturing, and Controls

Naropin™ contains ropivacaine HCL which is chemically described as S-(-)-1-propyl-2', 6'-10 pipecoloxylidide hydrochloride monohydrate. The drug substance is a white crystalline powder, with a chemical formula of C17H26N20.HCl.H20, molecular weight of 328.89. No new chemistry data has been submitted.

4.0 Animal Pharmacology and Toxicology[8]

The preclinical studies submitted focused on the evaluation of the metabolism and toxicity of ropivacaine following longer durations of exposure than for which the product is currently approved.

Preclinical studies performed on ropivacaine include the following:

Dogs

1. 4-week epidural (continuous infusion) tolerance study in the Beagle dog of ropivacaine and bupivacaine. July 18, 1995
2. Dose finding study of a fixed combination of ropivacaine and fentanyl given subcutaneously to dogs for up to 5 days. July 5, 1996
3. Maximal tolerated dose (MTD) of a fixed combination of ropivacaine and fentanyl given intravenously to dogs. July 5, 1996
4. Local effects of ropivacaine and fentanyl given to dogs as a single epidural injection. July 5, 1996
5. Ropivacaine/Bupivacaine + Fentanyl. Toxicity and local tolerance study in the Beagle dog after 1 month's continuous epidural infusion. April 15, 1998

Rats

6. Single dose toxicity of a combination of ropivacaine and fentanyl in rats after subcutaneous administration. July 12, 1996
7. Single dose subcutaneous toxicity study in the rat. Nov 4, 1997
8. Single dose intravenous toxicity study in the rat. October 22, 1997

Additionally, there were multiple efficacy studies in guinea pigs, mice, rats, rabbits, sheep, monkeys and dogs that compared the efficacy of ropivacaine to bupivacaine with respect to onset and duration of sensory and motor block. Routes of administration included, sciatic nerve block, lumbar spinal anesthesia, epidural anesthesia, infiltration anesthesia and corneal anesthesia.

Racemate analysis was performed using the R- (+)-ropivacaine, S -(-) ropivacaine, RS -(±)-ropivacaine forms of ropivacaine which showed no interconversion. In vitro conduction block studies were performed with frog sciatic nerves, rat vagus and phrenic nerves, and rabbit vagus nerves. Finally, reproduction toxicology, genotoxicology and ADME studies were performed in multiple large and small animal species.

[8] Excerpts from "Review and Evaluation of Pharmacology and Toxicology Data", by A. Goheer, Ph.D.

Overall ropivacaine was seen to be similar to bupivacaine in efficacy and safety. However, with higher intravenous doses, the cardiac toxicity of ropivacaine increased.

5.0 Description of Clinical Data Sources (Populations Exposed and Extent of Exposure)

Complications in anesthesia follow lines of similarity, i.e., maternal hypotension, and/or fetal bradycardia can complicate all labor epidural anesthetics, whereas respiratory depression is more common in narcotic-based epidural infusions during pain management. Appropriately, in an effort to ensure meaningful estimations of the incidence of adverse events occurring in the clinical trials, pooling of studies were made according to the type of anesthesia performed.

Efficacy Supplement[9]

Obstetrical Studies

Six Obstetrical Studies: Epidural Anesthesia (N = 530)

- All cesarean section
- 0.75% ropivacaine vs. 0.5 % bupivacaine
- Two open label non-comparative trials, one of which is a dose ranging trial with 0.75% ropivacaine (150,187.5, 225 mg)
- **Pivotal Studies:** Four clinical trials (Studies M8, M9, M10, M11, M12), ropivacaine 7.5 mg/ml (N=280) and bupivacaine 5 mg/ml (N=218)
- **Supportive Studies:** One open label (Study M4) Ropivacaine 7.5 mg/ml (N=32)

Regional Block Studies

Two Brachial Plexus Studies (N=207)

- 0.75% Ropivacaine (N=105) vs. 0.5% Bupivacaine (N=102)

Postoperative Pain Studies

72-hour Continuous Epidural Infusion (N=417)

- One non-comparative Ropivacaine (.5%, 0.2%, 0.3%) for post-orthopedic pain
- One 0.2% Ropivacaine ± fentanyl at 4-14 ml/hour
- One 0.2% Ropivacaine with fentanyl (1, 2, or 4 ug/ml)
- One clinical trial ropivacaine 2 mg/ml + fentanyl 1-4 ug/ml (N=244)

24 hour Continuous Epidural Infusion (N=278)

- One (Study 013) open label Ropivacaine 0.2% (N=69) vs. PCA Morphine (N=35)
- One (Study 014) Ropivacaine 0.2% ± PCA Morphine (N=44) vs. PCA Morphine (N=46)
- One (Study 012) Ropivacaine (N=27) 0.2% vs. Bupivacaine (N=27)

48-hour Continuous Epidural Infusion (N=88)

- Ropivacaine 0.2% or 1% vs. PCA Morphine

[9] Patient enumeration may change upon response from sponsor to Agency request for clarification.

5.1 Primary Source Data (Development Program)

5.1.1 Ropivacaine Exposure[10]

The subject efficacy supplement is designed to expand the duration and dose limits for epidural infusion of ropivacaine 2 mg/mL, and to prove the safety of the 7.5-mg/mL solution of ropivacaine for clinical applications previously approved for the 5-mg/mL solution, i.e., brachial plexus, cesarean section, lumbar and thoracic epidural.

The sponsor contends that the data submitted in this efficacy supplement supports the following **new dosage recommendations** for ropivacaine:

Ropivacaine 7.5 mg/mL for:

- Epidural anesthesia for **cesarean section** in a recommended dose of 150 mg (20 mL).
- Major nerve block, e.g. **brachial plexus block** in doses up to 40 mL (300 mg).
- **Thoracic epidural** administration of 5-10 mL (37.5-75 mg)
- The current label allows ropivacaine 5 mg/ml to be used in these procedures

Postoperative Pain:

- Extension of the epidural administration of ropivacaine 2 mg/mL to **72 hours** from 24 hours for postoperative pain management
- Increase in the epidural infusion rate for postoperative pain management to **6-14 mL/h** for both lumbar (from 6-10 to 6-14 ml/hour) **and thoracic** (from 4-8 ml/hour to 6-14 ml/hour) **administration.**

The proposed dosage recommendations are supported by the following **dose exposures**:

- **Cesarean section** - epidural ropivacaine 7.5 mg/mL (150 mg): 317 ropivacaine-exposed (mean dose – 164 mg) patients and compared to 218 bupivacaine- exposed (mean dose – 113 mg; 5 mg/ml) patients.
- **Brachial plexus block** 7.5% ropivacaine in doses up to 40 mL (300 mg): 102 ropivacaine-exposed (mean dose – 263 ± 38 mg) patients and compared to 100 bupivacaine- exposed (mean dose – 174 ± 25 mg) patients.
- **Thoracic epidural** administration of ropivacaine 7.5 mg/mL (37.5-75 mg):
- **Thoracic epidural** administration of ropivacaine 7.5 mg/mL (37.5-75 mg) at 6-14 ml/hour
- **Lumbar epidural** administration of ropivacaine at 6-14 ml/h
- **Postoperative pain management** (72-hour infusion; 6-14 ml/h): 116 ropivacaine-exposed (mean dose – 459 ± 189) patients versus 84 PCA morphine-exposed (mean dose 489 ± 130) patients.
- **Postoperative pain management** (72-hour infusion; 6-14 ml/h): 141 ropivacaine-exposed (mean dose – 1235 ± 189) patients versus 1252 ropivacaine + fentanyl-exposed (mean dose 1252 ± 522) patients.
- **Postoperative pain management** (24-hour infusion; 6-14 ml/h): 27 ropivacaine-exposed (mean dose – 1235 ± 189) patients versus 1252 ropivacaine + fentanyl-exposed (mean dose 1252 ± 522) patients.

---

[10] Extent of ropivacaine exposure may change upon response from sponsor to Agency request for clarification.

Table 2. Enumeration of Subjects Exposed

Enumeration of Patients for Ropivacaine Development Program		
Study Groups	**Treatment Groups**	
Cesarean Section: **Epidural Anesthesia: Dosages of 0.75% Ropivacaine vs. 0.5% Bupivacaine (mg)**		
	Ropivacaine (ISS) N=264	**Bupivacaine (ISS) N=218**
Mean Dose ± SD	164 ± 18	113 ± 18
Minimum		
Maximum		
Postoperative Pain Management: **Dosages of Ropivacaine (mg) vs. PCA Morphine (mg) for 72 Hours by Continuous Infusion**		
	Ropivacaine (ISS) N=116	**PCA Morphine (ISS) N=84**
Mean Dose ± SD	459 ± 189	489 ± 130
Minimum		
Maximum		
Postoperative Pain Management: **Dosages of Ropivacaine (mg) vs. Bupivacaine (mg) for 24 Hours by Continuous Infusion**		
	Ropivacaine (ISS) N=27	**Bupivacaine (ISS) N=27**
Mean Dose ± SD	448 ± 80	464 ± 27
Minimum		
Maximum		
Postoperative Pain Management: **Dosages of Ropivacaine (mg) ± Fentanyl for 72 Hours by Continuous Infusion**		
	Ropivacaine (ISS) N=141	**Ropivacaine + Fentanyl (ISS) N=265**
Mean Dose ± SD	1235 ± 621	1252 ± 522
Minimum		
Maximum		
Postoperative Pain Management: **Dosages of Ropivacaine (mg) for 72 Hours by Continuous Infusion**		
	Ropivacaine (ISS) N=445	
Mean Dose ± SD	1266 ± 562	
Minimum		
Maximum		

Table 3. Enumeration of Subjects Exposed (continued)

Enumeration of Patients for Ropivacaine Development Program (continued)		
Study Groups	**Treatment Groups**	
Postoperative Pain Management: Thoracic Epidural: Dosages of 0.75% Ropivacaine (mg)		
	Ropivacaine (ISS) N=173	
Mean Dose ± SD	84.9 ± 26.6	
Minimum		
Maximum		
Postoperative Pain Management: Thoracic Epidural: 72 Hour Infusion at 6-14 ml/h		
	Ropivacaine (mg) (ISS) N=173	
Mean Dose ± SD	1449 ± 342	
Minimum		
Maximum		
Mean Rate ± SD	10.4 ± 2.4 ml/hour	
Minimum		
Maximum		
Postoperative Pain Management: Lumbar Epidural – 72 Hour Infusion at 6-14 ml/h		
	Ropivacaine (mg) (ISS) N=11	
Mean Dose ± SD	1049 ± 288	
Minimum		
Maximum		
Mean Rate ± SD	7.5 ± 2.1 ml/hour	
Minimum		
Maximum		
Infiltration Nerve Block: Dosages of 0.75 % Ropivacaine vs. Bupivacaine		
	Ropivacaine (mg) (ISS) N=224	**Bupivacaine (mg) (ISS) N=218**
Mean Dose ± SD	300 ± 0.5	100 ± 0
Minimum		
Maximum		
Brachial Plexus Block: Dosages of 0.75% Ropivacaine vs. 0.5% Bupivacaine (mg)		
Mean Dose ± SD	263 ± 38	174 ± 25
Minimum		
Maximum		

5.1.2 Demographics

Awaiting response from sponsor.

