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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Dynastat® / Parecoxib sodium

PROTOCOL NO.: A3481066

PROTOCOL TITLE: Randomized, Double-Blind Study of the Morphine-Sparing Efficacy and Safety of Parecoxib Sodium 40 mg IV Followed by 20 mg IV Every 12 Hours in the Treatment of Pain Following Radical Prostatectomy

Study Centers: A total of 3 centers in Germany took part in the study and randomized subjects.

Study Initiation Date and Final Completion Date: 03 December 2006 to 24 September 2010. The study was terminated prematurely.

Phase of Development: Phase 4

Study Objectives:

Primary Objective: To demonstrate the opioid-sparing efficacy of parecoxib 40 mg intravenously (IV) given as a loading dose followed by 20 mg IV in the 24 hours after the end of surgery.

Secondary Objectives: To evaluate the overall safety and efficacy of multiple doses of parecoxib following radical prostatectomy. In particular, if administration of multiple doses of parecoxib was associated with an increased blood loss.

METHODS:

Study Design: This Phase 4, multiple-dose, randomized, double-blind, and placebo-controlled, parallel-group study was designed to evaluate the morphine-sparing effect of parecoxib sodium 40 mg administered IV followed by parecoxib 20 mg administered IV every 12 hours versus placebo administered IV every 12 hours until 48 hours after the end of radical prostatectomy surgery. The observation period for this study was 2 days (12, 24, 36, and 48 hours, respectively, after skin closure).

Due to the use of a new surgical method (da Vinci) for subjects undergoing prostatectomy that used laparoscopic methods rather than the more invasive open surgery approach, the study underwent slow recruitment and a decision was eventually made to terminate the study due to this slow recruitment. The schedule of study activities is presented Table 1.

Table 1. Schedule of Activities

	Preoperative Period		Postoperative Period					
	Screening	Day of Surgery	Baseline	Hours After Surgery				Follow-up
	-12 to -96 Hours		0 Hour	12 (±1 Hour)	24 (±1 Hour)	36 (±1 Hour)	48 (±1 Hour) or ET	Day of Discharge (-24 Hours)
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	X							
Medical and surgical history	X							
Physical examination	X							
Vital signs	X				X		X	
Inclusion/exclusion criteria	X		X					
Randomization			X[a]					
Study treatment dosing			X[b]	X	X	X	X	
PCA check[c]	X		X	X	X	X	X	
Assessment of morphine consumption[d]				X	X	X	X	
Pain assessment at rest and movement[e]				X	X	X	X	
Subject's global evaluation of study medication[f]							X	
Opiate-related symptom distress scale questionnaire[g]					X		X	
Modified-brief pain inventory (short form)[g]					X		X	
Overall analgesic benefit score					X		X	
Postoperative drainage fluid total amount (mL)			X	X	X	X	X	
Hemoglobin concentration		X	X		X		X	
Total RBC units substituted during surgery		X						
Total RBC units substituted during 48 hours after skin closure							X	
Collection and measurement of the fluid volume from suction and swab weights during surgery		X						
AE assessment[h]			X	X	X	X	X	X
Clinical laboratory[i]	X				X		X	X
Prior/concomitant medication[h]	X	X	X	X	X	X	X	X
Health care resource utilization[j]					X		X	
Time of last PCA dose				X	X	X	X	

AE = adverse event; ET = early termination; PCA = patient-controlled analgesia; RBC = red blood cell; SF = short form.

a. Subjects were randomized upon receipt of initial dose of study medication.
b. End of surgery, defined as application of last stitch to surgical wound.
c. PCA training prior to surgery and at connection of pump; PCA connection within 60 minutes after end of surgery.
d. Subjects could be disconnected from PCA if they had no recorded activity in the past 2 waking hours and indicated they did not need additional morphine when asked. However, subjects had to be monitored continuously through the whole study period until Visit 7 or ET. The intraoperative fentanyl consumption was to be recorded at the end of Visit 2.
e. Pain assessment was performed immediately prior and 30±10 minutes after administration of study medication. Movement was defined as sitting up from a lying position in bed to a sitting position in bed.
f. Subject's global evaluation of study medication was performed 30±10 minutes after administration of study medication at Visit 7.
g. To be collected immediately before administration of study medication.
h. Adverse events and concomitant medication were monitored throughout the study period.
i. Laboratory values were measured in a local lab.
j. The Health Care Resource Utilization question was answered by the supervising physician or nurse.

Number of Subjects (Planned and Analyzed): A total of 152 subjects (76 subjects per group) were planned to be enrolled into the study. A total of 105 subjects were randomized and received study treatment; 52 subjects in the parecoxib 40/20 mg group and 53 in the placebo group. All subjects who were randomized and received at least 1 dose of study treatment were analyzed.

Diagnosis and Main Criteria for Inclusion: Male subjects aged 18 years and older who were scheduled to undergo routine radical prostatectomy performed under a standardized regimen of general anesthesia, and were expected to experience moderate to severe postsurgical pain in the absence of postoperative analgesia, were eligible to be enrolled in the study. In addition, subjects had to have American Society of Anesthesiologists physical status 1 or 2 and a low risk (ie,<10%) of developing an acute coronary event within the next 10 years according to the Prospective Cardiovascular Münster Heart Study risk assessment calculator.

Study Treatment: Parecoxib sodium was supplied as a powder to be reconstituted with sodium chloride solution 9 mg/mL (0.9%) prior to administration. Sodium chloride solution 9 mg/mL (0.9%) was used as matching placebo; 2 mL for parecoxib 40 mg and 1 mL for parecoxib 20 mg.

