Time to First Ambulation

"The median time to first ambulation (all of the four steps were performed) was similar in both groups."

Table 24. Time to First Ambulation

GROUP	N	NMISS	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	64	12	25.86	8.73		20	23	29	
Ropi+2 fent	67	4	24.26	7.53		20	22	24	

[Sponsor's Table 46. Item 8, Vol. 42, p. 135]

Pain During Mobilization/Ambulation

"8 patients in the ropivacaine group and 2 patient in the ropivacaine + fentanyl group were never assessed for pain during mobilization. The median pain scores (VAS) during mobilization were higher in the ropivacaine group than in the ropivacaine + fentanyl group. The median pain score (VAS) during mobilization on the morning on the first postoperative day were 10 mm in the ropivacaine group (n-68) and 0 mm in the ropivacaine + fentanyl group (n=69). On the morning of third day the median pain scores during ambulation were 6 mm in the ropivacaine group (n=68) and 0 mm in the ropivacaine + fentanyl group (n=69)." [Note: no statistical analysis was performed].

[Item 8, Vol. 42, p. 136]

Discomfort during Mobilization/Ambulation

"87patients in the ropivacaine group and 2 patient in the ropivacaine + fentanyl group were never assessed for discomfort during mobilization/ambulation. The patients in the ropivacaine group reported a higher degree of discomfort during mobilization than patients in the ropivacaine + fentanyl group."

Patient Assessed Discomfort

"The results of patient – assessed discomfort for the different items (e.g., difficult in concentrating, constipation, poor appetite) were similar between the two groups, except for itching for which more discomfort was reported in the ropivacaine + fentanyl group, and pain when moving in which more discomfort was reported in the ropivacaine group. Discomfort for nausea was similar between groups."

[Item 8, Vol.42, p.140]

Urinary Catheter, Time to First Flatus and Nasogastric Tube

"The median times for catheter use and time to first micturition were similar between the two groups. However, the third quartile reveals a longer need for catheter in the ropivacaine + fentanyl group. The time until first flatus was shorter in the ropivacaine group compared to the ropivacaine + group. Time to withdrawal of nasogastric tube was similar between the groups."
[Item 8, Vol. 42, p. 142]

Table 25. Time to Urinary Catheter, Micturition, and Flatus

Variable	Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Catheter start time	Ropi	75	-2.7	2.0		-3.4	-2.6	-1.8	
	Ropi+2 fent	69	-2.9	1.9		-3.3	-2.5	-1.9	
Catheter end time	Ropi	74	91.3	40.9		68.0	90.0	115.9	
	Ropi+2 fent	71	127.6	157.9		70.8	89.7	139.8	
First flatus	Ropi	69	50.3	41.8		24.9	33.8	57.4	
	Ropi+2 fent	66	54.9	46.8		24.2	44.0	67.9	
First micturition	Ropi	68	95.9	41.8		72.1	93.5	118.8	
	Ropi+2 fent	65	126.4	152.6		72.8	93.0	138.5	

[Sponsor's Table 47, Item 8, Vol. 42, p. 142]

Table 26. Time to Withdrawal of Nasogastric Tube

Variable	Group	N	NMISS	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
TIME	Ropi	26	50	56.4	61.7		22.5	45.3	67.4	
	Ropi+2 fent	28	43	65.7	61.3		22.3	47.2	74.1	

[Sponsor's Table 48, Item 8, Vol. 42, p. 142]

Duration of Hospital Stay

"The median time (hours) spent in the theater preparation room, in the operating theater and at the Post Anesthesia Care Unit was similar in both groups. The median time until ready for discharge and actual discharge was shorter in the ropivacaine group, whereas stay in the hospital ward was similar between groups.

Regardless of whether the patients stayed at the intensive care unit or a step-down unit, the ropivacaine + fentanyl group required a more qualified postoperative care during a longer time than the ropivacaine group.

[Item 8, Vol. 42, p. 143]

The following are not protocol defined outcome measures; they will be considered as supportive to the overall efficacy analysis.

Mean Infusion Rate- Actual Infusion Time

"The median of each patient's mean infusion rate for the actual infusion time was 10.8 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. 103]

Table 27. Mean Infusion Rate- Actual Infusion Time

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	76	10.54	2.27		9.18	10.75	12.33	
Ropi+2 fent	71	9.21	2.15		8.00	9.29	10.67	

[Sponsor's Table 36., Item 8, Vol. 42, p. 103]

Figure 11. Mean Infusion Rate, Individual Values and Box Plots – Actual Infusion Time

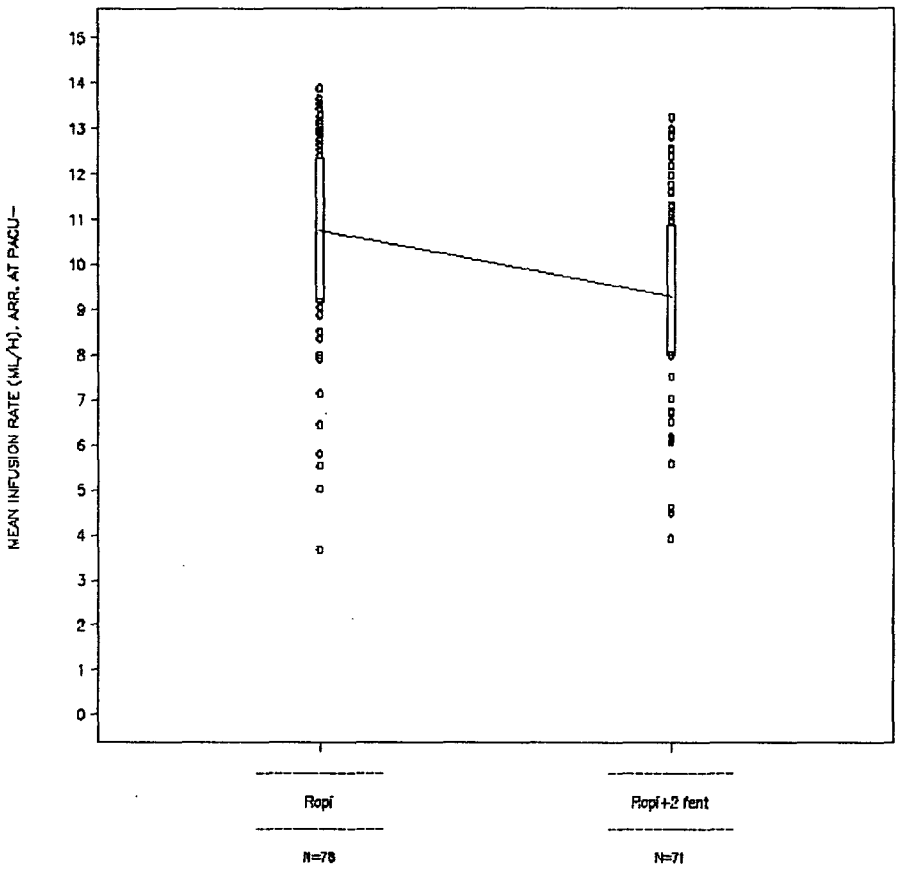


Figure 4. Mean infusion rate (ml/h) in the Ropi group and Ropi+2fent group. Individual values and box plots (Q1, median, Q3), median values connected (actual infusion time).

[Sponsor's Figure 4, Item 8, Vol. 42, p. 104]

Indicator of Mean Infusion Rate

"There were more patients in the ropivacaine group with a mean infusion rate above 10 ml/hour compared to the ropivacaine +fentanyl group. Statistically significant differences were found between the ropivacaine group and the ropivacaine + fentanyl group for the time intervals 0-24 hour (p=0.000), 0-48 hour (p=0.000), 0-72 (p=0.000) and for the actual infusion time 0-72 hour (p=0.000)."

[Item 8, Vol. 42, p. 105]

Figure 12. Cumulative Percentage of Indicator of Mean Infusion Rate by Treatment Group (0-72 Hour)

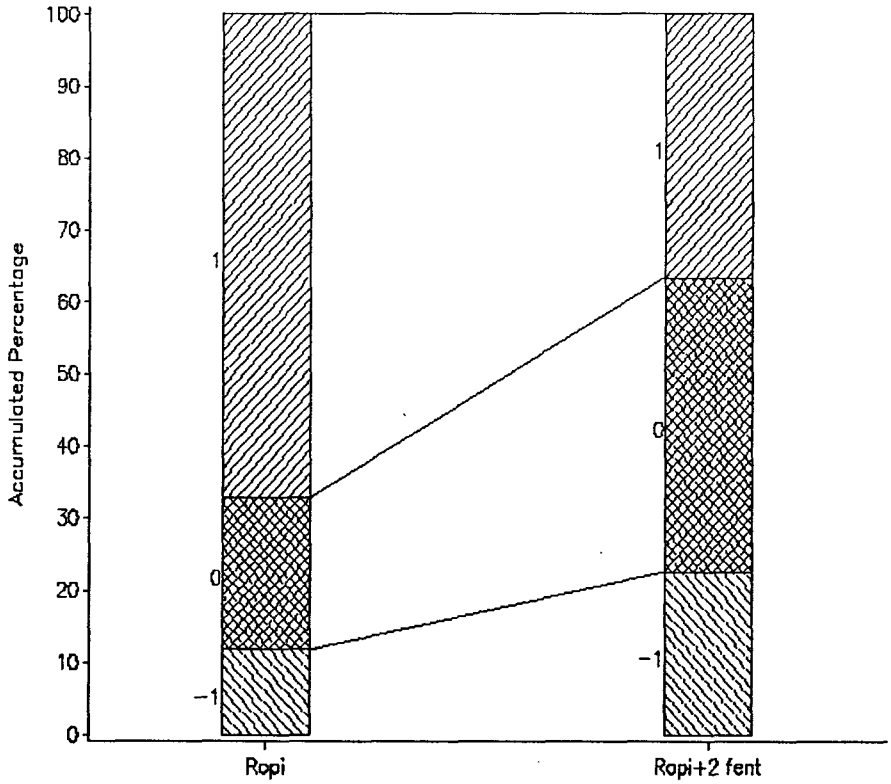


Figure 5. Cumulative percentage (%) of indicator of mean infusion rate in the Ropi group (n= 76) and Ropi+2fent group (n=71). -1 = below 6 ml/h; 0 = 6 to 10 ml/h; +1 = above 10 ml/h (0-72 h).

[Sponsor's Figure 5, Item 8, Vol. 42, p. 106]

Figure 13. Cumulative Percentage of Indicator of Mean Infusion Rate by Treatment Group (Actual Infusion Time)

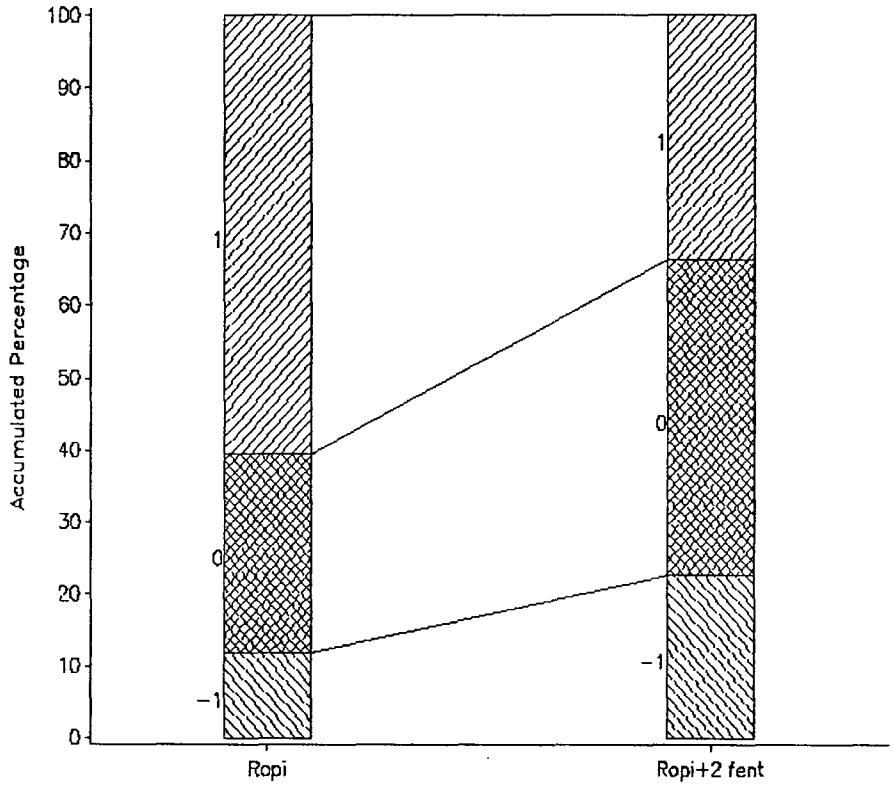


Figure 6. Cumulative percentage (%) of indicator of mean infusion rate in the Ropi group (n= 76) and Ropi+2fent group (n=71). -1=below 6 ml/h; 0=6 to 10 ml/h; +1 = above 10 ml/h (actual infusion time).

[Sponsor's Figure 6, Item 8, Vol. 42, p. 107]

Peak Infusion Rate

"There were more patients in the ropivacaine with a higher peak infusion rate compared to the ropivacaine +fentanyl group." [Note: no statistical analysis was performed of this variable]

[Item 8, Vol. 42, p. 108]

Table 28. Peak Infusion Rate by Treatment Group

ml/h	Ropi group (n=76)	Ropi+2fent group (n=71)
8	10	9
10	9	14
12	16	10
14	40	28
125*	1	

*Patient 411 (Ropi group) was by mistake administered 125 ml/h of the last 15 min of the 72-hour postoperative infusion.

[Sponsor's Table 37., Item 8, Vol. 42, p. 108]

Duration of Infusion

'Patients in the ropivacaine group discontinued earlier compared to the patients in the ropivacaine + fentanyl group. There were more patients who were discontinued earlier due only to lack of efficacy in the ropivacaine group compared to the ropivacaine + fentanyl group." [Note: No statistical analysis was performed of this variable].

[Item 8, Vol. 42, p. 108]

AUCM Actual Infusion Time – Pain at Rest

"The median AUCM values for pain at rest (VAS) using the actual infusion time were 9 mm in the ropivacaine group and 3 mm in the Ropi+2fent group (Table 41, Figure 11). A statistically significantly higher AUCM value was found in the ropivacaine group than in the Ropi+2fent group (p=0.000)."
[Item 8, Vol. 42, p. 115]

Table 29. AUCM Actual Infusion Time – Pain at Rest

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	75	15.24	17.83	——	3.33	9.44	19.94	——
Ropi+2 fent	71	6.24	8.75		0.27	2.76	7.83	

[Sponsor's Table 41, Item 8, Vol.42, p. 115]

Pain at Rest above 30 mm (VAS)

"The ropivacaine group had statistically significantly more patients with a VAS pain at rest ≥ 30 mm in all three time intervals (p=0.000). The percentages of the non-missing patient with a pain score ≥ 30 mm at rest for 0-24 hour were 55% (41/75) in the ropivacaine group and 28% (20/71) in the ropivacaine + fentanyl group. For 0-48 hour the percentages of patient were 68% (51/75) in the ropivacaine group and 41% (29/71) in the ropivacaine + fentanyl group. The corresponding values for 0-72 hour were 68% (51/750 and 45% (32/71)."