5.1.3 Extent of Exposure (dose/duration)

Not applicable – short term exposure (≤ 72 hours)

5.2 Secondary Source Data

None

5.2.1 Other Studies

None

5.2.2 Post-Marketing Experience

Ropivacaine was first approved for marketing in Sweden on September 15, 1995 and since has been approved for surgical anesthesia and acute pain management in forty countries, including the United States. The 7.5 mg/ml preparation is approved in all of these forty countries except the United States and Canada, where the 5.0 mg/ml concentration is recommended, and in Australia, where the use of ropivacaine was not approved for cesarean section.

Since is release, ropivacaine has not had any changes in labeling information or marketing status. Nine additional countries are currently evaluating ropivacaine for marketing.

5.2.3 Literature

1) Epidural Anesthesia and Analgesia. Their Role in Postoperative Outcome. Anesthesiology 1995;82:1474-1506 (X102)
2) Metabolism of s New Local Anesthetic, Ropivacaine, by Human Hepatic Cytochrome P450. Anesthesiology 1995;82(1):214-20 (x104)
3) Clinical Effects and Maternal and Fetal Plasma Concentrations of Epidural Ropivacaine versus Bupivacaine for Cesarean Section. Anesthesiology 1995;82: 1346-52 (X106)

6.0 Human Pharmacokinetics and Pharmacodynamics[11]

Eight clinical/pharmacokinetic studies, involving 119 subjects and patients ranging from 19 to 80 years of age, were conducted –postoperative pain management, epidural anesthesia for cesarean section, brachial plexus block and *in vivo* study of metabolic drug interaction with CYP1A2 (fluvoxamine) and CYP3A4 (ketoconazole) inhibitors.

The reviewing pharmacokineticist made the following conclusions and directed them to the reviewing medical officer:

1. Some patients, after 300 and 375-mg infiltration (however, in the package insert, dosage recommendation for the infiltration procedure is 2-200 mg) or 300mg brachial block, may approach the threshold for CNS toxicity.
2. A very long $t_{½}$ (> 30 h) was evidenced in a few patients, therefore, caution is needed with ropivacaine when used at high doses (e.g., 300 or 375 mg), upon repeated infiltration administration.
3. The plasma concentration ratio of umbilical venous/umbilical artery (UA/UV) or $UA_{unbound}/UV_{unbound}$ was about 0.8. Therefore, ropivacaine is distributed to the fetus.
4. BA [bioavailability] comparable between 5 and 7.5 mg/ml.
5. The plasma clearance of ropivacaine is reduced by 70% during co-administration of a selective and potent CYP1A2 inhibitor, fluvoxamine [treatment of obsessive compulsive disorder]. This reduction could be of clinical importance during long-term administration. A selective and potent inhibitor of CYP3A4 (ketoconazole) slightly reduces (about 15% decrease) the clearance of ropivacaine, therefore, this reduction may not likely be of clinical relevance.

In response to these pharmacokinetic concerns is the following:
All five of these above-mentioned comments warrant mention in the labeling of the product. Number one and five warrant additional comments from a medical perspective. With respect to number one, please see section8.1.12.4 "Summary of Potential Adverse Events Considered Related to Study Drug". Number 5 - the co-administration of ropivacaine and fluvoxamine and the possible reduced ropivacaine plasma clearance- the potential for patients with obsessive compulsive disorder treated with fluvoxamine needing local anesthetic blockade for surgery or delivery is a real one and one which is potentially life-threatening. The product label should reflect this level of severity.

Upon review of the supplemental NDA, on December 14, 1998, the following pharmacokinetic comments were forwarded to the sponsor, a response has yet to be received:

1. Please summarize any studies available in the literature on pharmacokinetic information in the geriatric population and update the information in the package insert according to 21 CFR 201.57 (f) (10) in the NDA.
1. Please submit in the NDA, summarization of study (ies) from the literature (along with articles) regarding the information of the effects of gender, race, age (e.g., pediatric use), renal and hepatic insufficiency on the pharmacokinetics of the drug. For those studies being currently conducted as a response to phase IV commitment, please provide the list of studies along with proposed timelines for completion.

The pharmacokineticist concluded that there are no significant drawbacks to make this submission unapprovable.

---

[11] Excepts from, "Clinical Pharmacology and Biopharmaceutics Review", S. Kim, Ph.D.

7.0 Review of Efficacy

7.1 Data Integrity

7.1.1 Division of Scientific Investigations

No investigation of the trial sites was performed. Due to the multiplicity of trial locations (sixteen clinical trials in multiple countries including Brazil, Canada, Norway, and South Africa, etc.) and the nature of the submission (efficacy supplement with primarily safety concerns), it was decided that the focus of the investigation into the integrity of the data would be performed on the case report forms and tabulations by the medical reviewer.

7.1.2 Case Report Forms and Tabulations

The case report forms submitted included efficacy and safety records from all patient deaths, discontinuations and serious adverse events. In an effort to establish the validity of data submitted, it was decided that a side by side comparison between the case report form efficacy records, e.g., primary and secondary efficacy endpoints, and those found in the data listings would be a valuable technique. It was further concluded that twenty percent of the individuals for which data was present, randomly selected, would be an adequate representation of the total database.

The results of this technique were favorable. The case report forms confirmed the integrity of the case report tabulations and vice versa. It can be concluded that the data was recorded and tabulated accurately twenty percent of the time and likely to have been for the remaining cases.

7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY:

7.2.1 STUDY # 94RO85 (O12)

7.2.1.1 Protocol Synopsis:

Title: "A Double-Blind Randomized Comparison between Continuous Epidural Infusion of Ropivacaine 2 mg/ml and Bupivacaine 2 mg/ml for the Prevention of Postoperative Pain after Total Knee Replacement"

Primary Objective: "To compare ropivacaine 2 mg/ml and bupivacaine 2 mg/ml, administered postoperatively after total knee replacement, with regard to both pain at rest and motor block."

Secondary Objective: "To compare the two treatments with regard to pain during movement, time from the end of treatment to the return of normal motor and sensory function, spread of sensory block, quality of pain relief and safety."

Study Design:

The study is designed as a randomized, double blind, parallel group comparative study of 2mg/ml ropivacaine versus 2 mg/ml bupivacaine administered for pain associated with total knee replacement. The protocol calls for two groups of twenty-six patients to each be randomly assigned to one of two treatment arms. All fifty-two patients are to be randomized at one center in Northern Ireland.

Group I	2 mg/ml ropivacaine
Group II	2 mg/ml bupivacaine

Eligible patients will be American Society of Anesthesiologists physical status I - III males or females between 18 and 75 years of age, weighing 50 –110 kg, providing written informed consent. Patients must have no prior history of significant medical illness, contraindication to epidural anesthesia, participation in clinical studies in the two week period prior to admission to the study, significant alcohol or drug abuse. Women who were pregnant or not practicing adequate contraception will be excluded from study participation.

Eligible patients will undergo a brief screening phase followed by placement of an epidural block to T10 with ropivacaine 5 mg/ml or bupivacaine 5 mg/ml. Surgery will then be performed under general anesthesia. Within 30 minutes of the end of surgery, an infusion of either ropivacaine 2 mg/ml or bupivacaine 2 mg/ml will commence and be maintained at a constant rate of 8 ml/h for 24 hours. A patient controlled analgesic device for the administration of morphine will be connected during the infusion.

Preoperatively, patient will receive temazepam 10 –20 mg or midazolam alternatively for patients unable to tolerate oral medications. Thrombosis prophylaxis will be administered to all patients according to hospital routines. All patients will receive ≥ 1000 ml of crystalloid or crystalloid colloid mixture (amendment 2) prior to the epidural block placement. General anesthesia will be induced with propofol, atracurium and fentanyl (maximum 200 μg) and maintained with isoflurane, nitrous oxide/oxygen, atracurium and fentanyl (50 μg when indicated). Neostigmine and glycopyrrolate will be administered to reverse muscle relaxation.

The epidural will be placed in accordance with the current standard of care. A 16-18-gauge needle will be introduced at L2-L4 vertebral interspace via the midline or paramedian approach with the patient in the sitting or lateral decubitus position. An epidural catheter will be inserted 4-5 cm in the cephalad direction and 3 ml of lidocaine 20 mg/ml with 5 μg/ml of epinephrine will be injected, provided that neither cerebrospinal fluid nor blood is aspirated. Five minutes later, if there are no signs of intravascular or spinal administration, a 10-20 ml dose of randomized drug will be administered, i.e., 5 mg/ml ropivacaine or bupivacaine, over a five minute period.

If sensory block at T10 is not achieved 30 minutes after injection of the main dose, an additional 5-ml of drug will be injected. If sensory block at T10 is still not obtained 15 minutes later (45 minutes after injection of the main dose), the patient will be withdrawn from efficacy assessments. The maximum total dose allowed will be 125 mg, i.e., a 10-20 ml bolus dose (50-100 mg) and possibly one additional 5 ml dose (25 mg) – by protocol amendment.

During surgery an additional 3-5 ml doses of randomized drug could be administered if the investigator assessed signs of inadequate block. Within 30 minutes of the end of surgery, ropivacaine 2 mg/ml or bupivacaine 2 mg/ml will be administered at a constant rate of 8 ml/h over 24 hours. The patient controlled morphine (PCA) will be connected when the patient is fully awake and set to deliver 1.0-mg boluses of morphine with a 5-minute lockout interval. No background infusion will be used. If a patient is unable to tolerate morphine, pethidine 10 mg [Note: pethidine is a meperidine analog] will be used with the same 10-minute lockout. Additional 1.0 mg doses of morphine (or pethidine) will be administered in instances of inadequate analgesia, as judged by the investigator, or if technical problems with the PCA device occur.

Figure 1. Study Schematic

Study Design	Actions before block	Induction of epidural block (min)				Surgery	0-24 hours of infusion		Discharge and follow-up
		0-5	5-10	10-	35		Every second hour from 2h		
Medical history									
Physical examination									
Premedication									
Preloading									
Test dose 3 ml									
Main dose 10-20 ml									
Additional dose 3-5 ml					1	2			
General Anaesthesia									
Cont. Infusion 8 ml/h									
PCA Morphine									
Pain Assessments									
Motor/Sensory block					1			3	
Patient satisfaction								5	
Blood pressure/Pulse								5	
Body Temperature								5	
ECG								4	6
Laboratory samples								4	6
Adverse Events									7

1. If block to T10 is not achieved
2. When indicated
3. Every hour until return of normal sensory and motor function
4. At the end of the epidural infusion
5. Every second hour until return of normal sensory and motor
6. At discharge from hospital
7. At discharge from hospital and at a follow up 3-4 weeks after surgery

[Item 8, Vol. 39, p. 117]

Postoperative pain assessments include the following:

1) Assessment of wound pain using the visual analogue scale (VAS).
2) Wound pain at rest using the VAS, the patient rated the pain experienced when resting on the bed every two hours during the epidural infusion beginning 2 hours after the start of the infusion.
3) Wound pain during movement using the VAS, the patient rated the pain experienced during a passive extension of the knee. Wound pain during movement was assessed every two hours during the epidural infusion, beginning 2 hours after the start of the infusion.