The first dose of study treatment (parecoxib 40 mg or placebo) was administered immediately after skin closure by the anesthesiologist responsible for the subjects' anesthesia. Consecutive doses of parecoxib 20 mg or placebo were administered by a study doctor or study nurse every 12 hours (±1 hour) until postoperative Day 2 (48±1 hour after skin closure), totaling 5 doses.

All subjects received standard patient-controlled analgesia (PCA) morphine administered via a PCA pump containing morphine (1 mg/mL) which was set to a lockout time of 10 minutes and PCA of 1.0 mg per dose to a maximum of 40.0 mg in any 4-hour period, as needed. If the subjects required analgesia before or after connection with the PCA pump was successfully completed, administration of 2 to 5 mg morphine by IV bolus was possible. For further rescue analgesia, additional IV bolus doses of morphine of 2 to 5 mg could be administered until pain control had been established. If a subject could not use the PCA pump, the subject was withdrawn from the study and provided with appropriate analgesia. Subjects were required to remain on PCA morphine for 48 hours postoperatively, until final assessment. Subjects requiring further analgesia at any time point in addition to the morphine and study medication were withdrawn from the study after collection of Visit 7 (48 hours) data and were recorded as treatment failures.

Efficacy, Safety, and Outcome Research Endpoints:

Primary Endpoint: The total cumulative amount of morphine administered (PCA and bolus) in the 24 hours after the end of surgery (ie, application of the last surgical stitch).

Secondary Endpoints:

- Blood loss, defined as:

- First: Number of red blood cell (RBC) units (RBCUs) transfused postoperatively;
- Second: ($[Hb\ g/dL]_{pra} + RBCU_{during48} - [Hb\ g/dL]_{at48}$), where $[Hb\ g/dL]_{pra}$ was the blood hemoglobin concentration preoperatively, $[Hb\ g/dL]_{at48}$ was the blood hemoglobin concentration 48 hours after skin closure, and $RBCU_{during48}$ was the number of RBCUs substituted during and after prostatectomy until 48 hours after skin closure;

- The total cumulative amount of morphine administered (PCA and bolus) in the 48 hours after the end of surgery;
- Time of last administration of morphine (PCA and/or bolus dose);
- Time specific pain intensity (categorical scales) at rest and at movement 12, 24, 36, and 48 hours after end of surgery (defined as application of the last surgical stitch);
- Subject's global evaluation of study medication 48 hours after skin closure;
- Subject global assessment of analgesic experience (Overall Analgesic Benefit Score [OABS]) 24 and 48 hours after skin closure;
- Modified Brief Pain Inventory-Short Form (mBPI-sf) after 24 and 48 hours;
- Opioid Related Symptom Distress Scale (OR-SDS) questionnaire after 24 and 48 hours;
- Health Care Resource Utilization (HCRU) 24 and 48 hours after surgery;
- Assessment of adverse events (AEs) 12, 24, 36, 48 hours after skin closure and at the follow-up visit.

Safety Evaluations: Safety assessments included monitoring of treatment-emergent AEs (TEAEs), vital signs, blood loss, and clinical laboratory tests (hematology, biochemistry, measurement of hemoglobin concentration and total amount of postoperative drainage fluid).

Statistical Methods: The full analysis set (FAS) was the primary analysis population which included those subjects who were randomized to treatment, received at least 1 dose of their assigned treatment and who had a valid postbaseline efficacy measurement.

The per protocol (PP) population included all subjects of the FAS for whom at least 1 valid post-baseline data were available with regard to the primary variable and did not violate the protocol in any fundamental manner including the violation of entry criteria and study drug non-compliance, that could influence the assessment of efficacy.

Modified intent-to-treat population (mITT) included all subjects of the FAS who provided morphine consumption data after the randomization and did not withdraw prior to 24 hours after the end of surgery.

Safety analysis set included all subjects who received at least 1 dose of the study drug. All safety endpoints were carried out on the safety analysis set.

All statistical tests were 2-sided and performed at the 5% level, unless otherwise stated.

The primary analysis was based on the FAS. The primary endpoint (cumulative amount of morphine used in each treatment group during the 24 hours after the end of surgery) was analyzed using an analysis of covariance (ANCOVA) model including terms for treatment and center.

The analysis of secondary endpoints was based on the FAS.

Cumulative Morphine: The total cumulative amount of morphine administered (PCA and bolus/mg) in the 48 hours after the end of surgery. Analysis was performed using an ANCOVA model, including terms for treatment and center.

Time to Last Administration of Morphine: This analysis was performed using methods of survival analysis. The time point for the analysis of time to last administration of morphine was 48 hours after the end of surgery.

Blood Loss: Postoperative blood loss was measured as the number of RBCUs transfused within the first 48 hours after the end of surgery. Data were summarized descriptively. The difference in blood loss between treatment groups and blood loss score were analyzed using an ANCOVA model, and including covariates. Treatment contrasts were computed with 2-sided 95% confidence limits for the treatment difference parecoxib and placebo.

Pain Intensity: The mean difference across time points, between the pain intensity pre- and post-study medication administration was analyzed using an ANCOVA model with treatment and center as covariates. This analysis was performed separately for the change at rest and for the change at movement.

mBPI-sf: mBPI was summarized descriptively for Questions 2 to 6 and for all parts of Question 7, at 24 and 48 hours after the end of surgery, and the pain severity and interference composite scores were calculated and summarized descriptively at each relevant time point. Both composite scores were analyzed using an ANCOVA model. If multiple responses were recorded for individual questions on the questionnaire scores then for the analyses a conservative approach was taken and the most severe (highest) score was used.

