Table 60. AUCM for pain upon coughing (VAS) at the time intervals 0-4, 0- 8 and 0-24 hours.

Period	group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3
0-4	Ropi	38	25.51	22.79		5.63	21.89	40.63
	Ropi+PCA	46	22.63	25.57		0.00	12.25	41.50
	PCA	46	51.63	21.46		40.00	50.19	70.00
0-8	Ropi	38	26.13	18.75		10.56	23.42	40.56
	Ropi+PCA	46	24.60	22.30		3.78	19.90	41.88
	PCA	46	50.67	20.59		37.25	48.53	66.00
0-24	Ropi	38	36.21	16.91		24.04	35.57	48.33
	Ropi+PCA	46	30.62	19.09		16.69	26.83	43.90
	PCA	46	48.82	20.63		31.19	49.78	64.29

[Item 8, Vol. 68, p. 71]

Pain upon coughing above 30 mm (VAS)

"There were statistically significant fewer patients with pain scores ≥ 30 mm (VAS) upon coughing in the ropivacaine group compared to the PCA group at the interval 0-4 h (p=0.003). In the ropivacaine +PCA group there were a statistically significantly lower number of patients that had pain scores ≥ 30 mm at the intervals 0-4 h (p=0.000) and 0-8 h (p=0.001) compared to the PCA group. No statistical differences were seen between the two groups receiving ropivacaine at any time during the therapy period, nor were there any statistically significant differences between the three groups at the interval 0-24 hours.

In some patients no pain scores (VAS) for pain upon coughing or for pain at rest were recorded up to 4 hours after surgery, as they were sleeping but easily aroused or difficult to arouse (degree of consciousness 3-4). The patients were nos. 211, 307, 606, and 662 in the ropivacaine +PCA morphine group and nos. 205, 220, 403, 406, 412, 502, 611, 614, 643, and 664 in the PCA group. In addition, in patient nos. 205 and 643 in the PCA group no pain scores were recorded for the first 8 hours after surgery." See Table below.

[Item 8, vol. 68, p. 75]

Table 61. Pain scores upon coughing ≥ 30 mm (VAS) at time intervals 0-4, 0- 8 and 0-24 hours.

Time interval	VAS ≥30 mm	Ropi (n=38)	Ropi+PCA (n=46)	PCA (n=46)
0-4 h	Yes	58%	46%	70%
	No	42%	46%	9%
	Not assessed	0%	9%	22%
0-8 h	Yes	79%	65%	89%
	No	21%	35%	7%
	Not assessed	0%	0%	4%
0-24 h	Yes	92%	89%	96%
	No	8%	11%	4%

[Item 8, vol. 68, p. 75]

Pain at rest (VAS)

"The PCA group had a markedly higher median pain score over time in the early part of the treatment, compared to the other two groups. The median pain scores for the ropivacaine group and ropivacaine + PCA group were similar The median pain scores over the 24-hour postoperative period varied between 6.9 and 20.5 mm in the ropivacaine group, between 0 and14.0 mm in the ropivacaine +PCA group, and 13.5 and 44.0 mm in the PCA group." See figure below.

[Item 8, vol. 68, p. 76]

Figure 19. Pain scores at rest (VAS, 0-100 mm) during the 24-hour postoperative period

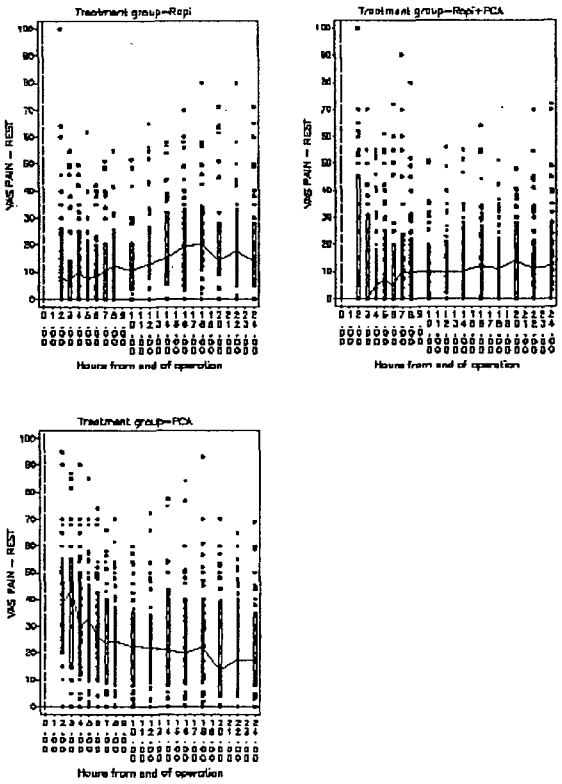


Figure 6. Pain scores at rest (VAS, 0-100 mm) during the 24-hour postoperative period in patients receiving ropivacaine (n=38), ropivacaine plus PCA morphine (n=45-46) or PCA morphine (n=46). Individual values and box plots (Q1, median, Q3); median scores joined.

[Item 8, vol. 68, p. 77]

AUCM for pain at rest (VAS)

"For AUCM for pain at rest (VAS), pairwise comparisons between the three groups 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=0.016). The 95% confidence intervals for the difference between these two groups were (14.8, 33.9), (11.6, 27.8) and (1.4, 15.1), respectively. The estimated difference over 4 hours was 25.6 mm, over 8 hours 20.8 mm and over 24 hours 8.2 mm.

Comparison of the ropivacaine +PCA group and the PCA group showed a statistically significantly lower AUCM value in the ropivacaine +PCA group at the time intervals 0-4 h (p=0.000), 0-8 h (p=0.000) and 0-24 h (p=0.002). The 95% confidence intervals at the respective time periods were (10.0, 35.0), (8.7, 27.6) and (4.5, 16.8). The estimated difference between the two groups over 4 hours was 26.4 mm, over 8 hours 18.1 mm and over 24 hours 11.0 mm.

There were no statistically significant differences between the ropivacaine group and ropivacaine +PCA group at any time interval."

[Item 8, vol. 68, p. 78]

Table 62. AUCM for pain at rest (VAS) at time intervals 0-4, 0-8 and 0-24 hours.

Period	group	N	MEAN	STD	MIN	Q1	MEDIAN	Q3	MAX
0-4	Ropi	38	14.60	18.17		0.00	8.69	23.88	
	Ropi+PCA	46	16.94	22.00		0.00	4.13	37.38	
	PCA	46	37.45	22.60		21.50	38.75	53.13	
0-8	Ropi	38	13.63	12.34		2.48	11.03	19.50	
	Ropi+PCA	46	16.23	18.33		1.74	9.84	25.75	
	PCA	46	32.90	19.60		17.88	36.27	45.00	
0-24	Ropi	38	17.99	10.68		10.79	16.36	25.42	
	Ropi+PCA	46	16.16	14.14		7.02	12.74	20.15	
	PCA	46	26.89	16.62		14.46	25.98	36.35	

[Item 8, vol. 68, p. 78]

Pain at rest above 30 mm (VAS)

"A statistically significantly lower number of patients with pain scores ≥30 mm in the ropivacaine group compared to the PCA group was found at the time intervals 0-4 hours (p=0.000) and 0-8 hours (p=0.006). Comparison between the ropivacaine +PCA group and PCA group showed statistically significantly fewer patients with pain scores ≥30 mm in the ropivacaine + PCA morphine group at the intervals 0-4 hours (p=0.000) and 0-8 hours (p=0.003). No statistical differences at any time interval were found between the ropivacaine group and ropivacaine +PCA group, nor were there any differences between the three groups over 24 hours." See Table below.

Table 63. Pain scores at rest ≥30 mm (VAS) at time intervals 0-4, 0-8 and 0- 24 hours.

Time interval	VAS ≥30 mm	Ropi (n=38)	Ropi+PCA (n=46)	PCA (n=46)
0-4 h	Yes	37%	35%	61%
	No	63%	57%	17%
	Not assessed	0%	9%	22%
0-8 h	Yes	47%	48%	74%
	No	53%	52%	22%
	Not assessed	0%	0%	4%
0-24 h	Yes	76%	70%	83%
	No	24%	30%	17%

[Item 8, vol. 68, p. 79]

Spread of Analgesia

"The spread of the sensory block over time was similar in the two groups receiving ropivacaine. The median upper segmental spread of sensory block for the ropivacaine group after the operation was T7 after 4 hours, T8/T7 after 8 hours and T10/T9 after 24 hours. The corresponding figures in the ropivacaine +PCA group were T6, T8 and T9. The lower median segmental spread of sensory block for the ropivacaine group was L5 after 4 and 8 hours and L5/L4 after 24 hours. For the ropivacaine +PCA group, the spread was L5 at the same time points. (See figure below)

[Item 8, vol. 68, p. 80]

Figure 20. Upper and lower spread of sensory block during the 24-hour postoperative period

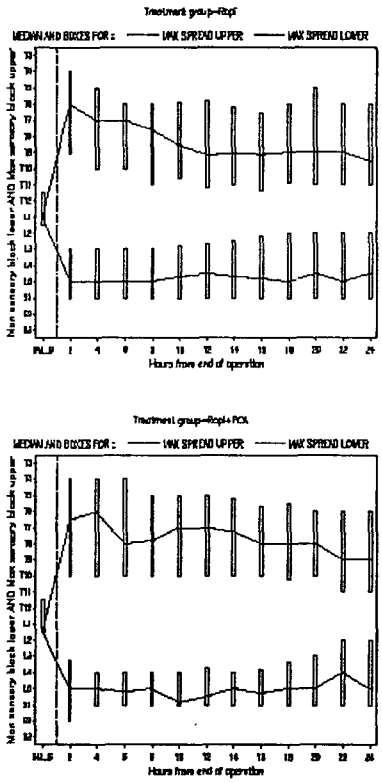


Figure 7. Upper and lower spread of sensory block during the 24-hour postoperative period in patients receiving ropivacaine (n=38) or ropivacaine plus PCA morphine (n=45-46) (Q1, median, Q3). INJ_S corresponds to the site of injection.

[Item 8, Vol. 68, p. 81]

Motor Block

"The motor block was attenuated over time during the postoperative infusion in the two groups receiving ropivacaine. 61% of the patients in the ropivacaine group and 51% in the ropivacaine +PCA group had no demonstrable motor block 4 hours after surgery according to the modified Bromage scale. At 8 hours the corresponding values were 68% and 60%. 24 hours after the end of surgery the percentage without motor block increased to 89% in the ropivacaine group compared to 71% in the ropivacaine +PCA group. Thus, there was totally less motor block in the patients who received only ropivacaine over 24 hours." (See figure below)

[Item 8, vol. 68, p. 82]

Figure 21. Cumulative frequency (%) of patients with different degrees of motor block

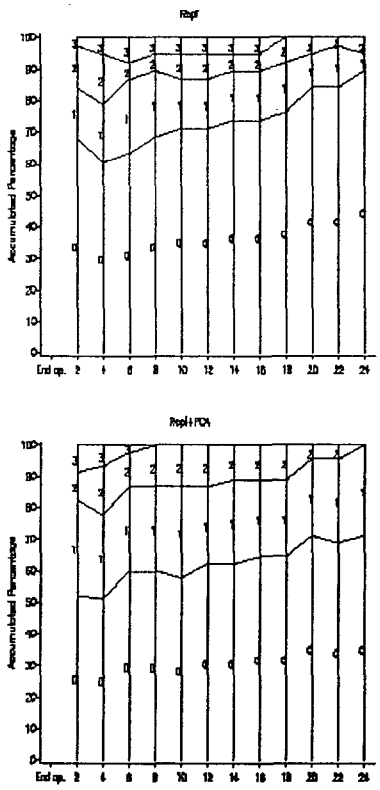


Figure 8. Cumulative frequency (%) of patients with different degrees of motor block (Bromage score 0-3; 0=no motor block) during the 24-hour postoperative period in patients receiving ropivacaine (n=38) or ropivacaine plus PCA morphine (n=45-46).