The spread of sensory block was determined bilaterally using ice for loss and return of sensation. Both upper and lower spreads (to S3) were recorded. The spread of the sensory block was assessed every five minutes from the end of injection of the main dose until the induction of general anesthesia. During the epidural infusion the spread of sensory block was determined every two hours beginning 2 hours after the start of the infusion. The spread of sensory block was to be assessed every hour from the end of the epidural infusion until the return of normal sensory function.

Motor block was determined bilaterally according to a **modified Bromage scale**:

0 = No motor block.
1 = Inability to raise the extended leg (just able to move knee).
2 = Inability to flex the knee (able to move foot only).
3 = Inability to flex the ankle joint (unable to move foot or knee).

It was assessed every five minutes from the end of the injection of the main dose until the induction of general anesthesia. During the epidural infusion motor block was to be determined every two hours beginning 2 hours after the start of the infusion until rated return of normal motor function.

At the end of the epidural infusion, the overall satisfaction in regard to pain relief during the epidural infusion was rated by the patient in response to the question: "How was your pain relief." The quality of pain relief was rated according to the following scale:

1- Excellent pain relief
2- Good pain relief
3- Fair pain relief
4- Poor pain relief
5- No pain relief

7.2.1.2 Statistical Analysis

Analyzed Data Sets

"An 'all patients treated' approach was used for efficacy variables, where 'treated,' means that the postoperative treatment had commenced for a patient. The postoperative treatment was considered to have commenced when the epidural infusion was started. Thus, a patient was not included in the "all patients treated" analysis if:

> The patient did not receive any postoperative epidural infusion. Technical failure occurred before the start of postoperative epidural infusion."

[Item 8, vol. 39, p. 30]

Clinical Variables

"The main efficacy variable was AUCM24 on a millimetre-scale based on the VAS measurements for pain at rest and the AUCM24 based on the Bromage score measurement.

The statistical analysis for each of these variables includes descriptive statistics and graphs for each treatment group, together with a comparison of the two groups using a Wilcoxon (mid) rank sum test, with corresponding point estimates and 95% confidence intervals for differences if the variable was continuous. The p-values reported correspond to two-sided tests, and a p-value less than 5% was considered to be significant for the primary comparison."

[Item 8, Vol.39 p.31-36]

7.2.1.3 Protocol Amendment:

A. Pain Assessments
- Pain at rest and during passive flexion of the knee has been changed to passive extension of the knee by amendment
- Wound pain during movement: the patient will rate the pain experienced during a passive knee hyper-extension instead of the previous passive knee flexion of between 40 and 50 degrees. *[Note: the clinical study reported pain experienced during passive knee extension not hyper-extension]*

B. Bolus Dose Administration
- The maximum bolus dose has been decreased from 20 to 15 ml. *[Note: the clinical study reported the maximum bolus dose as 20 ml]*

C. Maximum Total Dose
- The maximum total dose was increased from 100 mg to 125 mg.

D. Pre-loading
- A crystalloid/colloid mixture of ≥ 1000 ml was added as a possible choice for volume expansion pre – epidurally.

E. Administrative Corrections

- Multiple corrections have been made in this area including, numbering of captions, changes in personnel, typographical errors.

7.2.1.4 Conduct of Study

Patient Distribution/Disposition:

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

Demographics

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

Table 4. Demographics - Safety Evaluable Population

	STATISTICS	ROPIVACAINE	BUPIVACAINE
Age (years)	N	26	26
	mean	66	68
	median	66	69
	S.D.	7	5
	range	49-75	54-74
Men	N	7	8
Women	N	19	18
Weight (kg)	N	26	26
	mean	78	79
	median	78	77
	S.D.	14	11
	range	50-101	56-105
Height (cm)	N	26	26
	mean	163	164
	median	161	165
	S.D.	7	8
	range	152-180	152-183

[based on sponsor's Table 1, Item 8, Vol.39 p.40]

Patients' ages, heights and weights were similar in both groups. A significant number (18/56) of patients reported having cardiovascular disease, including essential hypertension, angina pectoris, and diseases of the mitral valve. By far the most frequently reported disease was essential hypertension; it occurred with equal frequency (9/26) in both groups. Preanesthetic medication included temazepam (anxiolytic) and cefamandole nafate (antibiotic) which was given to 24 and 25 patients in the ropivacaine and bupivacaine group, respectively.

Other medications were also given in equal percentages and included drugs to treat hypertension, asthma, iron deficiency anemia, and gastritis, for example.

7.2.1.5 Sponsor's Efficacy Results:

AUCM for Pain at Rest

The main efficacy variable was AUCM24 based upon VAS measurements for pain at rest and the AUCM24 based upon the Bromage score measurement.

"AUCM for pain at rest (VAS) comparisons between the ropivacaine and the bupivacaine group were performed at the time intervals 0-4, 0-8 and 0-24 hours. At 0-4 and 0-8 hours there were no statistical differences between the two groups. At 0-24 hours there was a statistically significantly higher AUCM score in the ropivacaine group than in the bupivacaine group (p=0.017). The 95% confidence interval for the difference of bupivacaine minus ropivacaine was (-14.6, -0.7). The estimated median difference over 24 hours between the groups was -5.6 mm."
[Item 8, Vol. 39, p.52]

Table 5. Comparative AUCM for Pain at Rest (VAS)

Period	Group	N	Mean	STD	MIN	Q1	Median	Q3	Max
0-4 h	Ropi	26	6.70	11.26		0.00	0.00	10.00	
	Bupi	26	3.86	10.98		0.00	0.00	0.00	
0-8 h	Ropi	26	10.78	11.83		0.00	6.56	21.25	
	Bupi	26	6.51	13.16		0.00	0.22	6.25	
0-24 h	Ropi	26	14.29	12.36		2.67	13.67	21.67	
	Bupi	26	7.42	10.86		0.42	2.92	12.33	

[Sponsor's Table 14. Item 8, Vol. 39, p. 52]

Pain at Rest (VAS)

"The pain scores at rest (VAS) were overall low during the therapy period for 24 hours in both groups. The median score at rest varied in the range 0-13.3 mm in the ropivacaine and 0-0.5 mm in the bupivacaine group during the infusion period (Figure 1). It could be noted that patient no.127 in the ropivacaine group had overall very high pain scores both at rest and during movement, but rated the quality of pain relief as good."

[Item 8, vol. 39, p.49]

No formal statistical analysis was performed.

Figure 1. Comparative VAS Pain Scores at Rest

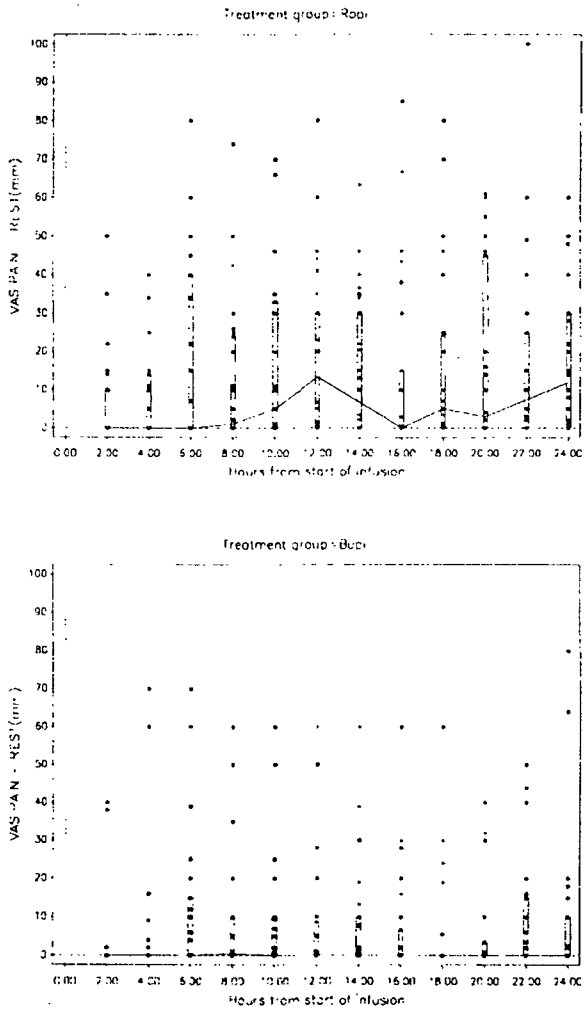

Figure 1. Pain score at rest (VAS) during the 24-hour postoperative infusion of ropivacaine 16 mg/h (n=26) or bupivacaine 16 mg/h (n=26). Individual values and boxplots (Q1, median, Q3); median scores connected.

[Sponsor's Figure 1. Item 8, Vol. 39, p.50]

Pain at Rest above 30 mm (VA S)

"There were no statistically significant differences between the two groups for the numbers of patients that had a pain score at rest ≥ 30 mm in the time intervals 0-4 and 0-8 hours. For the time interval 0-24 hours, there was a statistically significant higher number of patients in the ropivacaine group than in the bupivacaine group with a pain score at rest ≥ 30 mm (p=0.028)."
[Item 8, Vol. 39, p.51]

Table 6. Incidence of VAS scores ≥ 30 mm for each Time Interval

Table 13. Pain score at rest ≥30 mm (VAS) at time intervals 0-4, 0-8 and 0-24 hours. Yes or No (number of patients).