OR-SDS: OR-SDS questionnaire was analyzed for each symptom (fatigue, drowsiness, etc) descriptively by treatment group 24 and 48 hours after the end of surgery and the overall score was summarized at each relevant time point using standard summary statistics.

Subject's Global Evaluation of Study Medication: Each item of the subject's global evaluation of study medication (48 hours after end of surgery) was summarized descriptively using standard summary statistics.

The analyses of OABS and HCRU were not performed due to early termination of the study.

Safety data were reported for the safety population and were summarized descriptively.

RESULTS

Subject Disposition and Demography: Table 2 presents summary of subject disposition and subjects analyzed. Of the 105 randomized subjects, 50 (96%) from the parecoxib 40/20 mg group and 50 (94%) from the placebo group completed the study.

Table 2. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Parecoxib 40/20 mg	Placebo
Screened=111		
Assigned to study treatment=105		
Treated	52	53
Completed	50 (96.2)	50 (94.3)
Discontinued	2 (3.8)	3 (5.7)
Relation to study drug not defined	1 (1.9)	3 (5.7)
No longer willing to participate in study	0	3 (5.7)
Protocol violation	1 (1.9)	0
Related to study drug	1 (1.9)	0
Adverse event	1 (1.9)	0
Analyzed for efficacy:		
Per protocol analysis set	34 (65.4)	31 (58.5)
Full analysis set	52 (100.0)	53 (100.0)
Modified intent-to-treat	50 (96.2)	52 (98.1)
Analyzed for safety:		
Adverse events	52 (100.0)	53 (100.0)
Laboratory data	52 (100.0)	53 (100.0)

Discontinuations occurring outside the lag period were attributed to the last study treatment received.

Subjects were between the ages of 46 and 83 years with mean ages of 64.4 years in the parecoxib 40/20 mg group and 65.0 years in the placebo group. All subjects were White males. Table 3 summarizes the demographic characteristics.

Table 3. Demographic Characteristics

	Parecoxib 40/20 mg	Placebo
	Male	Male
Number (%) of subjects	52	53
Age in years, n		
<45	0	0
45-59	14 (27)	13 (25)
60-74	36 (69)	38 (72)
≥75	2 (4)	2 (4)
Mean	64.4	65.0
SD	7.5	7.2
Range	47-83	46-75
Race		
White	52 (100)	53 (100)

Percentage are rounded and therefore may not total 100%.
Subjects received parecoxib 40 mg IV given as a loading dose followed by parecoxib 20 mg IV in the 24 hours after the end of surgery.
IV = intravenous; n = number of subjects; SD = standard deviation.

Efficacy and Outcome Research Results:

Primary Endpoint Results: Table 4 summarizes the results for the primary efficacy endpoint (ie, cumulative amount of morphine administered in the first 24 hours following surgery).

The cumulative amount of morphine (bolus plus PCA) used in the parecoxib 40/20 mg group was statistically significantly lower than that used by subjects in the placebo group (least squares [LS] mean difference = −7.58 mL, p-value=0.035). Similar findings were observed using the analysis of variance (ANOVA) model for the mITT population, however, the differences were not significant (p-value=0.059).

Table 4. Cumulative Amount of Morphine Administered in the First 24 Hours Following Surgery - FAS Population

	Parecoxib 40/20 mg N=52	Placebo N=53	Overall p-Value
Cumulative Amount of Morphine (Bolus + PCA)			
Imputed Visit 24 hours			
n	52	53	
Mean	28.84	36.40	
SD	16.16	19.99	
Median	27.0	34.0	
Range, minimum, maximum	(0.0, 60.2)	(7.0, 117.2)	
LSM	26.24	33.82	
Parecoxib 40/20 mg minus placebo			
Difference in LSM	-7.58		0.035[a]
Difference in SE	3.55		
95% CI	(-14.63, -0.53)		

Subjects received parecoxib 40 mg or placebo administered IV given as a loading dose followed by parecoxib 20 mg or placebo administered IV every 12 hours until 48 hours after the end of surgery.
ANOVA = analysis of variance; CI = confidence interval; FAS = full analysis set; IV = intravenous; LSM = least squares mean; mITT = modified intent-to-treat; N = number of subjects in each group; n = number of evaluated subjects; PCA = patient controlled analgesia; SD = standard deviation; SE = standard error.
a. p-Values were based on ANOVA model with terms for treatment group and center.

Secondary Endpoints Results:

The blood loss in terms of number of RBCUs transfused postoperatively within the first 48 hours after the end of surgery is shown in Table 5.

Table 5. Blood Loss (RBC Transfused Units) - FAS Population

	Parecoxib 40/20 mg N=52 n (%)	Placebo N=53 n (%)
Blood loss 48 hours		
0 RBC transfused units	47 (90.4%)	51 (96.2%)
1 RBC transfused unit	1 (1.9%)	1 (1.9%)
2 RBC transfused units	4 (7.7%)	1 (1.9%)

Blood loss: number of RBC units transfused within the first 48 hours after surgery.
FAS = full analysis set; N = number of subjects in each group; n = number of subjects receiving RBC transfused units; RBC = red blood cell.

Table 6 presents the difference in blood loss for the FAS population.