[Item 8, Vol. 42, p. 117]

AUCM Actual Infusion Time – Pain upon Coughing

"The median AUCM values for pain upon coughing (VAS) for actual infusion time were 22 mm in the ropivacaine group and 8 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. 123]

Table 30. AUCM for Pain upon Coughing – Actual Infusion Time (VAS)

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	75	28.17	23.05		9.47	22.13	39.50	
Ropi+2 fent	71	14.55	15.60		3.21	8.39	23.59	

[Sponsor's Table 45, Item 8, Vol. 42, p. 123]

Pain upon Coughing above 30 mm (VAS)

"The percentages of the non-missing patients with a pain score ≥ 30 mm upon coughing for 0-24 hour were 71% (53/75) in the ropivacaine group and 46% (33/71) in the ropivacaine + fentanyl group. The difference was found to be statistically significant (p=0.001).

For the period 0-48 hour, the values were 79% (59/75) in the ropivacaine group and 54% (41/71) in the ropivacaine + fentanyl group. The difference was found to be statistically significant (p=0.003).

For the period 0-72 hour, the values were 79% (59/75) in the ropivacaine group and 61% (43/71) in the ropivacaine + fentanyl group. The difference was found to be statistically significant (p=0.006).

[Item 8, Vol. 42, p. 125]

7.2.2.6 Reviewer's Efficacy Discussion

The primary efficacy variable, mean infusion rate over the 72-hour postoperative period, was shown to be statistically in favor of ropivacaine + 2fentanyl and was consistently shown to be during each day or two of the 72 hour infusion period, i.e., 0-24 hours, 0-48 hours. Other protocol defined outcome measures, such as AUCM – pain at rest, pain upon coughing, quality of pain relief, pain during mobilization, patient assessed discomfort, were consistent with these findings.

The secondary measurements, urinary catheter, time to first flatus and nasogastric tube are indirect measures of the occurrence of common local anesthetic side effects, urinary retention, paralytic ileus and delay of gastric emptying, respectively. The results of this analysis were variable, i.e., in favor of ropivacaine in some instances, (urinary catheter, time to first flatus), and in favor of neither drug in other instances – nasogastric tube.

Additionally, the spread of analgesia and degree of motor block was similar in all groups.

The supportive outcome measures (not protocol defined) showed similar overall trends.

The clinical trial has demonstrated efficacy of ropivacaine when administered epidurally to patients following colonic resection. Evidence is present for improved efficacy when the product is administered in combination with fentanyl for postoperative pain.

7.2.3 STUDY # SP-ROA-0010 (O11)

7.2.3.1 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 Major Abdominal Surgery"

Primary Objective: "...to estimate treatment differences with respect to efficacy and safety variables in four treatment groups:

Group 1	ropivacaine 2 mg/ml alone,
Group 2	ropivacaine 2 mg/ml +1 μg/ml fentanyl,
Group 3	ropivacaine 2 mg/ml +2 μg/ml fentanyl and,
Group 4	ropivacaine 2 mg/ml + 4 μg/ml fentanyl,

when administered epidurally for postoperative pain management following major abdominal surgery. Ropivacaine 7.5 mg/ml will be bolused prior to the 2-mg/ml ropivacaine infusion, in all treatment groups. The dose-response group comparisons was thus with respect to the fentanyl concentrations."

[Item 8, Vol. 49, p. 22]

Study Design:

The study was double blind with four parallel treatment groups. Two hundred patients valid for efficacy and safety were enrolled over 12 centers in Australia and New Zealand. Patients scheduled for major abdominal surgery performed under general anesthesia were to be randomized in balanced blocks to one of the four treatment groups as shown above.

Eligible patients were age 18- 79 years, ASA risk category I- III, scheduled to receive elective major abdominal surgery, e.g., partial or total gastrectomy, biliary or pancreatic surgery and colonic resection, suitable for 72 hours of epidural analgesia postoperatively, had no planned ventilatory support of the patient for the postoperative period, weighed 50-110 kg, were under the care of a surgeon approving inclusion in the study and provided written informed consent.

Patients were excluded from study participation if they required major vascular abdominal surgery, rectal surgery, esophagogastrectomy, transdiaphragmatic surgery, nephrectomy not performed transabdominally, simple gynecological laparotomy and transvesical prostatectomy, had contraindications to epidural or general anesthesia, fentanyl or paracetamol, had a known history of allergy, sensitivity or any other form of reaction to local anesthetics of the amide type and/or to fentanyl, suspected of having an inability to comply with the study procedures, including language difficulties, medical history and/or concomitant disease, were suspected of significant alcohol, drug or medication use/abuse, were pregnant or lactating or who were not practicing adequate contraception.

Premedication consisted of benzodiazepines and prophylactic treatment for gastric reflux (proton pump inhibitors, H2 receptor antagonists or sodium citrate) administered at the discretion of the investigator. An intravenous infusion of a crystalloid solution was to be in progress before induction of the epidural block procedure and thrombosis prophylaxis was to be administered according to hospital routine.

Eligible patients received a combined general anesthesia and epidural block with ropivacaine 7.5 mg/ml.

General Anesthesia

Medications used for induction and muscle relaxation included: thiopental, fentanyl, atracurium/ vecuronium/ pancuronium/ rocuronium. Maintenance of anesthesia was performed with isoflurane/enflurane, fentanyl, nitrous oxide/oxygen or air/oxygen. Reversal of muscle relaxation was performed with neostigmine/atropine/glycopyrrolate.

Epidural Anesthesia

The epidural block was performed with a 16-18-gauge needle inserted between the T7 and T12 interspaces. The midline or paramedian approach was to be used with the patient in the sitting or lateral decubitus position. Following a negative aspiration of cerebrospinal fluid and blood, a 3-ml test dose of lidocaine15 mg/ml with epinephrine 5 µg/ml was injected. Five minutes later, if there were no signs of intravascular or intrathecal administration, an 8-15 ml main dose of ropivacaine 7.5 mg/ml (37.5-112.5 mg) was injected within a 5-minute period. [Note: According to protocol amendment #. 2, in order to avoid excessive block, the lower limit was changed to 5 ml ropivacaine 7.5 mg/ml].

All patients were to receive paracetamol 1 g x 4 /24 hour; the first dose of which was to be administered after arrival at the PACU or at the first suitable time thereafter. No rescue medication was to be administered during the postoperative infusion for up to 72 h.

Prior to the induction of general anesthesia, sensory block was assessed every five minutes from the end of injection of the bolus epidural ropivacaine dose until a sensory block appropriate for the intended area of incision was achieved. If adequate sensory block was not achieved 30 minutes after injection of the bolus dose, an additional 5-ml dose (37.5-mg) of ropivacaine was injected.

One hour after the induction of general anesthesia, the continuous epidural infusion of study drug commenced at a rate of 8 ml/h and continued throughout the surgical procedure.

The infusion rate could be modified in accordance with the following rules:

1. If the patient complained of inadequate pain relief during the postoperative period, the epidural infusion rate could be adjusted provided that it was constant for at least 30 minutes.
2. Each dose adjustment was to consist of a 4 ml top-up dose of ropivacaine followed by a 2 ml/h
   increase in infusion rate up to a maximum of 14 ml/h. If the maximum infusion rate of 14 ml/h was reached and the patient had received two 4 ml top-ups within a period of 12 hours and adequate pain relief had still not been obtained, the study treatment was to be terminated.
3. The epidural infusion rate was not to exceed 14 ml/h at any time during the 72-hour infusion period.
4. In instances of excessive block or unacceptable side effects, the infusion rate could be reduced by 2 ml/h to a minimum of 4 ml/h or the infusion could be discontinued until the block regressed to a desired level. The infusion was then to be recommenced at a rate of 2 ml/h lower than the previous rate, to a minimum of 4 ml/h.
5. If the epidural catheter was displaced or obstructed for less than one hour, at any time during the 72-hour infusion period, it could be reinserted. However, according to amendment # 2, the block is to be re-established with the estimated volume which had been missed (e.g. if the infusion had ceased for one hour, the catheter could be bolused with the previous hourly dose).
6. If the patient was unable to obtain adequate analgesia despite the maximum infusion rate and two boluses within the previous 12 hours, the catheter position was to be verified by a bolus of 4-6 ml of ropivacaine
   7.5 mg/ml. If a block could not be re-established with this dose, the catheter could be recited at the investigator's discretion.

The reference point (time 0) for the postoperative clinical assessments was to be the time of arrival at the PACU. Assessments were to be commenced one hour after the time of arrival at the PACU. This meant that every patient had an individual time schedule in chronological order, depending on the arrival at the PACU. In patients in whom the study treatment was discontinued before arrival at the PACU, sensory and motor block were to be recorded until the end of ropivacaine epidural block, if applicable.

The following variables were to be assessed 1, 2, 4, 6 and 8 hours after the time of arrival at PACU and thereafter every four hours until 72 hours after arrival. Assessments were not to be performed during the night between 22.00 and 08.00 hours:

1. Quality of pain management
2. Pain at rest
3. Pain on coughing
4. Sensory and motor block - (every hour after the end of infusion until return of normal function)

The patients used a visual analogue scale (VAS) ruler to rate wound pain at rest, when lying on the bed and upon coughing. It consisted of a 100-mm ungraduated horizontal scale, with the ends marked "no pain" (0 mm) and "worst pain" (100 mm).

The patients were asked to rate wound pain experienced during ambulation after each of the following steps was performed by use of the VAS ruler [Note: protocol amendment #. 1]:

1. Patient able to rise from a lying to a sitting position in bed
2. Patient able to sit with legs outside the bed
3. Patient able to ambulate with assistance from bed to chair
4. Patient able to ambulate with assistance (walk) for 5 m within the ward

On completion of the above the patient was asked to rate discomfort according to the following seven-graded Likert scale:

1. No discomfort at all
2. Minor discomfort
3. Mild discomfort
4. Moderate discomfort
5. Quite severe discomfort
6. Severe discomfort
7. Very severe discomfort

Patients were asked the following question at defined intervals: "How do you rate the quality of pain management you have experienced since the last assessment, i.e. since this morning or last night etc.?" The scale was as follows:

1. Excellent
2. Good
3. Fair
4. Poor

Sensory block was determined bilaterally using a cold pack (or ice). [Note: the term "cold stimulus" with the following examples e.g. ice, cold pack was provided by protocol amendment # 2]. Both upper and lower spread was recorded. In case of asymmetric block, the highest and lowest dermatome levels were recorded. Motor block was determined bilaterally according to a modified Bromage scale:

0= No motor block (full flexion of hips, knees and feet).
1= Inability to raise extended legs (just able to move knees and feet).
2= Inability to flex knees (able to move feet only).
3= Inability to flex ankle joints (unable to move hips, knees and feet).

In case of asymmetric block, the highest (numerical) value was to be recorded.
Patients rated their postoperative discomfort using a self-administered questionnaire about discomfort from sixteen symptoms associated with the postoperative course and side effects from pain management with opioids or local anesthetics. Each item was measured using a seven-graded Likert scale as follows:

1. No discomfort at all
2. Minor discomfort
3. Mild discomfort
4. Moderate discomfort
5. Quite severe discomfort
6. Severe discomfort
7. Very severe discomfort

The patients were asked to complete this questionnaire at the physical examination before surgery, and on days 2 (day after surgery), 3 and 4. The questionnaire was to be completed between 18.00 hrs and 22.00 hours on day 2 and 3. On day 4 the patient was to be asked to complete the questionnaire at the end of the 72-h period, before the end of the infusion. The questionnaire was to be completed prior to the clinical assessments scheduled in the protocol.

Table 31. 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 (hours)			72 h or at end of
		0-5	5-10	->	30	->	60				infusion
Physical examination + ECG	x										
Pre-anaesthetic infusion	x										
Test dose 3 ml		x									
Epidural dose 5-15 ml, ropi 7.5 mg/ml			x								
Additional 5 ml dose (if needed)				x							
Continuous infusion of study drug						x	x	x	x	x	x
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 (cold pack/ice)				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 mobilisation & discomfort								start day after surgery, twice daily.			
Criteria "fit for discharge" from hosp.											day 4->
Questionnaire (self assessment by pat.)	x								day 2**	day 3**	day 4
Other assessments+patient hosp.stay***	to be completed during the study										
Adverse events obs./rep / open ques	x	x	x	x	x	x	x	x	x	x	x

* Assessments between 08.00 and 22.00. BP/pulse/temp - 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 urine catheter
first micturition
passage of first flatus
withdrawal of nasogastric tube
perioperative blood loss

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

[Sponsor's Figure 1, Item 8, Vol. 49, p.24]

7.2.3.2 Statistical Analysis

"The analysis was based on the all patients treated data set, where treated means that a patient has at least arrived at the PACU with the epidural infusion of study treatment still in progress. The analysis and presentation of safety data were based on a safety data set.

Time zero for the clinical assessments in the postoperative period was the time of arrival at the PACU. In the case certain repeated assessments, a summary measure of the repeated measurements during the 72-hour postoperative period was calculated for a patient as follows. First the area under the curve based on the repeated measurements up to 72 hours was calculated using the trapezoidal rule. The summary in question was then defined as this area under the curve divided by the length of the time period on which it is based, so that it had the same scale as the underlying repeated measurements. This summary measure was denoted AUCM72. Similarly defined summary measures AUCM24 and AUCM48 based on the repeated measurements up to 24 hours and up to 48 hours were calculated."
[Item 8, Vol. 49, p.46]

Primary Efficacy Variable
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 the72-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 mobilisation and pain on mobilisation (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 ml/h throughout the entire 72-hour period, the variable was to be set equal to 0, otherwise its value was to be set to -1 or 1 if the first deviation outside these boundaries was below 6 or above 10 ml/h respectively.

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

[Item 8, Vol. 49, p.47]

"The statistical analysis includes descriptive statistics and graphs for each treatment group. Pairwise comparisons of groups were to be made for variables 1-6 and 8, using a stratified Wilcoxon (mid) rank sum test adjusting for centres, with corresponding point estimates and 95% confidence intervals for differences if the variable was continuous."
[Item 8, Vol. 49, p.54].