Time interval	VAS ≥ 30 mm	Ropivacaine n=26	Bupivacaine n=26
0-4 h	Yes	2	2
	No	24	24
0-8 h	Yes	9	4
	No	17	22
0-24 h	Yes	16	8
	No	10	18

[Sponsor's Table 23. Item 8, Vol. 39, p. 51]

Pain During Mobilization (VA S)

"Pain scores during mobilisation (VAS) were greater in the ropivacaine group than in the bupivacaine group. The median score varied over time in the range 0- 40.0 mm in the ropivacaine group and 0-16.0 mm in the bupivacaine group (Figure 2)."
[Item 8, Vol. 39, p.52]

Figure 2. Comparative Pain Scores During Mobilization (VAS)

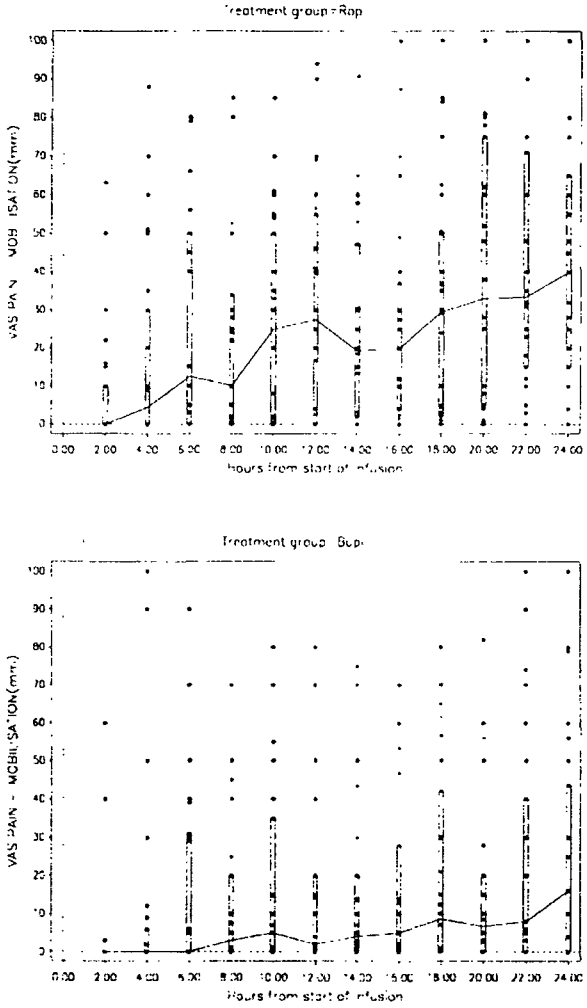

Figure 2. Pain score during mobilisation (VAS) during the 24-hour postoperative infusion of ropivacaine 16 mg/h (n=26) or bupivacaine 16 mg/h (n=26). Individual values and box plots (Q1, median, Q3); median scores connected.

[Sponsor's Figure2. Item 8, Vol. 39, p. 53]

Pain During Mobilization above 30 mm (VA S)

"There were no statistically differences between the two groups for the numbers of patients that had a pain score during mobilisation ≥30 mm (VAS) in the time intervals 0-4 and 0-8 hours. There was a statistically significantly higher number of patients in the ropivacaine group than in the bupivacaine group with a pain score ≥30 mm at the time interval 0-24 hours (p=0.040) (Table 15)."
[Item 8, Vol. 39, p.54]

Table 7. Comparative Pain Scores ≥ 30 mm During Mobilization

Table 15. Pain score during mobilisation ≥30 mm (VAS) at time intervals 0-4, 0-8 and 0-24 hours. Yes or No (number of patients).

Time interval	Indicator	Ropivacaine	Bupivacaine
0-4 h	Yes	3	2
	No	23	24
0-8 h	Yes	12	10
	No	14	16
0-24 h	Yes	21	14
	No	5	12

[Sponsor's Table 15, Item 8, Vol. 39, p. 54]

AUCM for Pain during Mobilization (VAS)

"AUCM comparisons between the ropivacaine and the bupivacaine group were performed at the time intervals 0-4, 0-8 and 0-24 hours during mobilisation. At 0-4 and 0-8 hours there were no statistically significant differences between the two groups. At 0-24 hours there was a significantly higher AUCM score in the ropivacaine group than in the bupivacaine group (p=0.016) (Table 16). The 95% confidence interval for the difference of bupivacaine minus ropivacaine was (-21.9, -1.7). The estimated median difference over 24 hours between the groups was -11.6 mm."
[Item 8, Vol. 39, p.55]

Table 8. Comparative AUCM for Pain during Mobilization (VAS)

Period	Group	N	Mean	STD	MIN	Q1	Median	Q3	Max
0-4 h	Ropi	26	10.59	15.31		0.00	2.38	18.75	
	Bupi	26	5.85	15.34		0.00	0.00	2.25	
0-8 h	Ropi	26	17.41	17.00		0.63	9.19	32.50	
	Bupi	26	10.62	17.89		0.00	1.44	11.75	
0-24 h	Ropi	26	27.02	19.47		12.50	24.08	36.42	
	Bupi	26	16.25	19.76		0.67	8.84	24.75	

[Sponsor's Table 16. Item 8, Vol. 39, p. 55]

Spread *of Sensory Block*

"The spread of sensory block over time was similar in both groups. The upper median segmental spread of sensory block after 2 hours was T7/T6 in the ropivacaine and T6/T5 in the bupivacaine group. After 24 hours of infusion the median upper sensory spread was L2/ LI for ropivacaine and L1 for bupivacaine (Figures 3 and 4). The lower median segmental spread of sensory block after 2 and 24 hours was S1 in each group."

[Item 8, Vol. 39, p.56]

Figure 3. Comparative Spread of Upper Level of Sensory Block During 24-h Infusion

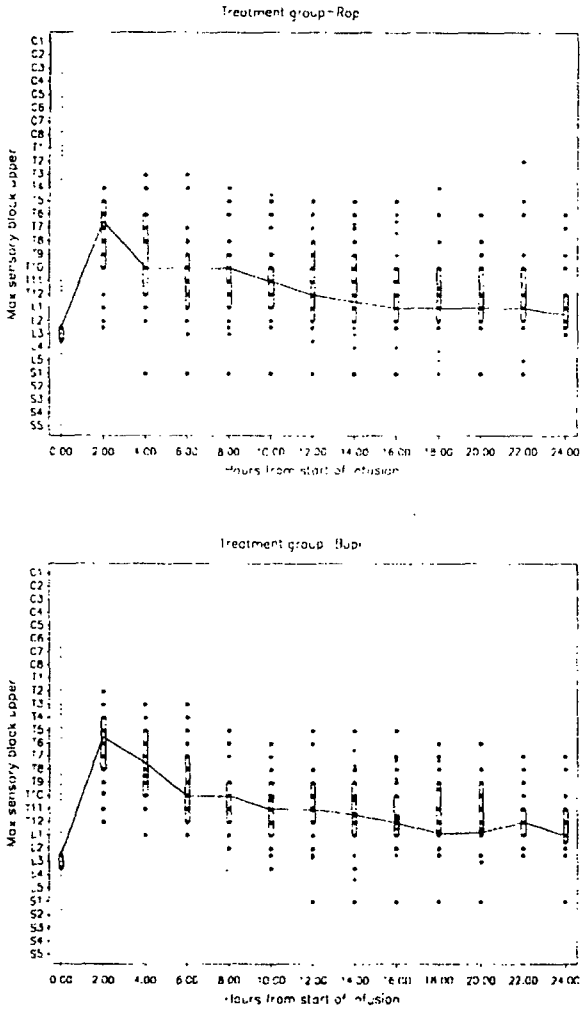

Figure 3. Upper segmental spread of sensory block during infusion of ropivacaine 16 mg/h (n=26) or bupivacaine 16 mg/h (n=26) for 24 hours of infusion. Individual values and box plots (Q1, median, Q3); median values connected. The value plotted at time 0 is the median of the site of injection.

[Sponsor Figure 3, Item 8, Vol. 39, p. 57]

Figure 4. Comparative Spread of Lower Level of Sensory Block During 24-h Infusion

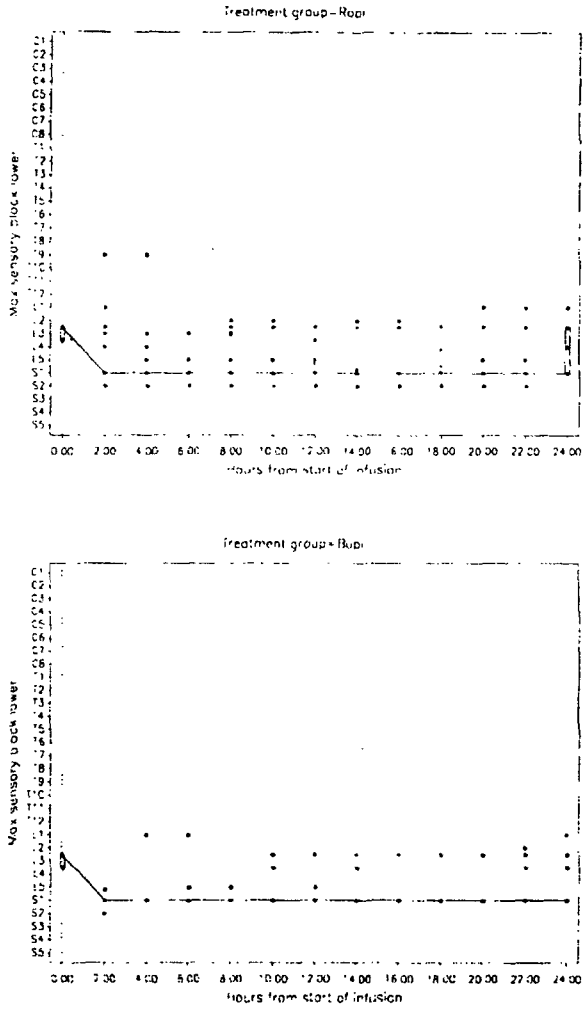

Figure 4. Lower segmental spread of sensory block for ropivacaine 16 mg/h (n=26) or bupivacaine 16 mg/h (n=26) for 24 hours of infusion. Individual values and box plots (Q1, median, Q3); median values connected. The value plotted at time 0 is the median of the site of injection.

[Sponsor's Figure 4. Item 8, Vol. 39, p. 58]

Number of Blocked Dermatomes

"AUCM comparisons of the number of blocked dermatomes between the ropivacaine and the bupivacaine group were performed over the time intervals 0-4, 0-8 and 0-24 hours. The ropivacaine group had more patients with a lower number of blocked dermatomes than the bupivacaine group. At 0-4 hour there was a statistically significantly lower AUCM score in the ropivacaine group than in the bupivacaine group (p=0.016). The 95% confidence interval for the difference of bupivacaine minus ropivacaine was (0.5, 4.5). Likewise, at the time interval 0-8 hour there was a statistically significant difference between the two groups (p=0.037) with a confidence interval of (0.13, 3.75). For the time interval 0-24 hours, there was no statistically significant difference between the two groups (Table 17)."
[Item 8, Vol. 39, p.59]

Table 9. Comparative AUCM for Number of Blocked Dermatomes

Table 17. AUCM for number of blocked dermatomes (n=number of patients).

Period	group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
0-4	Ropi	26	8.95	4.01		5.75	9.63	12.00	
	Bupi	26	11.65	2.55		9.50	11.63	14.00	
0-8	Ropi	26	8.20	3.32		5.63	8.56	10.13	
	Bupi	26	10.22	2.20		8.38	9.75	11.75	
0-24	Ropi	26	6.67	3.10		4.96	6.63	8.21.	
	Bupi	26	7.61	2.20		6.48	7.60	8.29	

The upper segemental spread of sensory block was recorded as being lower than the lower spread for patient 125 at 20 hours and patient 134 at 24 hours after start of postoperative infusion. In the calculations of AUCM these two points were excluded.