Table 6. Difference in Blood Loss - FAS Population

	Parecoxib 40/20 mg N=52	Placebo N=53	Overall p-Value
Difference in blood loss 48 hours			
N	52	53	0.810[a]
Mean	4.34	4.41	
SD	1.40	2.12	
Minimum-Maximum	(1.4, 7.8)	(1.1, 12.2)	
Median	4.2	4	
LS mean	4.35	4.42	
Parecoxib 40/20 mg minus placebo			
LS mean for difference	-0.07		
SE for difference	0.30		
95% confidence interval	(-0.68, 0.53)		

Difference in blood loss = ($[Hb\ g/dL]_{pra}$ + $RBCU_{during48}$ - $[Hb\ g/dL]_{at48}$), where $[Hb\ g/dL]_{pra}$ was the blood hemoglobin concentration preoperatively, $[Hb\ g/dL]_{at48}$ was the blood hemoglobin concentration 48 hours after skin closure, and $RBCU_{during48}$ was the number of RBCUs substituted during and after prostatectomy until 48 hours after skin closure.
ANCOVA = analysis of covariance; FAS = full analysis set; LS = least squares; N = number of subjects in each group; RBCU = red blood cell unit; SD = standard deviation; SE = standard error.

a. p-Values are based on ANCOVA model with terms for treatment group and center, and total RBCUs, total RBCUs substituted during surgery, baseline hemoglobin value, swab weights, lavage weight, and intraoperative blood loss fluid volume as covariates.

The cumulative amount of morphine administered (PCA and bolus) in the 48 hours after the end of surgery is presented in Table 7.

Table 7. Cumulative Amount of Morphine Administered in First 48 Hours - FAS Population

	Parecoxib 40/20 mg N=52	Placebo N=53	Overall p-Value
Cumulative amount of morphine (bolus + PCA)			
Imputed Visit 48 hours			
n	52	53	0.004[a]
Mean	42.13	57.03	
SD	25.02	28.07	
Median	39.1	50	
Minimum-maximum	(0.0, 107.0)	(16.2, 138.0)	
LSM	35.73	50.89	
Parecoxib 40/20 mg minus placebo			
Difference in LSM	-15.16		
Difference in SE	5.20		
95% CI	(-25.47, -4.85)		

ANOVA = analysis of variance; CI = confidence interval; FAS = full analysis set; IV = intravenous; LSM = least squares mean; N = number of subjects in each group; n = number of evaluated subjects; PCA = patient controlled analgesia; SD = standard deviation; SE = standard error.

a. p-Values are based on ANOVA model with terms for treatment group and center.

The results for time to last administration of morphine (PCA and/or bolus dose) is summarized in Table 8.

Table 8. Time to Last Administration of Morphine (PCA and/or Bolus Dose) - FAS Population

	Parecoxib 40/20 mg N=52	Placebo N=53
Was the subject censored?		
Yes	2 (4%)	3 (6%)
No	49 (94%)	49 (92%)
Total	51 (98%)	52 (98%)
Time to last administration (non-censored subjects only)		
Mean	48.39	47.08
Median	46.5	46.5
SD	20.58	10.76
Minimum	1.9	21.8
Maximum	123.7	90.3
n	48	49
Kaplan-Meier treatment comparison		
Median	46.6	46.48
95% CI	(44.77,48.07)	(45.28,47.62)
p-Value (log-rank test)		0.257

Calculated using a Kaplan-Meier analysis, with log-rank test stratified by center, to compare treatment groups.
Subjects who withdrew from the study were classified as censored observations using their last known time of morphine administration.
Differences in 'n's (n values) were due to missing values in result for any subject.
One subject (parecoxib) was not included as no morphine (bolus + PCA) was administered.
One subject (placebo) was not included as dates and times for morphine (bolus + PCA) were not recorded.
CI = confidence interval; FAS = full analysis set; N = number of subjects in each group; n = number of evaluated subjects; PCA = patient controlled analgesia; SD = standard deviation.

Table 9 presents results for the time specific pain intensity (categorical scales) at rest and at movement 12, 24, 36 and 48 hours after surgery for the FAS population.

Table 9. Time Specific Pain Intensity (Categorical Scales) at Rest and at Movement 12, 24, 36 and 48 Hours After Surgery-FAS Population