[Item 8, vol. 68, p. 83]

MORPHINE

Total morphine consumption
"There was a markedly higher morphine consumption in patients who were given PCA morphine only than in those administered ropivacaine plus PCA morphine. The median amount of morphine administered was 3.5 mg in the ropivacaine group and 19.0 mg in the ropivacaine +PCA groups whereas the PCA group took 51.2 mg during the study period." (See figure below)

[Item 8, vol. 68, p. 84]

Figure 22. Total morphine consumption (mg) during the study period per treatment group

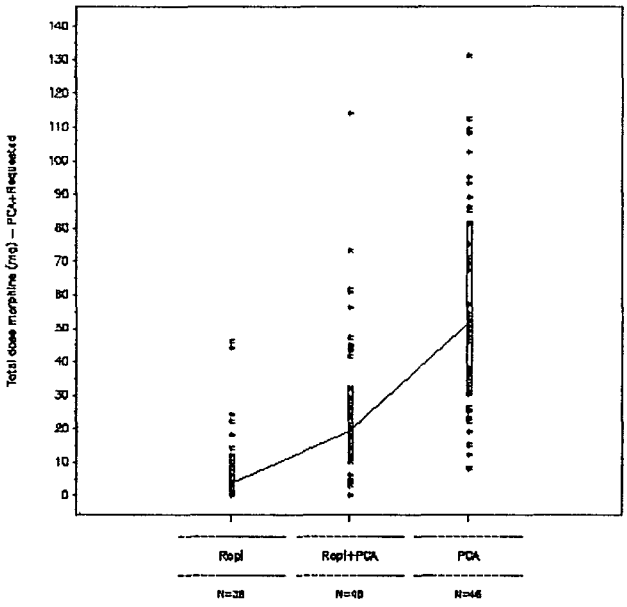


Figure 9. Total morphine consumption (mg) during the study period per treatment group (N=number of patients). Individual values and box plots (Q1, median, Q3); median values joined.

[Item 8, Vol. 68, p.85]

PCA morphine

"The median number of PCA attempts in the two groups receiving PCA morphine (groups 2 and 3), was 21 in the ropivacaine +PCA group, while the group that did not receive epidural ropivacaine had 78 attempts. The median total dose of morphine administered per patient was 18.5 mg in the ropivacaine +PCA group compared to 41 mg in the group that only received PCA morphine over the 24-hour period.

There were slightly more patients in the PCA group compared to the patients in the ropivacaine +PCA group who self-administered morphine at different time intervals. The amounts of morphine administered during different time intervals were greater in patients receiving only PCA morphine than those who received combined ropivacaine and PCA morphine. The number of PCA attempts at different time intervals was slightly higher in the PCA group than in the ropivacaine +PCA group

For patient nos. 306, 408 (ropivacaine + PCA morphine group) and 102, 503 (PCA group) registration of PCA morphine, one or zero mg were not made, instead the total amount of morphine was recorded at certain time points due to occasional problems with the PCA device. Hence, the attempts for PCA morphine could not be properly calculated for these patients, therefore they are excluded from tables/graphs over number of PCA attempts." (See Table below).

[Item 8, vol. 68, p. 86]

Table 64. Number of patients who self-administered PCA morphine at different time intervals.

Time interval (hours after end of surgery)	Ropi+PCA (n=46)	PCA (n=46)
0-4	15	38
4-8	29	43
8-12	34	45
12-16	33	43
16-20	32	43
20-24	39	44

[Item 8, vol. 68, p. 86]

Consciousness
"The degree of consciousness (sedation) over time was similar in all three groups. In patients given only ropivacaine, 18% at 4 hours, 26% at 8 hours and 92% at 24 hours after the end of the operation were awake and fully alert. The corresponding figures for the ropivacaine plus PCA morphine patients were 18%, 22% and 87%. In patients receiving PCA morphine alone, the values were 4%, 17% and 83%, respectively." (see figure below)

[Item 8, vol. 68, p. 91]

Figure 23. Cumulative frequency (%) of patients degree of consciousness in the 24-hour postoperative period

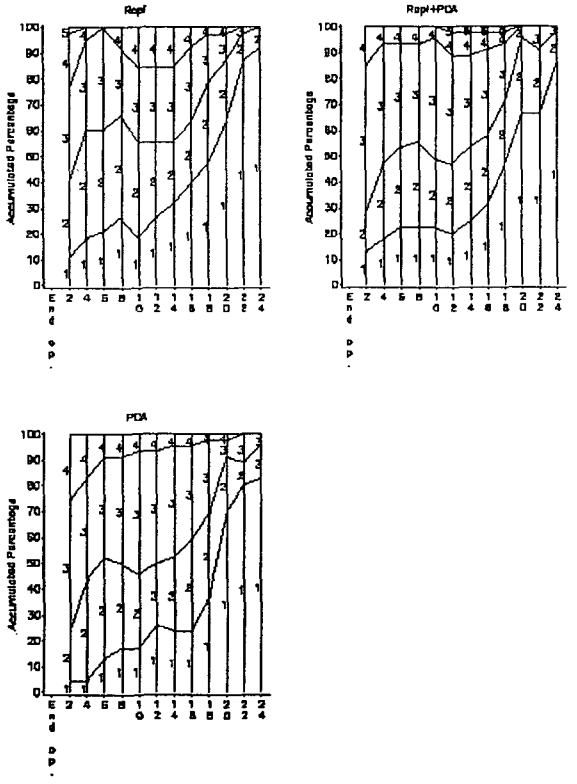


Figure 13. Cumulative frequency (%) of patients degree of consciousness in the 24-hour postoperative period in the ropivacaine group (n=38), ropivacaine plus PCA morphine group (n=45-46) or PCA morphine group (n=46) (1=awake, 2=drowsy, 3=easily aroused, 4=difficult to arouse, 5=asleep).

[Item 8, vol. 68, p. 92]

Quality of pain relief

"The quality of pain relief assessed at 22.00 hours on the day of surgery was rated as good or excellent in 84% of the ropivacaine patients and 87% of the ropivacaine plus PCA morphine patients, compared to 64% in patients given PCA morphine alone. At 8.00 hours on the day after surgery the corresponding values were 66%, 85% and 80%. At the end of the treatment period a similar quality of pain relief was seen. 79% in the ropivacaine group, 85% in the ropivacaine +PCA group, and 83% in the PCA group rated the quality of pain relief as good or excellent."

[Item 8, vol. 68, p. 93]

7.2.5.6 Reviewer's Efficacy Discussion

The clinical trial has demonstrated efficacy of ropivacaine when administered epidurally to patients following abdominal surgery. Evidence is present for improved efficacy of the product (without or with PCA morphine) over that of PCA morphine alone for controlling postoperative pain. No statistical differences were seen between the two groups receiving ropivacaine however.

The median pain scores over time upon coughing (VAS) (primary efficacy variable) were generally higher in the PCA group than in the other two groups receiving ropivacaine. This trend was repeated in the secondary outcome measures, AUCM for pain upon coughing (VAS), pain upon coughing above 30 mm (VAS), total morphine consumption, number of PCA attempts, quality of pain relief.

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.

7.2.6 STUDY # SP-ROA-0010 (O15)

7.2.6.1 Protocol Synopsis:

Title: "Two Approaches to Anesthesia and Postoperative Pain Management after Total Hip Replacement. A Comparison of Ropivacaine Epidural Anesthesia Followed by Epidural Ropivacaine and General Anesthesia Followed by PCA Morphine"

Objective: "...to evaluate the efficacy and tolerability of the following two approaches to anesthesia and postoperative pain management following total hip replacement:

1. Ropivacaine epidural anesthesia followed by epidural ropivacaine and
2. General anesthesia followed by PCA morphine;

The primary measure of efficacy was pain at rest.

[Item 8, Vol. 73, p. 22]

Study Design:
This was an open, randomized study with two parallel groups conducted in five centers in Germany. Eligible patients scheduled for unilateral total hip replacement, judged able to participate in physiotherapy on the day after surgery were randomized to receive anesthesia for surgery and postoperative treatment as follows:

Group 1: **Surgery:** Ropivacaine 10 mg/ml
Postoperative: Continuous infusion of ropivacaine 2mg/ml for 0-24 hours + top-ups 0-48 hours

Group 2: **Surgery:** General anesthesia
Postoperative: PCA morphine - 48 hours

Eligible patients were above age 18, ASA risk category I- III, scheduled to unilateral total hip replacement and judged able to participate in physiotherapy on the day after surgery, 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, metamizole, or diclofenac, 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 could be administered as premedication. Thrombosis prophylaxis was to be administered according to hospital routine. At least 500 ml of a crystalloid solution was to be administered intravenously prior to induction of anesthesia. No antiemetics were allowed

INDUCTION

Epidural Anesthesia (ropivacaine 10 mg/ml) - Group 1

Local infiltration of the skin using a local anesthetic other than ropivacaine could be performed. A 16-18-gauge needle was to be inserted at L1-L5, preferentially at L3-L4. The midline or paramedian approach was to be used with the patient in the sitting or lateral decubitus position. An epidural catheter was to be inserted cephalad and provided that neither cerebrospinal fluid nor blood was obtained on aspiration, a 3-ml test dose of 20-mg/ml lidocaine was to be injected. Five minutes later, if there were no signs of intravascular or intrathecal administration, a 12-15 ml main dose of ropivacaine 10 mg/ml (120-150 mg) was to be injected over a 5-minute period.

Surgery could commence when sensory block to T10 and adequate surgical anesthesia (measured by a pinch with forceps within the intended area of incision) had been achieved, as judged by the investigator. Midazolam could be used for sedation during surgery, at the discretion of the investigator. If adequate sensory block was not achieved 30 minutes after end of injection of the main dose, an additional 5-10 ml (50-100 mg) was to be injected. If adequate sensory block had not been achieved 45 minutes after the end of injection of the main dose, the patient could receive another anesthetic regimen at the discretion of the investigator.

During surgery, additional 5-ml doses (50 mg) of ropivacaine could be injected at signs/symptoms of inadequate block, as judged by the investigator, dependent on the dose required to establish the block. During the entire surgical procedure, a maximum dose of 250 mg was allowed. Patients who were classified as technical failures (defined as an incorrectly placed injection of the study drug, as judged by the investigator) or patients experiencing unilateral block judged inadequate for surgery, were to receive another anesthetic regimen at the discretion of the investigator.

General Anesthesia – Group 2

Induction and muscle relaxation:	thiopental/etomidate, fentanyl atracurium/vecuronium/succinylcholine/pancuronium
Maintenance:	isoflurane or enflurane, fentanyl nitrous oxide/oxygen or air/oxygen atracurium/vecuronium/ succinylcholine /pancuronium
Reversal of muscle relaxation:	neostigmine/atropine/glycopyrrolate

The dose of fentanyl should not exceed: 3-µg/kg-body weight for induction, 2-µg/kg-body weight/hour for maintenance.

POSTOPERATIVE TREATMENT

Group 1
The epidural infusion of ropivacaine 2 mg/ml was to commence as soon as possible after the end of surgery but not before the patient had a Bromage score for motor block < 2. The infusion was to commence at a rate of 4-6 ml/h (8-12 mg/h) and was to be kept constant at the chosen rate during 24 hours. Whenever the patient requested additional pain relief in this period, a 6-ml (12-mg) top-up dose was to be administered at the discretion of the investigator, but with a minimum of 30 minutes between each top-up.

In instances of excessive block, the infusion could be discontinued until regression of the block to a desired level had been achieved, as judged by the investigator. The infusion was to be recommenced with an infusion rate of 4-6 ml/h.

The continuous infusion was to be discontinued 24 hours after arrival at PACU. For the following 24 hours (between 24 and 48 hours after arrival at PACU), top-ups of 10 ml (20 mg) were to be administered at the discretion of the investigator, but with a minimum of 30 minutes between each top-up. The epidural catheter was to be withdrawn 48 hours after arrival at PACU.

In case of insufficient effect of the epidural, another local anesthetic at the discretion of the investigator was to be injected epidurally prior to withdrawal of the catheter in order to rule out catheter displacement.