7.2.3.3 Protocol Amendment:

Amendment 1 dated 7/25/96, Amendment 2 dated 9/19/96 and Amendment 3 dated 11/25/97 made the following changes:

A. Study Measurements
- Due to difficulties in standardizing the intensity of adverse events, this measurement will not be made.
- Rewording to clarify endpoint – wound pain duration
- Sensory block: the word "cold pack" has been replaced with "cold stimulus" with examples given.

B. Study Procedures
- No data will be collected of each general anesthetic given because comparable general anesthetics will be administered.

C. Administration
- Replacement of principal investigator – due to availability.
- Replacement of biostatistician
- Only patients exposed to study drug will have their adverse events recorded in the CRF

D. Epidural Block Procedure
- In order to avoid excessive block, the rate limit was changed to 5 –15 ml ropivacaine 7.5 mg/ml from 8-15 ml ropivacaine 7.5 mg/ml
- Infusion commencement time was specified as after incision or after decision was made about the type of surgery to be performed and thereby the inclusion or exclusion of the patient in study participation.

E. Postoperative Procedure
- The protocol for handling catheter blockade has been specified as follows: the block is to be re-established with the estimated volume which had been missed (e.g. if the infusion had ceased for one hour, the catheter could be bolused with the previous hourly dose).
- Fitness for discharge: to clarify that oral nutrition refers to both liquids and solids, examples have been provided.

[Item 8, Vol. 49 p. 238]

7.2.3.4 Conduct of Study

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

Demographics

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

Table 32. Baseline characteristics (number of patients)

	Ropi (n=62)	Ropi+1fent (n=62)	Ropi+2fent (n=64)	Ropi+4fent (n=67)
Race				
Caucasian	61	56	62	64
Mongoloid	.	2	1	1
Other	1	4	1	2
Sex				
Male	28	40	25	34
Female	34	22	39	33
ASA class				
I	9	9	9	14
II	40	39	43	43
III	13	14	12	10
Any history of allergy				
No	46	51	41	52
Yes	16	11	23	15

[Item 8, vol. 49, p. 60

Table 33. Patient demographics (number of patients)

Variable	Group	N	NMISS	MEAN	STD	MIN	MEDIAN	MAX
Age	Ropi	62	0		13.3	22	60.5	
	Ropi+1 fent	62	0		12.5	21	61.6	
	Ropi+2 fent	64	0		15.9	23	61.0	
	Ropi+4 fent	67	0		12.7	27	59.0	
Height	Ropi	60	2		10.7	150	167.5	
	Ropi+1 fent	60	2		8.9	150	170.0	
	Ropi+2 fent	62	2		9.0	151	165.5	
	Ropi+4 fent	66	1		10.0	136	166.5	
Weight	Ropi	62	0		13.5	50	72.5	
	Ropi+1 fent	62	0		13.9	50	75.5	
	Ropi+2 fent	64	0		12.9	45	73.5	
	Ropi+4 fent	67	0		13.5	45	73.0	

[Item 8, vol. 49, p. 60

The majority of patients were Caucasian of similar ASA class, age, height, and weight and with similar history of allergies. The majority of patients had current or past major medical conditions and had undergone major surgical procedures.

Equal numbers of patients in each treatment group received cefotetan (antibiotic), temazepam (sedative),aramine and ephedrine (vasopressors) as concomitant medication before and during surgery, as per protocol. Heparin (anticoagulant), maxolon and stemetil (antiemetics) were the most common drugs given postoperatively and were also equally distributed between treatment groups.

Sponsor's Efficacy Results:

Primary Efficacy Measurement:

The primary efficacy variable was defined for each patient 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]

INFUSION RATE:

Mean Infusion Rate 0-72 Hours

"The median of each patient's mean infusion rate for 0-72 h was 12.6 ml/h in the ropivacaine group, 12.2 ml/h in the ropivacaine +1fentanyl group, 11.2 ml/h in the ropivacaine +2fentanyl group and 11.1 ml/h in the ropivacaine +4fentanyl group.. Statistically significant differences were found between the ropivacaine group and ropivacaine +2fentanyl group (p=0.005), and between the ropivacaine group and the ropivacaine +4fentanyl group (p=0.001).
[Item 8, Vol. 49, p. 105]

Table 34. Mean Infusion Rate 0-72 Hour (ml/h)

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	60	11.79	2.09		10.89	12.62	13.21	
Ropi+1fent	59	11.61	1.96		10.18	12.16	13.46	
Ropi+2fent	62	10.86	2.21		9.24	11.23	12.60	
Ropi+4fent	63	10.73	2.42		9.12	11.06	12.68	

[Item 8, Vol. 49, p. 105]

Mean infusion rate 0-24 h

"The median of each patient's mean infusion rate for 0-24 h was 10.2 ml/h in the ropivacaine group, 9.8 ml/h ml in the ropivacaine +1fentanyl group, 9.5 ml/h in the ropivacaine +2fentanyl group and 9.3 ml/h in the ropivacaine +4fentanyl group. Statistically significant differences were found between the ropivacaine group and ropivacaine +2fentanyl group (p=0.049), and between the ropivacaine group and the ropivacaine +4fentanyl group (p=0.006)."

[Item 8, Vol. 49, p. 104]

Table 35. Mean Infusion Rate 0-24 Hour (ml/h)

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	60	10.19	2.23		8.62	10.19	11.65	
Ropi+1fent	59	9.98	2.40		8.00	9.83	12.38	
Ropi+2fent	62	9.39	2.29		8.00	9.53	11.09	
Ropi+4fent	63	9.29	2.22		8.00	9.26	10.67	

[Item 8, Vol. 49, p. 104]

Mean Infusion Rate 0-48 Hours

"The median of each patient's mean infusion rate for 0-48 h was 11.9 ml/h in the ropivacaine group, 11.3 ml/h in the ropivacaine +1fentanyl group, 10.7 ml/h in the ropivacaine +2fentanyl group and 10.3 ml/h in the ropivacaine +4fent group. Statistically significant differences were found between the ropivacaine group and ropivacaine +2fentanyl group (p=0.029), and between the ropivacaine group and the ropivacaine +4fentanyl group (p=0.002)."

[Item 8, Vol. 49, p. 101]

Table 36. Mean Infusion Rate 0-48 Hour (ml/h)

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	60	11.31	2.12		9.85	11.93	12.81	
Ropi+1fent	59	11.07	2.10		9.34	11.34	13.19	
Ropi+2fent	62	10.34	2.24		8.56	10.73	11.92	
Ropi+4fent	63	10.24	2.34		8.67	10.28	12.02	

[Item 8, Vol. 49, p. 104]

Figure 14. Mean Infusion Rate, Individual Values and Box Plots – 0-72 Hour

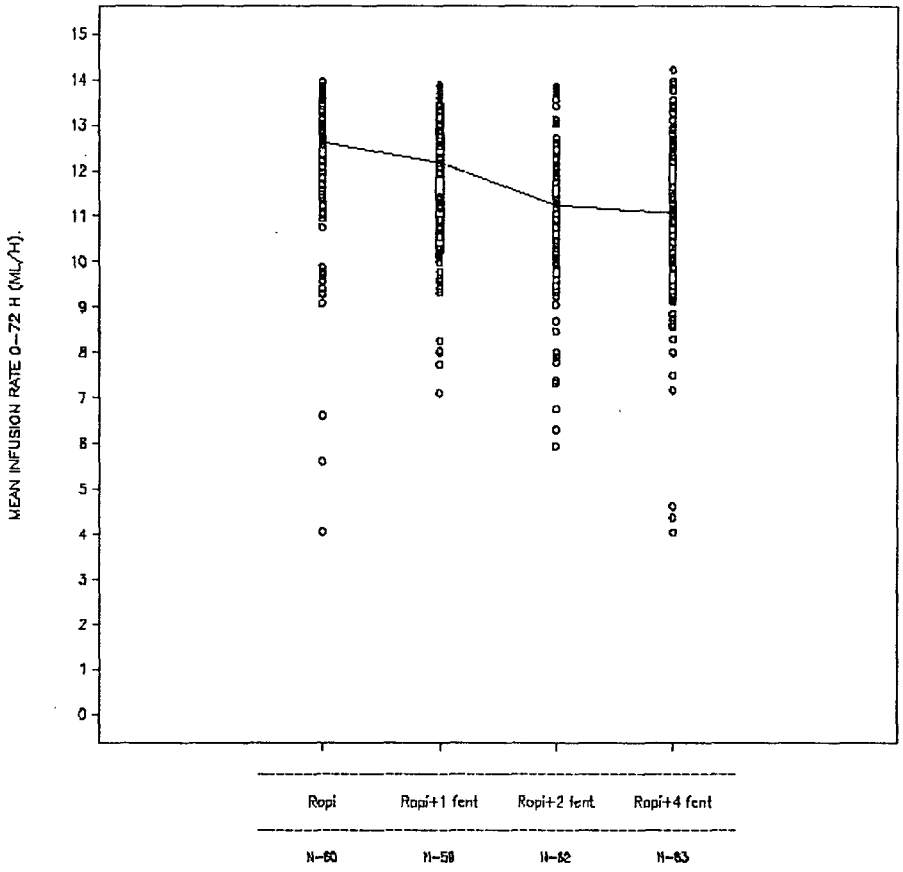


Figure 3. Mean infusion rate (ml/h) in the Ropi group, Ropi+1fent group, Ropi+2fent group and Ropi+4fent group. Individual values and box plots (Q1, median, Q3), medians connected (0-72 h).

[Sponsor's Figure 3, Item 8, Vol. 49, p. 106]

Postoperative Pain

Pain at Rest

"The median pain scores (VAS) were overall low in all four groups (primary and additional analysis).

Primary analysis
The median pain score at rest over the 72-hour period varied between 0 and 7 mm in the ropivacaine group (n=60), 0 and 10 mm in the ropivacaine +1fentanyl group (n=59), 0 and 7 mm in the ropivacaine +2fentanyl group (n=62) and 0 and 2 mm in the ropivacaine +4fentanyl group (n=61)

Additional analysis
The median pain score varied over time between 0 to 5 mm in the ropivacaine (n=60-30), 0 to 5 mm in the ropivacaine +1fentanyl group (n=59-33), 0 to 3 mm in the ropivacaine +2fentanyl group (n=62-34) and 0 to 2 in the ropivacaine +4fentanyl group (n=61-46)."

[Item 8, Vol. 49, p. 115]

AUCM 24 hour – Pain at Rest

"The median AUCM values for pain at rest (VAS) 0-24 h were 8 mm, 7 mm, 4 mm and 3 mm, in the ropivacaine, ropivacaine +1fentanyl, ropivacaine +2 fentanyl and ropivacaine +4fentanyl groups, respectively. A statistically significantly higher AUCM value was found in the ropivacaine group compared to the ropivacaine +4fentanyl group (p=0.000) and in the ropivacaine +1fentanyl group compared to the ropivacaine +4fentanyl group (p=0.005).

[Item 8, Vol.49, p. 118]

Table 37. AUCM 24 hour – Pain at Rest

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	60	13.03	14.59		1.73	8.07	21.21	
Ropi+1fent	59	12.26	17.15		2.25	7.38	14.58	
Ropi+2fent	62	10.79	16.54		0.19	4.24	14.85	
Ropi+4fent	61	5.95	8.29		0.00	3.06	7.21	

[Item 8, Vol.49, p. 118]

AUCM 48 hour – Pain at Rest

"The median AUCM values for pain at rest (VAS) 0-48 h were 11 mm, 8 mm, 4 mm and 4 mm in the ropivacaine, ropivacaine +1fentanyl, ropivacaine +2fentanyl and ropivacaine +4fentanyl groups, respectively. A statistically significantly higher AUCM value was found in the ropivacaine group compared to the ropivacaine +4fentanyl group (p=0.001) and in the ropivacaine +1fentanyl group compared to the ropivacaine +4fentanyl group (p=0.003).

[Item 8, Vol.49, p. 118]

Table 38. AUCM 48 hour – Pain at Rest

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	60	15.23	17.08		1.61	10.84	19.84	
Ropi+1fent	59	14.54	16.29		3.17	8.50	18.56	
Ropi+2fent	62	13.21	19.19		0.84	4.13	21.16	
Ropi+4fent	61	7.45	11.16		0.77	4.06	8.46	

[Item 8, Vol.49, p. 118]

AUCM 72 hour – Pain at Rest

"The median AUCM values for pain at rest (VAS) 0-72 h were 9 mm, 7 mm, 8 mm and 4 mm in the ropivacaine, ropivacaine +1fentanyl, ropivacaine +2fentanyl and ropivacaine +4fentanyl groups, respectively. A statistically significantly higher AUCM value was found in the ropivacaine group compared to the ropivacaine +4fentanyl group (p=0.002) and in the ropivacaine +1fentanyl group compared to the ropivacaine +4fentanyl group (p=0.011).

[Item 8, Vol.49, p. 119]

Table 39. AUCM 72 hour – Pain at Rest

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	60	15.87	19.53		1.72	8.93	19.03	
Ropi+1fent	59	14.94	19.89		2.67	6.57	17.03	
Ropi+2fent	62	15.74	21.50		1.83	7.62	20.74	
Ropi+4fent	61	7.38	12.04		1.11	4.03	8.22	

[Item 8, Vol.49, p. 119]

Mean Infusion Rate- Actual Infusion Time

"The median of each patient's mean infusion rate for actual infusion time was 11.3 ml/h in the ropivacaine group, 10.9 ml/h in the ropivacaine +1fentanyl group, 10.4 ml/h in the ropivacaine +2fentanyl group and 10.9 ml/h in the ropivacaine +4fentanyl group. A statistically significant difference was found between the ropivacaine group and the ropivacaine +2fentanyl group (p=0.023)."