	Parecoxib 40/20 mg N=52	Placebo N=53	Total N=105	Parecoxib 40/20 mg N=52	Placebo N=53	Total N=105
12 Hours Post Skin Closure		**At Rest**			**At Movement**	
Prior to administration						
n	51	51	102	51	52	103
Mean	1.31	1.69	1.5	2.12	2.63	2.38
SD	0.76	0.95	0.88	0.86	0.95	0.94
Minimum-Maximum	(0.0, 3.0)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)
Median	1	1	1	2	3	2
Post administration						
n	51	52	103	51	52	103
Mean	0.53	0.79	0.66	1.16	1.58	1.37
SD	0.67	0.78	0.74	0.88	1.02	0.97
Minimum-Maximum	(0.0, 3.0)	(0.0, 2.0)	(0.0, 3.0)	(0.0, 3.0)	(0.0, 3.0)	(0.0, 3.0)
Median	0	1	1	1	1.5	1
Change from prior to post administration						
n	51	51	102	51	52	103
Mean	-0.78	-0.9	-0.84	-0.96	-1.06	-1.01
SD	0.7	0.98	0.85	0.75	1.02	0.89
Minimum-Maximum	(-3.0, 0.0)	(-4.0, 2.0)	(-4.0, 2.0)	(-2.0, 0.0)	(-4.0, 0.0)	(-4.0, 0.0)
Median	-1	-1	-1	-1	-1	-1
24 Hours Post Skin Closure		**At Rest**			**At Movement**	
Prior to administration						
n	51	52	103	51	52	103
Mean	1	1.44	1.22	2.12	2.63	2.38
SD	0.82	0.94	0.91	0.86	0.77	0.85
Minimum-Maximum	(0.0, 3.0)	(0.0, 3.0)	(0.0, 3.0)	(0.0, 4.0)	(1.0, 4.0)	(0.0, 4.0)
Median	1	1	1	2	3	2
Post administration						
n	51	52	103	51	52	103
Mean	0.53	0.67	0.6	1.45	1.9	1.68
SD	0.76	0.73	0.75	1.05	0.96	1.02
Minimum-Maximum	(0.0, 3.0)	(0.0, 2.0)	(0.0, 3.0)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)
Median	0	1	0	2	2	2
Change from prior to post administration						
n	51	52	103	51	52	103
Mean	-0.47	-0.77	-0.62	-0.67	-0.73	-0.7
SD	0.64	0.81	0.74	0.77	0.95	0.86
Minimum-Maximum	(-2.0, 0.0)	(-3.0, 0.0)	(-3.0, 0.0)	(-3.0, 1.0)	(-3.0, 1.0)	(-3.0, 1.0)
Median	0	-1	0	-1	-1	-1
36 Hours Post Skin Closure		**At Rest**			**At Movement**	
Prior to administration						
N	51	51	102	51	51	102
Mean	0.86	1.04	0.95	1.59	2.12	1.85
SD	0.94	0.87	0.91	0.98	1.03	1.04
Minimum-Maximum	(0.0, 4.0)	(0.0, 3.0)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)
Median	1	1	1	2	2	2
Post administration						
n	51	51	102	51	51	102
Mean	0.45	0.59	0.52	1.04	1.51	1.27
SD	0.61	0.73	0.67	0.89	0.92	0.94
Minimum-Maximum	(0.0, 2.0)	(0.0, 2.0)	(0.0, 2.0)	(0.0, 3.0)	(0.0, 3.0)	(0.0, 3.0)
Median	0	0	0	1	2	1
Change from prior to post administration						
n	51	51	102	51	51	102
Mean	-0.41	-0.45	-0.43	-0.55	-0.65	-0.6
SD	0.61	0.67	0.64	0.73	0.87	0.8

Table 9. Time Specific Pain Intensity (Categorical Scales) at Rest and at Movement 12, 24, 36 and 48 Hours After Surgery-FAS Population

	Parecoxib 40/20 mg N=52	Placebo N=53	Total N=105	Parecoxib 40/20 mg N=52	Placebo N=53	Total N=105
Minimum-Maximum	(-2.0, 0.0)	(-3.0, 0.0)	(-3.0, 0.0)	(-3.0, 0.0)	(-3.0, 1.0)	(-3.0, 1.0)
Median	0	0	0	0	0	0
48 Hours Post Skin Closure		**At Rest**			**At Movement**	
Prior to administration						
n	51	51	102	51	51	102
Mean	0.67	0.82	0.75	1.47	2.31	1.89
SD	1.07	0.97	1.02	1.16	0.97	1.14
Minimum-Maximum	(0.0, 4.0)	(0.0, 3.0)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.0)
Median	0	0	0	1	2	2
Post administration						
n	51	51	102	51	51	102
Mean	0.29	0.29	0.29	0.88	1.41	1.15
SD	0.54	0.58	0.56	0.86	0.98	0.96
Minimum-Maximum	(0.0, 2.0)	(0.0, 2.0)	(0.0, 2.0)	(0.0, 3.0)	(0.0, 4.0)	(0.0, 4.0)
Median	0	0	0	1	2	1
Change from prior to post administration						
n	51	51	102	51	51	102
Mean	-0.33	-0.55	-0.44	-0.59	-0.9	-0.75
SD	0.77	0.88	0.83	0.83	0.78	0.82
Minimum-Maximum	(-4.0, 0.0)	(-3.0, 1.0)	(-4.0, 1.0)	(-2.0, 1.0)	(-3.0, 0.0)	(-3.0, 1.0)
Median	0	0	0	0	-1	-1

FAS = full analysis set; N = number of subjects in each group; n = number of evaluated subjects; SD = standard deviation.

Table 10 presents the results of ANCOVA analysis of the time specific pain intensity for the FAS population.

Table 10. Time Specific Pain Intensity: ANCOVA Analysis - FAS Population

	Parecoxib 40/20 mg N=52	Placebo N=53	Overall p-Value
At Rest			
Mean of differences			
Imputed Visit 48 hours			
n	51	52	0.070[a]
Mean	-0.5	-0.66	
SD	0.43	0.54	
Median	-0.5	-0.5	
Minimum-maximum	(-1.8, 0.0)	(-2.0, 0.3)	
LS mean	-0.33	-0.50	
Parecoxib 40/20 mg minus placebo			
LS mean for difference	0.17		
SE for difference	0.09		
95% Confidence Interval	(-0.01, 0.35)		
At Movement			
Mean of differences			
Imputed Visit 48 hours			
n	51	52	0.074[a]
Mean	-0.68	-0.83	
SD	0.45	0.51	
Median	-0.8	-0.8	
Minimum-maximum	(-2.0, 0.0)	(-2.0, 0.0)	
LS mean	-0.50	-0.66	
Parecoxib 40/20 mg minus placebo			
LS mean for difference	0.16		
SE for difference	0.09		
95% confidence interval	(-0.02, 0.33)		

ANCOVA = analysis of covariance; ANOVA = analysis of variance; FAS = full analysis set; LS = least squares; N = number of subjects in each group; n = number of evaluated subjects; SD = standard deviation; SE = standard error.
a. p-Values are based on ANOVA model with terms for treatment group and center.

Table 11 presents results for subject's global evaluation of study medication 48 hours after skin closure.