Group 2
A PCA device was to be connected when the patient was fully awake, as judged by the investigator. The device was to be set to deliver 1.0-mg i.v. bolus doses of morphine, with a 5 minute lockout time. The dose could be increased to 1.5 mg with the same lockout time, at the discretion of the investigator. The device was to be disconnected 48 hours after arrival at PACU.

Patients in group 2 were to be connected to a PCA device for i.v. administration of morphine. Before connection of the device, up to 10 mg morphine i.v. could be administered. Additional postoperative analgesics in both groups comprised metamizole i.v., to be administered at the discretion of the investigator. In case of insufficient effect, morphine i.v./i.m. could be administered at the discretion of the investigator.

The epidural catheter/the PCA device was to be disconnected 48 hours after arrival at PACU. Thereafter oral diclofenac was to be given as required until the patients were deemed ready for discharge from hospital. In case of insufficient effect, metamizole i.v. or morphine i.v./i.m. could be administered during this period, at the discretion of the investigator.

CLINICAL ASSESSMENTS

ASSESSMENTS BEFORE SURGERY (every 5 minutes)
Group 1: Time to sensory block at T10 after start of administration of the test dose and time to achieve adequate block for anesthesia in the intended area of incision were to be recorded.

ASSESSMENTS AFTER SURGERY:
The reference point (time 0) for the postoperative clinical assessments was the arrival at PACU. Assessments every 15 minutes until the patient was deemed ready for discharge from PACU:

- Vital signs
- Pain at rest

Assessments 2, 4, 6, 8 and 10 hours after the arrival at PACU and thereafter every morning between 8 and 10 a.m. and evening between 4 and 6 p.m. until the patient was deemed ready for discharge from hospital:

- Pain at rest
- Quality of pain relief

Assessments every morning between 8 and 10 a.m. and evening between 4 and 6 p.m. from the day after surgery until the patient was deemed ready for discharge from hospital:

- Pain on mobilization

Assessments the day before surgery and every evening from the day after surgery between 4 and 6 p.m. until the patient is deemed ready for discharge from hospital:

- Discomfort

The planned assessments each day in the morning between 8 and 10 a.m. and evening between 4 and 6 p.m. were to be performed in the following sequence:

1. Discomfort
2. Pain at rest
3. Quality of pain relief
4. Criteria for discharge from hospital
5. Adverse events
6. Pain on mobilization

ASSESSMENT OF POSTOPERATIVE PAIN
A 100-mm visual analogue scale (VAS) ruler was to be used to collect pain scores at rest when lying on the bed. During the time the patients stayed at PACU, a 10-point verbal scale was to be used in addition.

ATTEMPTS TO MOBILIZE PATIENTS

Day of surgery:

No mobilization or physiotherapy was to be performed.

Day after surgery 8-10 a.m. and 4-6 p.m.:

The patient was to be seated on the edge of the bed, then placed before the bed with a nurse's assistance. Standing exercises with a nurse's assistance were to be performed. This scheme was to be followed each day until the patient could walk short distances by means of human support. Thereafter, walking in heel-to-toe fashion every morning and evening with a load of 10 kg.
The attempts were to be documented in the CRF as successful or otherwise. Immediately after each these attempts, the patient had to rate the pain using the VAS ruler.

QUALITY OF PAIN RELIEF

The patient's overall satisfaction with regard to pain relief was to be evaluated by the patient, in response to the question, "How was your pain relief?", according to the following scale:

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

DISCOMFORT

A **modified Gastrointestinal Symptom Rating Scale** (GSRS) with additional items was to be used to evaluate discomfort. The patients were asked to complete the self-administered questionnaire.

Modified Gastrointestinal Symptom Rating Scale (GSRS – 5 dimensions

[**Note**: The numbered items refer to secondary efficacy variables – see below

Diarrhea Syndrome: items 11, 12, 14
Indigestion Syndrome: items 6, 7, 8, 9
Obstipation Syndrome: items 10,13,15
Abdominal Pain Syndrome: items 1, 4, 5
Reflux Syndrome: items 2, 3,

For each subject, each of these 15 items was to be assigned a numeric value 1, 2... or 7, with 1 for the first response option and 7 for the last one. The score on each of the 5 dimensions was then to be set equal to the mean of the scores from the items on which the dimension is based. These 5 dimensions' scores were to be considered as 5 response variables. The scores from the 15 underlying items and from the 6 additional were to be considered as separate response variables. There were thus 26 response variables associated with the discomfort assessments.

SENSORY AND MOTOR BLOCK

Sensory block was to be determined bilaterally by alcohol spray for loss and return of sensation. In instances of asymmetric block, the highest and lowest dermatome levels were to be registered.
Motor block was to be 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 instances of asymmetric block, the highest (numerical) value was to be recorded.

7.2.6.2 Statistical Analysis

Statistical Determination of Sample Size

A sample size of 40 patients (valid for the per-protocol analysis) in each group was obtained according to the study protocol using the variability information from a previous study where the standard deviation within groups of the variable AUCM21 based on VAS for pain at rest was about 16 mm (up to 22 mm within individual centers).

"Using the value 20 as an approximate upper bound for the standard deviation of the main efficacy variable AUCM24 considered in the present study, and assuming a difference of 13 mm or more between the two groups, the probability is at least 80% of getting a statistically significant result with 40 patients in each group.

In these power considerations, a simple unstratified two-sample t-test was used under normality assumptions. It was assumed that this provided a reasonable approximation for the sample size required for the stratified Wilcoxon test that was to be used.

In terms of a confidence interval for the mean difference between two groups, the sample size of 40 patients in each group and the standard deviation 20 led to the following: the length of a 95% confidence interval for the mean difference between two groups was at most 19 mm with power 80%. Here power was to be interpreted as a conditional probability given coverage with the confidence interval, as described in (18)."
[Item 8, vol. 73, p. 43]

STATISTICAL METHODS AND PLANS FOR ANALYSIS

Datasets to be analyzed

"The datasets to be analyzed were planned to be based on different patient populations according to evaluability in the study protocol. Two datasets were planned to be considered for the analysis of efficacy variables: the per-protocol (PP) dataset and the intention-to-treat (ITT) dataset.

The ITT dataset was to be based on all randomized patients except those who withdrew their consent before insertion of the epidural needle (group 1)/induction of general anesthesia (group 2). The PP dataset is a subset of the ITT dataset obtained by excluding patients in instances of:

- Violation of inclusion or exclusion criteria
- Technical failures
- Major protocol violations that influenced the validity of data or results in an extensive loss of primary efficacy data
- Patients' discontinuation from efficacy assessment that was not related to the treatment given and which resulted in an extensive loss of primary efficacy data.

The main analysis was planned to be based on the ITT dataset. In addition, an analysis was to be performed on the PP dataset."

[Item 8, vol. 73, p.44]

Clinical variables

"Time zero for the clinical assessments in the postoperative period was the arrival at PACU. For certain repeated assessments, a summary measure of the repeated measurements during the 24-hour postoperative 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. The summary measure considered was then defined as that 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. Similarly defined summary measures AUCM10 and AUCM48 based on the repeated measurements up to 10 hours and up to 48 hours were to be calculated."

[Item 8, vol. 73, p.44]

Primary efficacy variable

1. AUCM24 in mm-scale based on the VAS measurements for pain at rest.

Secondary efficacy variables

2. AUCM10 and AUCM48 based on the VAS measurements for pain at rest
3. Indicator of VAS-measurement for pain at rest, equal to or larger than 30 mm during 48 hours and until patients were deemed ready for discharge
4. VAS-measurements over time for pain at rest during 48 hours and until patients were deemed ready for discharge
5. Pain on mobilization until patients were deemed ready for discharge
6. Quality of pain relief until patients were deemed ready for discharge
7. Discomfort until patients were deemed ready for discharge
8. Time when patients were deemed ready for discharge from PACU
9. Time when patients were deemed ready for discharge from hospital, including time until return of bowel function
10. Consumption of metamizole during 48 hours (actually the complete second postoperative day was included as sometimes only the daily dose was documented in the CRF) and until patients were deemed ready for discharge
11. Consumption of morphine (administered in addition to PCA morphine) during 48 hours (until second postoperative day, see above) and until patients were deemed ready for discharge.

Other assessments

12. Incidence, intensity and type of adverse event
13. Nausea, vomiting and pruritus events
14. Peripheral oxygen saturation
15. Amount of ropivacaine consumed
16. Amount of PCA morphine consumed
17. Amount of diclofenac, metamizole i.v. and morphine i.v./i.m. administered from 48 hours after arrival at PACU (actually the consumption from the third postoperative day onwards was calculated as sometime only the daily dose was documented in the CRF) until patients were deemed ready for discharge from hospital
18. Upper and lower spread of sensory block, degree of motor block
19. Blood loss

[Item 8, vol. 73, p. 45-46]

20. Hospital resource utilization variables, i.e. the "time in" and the "time out" of the following
    - Theater preparation room
    - Operating theater
    - PACU
    - Intensive care unit
    - Hospital ward

21. Number of episodes with peripheral oxygen saturation less than 91%, 92-94% and above 95% (actually the limits were less than 91%, 91-95% and above 95% and the percentage of time within each of the three ranges was provided for each patient)
22. Dose of antiemetics administered.

Statistical Methods

"According to the study protocol, the statistical analysis of the efficacy variables 1 and 2 had to include descriptive statistics and graphs for each treatment group, and comparisons of the two groups using a stratified Wilcoxon (mid)rank sum test adjusting for centers, with corresponding point estimates and 95% confidence intervals for the differences between the groups. The p-values reported had to correspond to two-sided tests.

Descriptive statistics and graphs were to be used for variables/assessments 3 to 20 including, if relevant, boxplots and graphs showing the development over time for patients individually and for each group. Wilcoxon based comparisons could be made for some of these variables/assessments and further exploratory statistical analyses could be performed.

[Item 8, vol. 73, p. 46-47]

7.2.6.3 Protocol Amendment:

Amendment 1 dated 10/25/95, Amendment 2 dated 11/22/95, made the following changes:

A. Inclusion Criteria
   - Removed description of the hip replacement to enable greater patient inclusion

B. Study Procedures
   - Propofol has been removed from the list of induction agents due to its antiemetic properties.
   - A statement has been added which describes the technique to instruct patients on the proper use of the VAS ruler and the PCA device.
   - A doctor or nurse (instead of only a nurse) will be assisting patients to stand and exercise postoperatively.

7.2.6.4 Conduct of Study

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

Demographics

Of the 90 enrolled patients, 44 patients were male and 46 patients were female. The proportion of male patients was slightly lower in the Ropivacaine group (43.2%) than in the PCA morphine group (54.3%). Mean age, weight and height were similar in both groups. All patients were Caucasian. The majority was ASA II. The most frequent concomitant disease was essential hypertension (ropivacaine: 20.5% and PCA morphine 30.4%), followed by varicose veins. Concomitant medications included diclofenac, iron preparations, and levothyroxine and they were equally distributed between treatment groups.

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

Table 65. Baseline characteristics (number of patients)

all enrolled patients	Ropivacaine (n = 44)	PCA morphine (n = 46)
age [years]	62 ± 13	61 ± 10
weight [kg]	76 ± 12	75 ± 11
height [cm]	168 ± 8	169 ± 9

* arithmetic mean ± standard deviation

[Item 8, vol. 73, p. 55]

7.2.6.5 Sponsor's Efficacy Results:

Primary Efficacy Measurement:

"The mean AUCM24 for the wound pain at rest as the primary efficacy variable was 14.3 + 11.7 mm (median 13.2 mm) in the ropivacaine group and 24.0 + 17.0 mm (median 21.2 mm) in the PCA morphine group in the primary ITT analysis. This difference was statistically significant (p = 0.0072, stratified Wilcoxon (mid) rank sum test, two-sided)."

[Item 8, vol. 73, p. 82]

Table 66. AUCM24 using Different Calculations

[Item 8, Vol. 73, p. 82]

Similar results to the Intent-to-Treat analysis were also obtained for the per-protocol analysis.