[Item 8, Vol. 49, p. 107]

Table 40. Mean Infusion Rate- Actual Infusion Time

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	60	10.95	2.10		9.71	11.30	12.57	
Ropi+1fent	59	10.97	1.85		9.81	10.90	12.29	
Ropi+2fent	62	10.19	2.14		8.11	10.39	11.87	
Ropi+4fent	63	10.42	2.28		8.72	10.86	12.19	

[Item 8, Vol. 49, p. 107]

Figure 15. Mean Infusion Rate, Individual Values and Box Plots – Actual Infusion Time

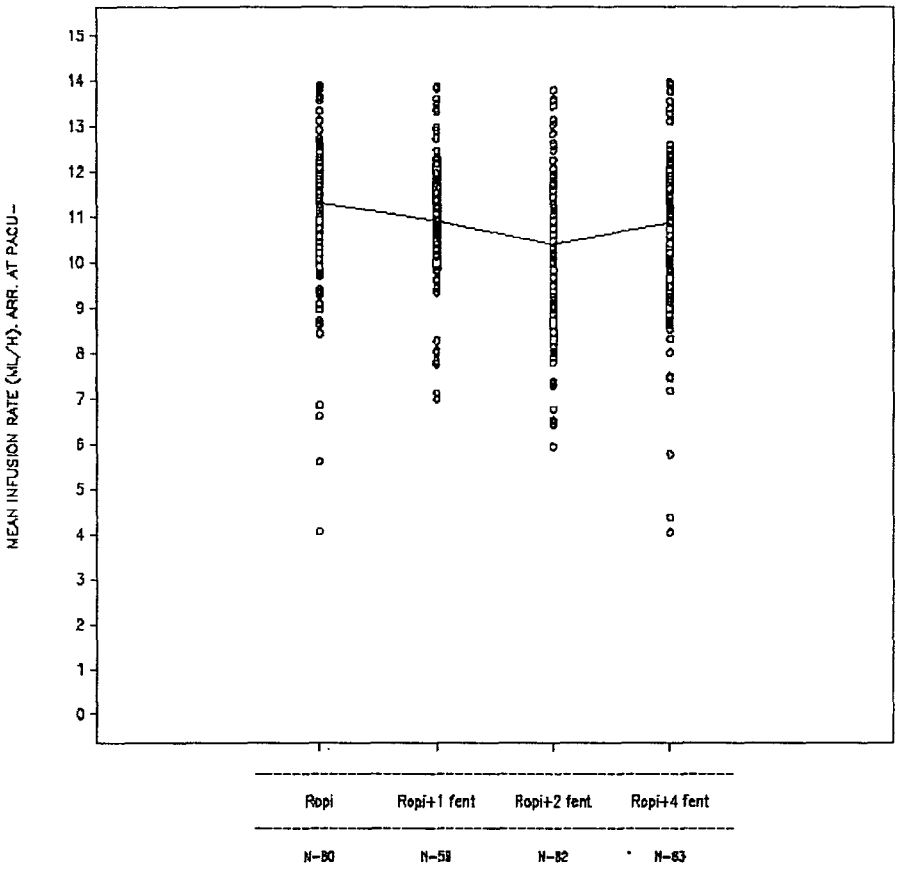


Figure 4. Mean infusion rate (ml/h) in the Ropi group, Ropi+1fent group, Ropi+2fent group and Ropi+4fent group. Individual values and box plots (Q1, median, Q3), medians connected (actual infusion time).

[Sponsor's Figure 4, Item 8, Vol. 49, p. 108]

Indicator of Mean Infusion Rate

"The following variable was used to indicate dose adjustments: if the mean infusion rate over a period was between 6-10 ml/h the variable was given the value 0, if it was above 10 ml/h it was given 1, and if it was below 6 ml/h, it was given the value -1. No statistically significant differences were found between any of the four groups for 0-72 h. For actual infusion times, a statistically significant difference was found between the ropivacaine +1fentanyl group and the ropivacaine +2fentanyl group (p=0.029). There were more patients in the ropivacaine +1fentanyl group that had a mean infusion rate above 10 ml/h compared to the ropivacaine +2fentanyl group."

[Item 8, Vol. 49, p. 109]

Figure 16. Cumulative Percentage of Indicator of Mean Infusion Rate by Treatment Group (0-72 Hour)

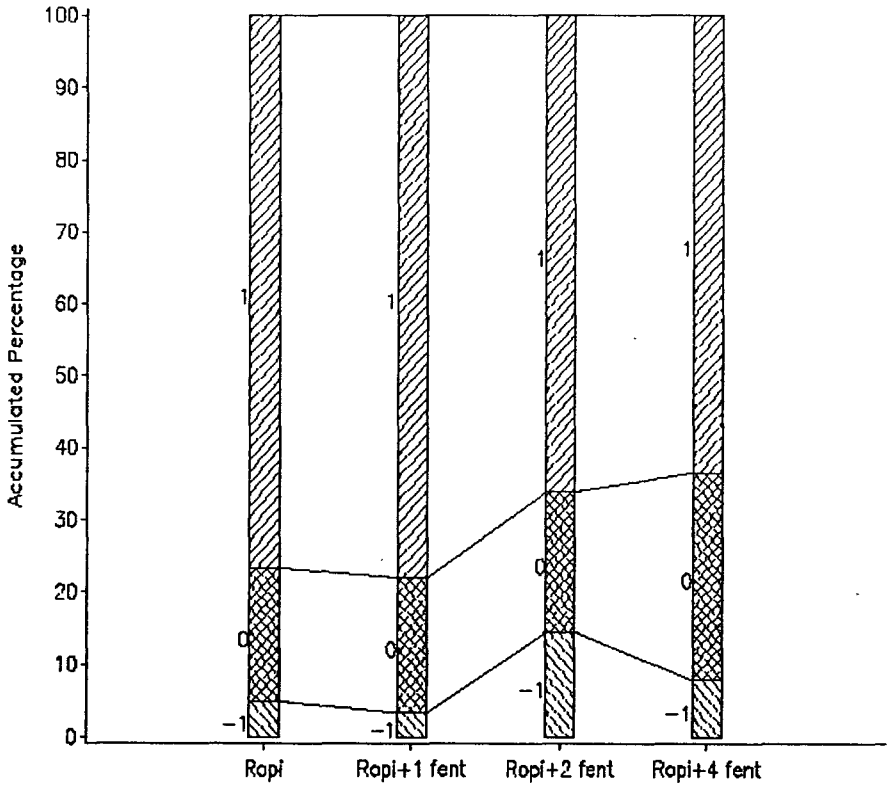


Figure 5. Cumulative percentage (%) of indicator of mean infusion rate in the Ropi group (n=60), Ropi+1fent group (n=59), Ropi+2fent group (n=62) and Ropi+4fent group (n=63). -1 = below 6 ml/ml; 0 = 6 to 10 ml/h; +1 = above 10 ml/h (0-72 h).

[Sponsor's Figure 5, Item 8, Vol. 49, p. 111]

Peak Infusion Rate

"There were more patients in the ropivacaine group that had a higher peak infusion rate compared to the ropivacaine +2fentanyl group and the ropivacaine +4fentanyl group."

[Item 8, Vol. 42, p. 108]

ml/h	Ropi (n=60)	Ropi+1fent (n=59)	Ropi+2fent (n=62)	Ropi+4fent (n=63)
8	2	3	6	9
10	7	7	9	7
11	0	0	2	0
12	4	5	12	11
14	47	44	32	35
16	0	0	1	0
18	0	0	0	1

Table 41. Peak Infusion Rate by Treatment Group

[Item 8, Vol. 49, p. 112]

Duration of Infusion

"Patients in the ropivacaine +4fentanyl group were discontinued later than the other three groups. There were more patients that were discontinued earlier due to lack of efficacy in the ropivacaine group than in the ropivacaine +4fentanyl group, whereas the other two groups (ropivacaine +1fentanyl group and ropivacaine +2fentanyl group) were in between.

[Item 8, Vol. 49, p. 112]

AUCM Actual Infusion Time – Pain upon Coughing

"The median AUCM values for pain upon (VAS) for actual infusion time were 18 mm, 18 mm, 17 mm and 11 mm in the ropivacaine, ropivacaine +1fentanyl, ropivacaine +2fentanyl and ropivacaine +4 fentanyl groups, respectively. A statistically significantly higher AUCM value was found in the ropivacaine group compared to the ropivacaine +4fentanyl group (p=0.002)."
[Item 8, Vol. 49, p. 131]

Table 42. AUCM for Pain upon Coughing – Actual Infusion Time (VAS)

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	59	24.90	18.24		13.38	18.30	35.47	
Ropi+1fent	59	25.59	22.54		6.74	18.45	43.33	
Ropi+2fent	61	20.13	16.16		6.39	16.67	31.82	
Ropi+4fent	61	15.06	13.18		5.74	11.49	19.29	

[Item 8, Vol. 49, p. 131]

Pain upon Coughing above 30 mm (VAS)

"The percentages of the non-missing patients with a pain score ≥ 30 mm upon coughing for 0-24 h were 75% (44/59) in the ropivacaine.group, 66% (39/59) in the ropivacaine +1fentanyl group, 61% (37/61) in the ropivacaine +2fentanyl group and 48% (29/61) in the ropivacaine +4 fentanyl group. Statistically significant differences were found between the ropivacaine group and the ropivacaine +4 fentanyl group (p=0.004) and between the ropivacaine group and ropivacaine +4fentanyl group (p=0.031).

For the period 0-48 h, the values were 81% (48/59), 75% (44/59), 70% (43/61) and 59% (36/61) in the ropivacaine, ropivacaine +1fentanyl, ropivacaine +2 fentanyl and ropivacaine +4 fentanyl groups, respectively. A statistically significant difference was seen between the ropivacaine group and the ropivacaine +4 fentanyl group (p=0.009).

For 0-72 h, the values were 83% (49/59), 75% (44/59), 77% (47/61) and 64% (39/61) in the four groups, respectively. A statistically significant difference was found between the ropivacaine group and the ropivacaine +4 fentanyl group (p=0.019)."

[Item 8, Vol. 49, p. 133]

Pain upon Coughing

"The pain score upon coughing was lower in the ropivacaine +4fentanyl group compared to the other three groups.

Primary analysis
The median pain score upon coughing over the 72 -hour period varied between 0 and 22 mm in the ropivacaine group (n=59), 0 and 25 mm in the ropivacaine +1fentanyl group (n=59), 0 and 24 mm in the ropivacaine +2fentanyl group (n=61) and 0 and 11 mm in the ropivacaine +4fentanyl group (n=61) (primary analysis)

Additional analysis
The median pain score varied over time between 0 to 20 mm in the ropivacaine group (n=59-30), 0 to 15 mm in the ropivacaine +1fentanyl group (59-33), 0 to 14 mm in the ropivacaine +2fentanyl group (n=61-34) and 0 to 11 mm in the ropivacaine +4fentanyl group (n=61-46)."
[Item 8, Vol. 49, p. 125]

AUCM 24h – Pain upon Coughing

"The median AUCM values for pain upon coughing 0-24 h (VAS) were 19 mm, 18 mm, 16 mm and 8 mm in the ropivacaine +1fentanyl, ropivacaine +2fentanyl and ropivacaine +4fentanyl groups, respectively. A statistically significantly higher AUCM value was found in the ropivacaine group compared to the ropivacaine +4fentanyl group (p=0.001) and in the ropivacaine +1fentanyl group compared to the ropivacaine +4fentanyl group (p=0.009)."

[Item 8, Vol. 49, p. 128]

Table 43. AUCM 24h – Pain upon Coughing

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	59	26.15	21.72		9.93	18.78	40.90	
Ropi+1fent	59	25.50	23.35		4.38	17.99	43.70	
Ropi+2fent	61	20.52	19.79		3.83	15.85	30.51	
Ropi+4fent	61	13.64	13.30		3.61	7.94	20.31	

[Sponsor's Table 42, Item 8, Vol. 49, p. 128]

AUCM 48h – Pain upon Coughing

"The median AUCM values for pain upon coughing 0-48 h (VAS) were 22 mm, 19 mm, 18 mm and 11 mm in the ropivacaine, ropivacaine +1fentanyl, ropivacaine +2fentanyl and ropivacaine +4 fentanyl groups, respectively. A statistically significantly higher AUCM value was found in the ropivacaine group compared to the ropivacaine +4fentanyl group (p=0.001) and in the ropivacaine +1fentanyl group compared to the ropivacaine +4fentanyl group (p=0.025)."

[Item 8, Vol. 49, p. 128]

Table 44. AUCM 48h – Pain upon Coughing

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	59	29.12	23.16		10.00	22.02	43.62	
Ropi+1fent	59	28.43	23.99		9.56	18.87	47.77	
Ropi+2fent	61	23.40	21.44		4.89	17.58	35.02	
Ropi+4fent	61	16.63	16.58		5.75	10.79	23.13	

[Item 8, Vol. 49, p. 128]

AUCM 72h – Pain upon Coughing

"The median AUCM values for pain upon coughing 0-72 h (VAS) were 20 mm, 22 mm, 18 mm and 11 mm in the ropivacaine, ropivacaine +1fentanyl, ropivacaine +2fentanyl and ropivacaine +4fentanyl groups, respectively. A statistically significantly higher AUCM value was found in the ropivacaine group compared to the ropivacaine + 4 fentanyl group (p=0.002) and in the ropivacaine +1fentanyl group compared to the ropivacaine +4fentanyl group (p=0.041)."

[Item 8, Vol. 49, p. 129]

Table 45. AUCM 72 – Pain upon Coughing

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	59	29.50	24.54		11.21	20.28	41.37	
Ropi+1fent	59	29.18	25.45		7.92	22.11	45.10	
Ropi+2fent	61	26.01	23.52		5.79	17.89	43.81	
Ropi+4fent	61	16.90	17.65		5.98	11.19	19.29	

[Item 8, Vol. 49, p. 129]

Spread of Analgesia

" Both analyses (primary and additional) showed similar results. The spread of both upper and lower sensory block over time was similar in all four groups .

[Item 8, Vol. 49, p. 127]

Table 46. Upper and lower spread of sensory block (primary analysis)

Sensory block	Ropi group (n=60)	Ropi+1fent group (n=59)	Ropi+2fent group (n=61)	Ropi+4fent group (n=62)
Upper spread				
24 h	T5	T5	T5	T4
48 h	T5	T6	T6	T5
72 h	T5	T5	T6	T6
Lower spread				
24 h	L3	L3	L2	L2
48 h	L2	L2	L1	L1
72 h	L2	L2	L1	L1

[Item 8, vol. 49, p. 135]

Table 47. Upper and lower spread of sensory block (additional analysis).

Sensory	Ropi group	Ropi+1fent	Ropi+2fent	Ropi+4fent
Sensory block	Ropi group (n=60)	Ropi+1fent group (n=59)	Ropi+2fent group (n=61)	Ropi+4fent group (n=62)
Upper spread				
24 h	T5	T5	T5	T4
48 h	T5	T6	T6	T5
72 h	T5	T5	T6	T6
Lower spread				
24 h	L3	L3	L2	L2
48 h	L2	L2	L1	L1
72 h	L2	L2	L1	L1

[Item 8, vol. 49, p. 135]

Motor Block

"Both analyses (primary and additional) showed similar results.
The motor block was low and similar between groups during the course of the postoperative infusion.

Primary analysis
In the ropivacaine group 87% (52/60) of the non-missing patients at 24 h, 92% (55/60) at 48 h and 92 % (55/60) at 72 h after postoperative infusion had no demonstrable motor block according to the modified Bromage scale. The corresponding figures for the ropivacaine + 1fentanyl group were 93% (55/59), 97% (57/59) and 98% (58/59), for the ropivacaine + 2fentanyl 95% (58/61), 95% (58/61) and 97% (59/61), and for the ropivacaine + 4fentanyl 94% (58/62), 97% (60/62) and 97% (60/62), at the same time points, respectively.