Table 11. Subject's Global Evaluation of Study Medication 48 Hours After Skin Closure - FAS Population

	Parecoxib 40/20 mg N=52 n (%)	Placebo N=53 n (%)
How would you rate the study medication you received for pain since your surgery (48 hours)?		
Poor	1 (1.9%)	3 (5.7%)
Fair	3 (5.8%)	5 (9.4%)
Good	19 (36.5%)	31 (58.5%)
Excellent	27 (51.9%)	11 (20.8%)
Missing	2 (3.8%)	3 (5.7%)

FAS = full analysis set; N = number of subjects in each group; n = number of subjects with specified criteria.

Table 12 presents ANCOVA results of mBPI-sf (Questions 2 to 5): pain severity composite score. Pain severity composite score was calculated from the mean of Questions 2 to 5 on the questionnaire.

Table 12. Modified Brief Pain Inventory-Short Form (mBPI-sf) Composite Measure: Pain Severity (Questions 2 to 5) After 24 and 48 Hours - FAS Population

	Parecoxib 40/20 mg N=52	Placebo N=53	Overall p-Value
Composite Measure mBPI-sf: Mean of Scores			
Imputed Visit 24 hours			
n	49	50	0.002[a]
Mean	2.08	2.78	
SD	1.17	1.06	
Median	2	3	
Minimum-maximum	(0.0, 5.0)	(1.0, 6.0)	
LS mean	1.90	2.61	
Parecoxib 40/20 mg minus placebo			
LS mean for difference	-0.71		
SE for difference	0.23		
95% confidence interval	(-1.16, -0.26)		
Imputed Visit 48 hours			
n	43	48	0.004[a]
Mean	1.6	2.31	
SD	1.26	1.17	
Median	1	2	
Minimum-maximum	(0.0, 5.0)	(1.0, 7.0)	
LS mean	1.42	2.15	
Parecoxib 40/20 mg minus placebo			
LS mean for difference	-0.73		
SE for difference	0.25		
95% confidence interval	(-1.22, -0.23)		

Q2: how much pain at its worst in the past 24 hours; Q3: how much pain at its least in the past 24 hours; Q4: how much pain at its average in the past 24 hours; Q5: how much pain right now.
Scores for Questions 2-5: scale from 0 (no pain) to 10 (pain as bad as you can imagine).
ANOVA = analysis of variance; FAS = full analysis set; LS = least squares; mBPI-sf = Modified Brief Pain Inventory-Short Form; N = number of subjects in each group; n = number of subjects evaluated; Q = question; SD = standard deviation; SE = standard error.
a. p-Values are based on ANOVA model with terms for treatment group and center.

Table 13 presents ANCOVA results of mBPI-sf (Question 7; Parts a-h): pain interference composite score.

Table 13. Modified Brief Pain Inventory-Short Form (mBPI-sf) Composite Measure: Pain Interference (Question 7, Parts a-h) After 24 and 48 Hours - FAS Population

	Parecoxib 40/20 mg N=52	Placebo N=53	Overall p-Value
Composite Measure mBPI-sf: Mean of Scores			
Imputed Visit 24 hours			
n	49	50	<0.001[a]
Mean	1.16	2.32	
SD	1.21	1.78	
Median	1.0	2.0	
Minimum-maximum	(0.0, 6.0)	(0.0, 9.0)	
LS mean	1.16	2.32	
Parecoxib 40/20 mg minus placebo			
LS mean for difference	-1.16		
SE for difference	0.30		
95% confidence interval	(-1.77, -0.56)		
Imputed Visit 48 hours			
n	43	48	0.006[a]
Mean	1.00	1.79	
SD	1.41	1.50	
Median	1.0	1.0	
Minimum-maximum	(0.0, 6.0)	(0.0, 7.0)	
LS mean	0.58	1.40	
Parecoxib 40/20 mg minus placebo			
LS mean for difference	-0.83		
SE for difference	0.30		
95% confidence interval	(-1.41, -0.24)		

Q7a: how much pain interfered with your: general activity; Q7b: how much pain interfered with your: mood; Q7c: how much pain interfered with your: walking ability; Q7d: how much pain interfered with your: relations with other people; Q7e: how much pain interfered with your: sleep; Q7f: how much pain interfered with your: coughing; Q7g: how much pain interfered with your: deep breathing; Q7h: how much pain interfered with your: concentration.
Scores for questions 7a to 7h are on a scale from 0 (does not interfere) to 10 (completely interferes).
ANOVA = analysis of variance; FAS = full analysis set; LS = least squares; mBPI-sf = Modified Brief Pain Inventory-Short Form; N = number of subjects in each group; n = number of subjects evaluated; Q = question; SD = standard deviation; SE = standard error.
a. p-Values are based on ANOVA model with terms for treatment group and center.

Table 14 presents OR-SDS overall composite scores after 24 and 48 hours. The overall composite score was calculated as the mean of each of the 10 individual mean symptoms' OR-SDS scores.

Table 14. OR-SDS Overall Score After 24 and 48 Hours - FAS Population

OR-SDS Overall Score	Parecoxib 40/20 mg N=52	Placebo N=53
After 24 hours		
n	51	52
Mean	0.50	0.55
SD	0.35	0.39
Minimum-Maximum	(0.0, 1.9)	(0.0, 1.3)
Median	0.4	0.5
Imputed Visit 48 hours		
n	51	52
Mean	0.26	0.34
SD	0.28	0.34
Minimum-Maximum	(0.0, 1.4)	(0.0, 1.4)
Median	0.3	0.2

N = number of subjects in each group; n = number of subjects evaluated; OR-SDS = Opioid Related Symptom Distress Scale; SD = standard deviation.