[Sponsor's Table. 17., Item 8, Vol. 39, p. 59]

Motor block for the Non-Operated Leg

"The motor block was attenuated over time during the therapy period for 24 hours. 50% of the patients in the ropivacaine group compared to 19% in the bupivacaine group did not have motor block two hours after surgery. After 24 hours the percentage without motor block had increased to 88% in the ropivacaine group compared to 56% in the bupivacaine group. Hence bupivacaine produced more frequent and intense motor block over 24 hours (Figure 5)."
[Item 8, Vol. 39, p.60]

Figure 5. Comparative Frequency of Degrees of Motor Block

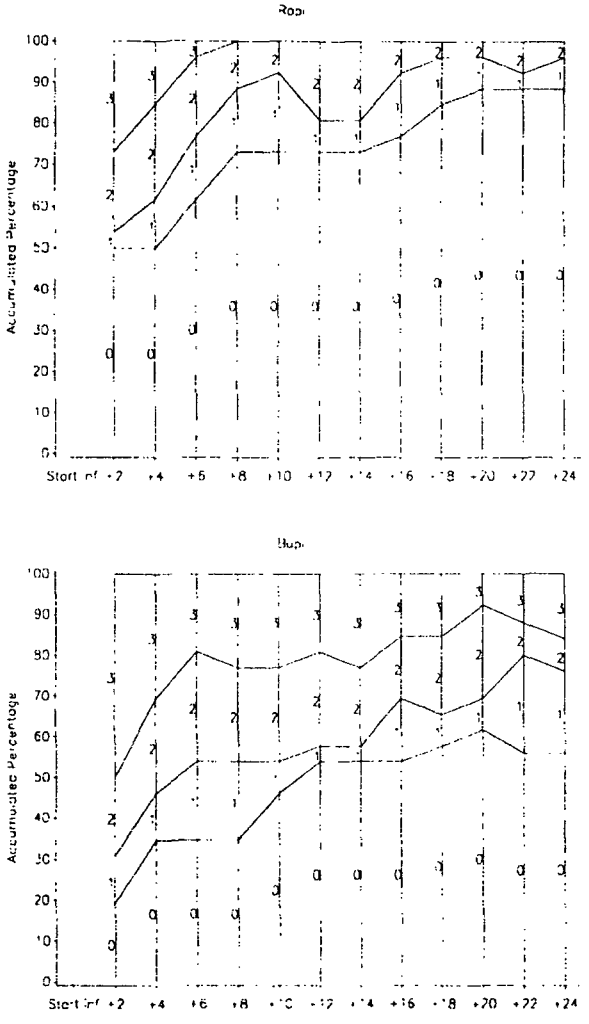

Figure 5. Cumulated frequency (%) of patients with different degrees of motor block (Bromage score 0-3) in the non-operated leg during 24 hours of ropivacaine 16 mg/ml (n=26) or bupivacaine 16 mg/ml (n=26) infusion.

[Sponsor's Figure 5, Item 8, Vol. 39, p. 61]

AUCM for Motor block in the Non-Operated Leg

"The AUCM for motor block (Bromage score) was calculated at the time intervals 0-4, 0-8 and 0-24 hours. The ropivacaine group had more patients with a lower degree of motor block in the non-operated leg than the bupivacaine group. There was a statistically significantly lower AUCM in the ropivacaine group than in the bupivacaine group at all three time intervals 0-4 (p=0.041), 0-8 (p=0.022) and 0-24 hours (p=0.015). (Table 18). The 95% confidence intervals for the difference of bupivacaine and ropivacaine were (0, 1.75) for the interval 0-4 hours, (0, 1.38) for the interval 0-8 hours and (0, 1.13) for the interval 0-24 hours."
[Item 8, Vol. 39, p.62]

Table 10. Comparative AUCM for Motor Block

Table 18. AUCM for motor block (Bromage score) for the non-operated leg at time intervals 0-4, 0-8 and 0-24 hours of infusion (n=number of patients).

Period	group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
0-4	Ropi	26	1.18	1.27		0.00	0.63	2.50	
	Bupi	26	1.88	1.17		0.75	2.13	3.00	
0-8	Ropi	26	0.92	1.00		0.00	0.63	1.88	
	Bupi	26	1.62	1.14		0.38	1.63	2.63	
0-24	Ropi	26	0.50	0.56		0.00	0.33	0.79	
	Bupi	26	1.16	1.00		0.25	1.04	2.23	

[Sponsor's Table 18. Item 8, Vol. 39, p.62]

Return of Normal Motor and Sensory Function

"The time until all patients had return of normal motor function in the non-operated leg was 4 hours in the ropivacaine group compared to 5 hours in the bupivacaine group (Figure 6). Normal sensory function for all patients returned in the ropivacaine group 5 hours after end of infusion, while for 96% of the patients in the bupivacaine group it had returned after 6 hours (Figure 7)"
[Item 8, Vol. 39, p.62]

Figure 6. Comparative Recovery of Motor and Sensory Function

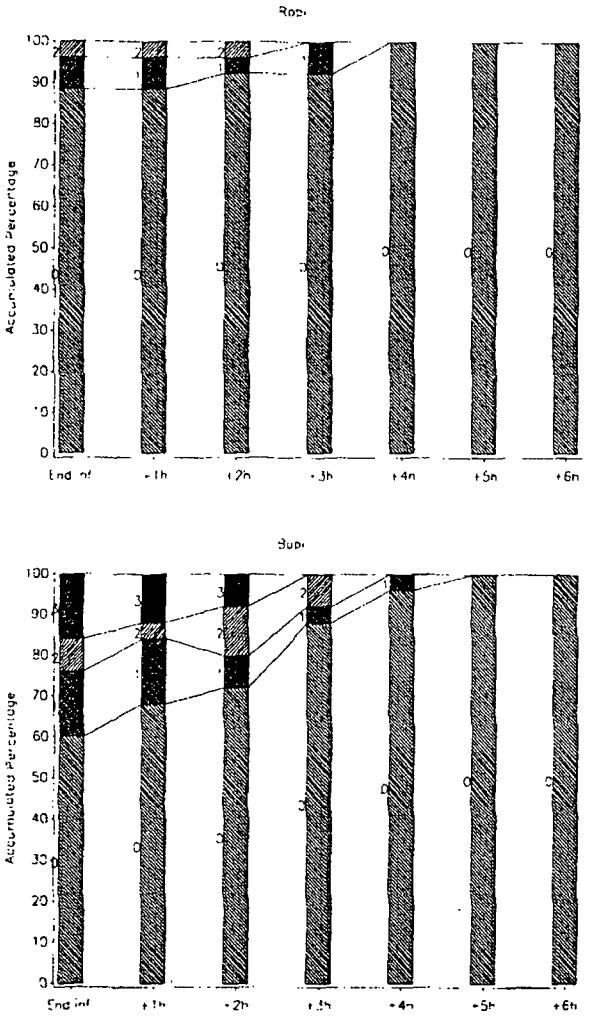

Figure 6. Cumulative frequency (%) of patients for the time (hours) until the return of normal motor function (Bromage score 0-3) after the end of the epidural infusion in the ropivacaine (16 mg/h) and bupivacaine (16 mg/h) groups.

[Sponsor's Figure 6, Item 8, Vol. 39, p. 63]

Figure 7. Comparative Recovery of Motor and Sensory Function

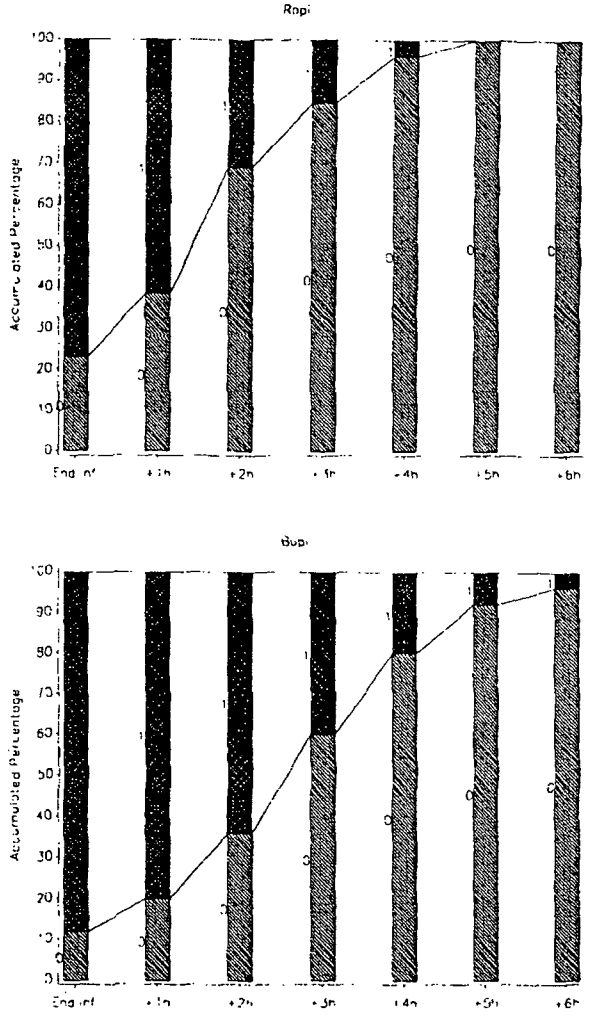

Figure 7. Cumulative frequency (%) of patients for the time (hours) until the return of normal sensory function (1=some sensory block, 0=no sensory block) after the end of the epidural infusion in the ropivacaine (16 mg/h) and bupivacaine (16 mg/h) groups.

[Sponsor's Figure 7, Item 8, Vol. 39, p. 64]

Morphine Consumption

"The median morphine consumption during the different time intervals is shown in Figure 8 and the number of patients that were given morphine is shown in Table 19. The median consumption for all patients during the therapy period was 30.7 mg in the ropivacaine group and 20.5 mg in the bupivacaine group. No patient received pethidine."
[Item 8, Vol. 39, p.65]

Table 11. Comparative Morphine Consumption

Table 19. Number of patients who received morphine.

Time interval (hours)	Ropivacaine	Bupivacaine
0-4 h	17	10
4-8 h	22	19
8-12 h	24	19
12-16 h	21	18
16-20 h	23	19
20-24 h	23	21
>24 h	3	4

[Sponsor's Table 19., Item 8, Vol. 39, p. 65]

Figure 8. Comparative Morphine Consumption

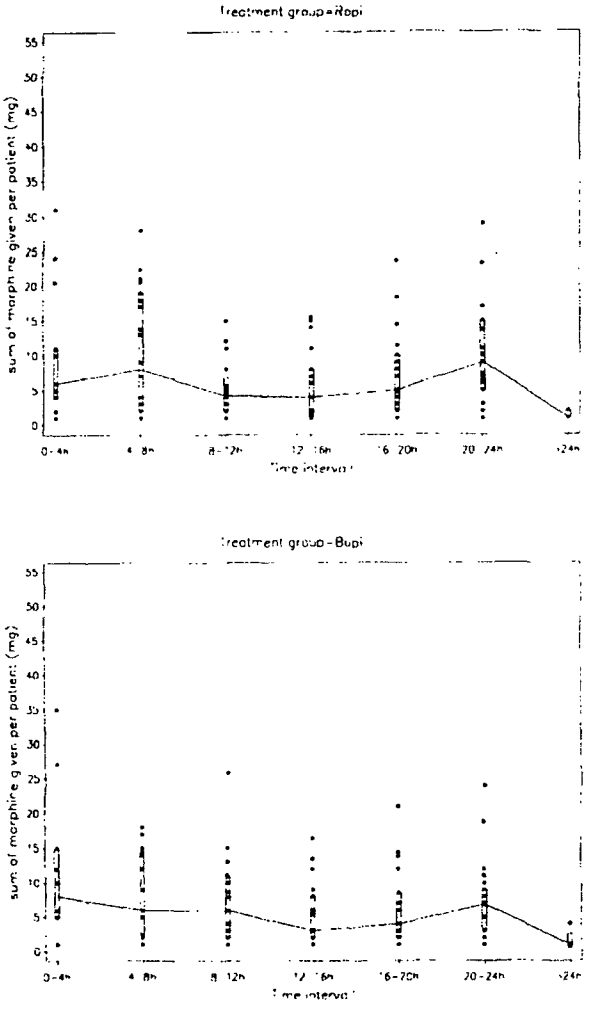

Figure 8. Amount of morphine consumption (mg) during the different time intervals in the ropivacaine group. Only patients who received morphine are included in the graphs. Individual values and box plots (Q1, median, Q3); median values connected.