Additional analysis
No demonstrable motor block according to the modified Bromage scale was found in 94% (44/47), 100% (35/35) and 100% (29/29) of the patients in the ropivacaine group, 92% (49/53), 94% (33/35) and 97% (32/33) in the ropivacaine + 1fentanyl group , 96% (48/50), 95% (38/40) and 97%, (33/34) in the ropivacaine + 2fentanyl and 94% (58/62), 98% (50/51) and 98% (46/47) in the ropivacaine + 4fentanyl, after 24 h, 48 h and 72 h of postoperative infusion, respectively."
[Item 8, Vol. 49, p. 139]

Quality of Pain Relief

Both analyses (primary and additional) showed similar results.

Primary analysis
"The quality of pain relief assessed at 24 h was rated as good or excellent in 80% (48/60) of the non-missing patients in the ropivacaine group, 78% (45/58) in the ropivacaine + 1fentanyl group , 83% (52/62) in the ropivacaine + 2fentany , and 87% (55/63) in the ropivacaine + 4fentanyl. At 48 h the corresponding values were 75% (45/60), 72% (42/58), 74% (46/62) and 86% (54/63), respectively. At 72h 73% (44/60) in the ropivacaine group, 71% (42/58) in the ropivacaine + 1fentanyl group, 68% (42/62) in the ropivacaine + 2fentanyl and 89% (56/63) in the ropivacaine + 4fentanyl rated the quality of pain relief as good or excellent."
[Item 8, Vol. 49, p. 142]

Additional analysis
"The quality of pain relief was rated as good or excellent in 85% (40/47) of the patients in the ropivacaine group, 81% (43/53) in the ropivacaine + 1fentanyl group, 90% (45/50) in the ropivacaine + 2fentanyl and 89% (54/61) in the ropivacaine + 4fentanyl. At 48 h the corresponding values were 91% (32/35), 97% (35/36), 92% (36/39) and 94% (48/51), respectively. At 72 h the quality of pain relief was rated good or excellent in 97% (29/30) of patients in the ropivacaine group, 100% (33/33) in the ropivacaine + 1fentanyl group, 88% (30/34) in the ropivacaine + 2fentanyl and 100% (47/47) in the ropivacaine + 4fentanyl."
[Item 8, Vol. 49, p. 142]

Time to First Ambulation
The median time to mobilization was similar between groups.

Table 48. Time to First Ambulation

GROUP	N	NMISS	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	32	28	34.16	18.25		20	24	48	
Ropi+1fent	40	19	34.43	13.62		21	35	44	
Ropi+2fent	38	24	32.79	15.16		21	27	43	
Ropi+4fent	49	14	31.71	16.62		19	24	43	

[Item 8, Vol. 49, p. 148]

Pain During Mobilization/Ambulation

The median pain score (VAS) during mobilization was higher in the ropivacaine group than in the other three groups (primary and additional analysis).

Primary analysis
"The median pain scores (VAS) on the morning of the first postoperative day were 10 mm in the ropivacaine group (n=48), 5 mm in the ropivacaine + 1fentanyl group (n=50), 0 mm in the ropivacaine + 2fentanyl (n=50), and 3 mm in the ropivacaine + 4fentanyl (n=59). The corresponding values on the morning of the third postoperative day were 11 mm in the ropivacaine group (n=48), 1 mm in the ropivacaine + 1fentanyl group (n=50), 3 mm in the ropivacaine + 2fentanyl (n=50) and 1 mm in the ropivacaine + 4fentanyl (n=59)."
[Item 8, Vol. 49, p. 149]

Additional analysis
"The median pain scores (VAS) on the morning of the first postoperative day were 10 mm in the ropivacaine group (n=48), 5 mm in the ropivacaine + 1fentanyl group (n=50), 0 mm in the ropivacaine + 2fentanyl (n=50), and 3 mm in the ropivacaine + 4fentanyl (n=59). The corresponding scores on the morning of the third postoperative day were 5 mm in the ropivacaine group (n=31), 0 mm in the ropivacaine + 1fentanyl group (n=34), 2 mm in the ropivacaine + 2fentanyl (n=35) and 1 mm in the ropivacaine + 4fentanyl (n=47). On the morning of the first postoperative day patients in the ropivacaine group had a higher pain score during mobilisation than in the other three groups."
[Item 8, Vol. 49, p. 149]

Patient Assessed Discomfort

Both analyses (primary and additional) showed similar results, and only the primary analysis is presented.

"At the baseline assessment the percentage of patients reporting any degree of discomfort varied between 10 and 30% for the different items. A maximum of 10% of the patients experienced moderate to severe discomfort. For some items (e.g. hard stools, constipation, not emptying the bowels), the postoperative scores were lower than baseline throughout study period. Compared to baseline, patients were more bothered by nausea, itching, difficulties in concentrating and pain when moving around during the postoperative infusion. Furthermore, there was a tendency towards more distress from itching with higher doses of fentanyl, and patients were more bothered by difficulties in concentrating with increasing doses of fentanyl."
[Item 8, Vol.49, p.155]

Urinary Catheter, Time to First Flatus and Nasogastric Tube

"The median start and end times for catheter use, time until first flatus and first micturition were shorter in the ropivacaine group than in the ropivacaine + 4fentanyl. The median time (hours) to withdrawal of the nasogastric tube was shorter in the ropivacaine group and ropivacaine + 1fentanyl group than in the ropivacaine + 2fentanyl and Ropi+4fent group."

[Item 8, Vol. 49, p. 160]

Table 49. Time from arrival at the PACU to placement/withdrawal of urinary catheter and to first micturition/first flatus (hours).

Variable	Group	N	NMISS	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Catheter start time	Ropi	59	1	-3.0	3.4	-	-2.9	-2.4	-1.7	
	Ropi+1 fent	58	1	-5.1	15.1		-3.7	-2.9	-2.0	
	Ropi+2 fent	58	4	-4.0	12.5	-	-4.0	-2.8	-2.1	
	Ropi+4 fent	63	0	-3.1	1.7	-	-3.9	-2.7	-2.1	
Catheter end time	Ropi	55	5	98.6	54.9		72.3	91.5	115.5	
	Ropi+1 fent	52	7	103.9	44.0		72.4	98.2	128.0	
	Ropi+2 fent	53	9	107.7	57.7		81.1	95.4	133.8	
	Ropi+4 fent	59	4	117.1	63.1		85.8	109.9	127.0	
First flatus	Ropi	50	10	48.6	42.2		22.1	38.0	59.6	
	Ropi+1 fent	46	13	51.3	35.9		23.6	43.6	68.8	
	Ropi+2 fent	47	15	61.5	42.1		31.9	45.2	89.6	
	Ropi+4 fent	55	8	54.5	36.4		27.6	47.3	69.4	
First micturition	Ropi	53	7	102.3	56.1		73.0	95.1	116.8	
	Ropi+1 fent	49	10	108.4	44.5		75.5	98.3	135.5	
	Ropi+2 fent	53	9	109.3	57.6		78.4	97.1	134.9	
	Ropi+4 fent	55	8	118.4	60.4		88.6	108.1	127.3	

[Item 8, Vol. 49, p. 160]

Table 50. Time to Withdrawal of Nasogastric Tube

Variable	Group	N	NMISS	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
TIME	Ropi	18	42	53.6	41.3		19.8	51.1	90.8	
	Ropi+1 fent	26	33	75.0	62.5		33.4	50.9	111.6	
	Ropi+2 fent	30	32	78.5	59.7		23.5	67.0	132.2	
	Ropi+4 fent	24	39	82.0	87.7		40.6	64.3	73.7	

[Item 8, Vol. 49, p. 160]

Duration of Hospital Stay

"The median time (hours) spent in the theatre preparation room, operating theatre and at the PACU was similar in all groups. The median times (days) for hospital ward and time until ready for discharge were shorter in the ropivacaine group than in the other groups, although the corresponding mean values were similar. The number of patients admitted to the intensive care unit differed between groups: none in the ropivacaine group, 2 patients in the ropivacaine + 1fentanyl group, 5 patients in the ropivacaine + 2fentanyl and 6 patients in the ropivacaine + 4fentanyl group. An analysis was made to check the times for the discontinued patients, which showed that they were deemed ready for discharge at similar time compared to the other patients. From this it can be concluded that any difference between the groups did not depend on the fact that there were more patients who discontinued in the ropivacaine group."
[Item 8, Vol. 49, p. 143]

Table 51. Time spent in theatre preparation room/operating theatre/PACU/intensive care unit (hours), and hospital ward, time from start of surgery until deemed ready for discharge from hospital and time from surgery to actual discharge (days).

Variable	Group	N	NMISS	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Theatre prep. room (hours)	Ropi	57	3	0.9	0.5		0.6	0.8	1.2	
	Ropi+1 fent	55	4	1.0	0.4		0.7	0.9	1.1	
	Ropi+2 fent	61	1	1.0	0.5		0.6	0.9	1.3	
	Ropi+4 fent	57	6	0.9	0.4		0.8	0.9	1.1	
Operating theatre (hours)	Ropi	60	0	2.9	1.4		2.0	2.7	3.3	
	Ropi+1 fent	59	0	3.3	1.3		2.5	3.1	3.9	
	Ropi+2 fent	62	0	3.0	1.6		1.9	2.7	3.6	
	Ropi+4 fent	63	0	3.3	1.5		2.2	2.9	4.5	
PACU (hours)	Ropi	60	0	2.0	0.9		1.3	1.8	2.5	
	Ropi+1 fent	59	0	2.1	0.9		1.5	1.9	2.5	
	Ropi+2 fent	62	0	1.9	0.8		1.3	1.7	2.5	
	Ropi+4 fent	63	0	2.3	3.4		1.3	1.8	2.5	
Intensive care unit (hours)	Ropi	0	60	.	.		.	.	.	
	Ropi+1 fent	2	57	22.0	3.4		19.7	22.0	24.4	
	Ropi+2 fent	5	57	21.5	15.1		18.8	20.2	20.5	
	Ropi+4 fent	6	57	44.4	38.4		22.7	33.4	44.6	
Hospital ward (days)	Ropi	57	3	10.1	6.4		6.6	7.9	10.8	
	Ropi+1 fent	54	5	9.4	5.2		6.9	8.2	9.8	
	Ropi+2 fent	57	5	10.0	5.0		6.7	8.5	12.7	
	Ropi+4 fent	63	0	10.1	5.2		6.8	9.3	11.0	
Ready for discharge (days)	Ropi	51	9	8.0	5.3		4.9	6.1	9.1	
	Ropi+1 fent	52	7	8.5	6.0		6.1	7.0	8.6	
	Ropi+2 fent	57	5	9.0	4.4		5.9	7.9	10.3	
	Ropi+4 fent	56	7	8.6	5.1		5.7	7.9	8.9	
Actual discharge (days)	Ropi	57	3	10.7	7.1		6.8	8.0	11.1	
	Ropi+1 fent	54	5	10.0	5.9		7.2	8.4	10.1	
	Ropi+2 fent	57	5	10.8	5.2		7.1	10.0	12.9	
	Ropi+4 fent	63	0	10.7	5.4		7.0	9.9	12.1	

[Item 8, vol. 49, p.143]

The following measurements were not protocol defined; however, will be considered for their contribution to the overall efficacy profile of the product:

AUCM Actual Infusion Time – Pain at Rest

"The median AUCM values for pain at rest (VAS) using the actual infusion time were 9 mm, 6 mm, 7 mm and 4 mm in the ropivacaine, ropivacaine +1fentanyl, ropivacaine +2fentanyl and ropivacaine +4fentanyl groups, respectively. A statistically significantly higher AUCM value was found in the ropivacaine group compared to the ropivacaine +4fentanyl group (p=0.000), in the ropivacaine +1fentanyl group compared to the ropivacaine +4fentanyl group (p=0.005) and in the ropivacaine +2fentanyl group compared to the ropivacaine +4fentanyl group (p=0.046)."

[Item 8, Vol. 49, p. 121]

Table 52. AUCM Actual Infusion Time – Pain at Rest

Group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
Ropi	60	11.95	13.20		2.88	8.80	17.14	
Ropi+1fent	59	12.53	16.65		2.67	6.44	14.32	
Ropi+2fent	62	11.09	12.71		1.83	7.26	16.63	
Ropi+4fent	61	6.16	8.20		0.67	3.99	6.94	

[Item 8, Vol.49, p. 121]

Pain at Rest above 30 mm (VAS)

"The percentages (%) of the non-missing patients with a pain score ≥ 30 mm at rest for 0-24 h were 53% (32/60) in the ropivacaine group, 47% (28/59) in the ropivacaine +1fentanyl group, 39% (24/62) in the ropivacaine +2fentanyl group and 25% (15/61) in the ropivacaine +4fentanyl group. Statistically significant differences were found between the ropivacaine group and the ropivacaine +4fentanyl group (p=0.001) and between the ropivacaine +1fentanyl group and the ropivacaine +4fentanyl group (p=0.008).

For 0-48 h the percentages of the non-missing patients having a pain score ≥ 30 mm at rest were 63% (38/60), 58% (34/59), 47% (29/62) and 41 % (25/61) in the ropivacaine, ropivacaine +1fentanyl, ropivacaine +2fentanyl and ropivacaine +4fentanyl groups, respectively. A statistically significant difference was seen between the ropivacaine group and the ropivacaine +4fentanyl group (p=0.012).

The corresponding values for 0-72 h were 67% (40/60), 58% (34/59), 58% (36/62) and 44% (27/61) in the four groups respectively. A statistically significant difference was seen between the ropivacaine group and the ropivacaine +4fentanyl group (p=0.014)."
[Item 8, Vol. 49, p. 123]

Ability to Ambulate

The number of patients with the ability to ambulate increased from the first day to the third postoperative day in all groups (primary and additional analysis).

Primary analysis
"On the morning of the first postoperative day 59% (30/51) of the non-missing patients in the ropivacaine group, 55% (29/53) in the ropivacaine + 1fentanyl group, 54% (28/52) in the ropivacaine + 2fentanyl and 57% (34/60) in the ropivacaine + 4fentanyl were able to walk five metres or walk from the bed to the chair. The corresponding values for the morning of the second postoperative day were 68% (35/51) in the ropivacaine group, 74% (39/53) in the ropivacaine + 1fentanyl group, 79% (41/52) in the ropivacaine + 2fentanyl and 88% (53/60) in the ropivacaine + 4fentanyl. On the morning of the third postoperative day the corresponding figures were 76% (39/51), 75% (40/53), 75% (39/52) and 90% (54/60) in the four groups, respectively."
[Item 8, Vol. 49, p. 145]

Additional analysis
"On the morning of the first postoperative day 59% (30/51) of the patients in the ropivacaine group, 55% (29/53) in the ropivacaine + 1fentanyl group, 54% (28/52) in the ropivacaine + 2fentanyl and 57% (34/60) in the ropivacaine + 4fentanyl were able to walk five metres or walk from the bed to the chair. The corresponding figures for the morning of the second postoperative day were 85% (29/34), 86% (32/37), 91% (39/43) and 90% (47/52) in the four groups respectively. On the morning of the third postoperative day the corresponding values were 97% (30/31), 91% (31/34), 91% (32/35) and 94% (45/48) in the four groups, respectively."
[Item 8, Vol. 49, p. 145]

Discomfort during Mobilization/Ambulation

The patients in the ropivacaine group reported higher discomfort scores during mobilization compared to the other three groups (primary and additional analysis).