The analyses of OABS and HCRU 24 and 48 hours after surgery were not performed due to early termination of the study.

The study was terminated prematurely due to this slow recruitment.

Safety Results: Table 15 summarizes the TEAEs (all causality and treatment-related).

Table 15. Summary of Treatment-Emergent All Causality and Treatment-Related Adverse Events

Number (%) of Subjects	Parecoxib 40/20 mg		Placebo	
	All Causality	Treatment-Related	All Causality	Treatment-Related
Subjects evaluable for AEs	52	52	53	53
Number of AEs	116	3	109	0
Subjects with AEs	43 (83)	3 (6)	42 (79)	0
Subjects with SAEs	12 (23)	1 (2)	5 (9)	0
Subjects with severe AEs	2 (4)	1 (2)	5 (9)	0
Subjects discontinued due to AEs	1 (2)	1 (2)	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	0	0

AEs include both serious and non-serious AEs, ie, AEs and SAEs are not separated out.
Subjects received parecoxib 40 mg or placebo administered IV given as a loading dose followed by parecoxib 20 mg or placebo administered IV every 12 hours until 48 hours after the end of surgery.
Includes data up to 30 days after the last dose of study treatment.
Except for the number of AEs, subjects were counted only once per treatment in each row.
AEs = adverse events; IV = intravenous; SAEs = serious adverse events.

All Causality TEAEs: Table 16 presents non-serious all causality TEAEs with an incidence rate of ≥5% in any treatment group. Non-serious TEAE occurring more frequently (3 or more subjects) in the parecoxib 40/20 mg arm than in the placebo arm was vomiting. None of these events were considered to be related to the study treatment. TEAEs occurring more frequently (3 or more subjects) in the placebo arm than in the parecoxib 40/20 mg arm included nausea, flatulence, diarrhea, constipation, pyrexia, and vertigo. None of these TEAEs were considered to be related to the study treatment.

The majority of all TEAEs were mild in severity (156 mild, 62 moderate, and 7 severe). There were 2 severe TEAEs (thrombocytosis and hyperhidrosis) in the parecoxib 40/20 mg arm and 5 (diarrhea, pyrexia, confusional state [in 2 subjects], and hemorrhage) in the placebo arm.

Table 16. Treatment-Emergent Non Serious Adverse Events (All Causalities) For Events Having a Frequency Rate ≥5% in Any Treatment Group

Number (%) of Subjects with Adverse Events by: System Organ Class MedDRA Preferred Term	Parecoxib 40/20 mg N=52	Placebo N=53
Number (%) of subjects evaluable for adverse events	52	53
Number (%) of subjects with adverse events	35 (67.3)	38 (71.7)
Blood and lymphatic system disorders	6 (11.5)	4 (7.5)
Anaemia	6 (11.5)	4 (7.5)
Ear and labyrinth disorders	0	3 (5.7)
Vertigo	0	3 (5.7)
Gastrointestinal disorders	26 (50.0)	30 (56.6)
Abdominal pain	3 (5.8)	1 (1.9)
Constipation	2 (3.8)	7 (13.2)
Diarrhoea	4 (7.7)	8 (15.1)
Flatulence	6 (11.5)	10 (18.9)
Nausea	12 (23.1)	16 (30.2)
Vomiting	9 (17.3)	4 (7.5)
General disorders and administration site conditions	1 (1.9)	4 (7.5)
Pyrexia	1 (1.9)	4 (7.5)
Infections and infestations	6 (11.5)	7 (13.2)
Urinary tract infection	6 (11.5)	7 (13.2)
Psychiatric disorders	3 (5.8)	1 (1.9)
Insomnia	3 (5.8)	1 (1.9)
Respiratory, thoracic and mediastinal disorders	3 (5.8)	2 (3.8)
Oropharyngeal pain	3 (5.8)	2 (3.8)
Vascular disorders	6 (11.5)	4 (7.5)
Hypertension	6 (11.5)	4 (7.5)

Subjects were only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (version 14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each group.

Treatment-Related TEAEs: Table 17 presents treatment-related TEAEs reported during the study. Three subjects had a TEAE that the Investigator considered to be related to the study treatment. All 3 events were reported in the parecoxib 40/20 mg arm (hypokalemia, acute renal failure, and hyperhidrosis). Of the 3 treatment-related AEs, acute renal failure was considered to be a serious event.

Table 17. Treatment-Related Treatment-Emergent Adverse Events

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA Preferred Term	Parecoxib 40/20 mg N=52	Placebo N=53
Total preferred term events	3	0
Metabolism and nutrition disorders	1 (1.9)	0 (0)
Hypokalemia	1 (1.9)	0 (0)
Renal and urinary disorders	1 (1.9)	0 (0)
Renal failure acute	1 (1.9)	0 (0)
Skin and subcutaneous tissue disorders	1 (1.9)	0 (0)
Hyperhidrosis	1 (1.9)	0 (0)

Adverse events and serious adverse events are not separated out.
Subjects received parecoxib 40 mg or placebo administered IV given as a loading dose followed by parecoxib 20 mg or placebo administered IV every 12 hours until 48 hours after the end of surgery.
Subjects were counted only once per treatment in each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (version 13.1) coding dictionary applied.
IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each group.

All-Causality and Treatment-Related SAEs: Table 18 presents treatment-emergent SAEs (all-causalities and treatment-related) reported during the study.

There was a discrepancy in the number of subjects having an SAE between the centralized safety database (Table 18) and the clinical study database (Table 15). According to the centralize safety database, there were 13 subjects in the parecoxib 40/20 mg arm and 7 subjects in the placebo arm who had 1 or more SAEs. The majority of the SAEs were AEs that led to prolongation of hospitalizations post therapy.