Table 67. AUCM using Per-Protocol Analysis Calculations

AUCM24* [mm] PP analysis	Ropivacaine (n = 38)	PCA morphine (n = 45)
missing values at arrival at PACU set to 0	14.3 ± 12.0 (13.1)	24.0 ± 17.0 (21.2)
all values at arrival at PACU set to 0	14.3 ± 12.0 (13.1)	23.8 ± 17.1 (20.9)
missing values at arr. at PACU repl. by 1st value	14.3 ± 12.0 (13.1)	24.2 ± 17.1 (21.2)

* arithmetic mean ± standard deviation (median); missing values at arrival at PACU set to 0

[Item 8,vol. 73, p. 83]

Secondary Efficacy Variables

AUCM10 and AUCM48

"The differences between the treatment groups towards a smaller AUCM for wound pain at rest in the Ropivacaine group were even more pronounced for the AUCM10 than for the AUCM24 (p = 0.0000, exploratory stratified Wilcoxon (mid) rank sum test, two-sided)."

[Item 8, vol. 73, p. 85]

Table 68. AUCM 10 – Intent-to-Treat Analysis

AUCM10* [mm] ITT analysis	Ropivacaine		PCA morphine	
center 1	n = 10	6.7 ± 12.0 (0.3)	n = 11	25.6 ± 15.6 (22.4)
center 2	n = 3	5.6 ± 9.8 (0.0)	n = 4	28.1 ± 11.0 (27.3)
center 3	n = 11	15.2 ± 8.8 (14.7)	n = 12	31.5 ± 22.7 (28.3)
center 4	n = 9	16.8 ± 19.1 (13.3)	n = 8	27.9 ± 15.4 (28.4)
center 5	n = 10	10.6 ± 10.7 (8.0)	n = 10	28.5 ± 16.7 (28.6)
total	n = 43	11.8 ± 12.9 (8.2)	n = 45	28.4 ± 17.1 (25.3)

* arithmetic mean ± standard deviation (median); missing values at arrival at PACU set to 0

Item 8, vol. 73, p. 85]

"The overall AUCM48 for wound pain at rest was still smaller in the Ropivacaine group than in the PCA morphine group and differences with regard to the arithmetic means were similar for the AUCM24 and the AUCM48, but they were less pronounced for the medians (p = 0.1003, exploratory stratified Wilcoxon (mid)rank sum test, two-sided). The arithmetic mean was still smaller in the Ropivacaine group in all centers, but the medians were slightly higher in the Ropivacaine group in centers 2 and 3."

Item 8, vol. 73, p. 86

Table 69. AUCM 48 – Intent-to-Treat Analysis

AUCM48* [mm] ITT analysis	Ropivacaine		PCA morphine	
center 1	n = 10	13.9 ± 12.9 (9.5)	n = 11	19.4 ± 14.4 (15.4)
center 2	n = 3	11.7 ± 11.7 (11.8)	n = 4	11.9 ± 5.6 (11.3)
center 3	n = 11	16.2 ± 6.5 (16.0)	n = 12	26.0 ± 25.3 (15.5)
center 4	n = 9	16.2 ± 12.0 (11.6)	n = 8	18.0 ± 16.0 (13.2)
center 5	n = 10	11.8 ± 3.9 (12.2)	n = 10	23.1 ± 12.9 (25.2)
total	n = 43	14.3 ± 9.3 (11.8)	n = 45	21.1 ± 17.4 (15.4)

* arithmetic mean ± standard deviation (median); missing values at arrival at PACU set to 0

[Item 8, vol. 73, p. 86]

Table 70. AUCM10 and AUCM48 –Per-protocol Analysis

PP analysis	Ropivacaine (n = 38)	PCA morphine (n = 45)
AUCM10* [mm]	12.5 ± 13.2 (9.2)	28.4 ± 17.1 (25.3)
AUCM48* [mm]	14.5 ± 9.4 (11.7)	21.1 ± 17.4 (15.4)

* arithmetic mean ± standard deviation (median); missing values at arrival at PACU set to 0

[Item 8, vol. 73, p.86]

Proportion of Patients with Pain Assessments Equal to or Larger than 30 mm

At the scheduled time points for pain assessment the proportion of patients with pain assessments for wound pain at rest equal to or larger than 30 mm was higher in the PCA morphine group until the evening of the fourth day. Afterwards only few patients had pain at rest equal to or larger than 30 mm. The situation for the first 48 hours is displayed below."

[Item 8, vol. 73, p.87]

Table 71. Proportion of patients with pain assessment for wound pain at rest ≥ 30 mm VAS)

ITT analysis	Ropivacaine (n = 43)		PCA morphine (n = 45)	
time after arrival at PACU*	n	%	n	%
< 2 hours	0	0.0	33	73.3
2 hours	1	2.3	27	60.0
4 hours	8	18.6	25	55.6
6 hours	7	16.3	17	37.8

PP analysis	Ropivacaine (n = 38)	PCA morphine (n = 45)
AUCM10* [mm]	12.5 ± 13.2 (9.2)	28.4 ± 17.1 (25.3)
AUCM48* [mm]	14.5 ± 9.4 (11.7)	21.1 ± 17.4 (15.4)

* arithmetic mean ± standard deviation (median); missing values at arrival at PACU set to 0

[Item 8, vol. 73, p. 87]

VAS-measurements for pain at rest

"Mean values were lower in the ropivacaine group during the first three days but differences were rather small after six hours. From day 4 onwards mean values were similar in both groups. The mean of interpolated values during 48 hours (11.94 + 8.30 vs. 26.93 + 16.17 mm) as well as until patients were deemed ready for discharge (9.36 + 5.91 vs. 20.20 + 14.28 mm) was lower in the ropivacaine group" No formal statistical analysis was performed."

[Item 8, vol. 73, p. 87-88]

Pain on mobilization

"Initially, higher mean values for pain at mobilization were reported in the PCA morphine group and from the afternoon of the second day onwards mean pain was slightly higher in the ropivacaine group. Taking into account the standard deviation the differences between the treatment groups were rather small. After day 5 assessments were always available for less than 20 patients per group. No formal statistical analysis was performed."

[Item 8, vol. 73, p. 88]

Table 72. Proportion of patients with pain assessment for pain after mobilization ≥ 50 mm (VAS)

ITT analysis	Ropivacaine (n = 43)		PCA morphine (n = 45)	
time after arrival at PACU*	n	%	n	%
day 1 (8-10 a.m.)	10	23.3	11	24.4
day 1 (4-6 p.m.)	10	23.3	16	35.6
day 2 (8-10 a.m.)	6	14.0	9	20.0
day 2 (4-6 p.m.)	6	14.0	6	13.3

* interpolated values at scheduled time points

[Item 8, vol. 73, p. 89]

Quality of pain relief

"After two hours the median for pain relief was 1 (excellent pain relief) in the ropivacaine group and 3 (fair pain relief) in the PCA morphine group for interpolated values at scheduled time points. On the following assessments the rounded median was 2 (good pain relief) in both groups for all time points with more than one patient assessing pain relief. The results in the PP analysis were again comparable to those of the ITT analysis". No formal statistical analysis was performed.

[Item 8, vol. 73, p. 89]

Table 73. Proportion of patients with excellent or good pain relief

ITT analysis	Ropivacaine (n = 43)		PCA morphine (n = 45)	
time after arrival at PACU*	n	%	n	%
3 - 5 hours	28	65.1	26	57.8
5 - 7 hours	30	69.8	31	68.9
7 - 9 hours	28	65.1	30	66.7
day 1 a.m.	29	67.4	32	71.1
day 1 p.m.	31	72.1	36	80.0
day 2 a.m.	32	74.4	36	80.0
day 2 p.m.	35	81.4	40	88.9

* values as documented for selected intervals

[Item 8, vol. 73, p. 90]

Discomfort according to modified GSRS

"Only minor differences between the treatment groups were observed. Except for the fact that the proportion of patients with a urinary catheter was slightly higher in the ropivacaine group, especially on the second postoperative day 31/43 (72.1%) patients vs. 19/45 (42.2%) patients, no relevant differences were observed between the treatment groups. In the first postoperative days mean values were highest (worst) for the item pain when moving around. The results for the PP analysis were again similar to those of the Intent-to-Treat." No formal statistical analysis was performed.

[Item 8, vol. 73, p. 90]

Time when deemed ready for discharge from PACU

"At least half the patients of the ropivacaine group were deemed ready for discharge from PACU according to the criteria specified in the study protocol at the time they arrived at PACU (median = 0 minutes). Some patients were even deemed ready for discharge before they actually arrived at PACU. For these patients a value of zero was used for calculating the mean time until patients were deemed ready for discharge. ...mean and median time until patients were deemed ready for discharge from PACU was shorter in the Ropivacaine group in all centers although there were marked differences between the centers." No formal statistical analysis was performed.

[Item 8, vol. 73, p. 91]

Table 74. Time to Deemed Ready for Discharge

ready for disch. from PACU* after [minutes] ITT analysis	Ropivacaine		PCA morphine	
center 1	n = 10	2.5 ± 4.9 (0.0)	n = 11	20.0 ± 12.5 (30.0)
center 2	n = 3	16.7 ± 24.7 (5.0)	n = 4	68.8 ± 38.8 (62.5)
center 3	n = 11	1.4 ± 3.2 (0.0)	n = 12	13.3 ± 24.1 (2.5)
center 4	n = 9	0.0 ± 0.0 (0.0)	n = 8	51.6 ± 38.8 (51.5)
center 5	n = 10	15.0 ± 0.0 (15.0)	n = 10	72.0 ± 52.8 (82.5)
total	n = 43	5.6 ± 8.9 (0.0)	n = 45	39.7 ± 41.5 (30.0)

* arithmetic mean ± standard deviation (median)

[Item 8, vol. 73, p. 91]

Table 75. Time to Actual Discharge

discharge from PACU* after [hours] ITT analysis	Ropivacaine		PCA morphine	
center 1	n = 10	1.6 ± 0.4 (1.5)	n = 11	1.7 ± 0.8 (1.5)
center 2	n = 3	21.5 ± 3.3 (21.8)	n = 4	21.9 ± 2.5 (21.9)
center 3	n = 11	48.4 ± 0.3 (48.3)	n = 12	50.5 ± 9.9 (48.3)
center 4	n = 9	1.3 ± 0.7 (1.2)	n = 8	2.1 ± 0.7 (2.0)
center 5	n = 10	6.5 ± 1.6 (7.5)	n = 10	6.0 ± 1.8 (6.7)
total	n = 43	16.0 ± 19.9 (5.2)	n = 45	17.5 ± 21.5 (5.3)

* arithmetic mean ± standard deviation (median)

[Item 8, vol. 73, p. 92]

As shown above, the time when patients were deemed ready for discharge (measured in minutes) from PACU was considerably shorter than the time patients actually spent at PACU (measured in hours.

Time when deemed ready for discharge from hospital

"Mean and median time until patients were deemed ready for discharge from hospital according to the criteria specified in the study protocol was slightly longer in the ropivacaine group than in the PCA morphine group, but again there were considerable differences between the centers." No formal statistical analysis was performed.