[Sponsor's Figure 8, Item 8, Vol. 39, p. 66]

Quality of Pain Relief

"The overall quality of pain relief at the end of treatment was rated as good or excellent in 77% of the ropivacaine patients and 80% of the bupivacaine patients. No statistically significant differences were found between the groups regarding quality of pain relief (Figure 9)."
[Item 8, Vol. 39, p.67]

Figure 9. Comparative Quality of Pain Relief

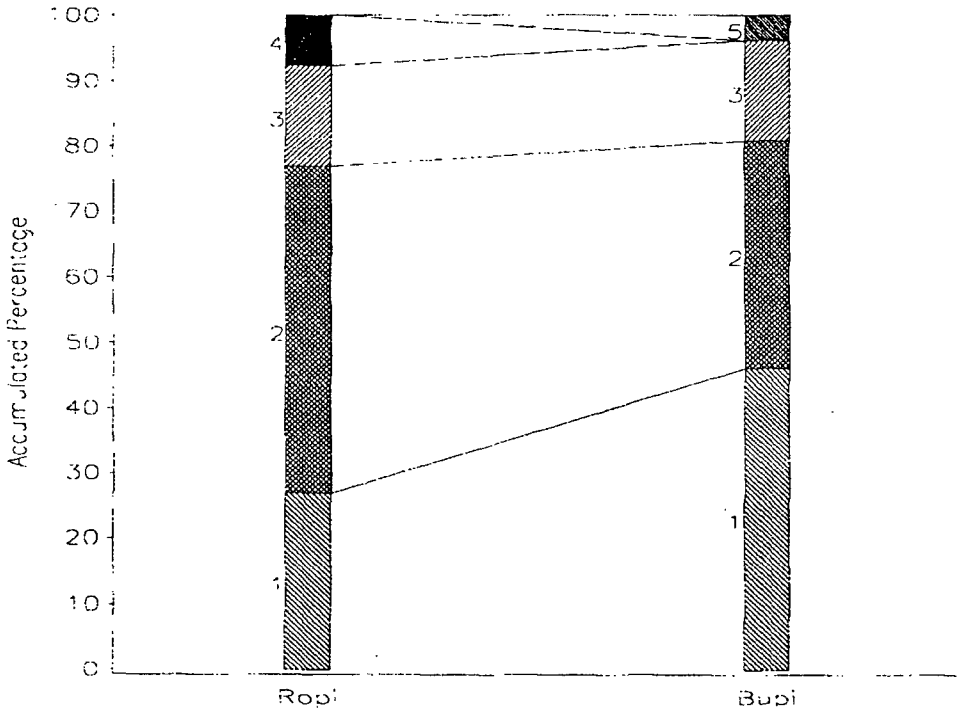

Figure 9. Cumulated frequency (%) of patients rating quality of pain relief in the ropivacaine (16 mg/h, n=26) or bupivacaine (16 mg/h, n=25) group at the end of the 24-h infusion (1=excellent, 2=good, 3=fair, 4=poor, 5=no).

[Sponsor's Figure 9., Item 8, Vol. 39, p. 67]

7.2.1.6 Reviewer's Efficacy Discussion

The main efficacy variable – "AUCM for pain at rest (VAS)" - was shown to be statistically significantly higher AUCM pain score in the ropivacaine group than in the bupivacaine group (p=0.017).

All other pain variables, e.g., pain score at rest (VAS) (no statistical analysis was performed), pain score at rest above 30 mm (VAS) 0-24 hours (p=0.028), pain scores during mobilization (no statistical analysis was performed), pain scores during mobilization above 30 mm (VAS) (p=0.040), AUCM for pain at rest 0-24 hours (p=0.017), AUCM for pain during mobilization 0-24 hours (p=0.016) were also suggestive of relatively less pain relief for those patients treated with ropivacaine.

Further support for this conclusion is found in the analysis of the endpoints, "the median morphine consumption for all patients" (no statistical analysis was performed), and, "the overall quality of pain relief at the end of treatment" (no statistical analysis was performed), both of which were in favor of the comparator. A possible explanation for these findings may be the found in the fact that the ropivacaine exposed patients had fewer blocked dermatomes than the bupivacaine exposed patients at 0-4 hours (p=0.016) and 0-8 hours (p=0.037).

Consistent with previous studies with ropivacaine in the original NDA, ropivacaine exposure was associated with less motor block compared to that seen following bupivacaine exposure. The spread of sensory block over time and the time to return of normal motor function was similar in both groups.

In conclusion, the clinical data suggests that the product, 2 mg/ml of ropivacaine when administered postoperatively for 24 hours following total knee replacement is less effective than bupivacaine in controlling pain.

7.2.2 STUDY # SP-ROA-0009 (O10)

7.2.2.1 Protocol Synopsis:

Title: "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"

Primary Objective: "To estimate treatment differences with respect to efficacy and safety variables in two treatment groups: ropivacaine 2 mg/ml alone and ropivacaine 2 mg/ml with fentanyl when administered for epidurally for postoperative pain management following colonic resection."

[Item 8, Vol. 42, p. 22]

Study Design:

The study is designed as a multicenter, randomized, double blind, two parallel groups, comparative study of ropivacaine 2 mg/ml alone and ropivacaine 2 mg/ml with fentanyl when administered for epidurally for postoperative pain management following colonic resection. The protocol calls for two groups of 10 patients to each be randomly assigned to one of two treatment arms.

Group I General anesthesia + ropivacaine epidural block followed by continuous 72 hour ropivacaine (2 mg/ml) infusion

Group II General anesthesia + ropivacaine epidural block followed by continuous 72 hour ropivacaine (2 mg/ml) + fentanyl (2 μg/ml) infusion

Eligible patients will be ASA Class I - III males or females 18-79 years of age, scheduled for colonic resection receiving no ventilatory support, suitable for 72 hours of epidural analgesia and under the care of an approving surgeon. Patients must not be scheduled for any surgery other than colonic, have contraindications to epidural, general anesthesia, fentanyl, or ketorolac administration, history of a hemorrhagic peptic ulcer, alcohol or drug abuse, participation in any clinical study in the two week period prior to study admission or previous enrollment or randomization in the present study, or be pregnant or lactating.

Preoperatively, patients will receive midazolam (≤ 2 mg) and or fentanyl (≤ 100 μg) gastric reflux prophylaxis (proton pump inhibitors, H_2 receptor antagonists or sodium citrate), crystalloids (approximately 1000 ml) and thrombosis prophylaxis according to hospital protocol.

All patients will receive general anesthesia combined with an epidural block with ropivacaine 7.5 mg/ml. Following placement of an epidural catheter between T8 and T11, and a negative test dose with 3 ml of lidocaine (15 mg/ml) with epinephrine (5 μg), 37.5 mg of ropivacaine will be injected over a one-minute. Sensory block (assessed every five minutes) of T6-L1 is considered acceptable for surgery and induction of anesthesia. If adequate sensory block is not achieved in 15 minutes following the first 5 ml injection, additional 5 ml doses every 15 minutes may be injected up to a maximum of 10 ml. If at this time, inadequate sensory blockade is assessed, the patient can receive an alternative analgesic and/or anesthetic at the discretion of the investigator.

Induction and maintenance of anesthesia will be performed using thiopental, fentanyl, vecuronium or pancuronium and isoflurane or enflurane, fentanyl and nitrous oxide/oxygen, respectively. Reversal of muscle relaxation will be performed using neostigmine, atropine or glycopyrrolate. All patients will receive ketorolac intramuscularly 30 mg initially upon arrival to the post-anesthesia care unit (PACU). Thereafter, 15 mg of ketorolac will be administered every 8 hours until 72 hours after arrival in the post anesthesia care unit.

Within one hour after the induction of general anesthesia, a continuous epidural infusion of either ropivacaine 2 mg/ml or ropivacaine 2 mg/ml with fentanyl 2 μg/ml will be instituted at 8 ml/h during the surgical procedure. The infusion is not to start until the incision has been made (by protocol amendment # 2).

The following will be assessed 1, 2, 4, 6, and 8 hours after arrival in the post anesthesia care unit, and thereafter every four hours until 72 hours after arrival (no assessments will be made during the night between 22:00 and 08:00):

- Quality of pain management
- Pain at rest
- Sensory and motor block (every hour after the end of the infusion until the return of normal function)

The following will be assessed 1 and 2 hours and then every second hour after arrival in the post anesthesia care unit during the infusion (both day and night)

- Respiratory rate
- Sedation

The following will be assessed 1, 2, 4, 6, and 8 hours after arrival in the post anesthesia care unit, and thereafter every four hours until 72 hours after arrival (during the night between 22:00 and 08:00), one value which is closest to 02:00 hours will be obtained from the hospital records)

- Pulse rate
- Blood pressure
- Temperature

Clinical measurements included a 100 mm visual analog scale (VAS) pain assessments, pin – prick assessment of sensory block, modified Bromage scale of motor block, and an assessment of patient discomfort during the postoperative recovery period. Laboratory measurements of clinical chemistry and hematology and urinalysis were to be performed.

Postoperatively, the epidural infusion is to continue at 8 ml/h for 72 hours unless modified in accordance with the following rules:

- If the patient complained of inadequate pain relief, the rate could be modified providing it had been constant for at least 30 minutes. Each dose adjustment consists of 4 ml top-up dose followed by a 2 ml/h increase in infusion rate up to a maximum of 14 ml/h. If the maximum infusion rate was reached and the patient had received two 4 ml top-up doses within 12 hours, and adequate pain relief had not been obtained, the infusion is to be terminated. By protocol amendment, at this time the catheter position could be verified by a bolus dose of 4-6 ml of ropivacaine 7.5 mg/ml. If a block is unable to be re-established with this dose, then the catheter may be re-sited at the discretion of the investigator.
- The re-siting procedure will be conducted similarly to the initial epidural catheter placement. The restart rate will be the rate that previously satisfied the patient preceded by a re-establishment dose, e.g., if the estimated missed volume is 6 ml/h then 6 ml will be given. However, if the block is re-established with this dose, then this is a sign that the epidural catheter is correctly placed and the patient should be discontinued.