Primary analysis
"The discomfort during mobilisation on the morning of the first postoperative day was rated as no, minor or mild by 73% (35/48) of the non-missing patients in the ropivacaine group, 80% (41/51) in the ropivacaine + 1fentanyl group, 80% (40/50) in the ropivacaine + 2fentanyl and 82% (49/60) in the ropivacaine + 4fentanyl. Moderate or quite severe discomfort was experienced by 15% (7/48), 20% (10/51), 16% (8/50) and 18% (11/60) of the non-missing patients, and severe or very severe discomfort by 12% (6/48), 0% (0/51), 4% (2/50) and 0% (0/60) patients in the ropivacaine group, ropivacaine + 1fentanyl group, ropivacaine+2fentanyl group, ropivacaine + 4fentanyl, respectively"
[Item 8, Vol.49, p.152]

Additional analysis
"The discomfort during mobilisation in the morning of the first postoperative day was rated as no, minor or mild by 35/48 in the ropivacaine group, 80% (41/51) in the ropivacaine + 1fentanyl group, 80% (40/50) in the ropivacaine + 2fentanyl and 82% (49/60) in the ropivacaine + 4fentanyl. Moderate or quite severe discomfort was experienced by 12% (6/48), 0% (0/51), 4% (2/50) and 0% (0/60) in the ropivacaine group, ropivacaine + 1fentanyl group, ropivacaine + 2fentanyl, ropivacaine + 4fentanyl, respectively."
[Item 8, Vol.49, p.152]

7.2.3.5 Reviewer's Efficacy Discussion

The clinical trial has demonstrated efficacy of ropivacaine when administered epidurally to patients following colonic resection.

Evidence is present for improved efficacy when the product is administered in combination with fentanyl for postoperative pain. Specifically, the primary efficacy variable – mean infusion rate over the 72-hour period was statistically in favor of ropivacaine with fentanyl, i.e., ropivacaine +2fentanyl ($p=0.049$) and ropivacaine + 4 fentanyl ($p=0.006$). AUCM - pain at rest, pain at rest $\geq$ 30 mm, and pain scores on coughing were also supportive of this overall conclusion.

The secondary measurements, urinary catheter, time to first flatus and nasogastric tube are indirect measures of the occurrence of common local anesthetic side effects, urinary retention, paralytic ileus and delay of gastric emptying, respectively. The results of this analysis were variable, i.e., in favor of ropivacaine in some instances, (urinary catheter, time to first flatus), and in favor of neither drug in other instances – nasogastric tube.

Additionally, the spread of analgesia and degree of motor block was similar in all groups.

The non-protocol defined measurements showed the same overall trends.

The clinical trial has demonstrated efficacy of ropivacaine when administered epidurally to patients following colonic resection. Evidence is present for improved efficacy when the product is administered in combination with fentanyl for postoperative pain.

7.2.4 STUDY # SP-ROA-0010 (O13)

7.2.4.1 Protocol Synopsis:

"A Comparison of Continuous Epidural Ropivacaine Following Epidural Ropivacaine for Surgery; Epidural Ropivacaine Plus PCA Morphine Following Epidural Ropivacaine for Surgery; and PCA Morphine Alone Following General Anesthesia, for the Management of Pain After Total Knee Replacement"

Objective: "...to compare the efficacy and tolerability of the following three treatments:

1. Epidural ropivacaine for surgery followed by continuous epidural ropivacaine for postoperative pain management;
2. Epidural ropivacaine for surgery followed by continuous epidural ropivacaine and PCA morphine for postoperative pain management;
3. General anesthesia for surgery followed by PCA morphine for postoperative pain management

The primary measure of efficacy was pain at rest."

[Item 8, Vol. 59, p. 11]

Study Design:

The study was open and randomized with three parallel treatment groups. Ninety-six patients valid for efficacy and safety were enrolled over 6 centers in Australia and New Zealand. Patients scheduled for total knee replacement performed under either general anesthesia or ropivacaine anesthesia were to be randomized in balanced blocks to one of the three treatment groups as shown above.

Eligible patients were age 18- 80 years, ASA risk category I- III, scheduled to receive elective total knee replacement, suitable for physiotherapy immediately after surgery, weighed 50-125 kg, and provided written informed consent.

Patients were excluded from study participation if there were any contraindications to epidural had a known history of allergy, sensitivity or any other form of reaction to local anesthetics of the amide type and/or to morphine, significant medical history and/or concomitant disease, were suspected of significant alcohol, drug or medication use/abuse, were pregnant or lactating or who were not practicing adequate contraception.

Premedication

Premedication consisted of midazolam and fentanyl and was administered at the discretion of the investigator. An intravenous infusion of a crystalloid solution (≥500-ml) was to be in progress before induction of anesthesia. Thrombosis prophylaxis and antiemetics was to be administered to patients in all treatment groups.

Groups Ropivacaine and Ropivacaine + PCA Morphine

A maximum of 5-mg midazolam, 250-ug fentanyl and 200 mg propofol was allowed, at the discretion of the investigator. No prophylaxis for nausea was allowed.

INDUCTION

General Anesthesia

Medications for induction, maintenance and reversal of general anesthesia were administered as required, as follows:

Induction and muscle relaxation: thiopental/propofol; atracurium / vecuronium bromide/succinylcholine / pancuronium bromide; fentanyl

Maintenance: isoflurane; nitrous oxide / oxygen or air/oxygen; atracurium/vecuronium bromide/suxamethonium/ pancuronium bromide; fentanyl.

Reversal of muscle relaxation: neostigmine/atropine / glycopyrrolate.

The maximum total dose of fentanyl during the entire surgical procedure was to be 10 mg/kg..

Epidural Anesthesia (Ropivacaine and Ropivacaine + PCA Morphine)

Epidural anesthesia was to be performed in accordance with the standard of care as follows: A 16-18-gauge needle was introduced at the L2-13 or L3-L4 interspace (midline or paramedian approach with the patient in the sitting or lateral decubitus position). The epidural space was identified by loss of resistance. An epidural catheter was to be inserted 4-5 cm cephalad and, provided that neither cerebrospinal fluid nor blood was obtained on aspiration, a 3-ml test dose of 15-mg/ml lidocaine with 5-ug/ml epinephrine was injected. Five minutes later, in absence of signs of intravascular or intrathecal administration, a 10-15-ml main dose of ropivacaine 10 mg/ml (150 mg) was to be injected in incremental doses over a 5-minute period.

Additional 10–ml or ropivacaine 10 mg/ml (100 mg) could be administered at the discretion of the investigator before or during surgery. If adequate sensory block was not achieved 45 minutes after the start of injection of the main dose, the patient was to be discontinued from further efficacy assessments.

POSTOPERATIVE

Groups ropivacaine and ropivacaine + PCA morphine:
A continuous epidural infusion was started when wound pain at rest was present (defined as VAS = 10 mm) or at the latest 2 hours after surgery. The infusion was to be started at a rate of 6 ml/h. Whenever VAS at rest exceeded 30 mm, a 6 ml top-up dose (12 mg) was to be administered, followed by an increase of the infusion rate of 2 ml/h. A minimum of 15 minutes between top-ups and correction of infusion rate had to elapse.

The infusion rate could also be decreased and/or discontinued periodically in case of excessive block, the maximum allowed rate being 14 ml/h (28 mg/h). If patients experienced pain during physiotherapy, a 6-ml top-up followed by a correction of the infusion rate could be administered at the discretion of the investigator.

Groups Ropivacaine + PCA morphine and PCA morphine:
PCA morphine was to be started when wound pain at rest was present (VAS > 10 mm). The PCA morphine was to be started 2 hours after surgery even if VAS score at rest was below 10 mm. The PCA device was set to deliver 1 mg bolus doses of morphine, with a lockout time of five minutes.

TREATMENT DURATION

Ropivacaine and Ropivacaine + PCA morphine Groups
Ropivacaine for epidural block for surgery in groups ropivacaine and ropivacaine + PCA morphine was administered as single main dose with a possibility of an additional dose before or during surgery. In these groups the continuous epidural infusion was to be discontinued 24 hours after the end of surgery. Analgesics were thereafter to be administered at the discretion of the investigator.

PCA Morphine Group
General anesthesia was administered as required. In this group and in group ropivacaine + PCA morphine, PCA morphine was to be continued for 24 hours after end of surgery, but could be continued, as judged by the investigator.

ASSESSMENTS

Assessment of Wound Pain
A visual analogue scale (VAS) device was used to measure pain scores. Generally a VAS score below 30 mm is considered as mild pain, between 30 and 60 mm as moderate pain and a VAS score of 60 mm or more is considered as severe pain.

Wound pain at rest
Patients used the VAS to rate their pain when resting in the bed.

Wound pain during physiotherapy
Using the VAS the patient rated the pain experienced immediately before and immediately after the use of physiotherapy (CPM). The CPM device was used on the day of surgery and the day after surgery.

As soon as possible after surgery, the patient's leg was placed into the CPM leg brace and then mounted into position on the machine. The machine was not switched on. The first mobilization period occurred for 1 hour between hour 7 and hour 8 from time 0 (end of surgery). The degree of flexion was set at 30 degrees and at the rate of approximately 45 cycles/hour. A pain score (VAS) was taken immediately before the machine was turned on and then immediately after the machine was turned off.

The second mobilization period occurred for 1 hour between hour 22 and hour 23 from time 0. Again the degree of flexion was set at 30 degrees with a rate of approximately 45 cycles/hour. A pain score was taken immediately before the machine was turned on and then immediately after the machine had been turned off.

It was to be understood that VAS at rest could not be performed during the period of physiotherapy. If the patient suffered from pain during physiotherapy (CPM), a 6-ml top-up dose followed by a correction of infusion rate could be given at the discretion of the investigator.

Quality of pain relief
The patient's overall satisfaction in regard to pain relief during the postoperative pain treatment was to be evaluated by the patient after the question "How was your pain relief?" related to defined intervals. The quality of the pain relief was to be assessed on the following scale:

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

Fitness for Discharge from PACU
Assessments of the following vital signs were performed every 15 minutes after end of surgery:

Respiration
2 = Able to breath and cough freely
1 = Dyspnea or limited breathing
0= Apnea

Circulation
2 =BP ± 20% of preanesthetic level
1 = BP ± 21-49% of preanesthetic level
0 = BP ± 50% of preanesthetic level

Color
2 = Pink
1 = Pale, dusky, blotchy, other
0 = Cyanotic

Consciousness
2 = Fully awake
1 = Arousal on calling
0 = Not responding

Nausea
2 = None
1 = Present, but responding to treatment
0 = Severe, i.e. not responding to treatment

Pain
2 = None
1 = Present (in spite of adequate ongoing pain treatment)
0 = Severe (in spite of morphine on request)

The patient was deemed ready for discharge from PACU when a total score of 9 - 12 was achieved.

Consciousness
The patient's degree of consciousness was to be assessed on the following scale:

1 =awake and fully alert
2 = awake but drowsy
3 = sleeping but easily aroused
4 = sleeping but difficult to arouse
5 = asleep and unresponsive to verbal or tactile stimulation

Sensory Block: Groups Ropivacaine and Ropivacaine + PCA morphine

Both upper and lower spread was assessed. Assessments were performed every 5 minutes until the start of preparation of the surgical site and then every 30 minutes (if possible), until the end of surgery. The maximum upper and maximum lower spread during surgery were recorded. Assessments were then performed and recorded every second hour until 22:00 hours on the day of surgery, at 02:00 on the night after surgery, and every two hours from 06:00 on the day after surgery until the return of normal sensation.

Motor Block Groups: Ropivacaine and Ropivacaine + PCA morphine

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

0 = No motor block.
1 = Inability to raise extended legs (just able to move knees and feet).
2 = Inability to flex knees (able to move feet only).
3 = inability to flex ankle joints (unable to move hips, knees and feet).

Quality of muscle relaxation: Groups Ropivacaine and Ropivacaine + PCA morphine

The overall quality of muscle relaxation was judged by the surgeon at the end of the surgery as excellent (no muscle Strain), satisfactory (disturbing, muscle strain, no need for general anesthesia) or unsatisfactory (unacceptable muscle strain, need for general anesthesia).

Other assessments

The time of and reason for, when a urinary catheter was inserted was to be recorded. If no urinary catheter was used, the time of the first micturation was to be recorded. The time to the first bowel movement was to be recorded."

Table 53. Schedule of Events

Figure 1. Study treatments and schedule of investigational events

Study code 94Ro81	Before surgery	Surgery	Hours after surgery						7-14 days after surgery (or at discharge)	3-4 weeks after surgery
			0	1	2	3	→	24		
Group Ropi		Ropi 10 mg/ml	Ropi 2 mg/ml 6 ml/h (top-ups/infusion rate change allowed) 1							
Group Ropi+PCA		Ropi 10 mg/ml	Ropi 2 mg/ml 6 ml/h(top-ups/infusion rate change allowed) + PCA morphine 1							
Group PCA		General anesthesia	PCA morphine 1							
Physical examination	x									
12-lead ECG	x							x		
Hematology/Clinical chemistry	x							x	x	
BP, PR, SpO_2	x	2	3							
Body temperature	x			4						
Sensory & motor block	x	5	6							
Pain at rest			7							
Criteria for PACU discharge			Every 15 min							
Mobilization pain			8					9		
Quality of pain relief				4						
Consciousness				4						
AE questionnaire									x	
AEs observed/reported		Continuously							x	x (phone)

1. Start when pain at rest = VAS ≥ 10 mm, or at the latest 2 h after surgery 2. At 5, 10, 15, 20, 30, 45 and 60 min + every 30 min 3;4. Every 2^{nd} h to 22:00, 02:00 A.M. + every 2^{nd} h from 06:00 until 24 h 5. Sensory block: every 5-30 min. 6. Sensory & motor block: every 2^{nd} h to 22:00 + 02.00 A.M.+ every 2^{nd} h from 06:00 until return of normal sensation/motor function 7. Every 15 min until VAS ≥ 10 mm + hourly to 22:00 + 02:00 A.M. + every 2^{nd} h from 06:00 until 24 h 8. 7-8 h after surgery 9. 22-23 h after surgery

Other assessments: blood loss, quality of muscle relaxation, time to the first bowel movement, time of discharge from PACU and hospital

[Sponsor's Figure 1, Item 8, Vol. 59, p.13]

7.2.4.2 Statistical Analysis

Data sets to be analyzed

An APT approach was to be used for efficacy variables, where "treated" means that the postoperative treatment had commenced for a patient. The postoperative treatment was to be considered to have commenced in groups ropivacaine and ropivacaine + PCA morphine if the infusion has been started, and in group PCA if the PCA morphine has been connected.