[Item 8, vol. 73, p. 93]

Table 76. Time until Deemed Ready for Discharge

ready for disch. from hospital* after [days] ITT analysis	Ropivacaine		PCA morphine	
center 1	n = 10	9.8 ± 5.1 (8.5)	n = 11	5.4 ± 0.8 (5.1)
center 2	n = 3	11.9 ± 1.1 (12.2)	n = 4	4.6 ± 1.3 (4.9)
center 3	n = 11	4.3 ± 0.9 (4.2)	n = 12	5.4 ± 1.5 (4.9)
center 4	n = 9	8.4 ± 2.9 (7.8)	n = 8	7.7 ± 3.1 (7.1)
center 5	n = 10	3.6 ± 1.3 (3.0)	n = 10	3.8 ± 0.9 (3.9)
total	n = 43	6.8 ± 4.1 (5.2)	n = 45	5.4 ± 2.0 (4.9)

[Item 8, vol. 73, p. 93]

Table 77. Time to Actual Discharge

discharge from hospital* after [days] ITT analysis	Ropivacaine		PCA morphine	
center 1	n = 10	24.5 ± 3.4 (25.4)	n = 11	29.7 ± 12.4 (25.0)
center 2	n = 3	11.8 ± 5.1 (14.8)	n = 4	12.6 ± 2.3 (11.7)
center 3	n = 11	20.2 ± 3.1 (21.0)	n = 12	20.3 ± 1.8 (20.9)
center 4	n = 9	19.8 ± 5.6 (16.9)	n = 8	27.3 ± 10.1 (23.5)
center 5	n = 10	15.5 ± 2.9 (15.1)	n = 10	16.1 ± 5.8 (13.9)
total	n = 43	19.4 ± 5.3 (20.1)	n = 45	22.2 ± 9.8 (21.0)

* arithmetic mean ± standard deviation (median)

[Item 8, vol. 73, p. 95]

"The median time until the return of bowel motility (first flatus) was shorter in the ropivacaine group (26 vs. 47 hours) and patients in the ropivacaine group were mentally clear and cooperative earlier, but otherwise no relevant differences for the seven criteria for discharge from hospital were observed. The stay in hospital was considerably longer than in the other patients (> 35 days) in three patients. These patients (nos. 9, 22, and 131) belonged to the PCA morphine group." No formal statistical analysis was performed.

[Item 8, vol. 73, p. 96]

Consumption of metamizole

"On the day of operation or during the first two postoperative days 20/43 (46.5%) patients of the Ropivacaine group received metamizole. The mean dose was 2.55 + 2.01 mg. In the PCA morphine group 14/45 (31.1%) patients received metamizole and the mean dose was 1.26 + 1.03 g.

Until patients were deemed ready for discharge from hospital 22/43 (51.2%) vs. 19/45 (42.2%) patients received metamizole. The mean doses were 2.69 + 2.26 vs. 1.64 + 1.58 g. From the third postoperative day onwards metamizole was administered to 2/43 (4.7%) vs. 2/45 (4.4%) patients and the mean dose was 1.50 + 0.71 vs. 1.25 + 1.06 g." No formal statistical analysis was performed.

[Item 8, vol. 73, p. 96]

Consumption of morphine (in addition to PCA morphine)
"On the day of operation or during the first two postoperative days 4/43 (9.3%) patients of the ropivacaine group received morphine. The mean dose was 9.75 + 4.11 mg. In the PCA morphine group 30/45 (66.7%) patients received morphine in addition to PCA morphine and the mean dose was 8.47 + 3.51 mg.

Until patients were deemed ready for discharge from hospital the same patients received morphine (in addition to PCA morphine in the PCA morphine group). The mean doses were 14.75 + 7.32 vs. 8.47 + 3.51 mg. From the third postoperative day onwards parenteral morphine was only administered to 2/43 (4.7%) patients in the Ropivacaine group and each of the two patients received 10 mg." No formal statistical analysis was performed.
[Item 8, vol. 73, p. 96]

Consumption of diclofenac
"From the third postoperative day onwards diclofenac was administered to 28/43 (65.1%) vs. 29/45 (64.4%) patients and the mean dose was 391 + 288 vs. 371 + 267 mg. The results for the PP analysis for consumption of these analgesics were similar." No p-value was provided.
[Item 8, vol. 73, p. 96]

7.2.6.6 Reviewer's Efficacy Discussion

The clinical trial has demonstrated efficacy of ropivacaine when administered epidurally to patients following total hip replacement. With respect to the primary efficacy variable, "mean AUCM24 for the wound pain at rest," there is statistical evidence for improved efficacy of the product over that of PCA morphine for controlling postoperative pain (p=0.007).

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 comment made by the statistical reviewer for this submission, "radical differences in technique "; 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.

STUDY # 94RO84 (09)

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

–Discontinued due to high incidence of fever See Integrated Review of Safety below for details.

Note to Reader

The following review of the cesarean section and brachial plexus trials was conducted by medical reviewer, Patricia Hartwell, M.D., MBA Throughout the process of this review and upon final efficacy analyses, both Dr. Hartwell and I have been in collaboration. In as much, we have come to the same conclusions about the efficacy of the product ropivacaine, for the indications studied.

Monica Roberts, M.D.

7.2.7 STUDY SP-ROA-007 (P11)

7.2.7.1 Protocol Synopsis

Title:

A Clinical Study of Ropivacaine 7.5 mg/ml and Bupivacaine 5.0 mg/ml for Brachial Plexus Block in Patients Undergoing Surgery of the Upper Limb

Objectives:

"The primary objective of the study is to investigate the efficacy of ropivacaine 7.5 mg/ml compared with bupivacaine 5 mg/ml when used for subclavian perivascular brachial plexus block."

"The secondary objectives are to investigate the tolerability of ropivacaine" by measuring "the incidence and severity of adverse events, blood pressure, and heart rate."
[Item 8, Vol. 96, p. 110]

Study Design:

This study is a multicenter, randomized, double blind, parallel group design. One hundred patients are to be enrolled at four centers and randomized to receive a subclavian perivascular brachial plexus block of 30 mL of ropivacaine 7.5 mg/ml (225 mg) or 30 mL of bupivacaine 5 mg/ml (150 mg) with equal probability of receiving the two drugs.

Patients eligible for the study will be male or female patients undergoing surgery of the arm or hand using the subclavian perivascular brachial plexus block technique for anesthesia. They will be 18 to 75 years of age, inclusive, will be 50 to 100 kg in weight, inclusive, will be ASA risk category I to III, and will have given written acknowledgement of informed consent. Patients will be excluded if they have a known history of allergy, sensitivity or reaction to amide local anesthetics, a contraindication to brachial plexus block, atrio-ventricular block, significant neurological disorder or injury in the upper extremity, advanced diabetes, renal insufficiency, psychiatric or medical history leading to unreliability in assessments, current alcohol, drug or medication abuse, or suspected inability to comply with the protocol. Pregnant or lactating women, participants in clinical studies 14 days prior to admission to this study, patients previously included in the study, or patients requiring surgery expected to last 3 hours or more will also be excluded.

Figure 1. Study Schemata

Assessments																	
	Pre-op	Pre-anaest	Induction of anaesthesia (minutes)						Surgery (minutes)							Postop	Follow-up
	≤14 days		0	10	20	30	40	50	60	90	120	150	180	210	240		12 ±2 days
Incl/excl criteria	x																
Informed consent	x																
Clin examination	x																
Med/surg history	x																
Pulse, BP		x		x	x	x	x	x	x	x	x	x	x	x	x		
Drug administration			x														
Sensory block				x	x	x	x	x							x	x*	
Motor block		x		x	x	x	x	x							x	x*	
Adverse events			x	----	----	----	----	----	----	----	----	----	----	----	----	------	x
Quality of anaesthesia															x		

* thereafter at 6, 8, 10, 13, 16, 19 and 22 hours, then every 2 hours until end of block

[From sponsor's Figure 1, Item 8, Vol. 96, p. 12]

At the preoperative visit, patients will be assessed for inclusion or exclusion to the study, informed consent will be given, and a history and physical exam will be obtained. Pre-anesthetic baseline measurements will include pulse, blood pressure, and an assessment of motor function in the affected limb.

Prior to beginning the surgical procedure, a subclavian perivascular brachial plexus block with the previously defined dose of the randomized study drug will be performed according to standard technique (identification of the interscalene groove; plexus localization by paresthesia, nerve stimulator, or test injection; drug injection in incremental doses, post-injection caudal massage). Time zero is considered to be the start of injection of the drug. Premedication with midazolam (1-2 mg IV) and fentanyl (50-100 µg IV) and intraoperative medications such as propofol, midazolam, fentanyl and other necessary medications may be used at the investigator's discretion.

Sensory blockade will be evaluated by pin-prick in the cutaneous area of the axillary nerve, median nerve, radial nerve, ulnar nerve, and musculocutaneous nerve and will be graded according to a scale 0 = no analgesia, 1 = analgesia, 2 = anesthesia. Motor blockade will be assessed by nerve-distribution-specific voluntary maneuvers and graded according to a scale 0 = no motor block, 1 = partial motor block, and 2 = complete motor block. The quality of analgesia and muscle relaxation will be subjectively judged by the surgeon and the investigator at the end of surgery and graded as "excellent", "satisfactory", or "unsatisfactory".

After injection of the study drug, time-controlled measurements of pulse, blood pressure, sensory and motor blockade, and adverse event appearance will be recorded. At the start of the surgical procedure and throughout the procedure at designated time intervals, pulse, blood pressure, and the appearance of adverse events will be recorded. The presence or absence of tourniquet pain, where applicable, and the time of appearance will be recorded intraoperatively. At the end of the procedure the surgeon and the investigator will make an assessment of the quality of anesthesia.

Post-operatively, the sensory and motor blockades will be monitored at designated time intervals until complete regression. Appearance of adverse events will be recorded intraoperatively and will also be elicited during a telephone follow-up 12 ± 2 days after the surgical procedure.

Section 7.2.1.2 Statistical Analysis

According to the original protocol, the single primary efficacy variable is onset of analgesia in each of five nerves (axillary, radial, musculocutaneous, median, and ulnar). There will be 5 different onset times (time of analgesia x No. of nerves) for each patient. Since measurements are performed in 10-minute intervals, actual onset times will not be observed and will be estimated by calculating the arithmetic mean of the assessment times before and after the block occurred. The difference between the groups with regard to median time to event will be estimated using confidence intervals. [Item 8, Vol. 96, pp. 125-127]

Secondary efficacy variables and their planned analysis are as follows:

- Onset of anesthesia, partial motor block, and complete motor block in each of the five nerves. There will be 15 different onset times (No. of block types x No. of nerves) for each patient. Since measurements are performed in 10-minute intervals, actual onset times will not be observed and will be estimated by calculating the arithmetic mean of the assessment times before and after the block occurred.
- Individual duration in each nerve for each type of block. There will be 20 such measurements for each patient. Individual duration is defined as the time the block disappears minus the time of onset. Time of disappearance is estimated by calculating the arithmetic mean of the assessment times before and after the block disappears.
- Time from start of injection until regression of analgesia for each nerve. There will be 5 such measurements for each patient and this time interval is defined as the onset time plus the individual duration.
- Time from start of injection until the first request for postoperative analgesics
- Quality of analgesia
- Quality of muscle relaxation
- Tourniquet pain
- Amount of concomitant sedative or analgesic medications administered during surgery. These amounts are defined as propofol (0-100, >100-200, >200 mg/hr), midazolam (0-5, >5-10, >10 mg/hr), and fentanyl (0-100, >100-200, >200 μg/hr) and are the mean amounts given during the surgical procedure.