Table 12. Schedule of Events

Figure 1. Schedule of events						Day 1		Day 2 & 3	Day 4				
Procedures	Before surgery	epidural block (minutes)				GA+surgery		Time from arrival at PACU Postoperative period			72 h or at end of infusion	Days	Weeks
		0-5	5-6	21	35	->51	60					5-10	3-4
Physical examination + ECG	x												
Pre anesthetic infusion	x												
Test dose 3 ml		x											
Epidural dose 5 ml, ropi 7.5 mg/ml			x										
Additional 5 ml doses (if needed)				x	x								
Continuous infusion of study drug						x	x	x	x	x	x		
Complementary analgesics (ketorolac)								30 mg im. then 15 mg every 8 h					
Respiratory rate & sedation	x							1h and then every 2 h.(day & night)			x		
Quality of pain management								1, 2, 4, 6, 8 -> every 4 h*			x		
BP / pulse / temperature	x							1, 2, 4, 6, 8 -> every 4 h*			x		
Pain at rest & at coughing (VAS)								1, 2, 4, 6, 8 -> every 4 h*			x		
Sensory block (pin-prick)				x	x			1, 2, 4, 6, 8 -> every 4 h*			x		
Motor block (Bromage score)								1, 2, 4, 6, 8 -> every 4 h*			x		
Pain on mobilization & discomfort								start day after surgery, twice daily.					
Criteria "fit for discharge" from hosp.											day 4 >	x	
Questionnaire (self assessment by pat.)	x								day 2**	day 3**	day 4		
Other assessments + patient hosp.stay***	to be completed during the study												
Laboratory assessments (blood, urine)	x										x	8 ↓2	
Adverse events obs./rep./ open ques.	x	x	x	x	x	x	x	x	x	x	x	x	x

* Assessments between 08.00 and 22.00. BP/ pulse/ temperature one additional value, which lies closest to 02.00, from the night chart.

**Between 18.00 and 22.00

*** Other assessments include time of placement/ withdrawal of urinary catheter first mobilization passage of first flatus withdrawal of nasogastric tube perioperative blood loss

Patient hospital stay includes "time in" and "time out" for theater preparation room operating theater PACU intensive care unit hospital ward

Sponsor's Figure 1. Item 8, Vol. 42, p. 23]

7.2.2.2 Statistical Analysis

The sponsor submits the following description of the planned statistical analysis:

Primary efficacy variable

1. The primary efficacy variable was defined for each patient as the mean infusion rate over the 72-hour postoperative period*.

Secondary efficacy variables

(1) The mean infusion rate over 48 hours and 24 hours.
(2) Need for dose adjustments of more than 2 ml/h upward or downward**.
(3) AUCM72, AUCM48 and AUCM24 based on the VAS measurements for pain upon coughing
(4) AUCM72, AUCM48 and AUCM24 based on the VAS measurements for pain at rest
(5) Indicator of VAS score equal to or larger than 30 mm during the 72-hour period for pain upon coughing and similarly for pain at rest
(6) VAS scores over time up to 72 hours, for pain upon coughing and for pain at rest
(7) Time to mobilization and pain on mobilization (patient ambulation)
(8) Upper and lower spread of sensory block
(9) Degree of motor block
(10) Quality of pain management

**The idea behind this variable was that an increase in infusion rate reflects pain, whereas a decrease reflects unacceptable side effects,* e.g. *motor block or adverse events.*

***This is a simple categorical variable that is related to the mean infusion rate in that it is also sensitive to whether a patient tends to deviate upward or downward from the initial rate of 8 ml/h. If the patient's infusion rate remained between the two boundary rates 6 and 10 m/h throughout the entire 72-hour period, the variable was set equal to 0, otherwise its value was set to -1 or 1 if the first deviation outside these boundaries was below 6 or above 10 ml/h respectively. Straightforward descriptions and comparisons of treatment groups could then be made in terms of the three within-group proportions corresponding to the three values 0 and +/- 1, i.e. to patients that (a) needed no or little adjustment of the initial infusion rate, (b) needed a certain upward adjustment, and* (c) *needed a certain downward adjustment.*

Other variables

12. Times of placement and withdrawal of urinary catheter
13. Time to first micturition
14. Bowel motility returned (passage of flatus)
15. Time when patients were deemed fit for discharge from hospital
16. Patient's stay in hospital
17. Time to withdrawal of nasogastric tube
18. Patient's self-assessment of discomfort

[Item 8, Vol. 42 pp. 46-48]

Statistical Methods

According to the protocol
"The statistical analysis included descriptive statistics and graphs for each treatment group. Comparisons of groups was to be used for variables 1-6, 8, 10 and 11, using a stratified Wilcoxon (mid) rank sum test adjusting for centers, with corresponding point estimates and 95% confidence intervals for differences if the variable was continuous.

For statistical descriptions of continuous data at selected target times (e.g. for VAS for pain, blood pressure, pulse rate and body temperature), missing data at the target times were to be handled as follows. In case of premature patient discontinuations leading to missing data, the last (valid) observation carried forward (LOCF) principle was to be used to impute data to missing values, where possible. In case of missing data within a sequence, with available values before and after, linear interpolation was to be used to impute values. Such an intermediate missing value could occur either because a scheduled assessment had not been performed at all or because the time at which the assessment had been performed was more or less incorrect relative to the scheduled time.

In the calculation of the areas under the curves using the trapezoidal rule for VAS measurements up to 72 hours, only actually observed values and time points were used, with two exceptions: (1) a VAS value of zero at time zero was to be used for each patient: and (2) if the 72 hour assessment was measured somewhat later than scheduled, linear interpolation was used, whereas if the 72-hour assessment was missing or performed before schedule, the LOCF principle was used to impute a value at 72 hours (and similarly at 48 and 24 hours)."

[Item 8, vol. 42, p. 52-53]

7.2.2.3 Protocol Amendment:

Amendment 1 dated 2/5/97 and Amendment 2 dated August 4, 1997 made the following changes:

A. Inclusion Criteria
   - The addition of minor procedures, e.g., appendectomy, will be included
B. Epidural Infusion
   - To prevent starting the infusion too early, e.g., in the event of a change in type of surgical procedure, a clause has been included which states that the infusion is not to be started until the incision has been made.
   - If the maximum infusion rate was reached and the patient had received two 4-ml top-up doses within 12 hours, and adequate pain relief had not been obtained, the infusion is to be terminated. By protocol amendment, at this time the catheter position could be verified by a bolus dose of 4-6 ml of ropivacaine 7.5 mg/ml. If a block is unable to be re-established with this dose, then the catheter may be re-sited at the discretion of the investigator.
   - Clarification of treatment failure, i.e., if the block is re-established with additional dosing then the catheter is correctly placed and the patient should be discontinued
   - The restart rate will be estimated by the missing volume, i.e., if the estimated missed volume is 6 ml/h then 6 ml will be given

Additionally, the amendments call for administrative changes in the areas of reporting procedures, contact persons, and typographical errors.

7.2.2.4 Conduct of Study

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

Demographics

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

Table 13. Baseline Demographics – Age, Height and Weight

Variable	Group	N	NMISS	MEAN	STD	MIN	MEDIAN	MAX
Age (year)	Ropi	79	0	58.9	14.7		64.0	
	Ropi+2 fent	72	0	59.6	13.0		60.0	
Height (cm)	Ropi	79	0	165.1	8.9		165.0	
	Ropi+2 fent	72	0	166.9	7.5		167.0	
Weight (kg)	Ropi	79	0	70.1	13.8		68.0	
	Ropi+2 fent	72	0	72.8	13.0		73.0	

Table 14. Baseline Demographics – Race, Sex, ASA, and Allergy

	Ropi (n=79)	Ropi+2fent (n=72)
Race		
Caucasian	78	71
Negroid	.	1
Other	1	.
Sex		
Male	34	34
Female	45	38
ASA class		
I	16	11
II	47	45
III	16	16
Any history of allergy		
No	54	53
Yes	25	19

[Sponsor's Table 1 and 2., Item 8, Vol. 42, p. 59]

The majority of evaluable patients was Caucasian and had a history of major medical diseases, such as myocardial infarction, meningitis, lymphoma, cerebral vascular disease, prostate cancer, diabetes mellitus, and hypothyroidism. American Society of Anesthesiologists physical status, age, height, weight and positive history of allergy were similar between treatment groups.

Physical examination of the study population revealed abnormalities in multiple body systems including, the heart, lungs, nervous system, thyroid, lymph nodes, general appearance and the abdomen (as would be expected). The areas with the most abnormalities were the abdomen (Ropivacaine N=34, Ropivacaine +fentanyl N=28), Mouth/teeth and throat (Ropivacaine N=32, Ropivacaine +fentanyl N=28), general appearance (Ropivacaine N=25, Ropivacaine +fentanyl N=21), and heart (Ropivacaine N=15, Ropivacaine +fentanyl N=5).

The most commonly administered medications given before and during surgery, in descending order, were the following: heparin (Ropivacaine N=44, Ropivacaine +fentanyl N=46), flagyl (Ropivacaine N=42, Ropivacaine +fentanyl N=34), ephedrine (Ropivacaine N=38 Ropivacaine +fentanyl N=35), midazolam (Ropivacaine N=18, Ropivacaine +fentanyl N=25), ansef (Ropivacaine N=20, Ropivacaine +fentanyl N=16), and xylocaine (Ropivacaine N=21, Ropivacaine +fentanyl N=22)

Postoperatively, the medications given with the most frequency include the following: heparin (Ropivacaine N=61, Ropivacaine +fentanyl N=56), gravol (Ropivacaine N=30, Ropivacaine +fentanyl N=22), flagyl (Ropivacaine N=23, Ropivacaine +fentanyl N=18), oxygen (Ropivacaine N=22, Ropivacaine +fentanyl N=17), and gentamycin (Ropivacaine N=17, Ropivacaine +fentanyl N=11). Ketorolac was given to all patients postoperatively.

7.2.2.5 Sponsor's Efficacy Results:

Primary Efficacy Measurement:

INFUSION RATE:

The primary efficacy variable is defined as the mean infusion rate over the 72-hour postoperative period. [**Note**: The sponsor has performed a statistical analysis of the median of the mean instead of the protocol-specified mean for certain efficacy variables. Upon discussion with the reviewing statistician, Dr. T. Permutt, it has been determined that this analysis is logical statistically and does not misrepresent the study results]

Mean Infusion Rate 0-72 Hours

"The median of each patient's mean infusion rate for 0-72 hour was 11.5 ml/hour in the ropivacaine group and 9.3 ml/hour in the ropivacaine + fentanyl group. The difference was found to be statistically significant (p=0.000)."