Thus, a patient was not to be included in the APT analysis in the following circumstances:

The patient did not receive any postoperative treatment, i.e. for groups ropivacaine and ropivacaine + PCA morphine the postoperative infusion of ropivacaine was not started and for group PCA the PCA morphine device was not connected.

- The occurrence of technical failure before the start of postoperative treatment.

All patients were to be included in the safety analysis except the patients who did not receive any treatment, i.e. no treatment for surgery and accordingly no treatment postoperatively. They were to be described separately.

APT analysis was conducted in the following two ways:

a. APT analysis using all observations up to and including the last valid efficacy time point.
b. APT analysis using all observations up to and including the 24-hour after surgery time point.

Statistical methods

For certain repeated assessments, a summary measure of the repeated measurements during the 24-hour postoperative treatment period was to be calculated for a patient as follows:

"First the area under the curve based on the repeated measurements up to 24 hours was to be calculated using the trapezoidal rule (extended to the 24-hour point by extrapolation if necessary). The summary measure considered was then to be defined as this area under the curve divided by the length of the time period on which it was based, so that it had the same scale as the underlying repeated measurements. This summary measure is denoted AUCM24"
[Item 8, vol. 59, p.31-32]

The main efficacy variable was to equal the AUCM24 in mm-scale based on the VAS measurements for pain at rest.

"In addition, similarly defined variables, AUCM4 and AUCM8, based on VAS measurements for pain at rest up to 4 hours and up to 8 hours were to be considered.

An indicator of whether or not the VAS measurements for pain at rest up to 24 hours for a patient have reached a value equal to or larger than 30 mm was to be used as an additional summary measure for these VAS measurements."

[Item 8, vol. 59, p.33]

"The statistical analysis for each of these variables was to include descriptive statistics and graphs for each treatment group, and pairwise comparisons of groups using a stratified Wilcoxon (mid) rank sum test adjusting for centers, with corresponding point estimates and 95% confidence intervals for differences if the variable is continuous. The p-values reported were to correspond to two-sided tests. A formal correction for multiplicity (leading to a type I family wise error rate of 5%) was to be made only for the main efficacy variable, to take into account the fact that three pairwise comparisons of groups were to be made."

[Item 8, Vol. 59, p.33]

7.2.4.3 Protocol Amendment:

Amendment 1 dated 7/26/95, Amendment 2 dated 10/27/95 and Amendment 3 dated 6/5/96 made the following changes:

A. Number of Patients
- Fifteen instead of eighteen patients will be enrolled at each center. The reason given for the change, "15 patients at each center was considered to be enough"[Item 8, vol., 59, p.116-117]

B. Study Procedures
- To clarify the start of continuous epidural infusion and due to allow for the possibility to give a top-up followed by a correction of infusion rate for pain relief during mobilization, the continuous epidural infusion in Group 1 and Group 2 will be started 2 hours after last suture even if VAS at rest is below 10 mm.
- If the patient in Group 1 and Group 2 suffers from pain during physiotherapy (CPM), a 6-ml top-up dose followed by a correction of infusion rate may be given at the discretion of the investigator.
- To allow for anesthetic flexibility, the main dose of ropivacaine has been decrease from 15 ml of 10-mg/ml ropivacaine to 10-15 ml.
- The dosage of droperidol has been corrected to read: Droperidol 0.625-mg i.v.

C. Assessments
- Change in when wound pain during physiotherapy assessments should be performed, i.e., immediately before and after, instead of during, to refine statistical time points and correct rate used in CPM device. This correction will allow for the possibility of giving a top-up followed by correction of infusion rate
- Clarification of assessment times – no change in times however.

F. Statistical Analysis
- Clarification of technical details.
-

G. Administrative
- Addition of appendices,
- Change in the routine of data coding and entry.

H. Inclusion Criteria
- Increase in the acceptable maximum weight from 11o to 125 kg in order to improve enrollment.

7.2.4.4 Conduct of Study

Awaiting a response from the sponsor. When the data is available it will be reviewed as an amendment to this efficacy supplement.

Demographics

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

Table 54. Baseline characteristics (number of patients)

		TREATMENT			
		ROPI (N= 27)	ROPI+PCA (N= 34)	PCA (N= 35)	TOTAL (N= 96)
AGE (yrs)	N	27	34	35	96
	MEAN	62.9	65.5	64.8	64.5
	MEDIAN	63.0	65.0	67.0	65.0
	STD	13.5	8.1	10.3	10.6
	MIN	20	49	28	20
	MAX	86	80	81	86
SEX, N(%)	MALE	8 (30%)	18 (53%)	13 (37%)	39 (41%)
	FEMALE	19 (70%)	16 (47%)	22 (63%)	57 (59%)
RACE, N(%)	CAUCASIAN	16 (59%)	19 (56%)	21 (60%)	56 (58%)
	BLACK	7 (26%)	6 (18%)	9 (26%)	22 (23%)
	OTHER	4 (15%)	9 (26%)	4 (11%)	17 (18%)
	ASIAN	0 (0%)	0 (0%)	1 (3%)	1 (1%)
WEIGHT (kg)	N	27	34	35	96
	MEAN	81.0	89.4	82.3	84.5
	MEDIAN	82.0	86.5	80.0	82.0
	STD	19.8	17.7	16.7	18.2
	MIN	43	61	51	43
	MAX	114	127	126	127
HEIGHT (cm)	N	27	33	35	95
	MEAN	164.0	168.4	165.5	166.1
	MEDIAN	163.0	168.0	165.0	165.0
	STD	10.8	9.9	10.5	10.4
	MIN	145	147	142	142
	MAX	185	185	193	193
ASA GROUP, N(%)	I	1 (4%)	4 (12%)	2 (6%)	7 (7%)
	II	23 (85%)	24 (71%)	24 (69%)	71 (74%)
	III	3 (11%)	6 (18%)	9 (26%)	18 (19%)
HISTORY OF ALLERGY, N (%)	YES	12 (44%)	11 (32%)	8 (23%)	31 (32%)
	NO	15 (56%)	23 (68%)	27 (77%)	65 (68%)

Source data: Appendix 4, PDL 2

[Item 8, vol. 59, p. 40

The majority of patients were Caucasian, ASA class II, mean age of 64.5, height of 166.1 cm, weight of 84.5 kg and had no allergies. On physical examination, the majority of patients had abnormalities in the following systems, in decreasing order: locomotor (90%), mouth/teeth (23%), cardiovascular (19%), eyes (17%).

Ninety –three percent of patients had at least one condition. Fifty-two percent of which had essential hypertension and forty-six percent had osteoarthritis. Concomitant medications were equally distributed between treatment groups.

7.2.4.5 Sponsor's Efficacy Results:

Primary Efficacy Measurement:

The primary efficacy variable was defined for each patient as the AUCM24 in mm-scale based on the VAS measurements for pain at rest.

POSTOPERATIVE PAIN

Wound pain at rest VAS AUCM

The PCA group showed a statistically significant higher AUCM value than both the ropivacaine and the ropivacaine + PCA morphine group. No statistically significant difference was found between ropivacaine and ropivacaine + PCA morphine however.

Table 55. Wound pain at rest (VAS AUCM for 24 hours): statistical analysis results of pairwise comparison of treatment groups:

Treatment groups	Statistically significant?	Implication
Ropi vs Ropi+PCA	No (p-value = 1.000)*	Both treatments provided similar pain relief
Ropi vs PCA	Yes (p-value = 0.003)*	The Ropi group patients had less pain than the PCA group patients
Ropi +PCA vs PCA	Yes (p-value = 0.001)*	The Ropi+PCA group patients had less pain than the PCA group patients

* P-values were adjusted using Bonferroni multiple comparison method.

[Item 8, vol. 59, p. 60]

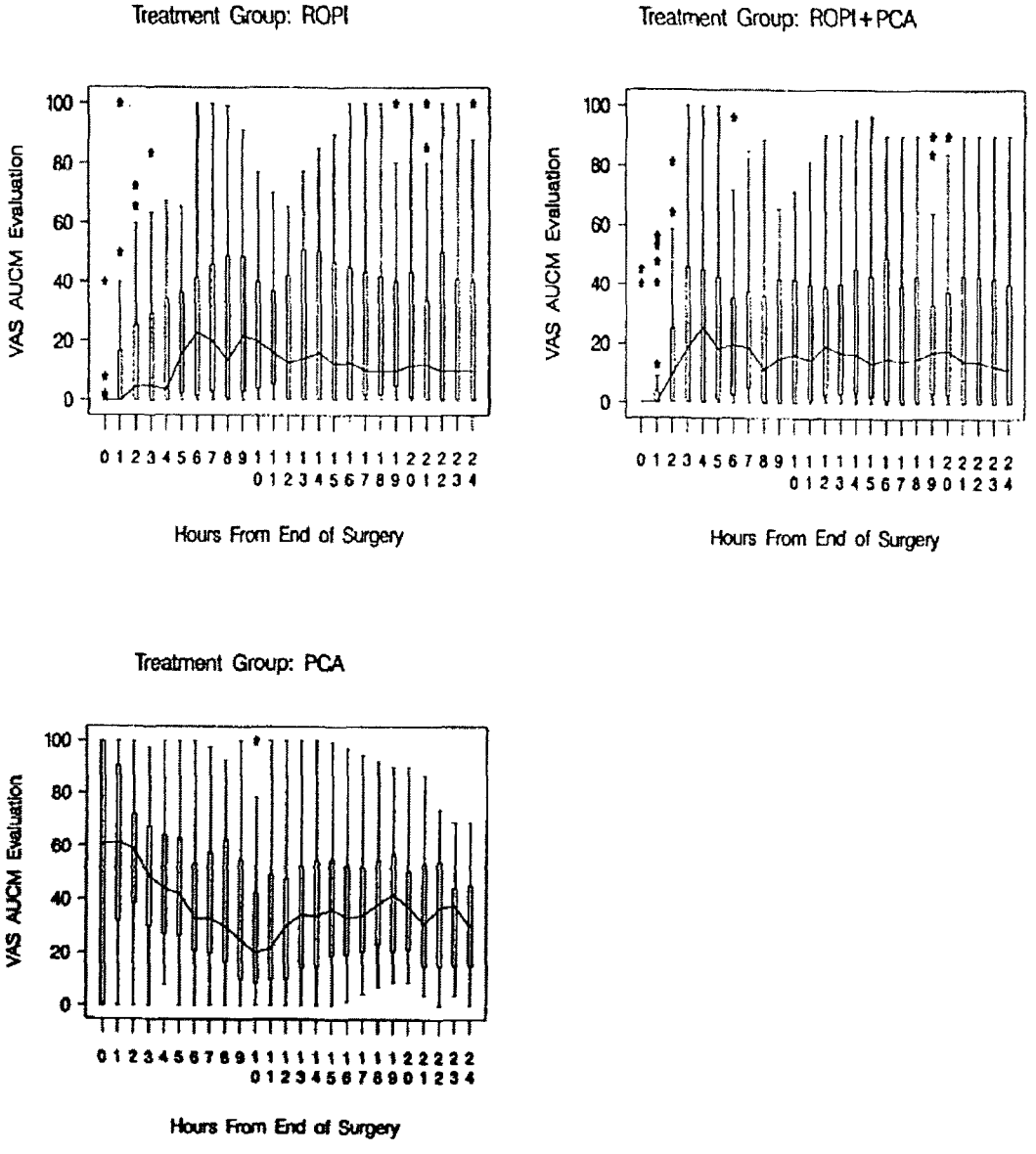
"At both 0-4h and 0-8h, the analyses also showed statistically significant higher AUCM value in the PCA group than in the ropivacaine and ropivacaine + PCA morphine groups. No statistically significant difference was found between the two latter groups. The PCA group had more pain at rest than the ropivacaine and the ropivacaine + PCA morphine groups."[**Note:** no p-values were provided]

[Item 8, Vol. 59, p. 60]

Wound pain at rest - VAS scores

The scores were similar in the ropivacaine and ropivacaine + PCA morphine groups and markedly lower than those in the PCA group. The PCA morphine group had more pain in the initial postoperative period and required over 10 hours to reach a near steady state. Whereas the ropivacaine and ropivacaine + PCA morphine groups had good initial pain relief which waned with time.

Figure 17. Pain VAS Scores at Rest during the 24-h Postoperative Period



[Item 8, Vol. 59, p. 62]

Wound pain at rest - VAS equal to or above 30 mm

"The proportion scoring ≥ 30 mm was generally lowest in the ropivacaine group and highest in the PCA group, the differences being most pronounced at the 0-4 hour interval."

[Item 8, vol. 59, p. 62]

Table 56. Proportion of patients with pain assessments for wound pain at rest equal to or larger than 30 mm (VAS) at time intervals 0-4, 0-8 and 0-24 hours by treatment group

Time Interval	VAS Score ≥= 30mm	TREATMENT ROPI (N= 27)	ROPI+PCA (N= 34)	PCA (N= 35)
0-4 Hours	Yes	12 (44%)	18 (53%)	28 (80%)
	No	15 (56%)	16 (47%)	7 (20%)
0-8 Hours	Yes	20 (74%)	24 (71%)	30 (86%)
	No	7 (26%)	10 (29%)	5 (14%)
0-24 Hours	Yes	23 (85%)	28 (82%)	33 (94%)
	No	4 (15%)	6 (18%)	2 (6%)

Source Data: Appendix 5, PDL 13

[Item 8, Vol. 59, p. 63]

Wound pain after physiotherapy

"The pain scores were generally low both before and after physiotherapy and there were no consistent differences between the three groups."
[Item 8, Vol. 59, p. 64]

7.2.4.6 Reviewer's Efficacy Discussion

The clinical trial has demonstrated efficacy of ropivacaine when administered epidurally to patients following total knee replacement. Evidence is present for improved efficacy of the product over that of PCA morphine for controlling postoperative pain.

Statistically significant results were found in favor of the ropivacaine groups, (ropivacaine alone and ropivacaine + PCA morphine) for the primary efficacy variable, (AUCM24 in mm-scale based on the VAS measurements for pain at rest), as well as the secondary efficacy variables (wound pain at rest - VAS scores and wound pain at rest - VAS equal to or above 30 mm).