[Item 8, Vol. 96, p. 126]

The analysis of these variables will include descriptive statistics and/or graphs for each treatment group. The primary efficacy variable and the first three secondary variables will be presented using plots of the survival function (proportion of patients for whom the event has not yet occurred plotted against time. The difference between groups with regard to median time to event will be estimated, preferably with confidence intervals. Treatments will also be compared by use of hypothesis tests such as the log rank test and the effect of center differences will be considered in the analysis.[Item 8, Vol. 96, p. 127]

7.2.7.2 Protocol Amendments

Amendment 1:

This amendment, dated 10/23/96, consists of a change to the inclusion criteria. The change to these criteria is the following:

- Weight ≥60 and ≤100 kg to Weight ≥50 and ≤100 kg

Amendment 2:

This amendment, dated 11/11/96, consists of several features:

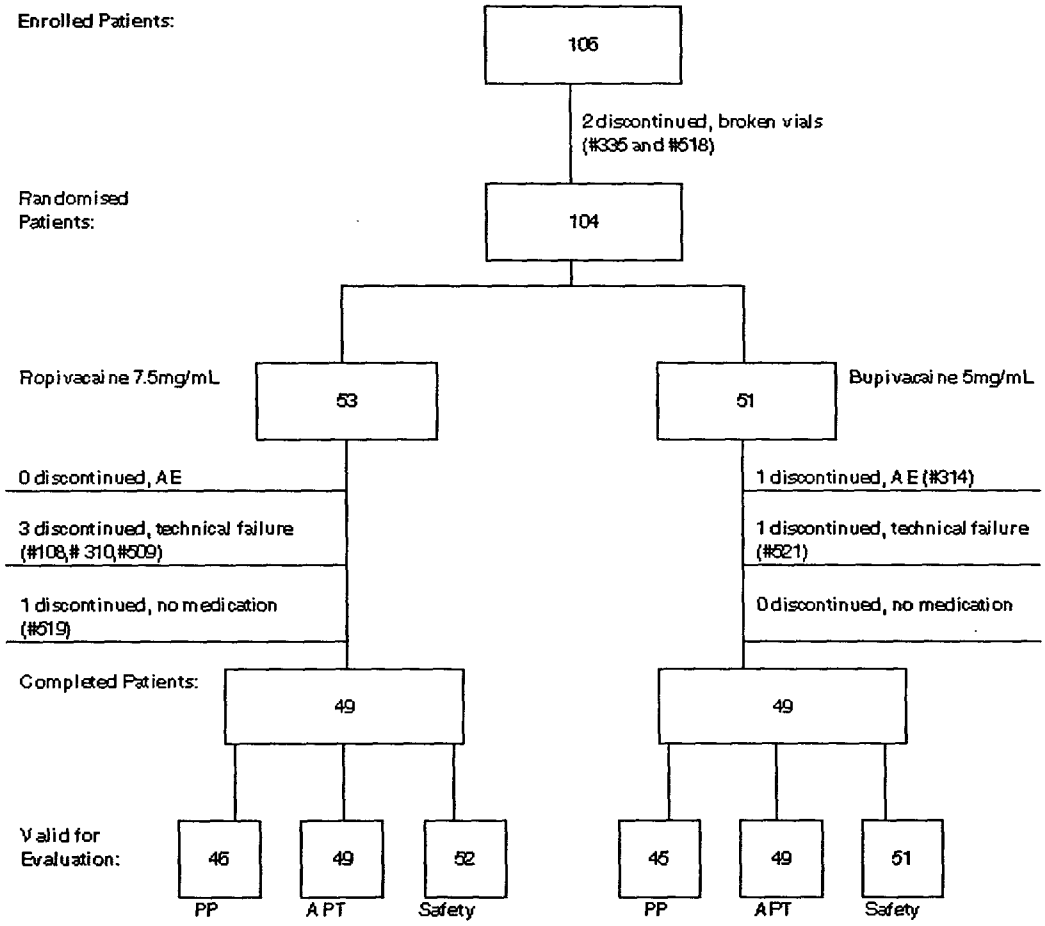
- Replacement of the Canadian Study Coordinator
- Updates to contact information for investigators
- Addition of two additional centers to the study, requiring a change in study design to read "It is planned that *six* centers will participate and enroll a total of 100 valid patients."
- Addition of two additional centers to the study, requiring a change in study design to read "aim is to have 50 patients in each treatment group, distributed evenly over the *six* centers, with at least *twelve* and at most 30 patients per center"

7.2.7.3 Conduct of Study

Patient Distribution/Disposition:

Of the 106 patients enrolled in the study, 104 were randomized to receive ropivacaine (53) and bupivacaine (51). One patient in the ropivacaine group did not receive study drug after the surgeon overruled their participation. Three patients in the ropivacaine group and one in the bupivacaine group were withdrawn from efficacy analysis due to technical failures and one patient in the bupivacaine group was withdrawn due to an adverse event. Data from the remaining 98 patients was utilized for the efficacy analysis.

Figure 2 Patient Disposition



[Based on sponsor's Figure 2, Item 8, Vol. 96, p. 37]; PP = Per Protocol, APT = All Patients Treated

Data from three patients in the ropivacaine group was considered invalid for PP data analysis – one due to use of another anesthetic regimen and two due to insufficient duration of analgesia prior to surgery. Data from four patients in the bupivacaine group was considered invalid for PP analysis – one due to an inclusion criteria violation, one due to insufficient duration of analgesia prior to surgery, and two due to the use of another anesthetic regimen. According to the investigators, "these violations were of minor importance and were not considered to have an effect on the APT data analysis" and all were included in the analysis of efficacy. Protocol violations for individual patients are summarized in the table below.

Table 1. Protocol Violations

Patient Number	*Protocol Violation*	*Ropivacaine*	*Bupivacaine*
202	Other Anesthetic Regimen (bupivacaine infiltration)	X	
112	Other Anesthetic Regimen (lidocaine infiltration)		X
201	Other Anesthetic Regimen (bupivacaine infiltration)		X
320	Duration of Analgesia (36 minutes)	X	
528	Duration of Analgesia (40 minutes)	X	
520	Duration of Analgesia (37 minutes)		X
507	Violation of Inclusion Criteria (weight 48kg)		X

[Item 8, Vol. 96, p. 48)

Three other patients, in addition to the original 106, entered the study. According to the sponsor, "as it was discovered that these patients were not given study information or consented according to the stipulations of the protocol, all data concerning these three patients were removed from the database and were not included in any analyses" [Item 8, Vol. 96, p.36]. These three patients are listed in Appendix 4 to Clinical Study Report [Item 8, Vol. 97, p. 347] and are summarized below:

Patient 330

62 year old male; withdrawn from the study prior to study drug administration; no adverse effects recorded

Patient 332

39 year old female; mild intensity adverse effects recorded were vomiting, headache, nausea, small bleeding left hand, constipation, and dizziness; all adverse effects resolved except constipation for which the date and time are unknown

Patient 334

63 year old male; mild intensity adverse effects recorded were bleeding from the surgical site, swelling of fingers on the right hand; both adverse effects resolved

Demographics

The following tables summarize the general demographic characteristics of the two study populations used in the safety evaluations:

Table 2 Age, Height, and Weight

Variable	Treatment	N	Mean	SD	Minimum	Maximum
Age (yr)	Ropi 7.5 mg/mL	52	46.7	15.7		
	Bupi 5.0 mg/mL	51	51.4	16.9		
Height (cm)	Ropi 7.5 mg/mL	52	170.2	9.2		
	Bupi 5.0 mg/mL	51	168.4	10.6		
Weight (kg)	Ropi 7.5 mg/mL	52	74.3	13.2		
	Bupi 5.0 mg/mL	51	73.4	13.0		

[From sponsor's Table 1, Item 8, Vol. 96, p. 38]

Table 3 Sex, Race, ASA Classification, and Allergy

[From sponsor's Table 2, Item 8, Vol. 96, p. 38]

	Ropivacaine 7.5 mg/mL (n=52)	Bupivacaine 5.0 mg/mL (n=51)
Sex		
Male	32	23
Female	20	28
Race		
Caucasian	50	51
Black	1	0
Other	1	0
ASA		
ASA I	22	13
ASA II	25	32
ASA III	5	6
Allergy		
No	34	28
Yes	18	23

The incidence of significant findings in medical history and on physical exam was similar between the two study groups. Borderline or abnormal electrocardiogram recordings, current and/or past major disease or condition, previous major surgery, and abnormal physical exam findings were noted and are summarized in the following table. The investigators considered none of these documented or confounding factors to have a significant influence on the study evaluations.

Table 4 Abnormal History and Physical Findings

Abnormality	*Number of Patients* Ropivacaine 7.5 mg/ml	Bupivacaine 5.0 mg/ml
Abnormal Physical Exam	16	17
Borderline ECG	8	4
Abnormal ECG	5	9
Other Diseases	30	38
Surgical History	43	39

[Item 8, Vol. 96, pp. 39-41]

The two study groups were similar when compared for time from start of drug injection to the start of surgery, with a median time of 54 minutes for the ropivacaine group and 55 minutes for the bupivacaine group, and for surgical duration, with a median time of 73 minutes and 67 minutes respectively. Duration of treatment administration, with a median time of 3 minutes in both groups, and time from end of surgery to discharge, with a median of 26.3 hours for ropivacaine and 26.1 hours for bupivacaine, were also comparable. These results are summarized in the following table.

Table 5 Pertinent Time Comparisons

Measured Variable	*N*	*Median*	*Minimum*	*Maximum*
Start Injection to Start Surgery (minutes)				
Ropivacaine 7.5 mg/ml	49	54		
Bupivacaine 5 mg/ml	49	55		
Duration of Surgery (minutes)				
Ropivacaine 7.5 mg/ml	49	73		
Bupivacaine 5 mg/ml	49	67		
Duration of Administration (minutes)				
Ropivacaine 7.5 mg/ml	49	3		
Bupivacaine 5 mg/ml	49	3		
Time to Discharge (hours)				
Ropivacaine 7.5 mg/ml	49	26.3		
Bupivacaine 5 mg/ml	49	26.1		

[From sponsor's Tables 5, 6, 7, & 8, Item 8, Vol. 96, pp. 41-45]

7.2.7.4 Sponsor's Efficacy Results

Primary Efficacy Variable:

Nerve-Specific Time to Onset of Analgesia

Differences between the onset times to development of analgesia between the ropivacaine group and the bupivacaine group were not clinically significant for any of the tested nerves. It was observed that the median difference between the two groups was less than 10 minutes, with individual variation from 4 minutes to more than an hour. The following table summarizes these results.

Table 6 Analgesia Onset Time (minutes)

Nerve	*Analgesia*		
	Mean	SD	Median
Axillary			
Ropivacaine	13.2	11.0	7.0
Bupivacaine	15.4	12.5	15.0
Median			
Ropivacaine	12.3	12.6	5.0
Bupivacaine	11.6	8.3	6.5
Musculocutaneous			
Ropivacaine	10.8	10.2	5.0
Bupivacaine	12.9	10.2	7.0
Radial			
Ropivacaine	10.8	9.2	5.0
Bupivacaine	11.7	9.3	6.8
Ulnar			
Ropivacaine	9.1	6.8	5.0
Bupivacaine	12.6	10.7	6.5

[From sponsor's Table 1 "Summary Statistics", Item 8, Vol. 97, pp. 308-311]

Confidence intervals for the difference in medians between the two treatments were calculated with the bootstrap technique are summarized in the table below.

Table 7 95% Confidence Intervals – Onset of Analgesia

Nerve	*Lower Bound*	*Upper Bound*	*Median Difference*
Axillary	-8.50	10.25	0.00
Median	-3.00	7.50	-2.50
M-cutaneous	-7.50	7.50	-2.50
Radial	-10.0	8.00	-2.00
Ulnar	-10.00	8.00	-2.00

[From sponsor's Table 12, Item 8, Vol. 96, p. 60]

Secondary Efficacy Variables:

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

There was no clinically significant difference in the onset times to development of anesthesia, partial motor block, and complete motor block between the ropivacaine group and the bupivacaine group for all nerves tested. The following table, ordered by type of block, summarizes these results.