[Item 8, Vol. 42, p. 101]

Table 15. Mean Infusion Rate 0-72 Hour (ml/h)

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	76	11.00	2.34		9.62	11.52	12.94	
Ropi+2 fent	71	9.38	2.26		8.00	9.29	11.09	

[Sponsor's Table 35., Item 8, Vol. 42, p. 101]

Mean Infusion Rate 0-24 Hours

"The median of each patient's mean infusion rate for 0-24h was 10.0 ml/h in the ropivacaine group and 8.0 ml/h in the ropivacaine +fentanyl group. This difference was found to be statistically significant (p=0.000)."
[Item 8, Vol. 42, p. 101]

Table 16. Mean Infusion Rate 0-24 Hour (ml/h)

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	76	9.59	2.48		8.00	9.96	11.58	
Ropi+2 fent	71	8.14	1.80		7.53	8.00	9.21	

[Sponsor's Table 33, Item 8, Vol. 42, p. 101]

Mean Infusion Rate 0-48 Hours

"The median of each patient's mean infusion rate for 0-48 hour was 11.0 ml/hour in the ropivacaine group and 8.9 ml/hour in the ropivacaine + fentanyl group. The difference was found to be statistically significant (p=0.000)."

[Item 8, Vol. 42, p. 101]

Table 17. Mean Infusion Rate 0-48 Hour (ml/h)

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	76	10.54	2.40		8.92	11.05	12.41	
Ropi+2 fent	71	8.87	2.06		7.99	8.88	10.24	

[Sponsor's Table 34., Item 8, Vol. 42, p. 101]

Figure 10. Mean Infusion Rate, Individual Values and Box Plots – 0-72 Hour

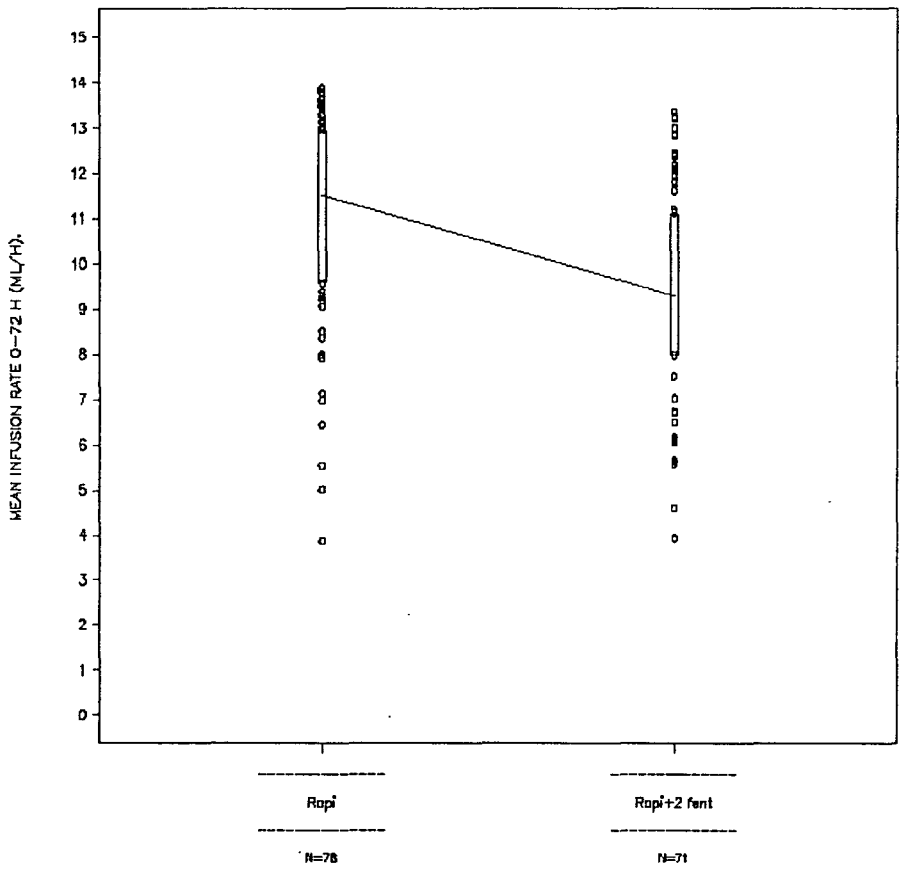

Figure 3. Mean infusion rate (ml/h) in the Ropi group and Ropi+2fent group. Individual values and box plots (Q1, median, Q3), median values connected (0-72 h).

[Sponsor's Figure 3, Item 8, Vol. 42, p. 102]

Postoperative Pain

Pain at Rest

"The median pain score at rest over the 72-hour period varied between 0 and 12 mm in the ropivacaine group (n=75) and 0 and 2 mm in the ropivacaine + fentanyl group (n=71). [Note: This variable was not in the protocol defined outcomes and it was not analyzed statistically].

[Item 8, Vol. 42, p. 111]

AUCM 24 hour – Pain at Rest

"The median AUCM values for pain at rest (VAS) 0-24 hour were 9 mm in the ropivacaine group and 1 mm in the ropivacaine + fentanyl group. A statistically significantly higher AUCM value was found in the ropivacaine group than in the ropivacaine + fentanyl group (p=0.000)."

[Item 8, Vol.42, p. 113]

Table 18. AUCM 24 hour – Pain at Rest

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	75	15.34	17.94		2.82	8.54	21.54	
Ropi+2 fent	71	4.56	7.01		0.00	0.83	7.25	

[Sponsor's Table 38. Item 8, Vol.42, p. 113]

AUCM 48 hour – Pain at Rest

"The median AUCM values for pain at rest (VAS) 0-48 hour were 11 mm in the ropivacaine group and 2 mm in the ropivacaine + fentanyl group. A statistically significantly higher AUCM value was found in the ropivacaine group than in the ropivacaine + fentanyl group (p=0.000)."

[Item 8, Vol.42, p. 113]

Table 19. AUCM 48 hour – Pain at Rest

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	75	19.44	22.46		3.84	11.13	27.68	
Ropi+2 fent	71	6.67	10.34		0.00	2.39	8.58	

[Sponsor's Table 39. Item 8, Vol.42, p. 113]

AUCM 72 hour – Pain at Rest

"The median AUCM values for pain at rest (VAS) 0-72 hour were 10 mm in the ropivacaine group and 3 mm in the ropivacaine + fentanyl group. A statistically significantly higher AUCM value was found in the ropivacaine group than in the ropivacaine + fentanyl group (p=0.000)."

[Item 8, Vol.42, p. 113]

Table 20. AUCM 72 hour – Pain at Rest

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	75	20.74	26.16		3.35	9.50	27.21	
Ropi+2 fent	71	8.76	14.17		0.27	3.06	10.32	

[Sponsor's Table 40. Item 8, Vol.42, p. 113]

AUCM 24h – Pain upon Coughing

"The median AUCM values for pain upon coughing 0-24 hour (VAS) were 24 mm in the ropivacaine group and 6 mm in the ropivacaine + fentanyl group. The difference was found to be statistically significant (p=0.000)."
[Item 8, Vol. 42, p. 121]

Table 21. AUCM 24h – Pain upon Coughing

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	75	27.51	23.54		8.39	24.21	36.12	
Ropi+2 fent	71	13.05	15.18		0.99	6.33	17.78	

[Sponsor's Table 42, Item 8, Vol. 42, p. 121]

AUCM 48h – Pain upon Coughing

"The median AUCM values for pain upon coughing 0-48 hour (VAS) were 24 mm in the ropivacaine group and 10 mm in the ropivacaine + fentanyl group. The difference was found to be statistically significant (p=0.000)."
[Item 8, Vol. 42, p. 121]

Table 22. AUCM 48h – Pain upon Coughing

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	75	31.27	25.18		10.52	23.76	46.14	
Ropi+2 fent	71	15.52	17.06		2.83	10.00	22.27	

[Sponsor's Table 43, Item 8, Vol. 42, p. 121]

AUCM 72h – Pain upon Coughing

"The median AUCM values for pain upon coughing 0-72 hour (VAS) were 23 mm in the ropivacaine group and 10 mm in the ropivacaine + fentanyl group. A statistically significantly higher AUCM value was found in the ropivacaine group than in the ropivacaine + fentanyl group (p=0.000)."
[Item 8, Vol. 42, p. 121]

Table 23. AUCM 72 – Pain upon Coughing

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	75	32.50	27.36		12.27	22.90	47.06	
Ropi+2 fent	71	16.68	18.68		3.11	9.78	25.45	

[Sponsor's Table 44, Item 8, Vol. 42, p. 121]

Pain upon Coughing

"The pain score upon coughing (VAS) was lower in the ropivacaine + fentanyl group than in the ropivacaine group. The median pain score upon coughing over the 72-hour period varied between 10 and 30 mm in the ropivacaine group and 0 and 10 mm in the ropivacaine + fentanyl group." [Note: no statistical analysis was performed.]

[Item 8, Vol. 42, p. 119]

Spread of Analgesia

"The medians of the upper sensory block for the ropivacaine group were T5 at 24 hour (n=76), T6 at 48 hour (n=76) and T7 at 72 hour (n=76). The corresponding values for the ropivacaine + fentanyl group were T6 at 24 hour (n=71) at the same time points. The spread of both upper and lower sensory block over time remained stable and was similar in the both groups"
[Note: no statistical analysis was performed]

[Item 8, Vol. 42, p. 127]

Motor Block

"The ropivacaine group 92% (70/76) of the patients at 24 hour, 96% (73/76) at 48 hour and 96% (73/76) at 72 hour of the postoperative infusion had no motor block according to the modified Bromage scale. The corresponding values for the ropivacaine + fentanyl group were 99% (70/71), 97% (69/71) and 100% (71/71) at the same time points." [Note: no statistical analysis was performed]

[Item 8, Vol. 42, p. 129]

Quality of Pain Relief

"The quality of pain relief assessed at 24 hour was rated as good or excellent in 79% (60/76), at 48 hour 68% (52/76) and at 72 hour 67% (51/76) of the patients in the ropivacaine group. The corresponding figures in the ropivacaine + fentanyl group were 90% (64/71), 89% (63/71) and 82% (58/71), at 24 hour, 48 hour and 72 hour." [Note: no statistical analysis was performed].

[Item 8, Vol. 42, p. 131]

Ability to Ambulate

"6 patients in the ropivacaine group and 1 patient in the ropivacaine + fentanyl group were never assessed for their ability to ambulate. The ability to ambulate was similar for both groups during the postoperative infusion. On the morning of the first postoperative day 81% (57/70) of the assessed patients in the ropivacaine group and 91% (64/70) of the assessed patients in the ropivacaine + fentanyl group were able to walk form bed to chair or walk five meters. On the morning of third day after surgery 84% (59/70) of the assessed patients in the ropivacaine group and 91% (64/70) in the ropivacaine + fentanyl group were able to walk from bed to chair or walk five meters." [Note: no statistical analysis was performed].

[Item 8, Vol. 42, p. 133]