The blinding of the trial deserves special mention.

This reviewer questions the validity of the study results based upon the lack of blinding. The potential for patient, and investigator bias can only be guarded against by the appropriate use of blinding. One argument against this point of view is the following comment made by the statistical reviewer for this submission, "given the radical differences in technique between treatments, I believe the open-label design was appropriate". However, the differences in technique only confirms, for both the investigator and the patient, which drug is being administered thereby coloring responses made to subjective endpoint assessments such as pain scores.

7.2.5 STUDY # SP-ROA-0010 (O14)

7.2.5.1 Protocol Synopsis:

Title: "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"

Objective: "...to compare the efficacy and tolerability of the following three treatments for 24 hours following major abdominal surgery:

1. Continuous epidural infusion of ropivacaine 2 mg/ml
2. Epidural ropivacaine 2 mg/ml and PCA morphine;
3. PCA morphine

The primary measure of efficacy was pain experienced (VAS score) upon coughing.

[Item 8, Vol. 68, p. 15]

Study Design:

The study was open and randomized with three parallel groups conducted in six centers in France. Patients scheduled for major abdominal surgery performed under general anesthesia were randomized to one of the following groups to received treatment for 24 hours postoperatively as follows:

Group 1: Continuous infusion of ropivacaine 2 mg/ml
Group 2: Continuous infusion of ropivacaine 2 mg/ml + PCA morphine
Group 3: PCA morphine

Eligible patients were age 18- 75 years, ASA risk category I- III, scheduled to receive laparotomies, e.g., cystectomy, radical hysterectomy, colon resection or rectum amputation, weighed 50-110 kg, and provided written informed consent.

Patients were excluded from study participation if there were any contraindications to epidural had a known history of allergy, sensitivity or any other form of reaction to local anesthetics of the amide type and/or to morphine, significant medical history and/or concomitant disease, were suspected of significant alcohol, drug or medication use/abuse, were pregnant or lactating or who were not practicing adequate contraception.

PREMEDICATION
Benzodiazepines were to be administered as at the discretion of the investigator. Thrombosis prophylaxis was to be given according to the hospital routine and an i.v. electrolyte solution was to be in progress prior to the induction of general anesthesia.

INDUCTION

General Anesthesia – All Groups

Induction and muscle relaxation: thiopental, fentanyl, atracurium/ vecuronium bromide/ suxamethonium/pancuronium

Maintenance: isoflurane, nitrous oxide/oxygen (40-60%) (*protocol amendment no. 1, 1995-02-03*) atracurium/vecuronium bromide/suxamethonium/ pancuronium, fentanyl

Reversal of muscle relaxation: neostigmine/atropine/glycopyrrolate

POSTOPERATIVE - 24 Hour Infusion

Epidural - Group 1 and Group 2

Local infiltration of the skin with a local anesthetic other than ropivacaine could be performed. A 16-18-gauge needle was to be introduced at the chosen interspace. The chosen interspace was to be located at the center of the corresponding specific dermatome appropriate for surgery *(protocol amendment no. 2, 1995-05-15)*. The midline or paramedian approach was to be used, with the patient in the sitting or lateral decubitus position. The epidural space was to be identified by loss of resistance. An epidural catheter was to be inserted 4-5 cm cephalad and, provided that neither cerebrospinal fluid nor blood was obtained on aspiration, a 3-ml test dose of lidocaine 2% with 12.5 mg/ml (epinephrine) was to be injected. Five minutes later, if there were no signs of intravascular or intrathecal administration, general anesthesia was to be induced followed by the surgical procedure.

Surgery was preferably to be started before 12.00 hours. Within 30 minutes of surgery (last suture) a 20-ml bolus of ropivacaine 2 mg/ml was to be administered through the epidural catheter, immediately after which a continuous infusion of ropivacaine 2 mg/ml at a rate of 10 ml/hour was to be started. The infusion was to continue for 24 hours after surgery.
The rate of infusion was not to exceed 10 ml/h at any time during the 24 hours of study treatment.

In case of excessive block, the infusion rate could be reduced to 6 ml/hour (or the infusion suspended) until regression of the block to a desired level (*protocol amendment no. 1, 1995-02-03*). The recommencement of the epidural infusion is at the discretion of the investigator. In case of technical failure, the patient was to be withdrawn from efficacy assessments and replaced.

PCA Morphine - Group 2 and Group 3

A PCA device was to be connected 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 lockout time of 5 minutes. Background infusions of morphine were not allowed.

Rescue medication in all three groups consisted of morphine i.v. 1 - 2 mg bolus doses, which were to be administered at the request of the patient and at the discretion of the investigator in case of wound pain.

Assessments were to begin 2 hours after the end of surgery (the last suture) and were to be performed as follows:

Every hour until 22.00 hours on the day of surgery:
- wound pain at rest
- wound pain upon coughing

Every 2 hours from 22.00 hours (between 22.00 and 08.00 hours only if the patient was awake) until 24 hours after surgery:
- wound pain at rest
- wound pain upon coughing

Every 2 hours (except between 22.00 and 08.00 hours) until 24 hours after surgery:
- consciousness
- sensory and motor block (Groups 1 and 2)

Assessments of sensory and motor block in Group 1 and Group 2 were to be continued hourly after the end of infusion until the return of normal sensation and motor function.

The patients' overall satisfaction in regard to pain relief during the postoperative pain treatment was to be assessed:
- 22.00 hours on the day of surgery
- 08.00 hours on the morning after surgery
- 24 hours after the end of surgery.

Table 57. Schedule of Events

Study Design 94R082	Actions before surgery	Induction of anesthesia 0-5 (min)	Surgery	Hours after surgery 0	1	2	3	→	24	7-14 days after surgery	3-4 weeks after surgery
Physical examination											
Medical history											
Laboratory Assessments/ECG											
Premedication											
Preanesthetic Infusion											
Test dose 3 ml lidocaine 2%		1.									
General Anesthesia											
Bolus dose 20 ml ropi. 2 mg/ml				1.							
ContInfusion 10 ml/h				1.							
Morphine i.v. by PCA				2.							
Morph. i.v. upon request				3.							
Pain assessments						4.					
Motor/Sensory block						6.					
Quality of pain relief				At 22.00 and 08.00							
Blood pressure/Pulse rate						7.					
Peripheral oxygen						7.					
Body temperature						7.					
Consciousness						6.					
Adverse Events open/active Q						5.					
Adverse Events											follow-up by phone

1. Group 1 and Group 2.
2. Group 2 and Group 3.
3. At the discretion of the Investigator
4. Wound pain at rest on coughing: Every hour until 22.00 hours on the day of surgery and then every 2nd hour until 24 hours after surgery (during 22.00 and 08.00 only if the patient was awake).
5. Every 2nd hour from 22:00 hours on the day of surgery until 24 hours after surgery (during 22.00 and 08.00 hours only if the patient is awake).
6. Every 2nd hour until 24 hours after surgery (except 22.00 and 08.00 hours).
7. Every 2 hours until 24 hours after surgery.

[Sponsor's Figure 1, Item 8, Vol. 68, p.19]

7.2.5.2 Statistical Analysis

Data sets to be analyzed
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 to be considered to have commenced in Groups 1 and 2 if the infusion had been started, and in Group 3 if the PCA morphine was connected.

Thus, a patient was not to be included in the "all patients treated" analysis in the following circumstances:

1. The patient did not receive any postoperative treatment, i.e. for Groups 1 and 2 the postoperative infusion of ropivacaine was not started and for Group 3 the PCA morphine device was not connected.
2. The occurrence of technical failure before the start of postoperative treatment.

All patients were to be included in the safety analysis apart from the patients who did not receive any treatment, i.e. no test dose before surgery and accordingly no treatment postoperatively or no PCA device connected. They were to be described separately.

Clinical variables
"For certain repeated assessments, a summary measure of the repeated measurements during the 24-hour postoperative treatment period was calculated for a patient as follows.

> First, the area under the curve based on the repeated measurements up to 24 hours was calculated using the trapezoidal rule (extended to the 24-hour point by extrapolation if necessary). The summary measure considered was then defined as this area under the curve divided by the length of the time period on which it was based, so that it had the same scale as the underlying repeated measurements. This summary measure was denoted AUCM24."

[Item 8, Vol. 68, p.34]

The main efficacy variable was to equal the AUCM24 on a millimeter scale based on the VAS measurements for pain upon coughing.

"The variable AUCM24 based on VAS measurements at rest was also to be considered. In addition, similarly defined variables, AUCM4 and AUCM8, based on VAS measurements for pain upon coughing and at rest up to 4 hours and up to 8 hours, were considered. An indicator of whether or not the VAS measurements for pain upon coughing up to 24 hours for a patient had reached a value equal to or larger than 30 mm was used as an additional summary measure for these VAS measurements. A similar indicator based on the VAS measurements for pain at rest was considered.

The statistical analysis for each of these variables includes descriptive statistics and graphs for each treatment group, and pairwise comparisons of groups using a stratified Wilcoxon (mid)rank sum test with adjustments for centers, with corresponding point estimates and 95% confidence intervals for differences if the variable was continuous. The p-values reported correspond to two-sided tests. A formal correction for multiplicity (leading to a type I familywise error rate of 5%) was made only for the main efficacy variable, to take into account the fact that three pairwise comparisons of groups were made."

[Item 8, Vol. 68, p.35]

7.2.5.3 Protocol Amendment:

Amendment 1 dated 2/3/95, Amendment 2 dated 5/15/95, Amendment 3 dated 6/30/95 and Amendment 4 dated 9/12/95 made the following changes:

A. Inclusion Criteria
- Radical abdominal hysterectomy has been included as an acceptable laparotomy.

B. Study Procedures
- Clarification of the rate to which the infusion made be reduced to 6 ml/min the case of excessive epidural block, as well as clarification that the change may be temporary.
- The temporal relationship between the bolus doses of morphine and the connection of the PCA device was defined.
- Lorazepam 1-2 mg has be specified as the benzodiazepine of choice for premedication.
- Enflurane has been eliminated as an option for maintenance of anesthesia.
- The concentration of N_2O/O_2 has been specified – 40 to 60 %
- It has been determined that the epidural space must lie at the center of the specific dermatome appropriate for surgery.
- If patients are asleep, provisions had been made to perform assessments at alternate times

C. Assessments
- If patients are asleep, provisions had been made to perform assessments at alternate times

7.2.5.4 Conduct of Study

Awaiting response from the sponsor. When all data is available it will be reviewed as an addendum to this efficacy supplement.

Demographics

All of the patients were Caucasian, except for one patient in the ropivacaine group (no. 658) and two patients in ropivacaine + PCA group (nos. 602 and 662) who were Black. Age (mean 56 years), height and weight were similar in all three groups. The majority of patients were ASA I or II. The types of surgical procedures were equally distributed among treatment groups, with the majority of patients requiring radical abdominal hysterectomy, sigmoidectomy, APR of the rectum or hemicolectomy.

On physical examination, the abnormality most commonly found was in the genitourinary system (n=10: ropivacaine 2/38, ropivacaine + PCA morphine 5/46, PCA morphine 3/46), followed by the cardiovascular system (n=9: ropivacaine 4/38, ropivacaine + PCA morphine 3/46, PCA morphine 2/46) and general condition (n=9: (ropivacaine 4/38, ropivacaine + PCA morphine 2/46, PCA morphine 3/46).

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

Table 58. Baseline characteristics (number of patients)

	Ropi (n=38)	Ropi+PCA (n=46)	PCA. (n=46)
Race			
CAUCASIAN	37	44	46
BLACK	1	2	
Sex			
MALE	15	19	30
FEMALE	23	27	16
Allergies			
NO	21	29	37
YES	17	17	9
ASA group			
GROUP 1	20	22	23
GROUP 2	18	21	22
GROUP 3		3	1

[Item 8, vol. 68, p. 42

Table 59. Baseline Characteristics (continued)

Variable	Group	N	MEAN	STD	MIN	MEDIAN	MAX
Age (years)	Ropi	38	56.9	12.4		60.0	
	Ropi+PCA	46	58.6	11.8		60.5	
	PCA	46	55.8	13.3		56.5	
Height (cm)	Ropi	38	165.7	9.3		163.0	
	Ropi+PCA	46	166.3	7.6		165.0	
	PCA	45	169.5	7.6		170.0	
Weight (kg)	Ropi	38	70.8	12.4		70.0	
	Ropi+PCA	46	68.5	13.8		65.0	
	PCA	46	71.0	12.1		70.5	

[Item 8, vol. 68, p. 42

7.2.5.5 Sponsor's Efficacy Results:

Primary Efficacy Measurement:

The primary efficacy variable was defined for each patient as the AUC pain on coughing over 24 hours.

POSTOPERATIVE PAIN

Pain upon coughing (VAS)
"The median pain scores over time upon coughing (VAS) were generally higher in the PCA group than in the other two groups receiving ropivacaine. The median values for the ropivacaine group and ropivacaine +PCA group were similar over time.

The median pain scores over time varied between 19.2 and 50.8 mm in the ropivacaine group, 9.5 and 35.0 mm in the ropivacaine +PCA group, and 42.0 and 54.0 mm in the PCA group." See Figure below.

[Item 8, vol. 68, p.69]

Figure 18. Pain scores upon coughing (VAS) during the 24-hour postoperative period

[Item 8, vol. 68, p. 70]

Secondary Efficacy Measurements:

AUCM for pain upon coughing (VAS)
"Pairwise comparisons between the three groups for AUCM for pain upon coughing were performed at the time intervals 0-4, 0-8 and 0-24 hours. A statistically significantly lower AUCM value in the ropivacaine group compared to the PCA group was found at the time intervals 0-4 h (p=0.000), 0-8 h (p=0.000) and 0-24 h (p=0.024; Bonferroni correction). The 95% confidence intervals for the difference between these two groups were (16.3, 37.6), (16.0, 33.8) and (3.0, 21.5), respectively. The estimated difference over 4 hours was 25.5 mm, over 8 hours 24.4 mm and over 24 hours 12.0 mm.

The ropivacaine +PCA group showed a statistically significantly lower AUCM value compared to the PCA group at the time intervals 0-4 h (p<0.000), 0-8 h (p=0.000) and 0-24 h (p=0.003; Bonferroni correction). The 95% confidence intervals at the respective time period were (20.4, 43.8), (17.4, 38.5) and (8.8, 30.7). The estimated difference between the two groups over 4 hours was 35.6 mm, over 8 hours 28.0 mm and over 24 hours 17.5 mm. There were no statistically significantly differences between the ropivacaine group and ropivacaine +PCA group at any time interval." See Table below. [Item 8, vol. 68, p. 71]