Table 8 Block Onset Time (minutes)

Nerve	*Anesthesia*			*Partial Motor Block*			*Complete Motor Block*		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Axillary									
Ropivacaine	20.9	10.3	19.0	6.9	4.0	5.0	13.7	10.4	15.0
Bupivacaine	22.7	14.6	15.0	8.6	6.0	5.0	19.4	13.1	15.
Median									
Ropivacaine	17.9	10.5	15.0	9.6	8.5	5.0	16.4	10.7	15.0
Bupivacaine	24.7	16.0	25.0	13.7	11.3	7.5	22.7	15.1	18.0
M-cutaneous									
Ropivacaine	17.5	11.1	15.0	9.7	7.6	5.0	14.9	11.4	15.0
Bupivacaine	21.9	15.8	22.0	10.1	9.4	5.5	12.6	12.6	16.0
Radial									
Ropivacaine	16.0	10.6	15.0	8.6	6.5	5.0	14.9	10.7	15.0
Bupivacaine	21.4	14.6	22.0	10.5	9.8	5.0	17.8	11.2	15.0
Ulnar									
Ropivacaine	19.1	11.5	15.0	9.2	7.8	5.0	13.4	7.7	15.0
Bupivacaine	23.2	16.1	25.0	11.9	9.9	5.0	17.9	14.9	15.0

[From sponsor's Table 1 "Summary Statistics", Item 8, Vol. 97, pp. 308-311]

Confidence intervals for the difference in the medians between treatment groups were calculated by the bootstrap method and are summarized in the table below:

Table 9 95% Confidence Intervals – Onset Anesthesia, Partial Motor Block and Complete Motor Block

Type of Block	*Lower Bound*	*Upper Bound*	*Median Difference*
Anesthesia			
Axillary	-6.00	13.00	-6.50
Median	-11.50	11.50	-11.50
M-cutaneous	-14.00	14.00	-14.00
Radial	-18.50	15.00	-18.50
Ulnar	-16.00	0.50	-16.00
Partial Motor			
Axillary	-0.50	1.50	0.00
Median	-0.50	1.50	0.00
M-cutaneous	-9.50	7.50	-1.50
Radial	-2.50	3.75	-1.00
Ulnar	-9.50	7.00	-3.00
Complete Motor			
Axillary	-13.00	10.00	-10.00
Median	-10.50	11.50	-11.50
M-cutaneous	-20.00	19.50	-10.00
Radial	-22.00	10.00	-10.00
Ulnar	-16.00	10.00	-16.00

[From sponsor's Table 12, Item 8, Vol. 96, pp. 60-62]

Nerve-Specific Duration of Sensory and Motor Blockade

There was no clinically significant difference in the duration of blockade, or time of disappearance minus time of onset, between the ropivacaine group and the bupivacaine group for any of the tested nerves. The median differences for duration between the two groups differed by less than 6 hours, with ranges as wide as 0-2 hours to 23-38 hours, depending on the nerve. These results are summarized in the following table.

Table 10 Block Duration (hours)

Nerve	*Analgesia*			*Anesthesia*			*Partial Motor Block*			*Complete Motor Block*		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Axillary												
Ropi	11.1	5.7	11.4	8.4	4.0	8.5	13.9	5.4	14.4	10.8	4.0	11.3
Bupi	12.4	7.8	12.4	9.1	5.3	8.9	16.0	5.2	17.1	12.0	4.9	12.2
Median												
Ropi	13.8	5.0	14.1	9.7	3.7	9.3	13.4	36.	14.2	9.6	3.8	9.3
Bupi	14.7	6.0	15.6	11.4	4.8	10.9	15.0	6.1	14.4	11.9	4.8	12.1
M-cutan												
Ropi	13.6	6.2	14.4	10.2	3.8	11.1	13.9	5.5	14.3	11.5	3.5	11.4
Bupi	15.3	7.0	17.3	12.2	5.3	13.9	16.4	5.2	17.3	13.5	3.7	13.9
Radial												
Ropi	13.5	6.5	14.3	10.5	3.7	11.1	13.6	4.2	14.4	11.1	3.0	11.4
Bupi	16.2	6.9	17.3	12.8	4.8	11.6	17.4	5.9	17.4	14.1	5.5	13.9
Ulnar												
Ropi	14.1	4.2	14.2	9.8	3.8	9.3	14.4	4.2	14.4	10.3	36.	10.7
Bupi	13.5	7.4	13.4	11.6	5.5	12.1	15.2	6.4	17.1	11.8	4.8	12.1

[From sponsor's Table 1 "Summary Statistics", Item 8, Vol. 97, pp. 308-311]

Confidence intervals for the difference in the medians between treatment groups were calculated by the bootstrap method and are summarized in the table below:

Table 11 95% Confidence Intervals – Duration Analgesia, Anesthesia, Partial Motor Block and Complete Motor Block

Type of Block	*Lower Bound*	*Upper Bound*	*Median Difference*
Analgesia			
Axillary	-6.48	5.48	0.15
Median	-4.33	4.00	-1.67
M-cutaneous	-4.83	2.83	-2.83
Radial	-5.61	7.05	-2.83
Ulnar	-3.17	5.83	0.00
Anesthesia			
Axillary	-4.67	4.33	2.00
Median	-4.66	3.51	-0.66
M-cutaneous	-8.70	3.72	-1.62
Radial	-3.98	2.86	-1.47
Ulnar	-4.54	8.13	4.04
Partial Motor			
Axillary	-2.67	3.00	-2.67
Median	-4.71	2.53	-2.79
M-cutaneous	-1.57	3.42	-1.58
Radial	-6.11	3.17	-6.00
Ulnar	-5.63	3.33	2.67
Complete Motor			
Axillary	-2.79	2.73	-0.67
Median	-6.96	5.29	1.79
M-cutaneous	-1.38	3.24	-0.92
Radial	-1.86	4.42	-0.83
Ulnar	-4.92	6.44	4.00

[From sponsor's Table 12, Item 8, Vol. 96, pp. 60-62]

Nerve-Specific Time to Regression of Sensory and Motor Blockade

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

Time to First Postoperative Analgesic Request

A total of 44 patients in the ropivacaine group and 41 patients in the bupivacaine group requested postoperative analgesics. The median time to first request was 11.0 and 12.2 hours in the ropivacaine and bupivacaine groups respectively. These results are summarized in the following table.

Table 12 First Analgesic Request (hours)

Treatment	N	Median	Minimum	Maximum
Ropivacaine 7.5 mg/mL	44	11.0		
Bupivacaine 5.0 mg/mL	41	12.2		

[From sponsor's Table 19, Item 8, Vol. 96, p. 69]

Quality of Analgesia and Muscle Relaxation

Both surgeon and investigator evaluated the quality of analgesia and muscle relaxation at the end of the surgical procedure. No statistically significant difference was found between the two study groups for either assessment. These results are summarized in the following table.

Table 13 Quality of Analgesia and Muscle Relaxation

Assessment	Ropivacaine 7.5 mg/mL (n=49)	Bupivacaine 5.0 mg/mL (n=49)	p-value
Analgesia, by Investigator			p = 0.20
Excellent	33	26	
Satisfactory	2	6	
Unsatisfactory	14	17	
Muscle Relaxation, by Investigator			p = 0.51
Unassessed	0	1	
Excellent	35	30	
Satisfactory	2	4	
Unsatisfactory	12	14	
Analgesia, by Surgeon			p = 0.79
Unassessed	0	2	
Excellent	33	27	
Satisfactory	1	7	
Unsatisfactory	15	13	
Muscle Relaxation, by Surgeon			p = 0.70
Unassessed	0	2	
Excellent	34	29	
Satisfactory	4	6	
Unsatisfactory	11	12	

[From sponsor's Table 16, Item 8, Vol. 96, p. 67]

Tourniquet Pain

Tourniquet pain was assessed by the investigator in applicable patients. Thirty-four patients in the ropivacaine group and 31 patients in the bupivacaine group were evaluated for its presence. Three patients in the ropivacaine group experienced pain with a median onset of 2.0 hours, as did 6 patients in the bupivacaine group with a median onset of 1.6 hours. The following tables summarize these results.

Table 14 Incidence of Tourniquet Pain

Assessment	Ropivacaine 7.5 mg/mL (n=49)	Bupivacaine 5.0 mg/mL (n=49)	P-value
Tourniquet pain			p = 0.85
Unassessed (not applicable or unavailable)	15	18	
Absent	31	25	
Present	3	6	

[From sponsor's Table 17, Item 8, Vol. 96, p.68]

Table 15 Onset Time of Tourniquet Pain (hours)

Treatment	N	Median	Minimum	Maximum
Ropivacaine 7.5 mg/mL	3	2.0	—	—
Bupivacaine 5.0 mg/mL	6	1.6		

[From sponsor's Table 18, Item 8, Vol. 96, p. 68]

Amount of Concomitant Fentanyl, Midazolam, and Propofol:

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

Table 16 Use of Concomitant Medications (Fentanyl µg/h, Midazolam mg/h, Propofol mg/h)

Therapy	Dose	Treatment	N	Median	...mum	Maximum
Fentanyl	0 - 100	Ropi 7.5 mg/mL	12	46.5		
		Bupi 5.0 mg/mL	14	48.8		
Fentanyl	> 100 - 200	Ropi 7.5 mg/mL	1	157.9		
Midazolam	0 - 5	Ropi 7.5 mg/mL	6	0.9		
		Bupi 5.0 mg/mL	4	0.9		
Midazolam	> 5 - 10	Ropi 7.5 mg/mL	2	8.3		
Midazolam	> 10	Bupi 5.0 mg/mL	1	18.0		
Propofol	0 - 100	Ropi 7.5 mg/mL	5	57.9		
		Bupi 5.0 mg/mL	3	37.8		
Propofol	> 100 - 200	Ropi 7.5 mg/mL	1	138.5		
		Bupi 5.0 mg/mL	4	132.3		
Propofol	> 200	Ropi 7.5 mg/mL	3	228.6		
		Bupi 5.0 mg/mL	2	653.8		

[From sponsor's Table 9, Item 8, Vol. 96, p. 46]

Reviewer's Efficacy Discussion

In this study the sponsor chose the onset of analgesia in 5 distinct nerves as the primary variable to be measured and analyzed for efficacy comparison of ropivacaine and bupivacaine in brachial plexus blockade. Analysis of the results does not support a conclusion that either study drug is more effective in producing analgesia in this nerve plexus.

Numerous secondary efficacy variables were measured, including duration of analgesia, onset and duration of anesthesia and motor blockade, and use of concomitant sedative or analgesic medication. The results do not support a finding that one study drug is clinically more effective than the other. Additional secondary efficacy variables, time to first request of analgesics and quality of anesthesia or motor blockade, were measured and no clinically or statistically significant difference was found between the two study groups.

Of interest is the sponsor's choice to compare two different dosages of these agents, 7.5 mg/ml of ropivacaine and 5 mg/ml of bupivacaine in their efficacy study. Any differences in measured variables that might occur, whether or not they were statistically significant, would potentially be biased by dosage effect and could not reliably be used to support a finding of increased efficacy with the tested agent.

Another area of concern in this study is the disposition of patients #330, #332, and #334. According to the sponsor, these three patients entered the study but, when it was discovered that they had not received study information or proper informed consent, they were removed from the study and were not included in any analyses. Information about these patients is unavailable in the summary data and only appears as abbreviated case reports in the final appendix to the study, referenced in the patient enrollment section [Item 8, Vol. 96, p. 36]. They are not included in any of the diagrams or tables describing patient disposition or protocol violations. It appears that while one patient received no study medication, two of the patients did. Adverse events were listed for these two patients but there was no mention as to how far along in the study they were before data collection ceased. Although it would not be expected that the data of two patients would make a significant difference in the study results, it would have been helpful to confirm this expectation.

This study supports the conclusion that neither 225 mg of ropivacaine 7.5 mg/ml nor 150 mg of bupivacaine 5 mg/ml is more or less effective than the other for subclavian perivascular brachial plexus block when the stated efficacy variables are measured.

7.2.8 STUDY SP-ROA-0008 (P12)

7.2.8.1 Protocol Synopsis

Title:

A Clinical Study of Ropivacaine 7.5 mg/ml and Bupivacaine 5.0 mg/ml for Brachial Plexus Block in Patients Undergoing Surgery of the Upper Limb

Objectives:

"The primary objective of the study is to investigate the efficacy of ropivacaine compared with bupivacaine when used for axillary brachial plexus block."

"The secondary objective is the tolerability of ropivacaine."
[Item 8, Vol. 98, p. 134]

Study Design:

This study is a multicenter, randomized, double-blind, parallel group design. One hundred patients are to be enrolled at four centers and randomized to receive an axillary brachial plexus block of 40 mL of ropivacaine 7.5 mg/ml (300 mg) or 40 mL of bupivacaine 5 mg/ml (200 mg) with equal probability of receiving the two drugs.

Patients eligible for the study will be patients undergoing elective surgery of the arm or hand using the axillary brachial plexus block technique for anesthesia. They will be 18 to 75 years of age, inclusive, 60 to 100 kg in weight, inclusive, 150 cm or more in height, and ASA risk category I to III. They will have given written acknowledgement of informed consent. Patients will be excluded if they have a known history of allergy, sensitivity or reaction to amide local anesthetics as judged by the investigator, a contraindication to brachial plexus block as judged by the investigator, atrio-ventricular block, significant neurological disorder or nerve injury in the upper extremity, advanced diabetes, renal insufficiency, psychiatric or medical history/disease leading to unreliability in assessments, current alcohol, drug or medication abuse leading to unreliability in assessments, or suspected inability to comply with the protocol. Pregnant or lactating women, participants in clinical studies 14 days prior to admission to this study, patients previously included in the study, or patients requiring surgery expected to last 3 hours or more will also be excluded.

Figure 1. Study Schemata

Assessments																	
	Pre-op	Pre-anaesth	Induction of anaesthesia (minutes)						Surgery (minutes)							Postop	Follow-up
	≤14 days		0	10	20	30	40	50	60	90	120	150	180	210	240		12 ±2 days
Incl./excl. criteria	x																
Informed consent	x																
Clin. examination	x																
Med./surg. history	x																
Clin haem/chem.	x																x
Pulse, BP		x		x	x	x	x	x	x	x	x	x	x	x	x		
Body temp		x													x	x*	
Drug administration			x														
Sensory block				x	x	x	x	x							x	x*	
Motor block		x		x	x	x	x	x							x	x*	
Adverse events			x**	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	----------	x
Quality of anaesthesia															x		

*Thereafter at 6, 8, 10, 13, 16, 19, and 22 hours, then every 2 hours until the end of block
**Adverse events continuously monitored during the hospital stay
[From sponsor's Figure 1, Item 8, Vol. 98, p. 33]

At the preoperative visit, patients will be assessed for inclusion or exclusion to the study, informed consent will be given, and a history and physical exam will be obtained. Pre-anesthetic baseline measurements will include pulse, blood pressure, temperature and an assessment of motor function in the affected limb.

Prior to beginning the surgical procedure, an axillary brachial plexus block with the previously defined dose of the randomized study drug will be performed according to standard technique (identification of the brachial artery pulse, insertion of needle parallel to artery, plexus localization by paresthesia, nerve stimulator, fascial click, or test injection; drug injection in incremental doses over 3-7 minutes with application of distal pressure). Time zero is considered to be the start of injection of the drug. Premedication with midazolam (1-2 mg IV) and diazepam (10 mg po) and intraoperative medications such as propofol, midazolam, fentanyl and other necessary medications may be used at the investigator's discretion.

Sensory blockade will be evaluated by pin-prick in the cutaneous area of the axillary nerve, median nerve, radial nerve, ulnar nerve, and musculocutaneous nerve and will be graded according to a scale 0 = no analgesia, 1 = analgesia, 2 = anesthesia. If adequate analgesia has not occurred in the surgical area 50 minutes after administration of the block, the investigator may perform supplemental blockade with a short-acting local anesthetic (lidocaine, prilocaine). The supplemented area will not be included in anesthesia/analgesia assessment. Motor blockade will be assessed by nerve-distribution-specific voluntary maneuvers and graded according to a scale 0 = no motor block, 1 = partial motor block, and 2 = complete motor block. The quality of analgesia and muscle relaxation will be subjectively judged by the surgeon and the investigator at the end of surgery and graded as "excellent", "satisfactory", or "unsatisfactory".

After injection of the study drug, time-controlled measurements of pulse, blood pressure, temperature, sensory and motor blockade, and adverse event appearance will be recorded. At the start of the surgical procedure and throughout the procedure at designated time intervals, pulse, blood pressure, and the appearance of adverse events will be recorded. The presence or absence of tourniquet pain, where applicable, and the time of appearance will be recorded intraoperatively. At the end of the procedure the surgeon and the investigator will make separate assessments of the quality of anesthesia.

Post-operatively, the sensory and motor blockades will be monitored at designated time intervals until complete regression. Appearance of adverse events will be recorded intraoperatively and postoperatively and will also be elicited during a follow-up visit 12 ± 2 days after the surgical procedure.

7.2.8.2 Statistical Analysis

According to the original protocol, the single primary efficacy variable is onset of analgesia in each of five nerves (axillary, radial, musculocutaneous, median, and ulnar). There will be 5 different onset times (time of analgesia x No. of nerves) for each patient. Since measurements are performed in 10 minute intervals, actual onset times will not be observed and will be estimated by calculating the arithmetic mean of the assessment times before and after the block occurred. The difference between the groups with regard to median time to event will be estimated using confidence intervals. [Item 8, Vol. 98, pp. 152-153]

Secondary efficacy variables and their planned analysis are as follows:

- Onsets of anesthesia, partial motor block, and complete motor block in each of the five nerves. There will be 15 different onset times (No. of block types x No. of nerves) for each patient. Since measurements are performed in 10-minute intervals, actual onset times will not be observed and will be estimated by calculating the arithmetic mean of the assessment times before and after the block occurred.
- Individual duration in each nerve for each type of block. There will be 20 such measurements for each patient. Individual duration is defined as the time the block disappears minus the time of onset. Time of disappearance is estimated by calculating the arithmetic mean of the assessment times before and after the block disappears.
- Time from start of injection until regression of analgesia for each nerve. There will be 5 such measurements for each patient and this time interval is defined as the onset time plus the individual duration
- Time from start of injection until the first request for postoperative analgesics
- Quality of analgesia
- Quality of muscle relaxation
- Tourniquet pain
- Amount of concomitant sedative or analgesic medications administered during surgery. These amounts are defined as propofol (0-100, >100-200, >200 mg/hr), midazolam (0-5, >5-10, >10 mg/hr), and fentanyl (0-100, >100-200, >200 µg/hr) and are the mean amounts given during the surgical procedure.[Item 8, Vol. 98, p. 152]

The analysis of these variables will include descriptive statistics and/or graphs for each treatment group. The primary efficacy variable and the first three secondary variables will be presented using plots of the survival function (proportion of patients for whom the event has not yet occurred plotted against time. Confidence intervals will be used to evaluate the difference between treatment groups for median time to event. Treatments will also be compared by use of hypothesis tests such as the log rank test and the effect of center differences will be considered in the analysis. [Item 8, Vol. 98, p. 153]

7.2.8.3 Protocol Amendments

Amendment 1:

This amendment, dated 05/20/96, consists of the following changes:

- Administrative features – change in phone, address
- Addition of the wording "sensory block will be evaluated by pin-prick *using the blunt end of a 27 G dental needle...*"
- Addition of the wording "adverse effects...at the follow-up visit *or telephone follow-up* 12 ± 2 days after surgery."
- Addition of the statement " *The investigator will report serious and/or frequent adverse events directly to the Norwegian Medicines Control Authority (Sttens Legemiddel-kontroll) as soon as possible."*

Amendment 2:

This amendment, dated 08/15/96, consists of the following changes:

- Replacement of the statement "before insertion of the needle, the skin is infiltrated with 0.5 to 1 mL of...." with the statement "before insertion of the needle, the skin *may* be infiltrated..."

Amendment 3:

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

- Addition of one additional center to the study, requiring a change in study design to read "The aim is to have 50 patients in each treatment group distributed evenly over the *five* centers."

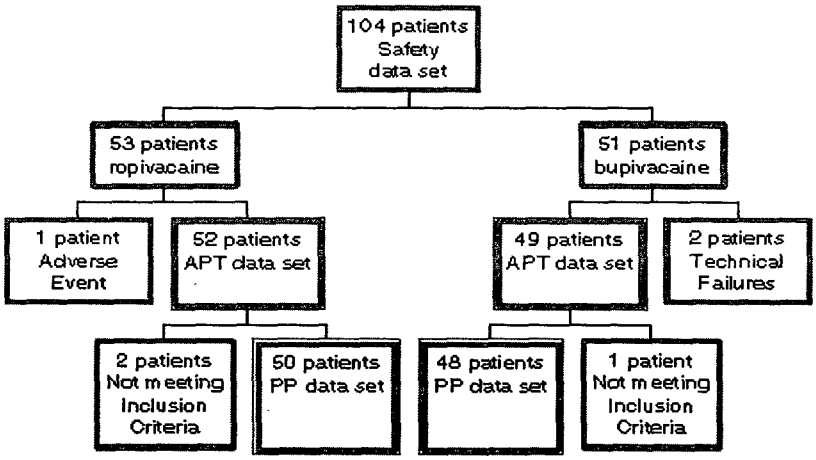
7.2.8.4 Conduct of Study

Patient Distribution/Disposition:

Of the 104 patients enrolled in the study, all were randomized to receive either ropivacaine (53) or bupivacaine (51). Two patients in the bupivacaine group were withdrawn from efficacy analysis due to technical failures and one patient in the ropivacaine group was withdrawn due to an adverse event (seizure activity from intravascular injection). Data from the remaining 101 patients was utilized for the efficacy analysis (APT data set).

Figure 2 Patient Disposition

[Based on sponsor's Figure 2, Item 8, Vol. 98, p. 62; PP = Per Protocol, APT = All Patients Treated]



Two patients in the ropivacaine group and one in the bupivacaine group did not meet the inclusion criteria and their data was not considered valid for PP data analysis – one patient weighed more than 100 kg and two patients weighed less than 60 kg. However, 34 additional patients, listed as protocol deviations, are included in the PP data set. According to the investigators, "the protocol deviations that were found in the study were all considered to be of minor importance." [Item 8, Vol. 98, p. 69-70] Protocol deviations for individual patients are summarized in the following table.

Table 1.

Protocol Deviation	*Patient #*	*Ropivacaine*	*Bupivacaine*	*Included in PP Data Set*
Duration of injection (>7 min)	212, 519	X		X
Duration of injection (>7 min)	219		X	X
Dose of study drug (<40 mL)	210, 213, 225, 507		X	X
Premedication (propofol)	202		X	X
Premedication (fentanyl)	120		X	X
Other regimen (failed block was repeated)	227		X	X
Additional analgesic (alfentanil)	201	X		X
Additional analgesic (alfentanil)	202		X	X
Laboratory testing (omitted)	201, 121, 206, 208, 217, 220, 229, 230, 405, 406,	X		X
Laboratory testing (omitted)	204, 402, 107, 115, 205, 209, 211, 227, 228, 316, 404		X	X
Inclusion criteria (weight)	514, 212	X		
Inclusion criteria (weight)	210		X	X

[Item 8, Vol. 98, pp. 69-70)

Demographics

The following tables summarize the general demographic characteristics of the two study populations used in the safety evaluations.

Table 2 Age, Height, and Weight

Variable	Group	N	MEDIAN	MIN	MAX
AGE	ROPI 7.5	53	48.2	18.7	73.1
	BUPI 5.0	51	49.7	21.9	75.6
Height	ROPI 7.5	53	176.0	158.0	195.0
	BUPI 5.0	51	175.0	155.0	190.0
Weight	ROPI 7.5	53	75.0	54.0	105.0
	BUPI 5.0	51	80.0	56.0	100.0

[From sponsor's Table 1, Item 8, Vol. 98, p. 62]

Table 3 Sex, Race, ASA Classification, and Allergy

Variable	Ropi 7.5 (n=53)	Bupi 5.0 (n=51)
Sex		
Male	31	32
Female	22	19
Race		
Caucasian	53	51
ASA		
ASA I	28	23
ASA II	22	26
ASA III	3	2
Allergy		
No	47	40
Yes	6	11

[From sponsor's Table 2, Item 8, Vol. 98, p. 63]

The two groups were also similar with respect to the incidence of significant findings in medical history and on physical exam. Borderline or abnormal electrocardiogram recordings, current and/or past major disease or condition, previous major surgery, and abnormal physical exam findings were noted and are summarized in the following table. The investigators considered none of these documented or confounding factors to have a significant influence on the study evaluations.