According to the Investigator, 1 subject from the parecoxib 40/20 mg arm had 2 SAEs that were considered to be related to the study treatment (Table 18). A 64-year-old White male subject was diagnosed with prostate cancer (duration of 0.13 years). The subject had a past history of appendicitis and present histories for hyperuricemia and seasonal allergy. The subject received his last dose of parecoxib on Day 3. On Day 9, the subject had an infected lymphocele and urinary tract infection that were serious and related to the surgical procedure. The subject also had pyrexia on Day 9 and wound infection on Day 10 that were both related to the surgical procedure. On Day 15 the subject had acute renal failure that was serious and related to the study treatment. The subject had an abnormal creatinine level of 2.0 mg/dL (normal range = 0-1.2 mg/dL) on Day 26. On Day 32, he had a gastric ulcer that was serious and related to the study treatment.

SAEs from all other subjects were considered to be unrelated to the study treatment.

Table 18. Serious Adverse Events

Serial Number	MedDRA Preferred Term	Therapy Stop Day	SAE Start Day	SAE Stop Day	Inv/Spon Causality	Outcome
Parecoxib 40/20 mg						
1	Urinary tract infection	3	10	14	Unr/Unr	Recovered/Resolved
2	Deep vein thrombosis	3	9	N/A	Unr/Unr	Not recovered/Not resolved
3	Lymphoedema	3	3	15	Unr/Unr	Recovered/Resolved
4	Fistula	3	5	27	Unr/Unr	Recovered/Resolved
5	Pelvic hematoma	3	7	7	Unr/Unr	Recovered/Resolved
6	Urinary retention	3	6	11	Unr/Unr	Recovered/Resolved
7	Lymphocele	3	8	10	Unr/Unr	Recovered/Resolved
8	Angina pectoris	3	5	6	Unr/Unr	Recovered/Resolved
	Paresthesia	3	5	6	Unr/Unr	Recovered/Resolved
9	Lymphocele	3	7	9	Unr/Unr	Recovered/Resolved
	Urinary retention	3	17	17	Unr/Unr	Recovered/Resolved
10	Urinary retention	3	10	17	Unr/Unr	Recovered/Resolved
11	Lymphocele	3	14	15	Unr/Unr	Recovered/Resolved
12	Infected lymphocele	3	9	11	Unr/Unr	Recovered/Resolved
	Renal failure acute	3	15	25	Rel/Rel	Recovered/Resolved
	Urinary tract infection	3	10	26	Unr/Unr	Recovered/Resolved
	Anemia	3	27	28	Unr/Rel	Recovered/Resolved
	Gastric ulcer	3	32	N/A	Rel/Rel	Recovering/Resolving[a]
13	Lymphocele	3	10	12	Unr/Unr	Recovered/Resolved
Placebo						
14	Confusional state	3	4	5	Unr/Unr	Recovered/Resolved
15	Infected lymphocele	3	22	28	Unr/Unr	Recovered/Resolved
16	Lymphocele	3	8	11	Unr/Unr	Recovered/Resolved
17	Lymphocele	3	15	21	Unr/Unr	Recovered/Resolved
	Genitourinary tract infection	3	15	30	Unr/Unr	Recovered/Resolved
	Renal failure	3	15	42	Unr/Unr	Recovered/Resolved
	Anemia	3	15	N/A	Unr/Unr	Recovering/Resolving[a]
	Diarrhea	3	15	32	Unr/Unr	Recovered/Resolved
18	Lymphocele	3	17	19	Unr/Unr	Recovered/Resolved
	Wound infection	3	17	19	Unr/Unr	Recovered/Resolved
19	Tachycardia	3	2	3	Unr/Unr	Recovered/Resolved
20	Hemorrhage	1	12	13	Unr/Unr	Recovered/Resolved

Subjects received parecoxib 40 mg or placebo administered IV given as a loading dose followed by parecoxib 20 mg or placebo administered IV every 12 hours until 48 hours after the end of surgery.
IV = intravenous; Inv = Investigator; MedDRA = Medical Dictionary for Regulatory Activities Version 13.1; N/A = not available or not applicable; Rel = related; SAE = serious adverse event; Spon = Sponsor; Unr = unrelated.
a. at the time of last follow-up or study completion.

Deaths: There were no deaths in the study.

Permanent Discontinuations due to AEs: One subject from the parecoxib 40/20 mg arm discontinued the study due to severe hyperhidrosis. The AE developed 20 minutes after the subject received the study treatment and lasted for 3 days (Days 1 to 3). The Investigator considered the event to be related to the study treatment but not serious.

Dose Reductions or Temporary Discontinuations due to AEs: There were no dose reductions or temporary discontinuations due to AEs.

Blood Loss: The difference in blood loss between treatments was not statistically significant (LS mean difference [parecoxib 40/20 mg-placebo] in blood loss was -0.07, p-value=0.810) (Table 6). One (2%) subject from each group had 1 unit of blood transfused within the first

48 hours after surgery. Four (8%) subjects from the parecoxib 40/20 mg group and 1 (2%) subject from the placebo group had 2 units of blood transfused within the first 48 hours after surgery (Table 5).

Safety Related Findings in Vital Signs and Clinical Laboratory Tests: None of the changes in vital signs were of clinical concern.

Forty-three (83%) out of 52 subjects in the parecoxib 40/20 mg arm and 36 (68%) out of 53 subjects in the placebo arm had 1 or more abnormal laboratory values. The majority of the laboratory abnormalities were the types of abnormalities consistent with an individual who had just undergone a surgical procedure (decreases in hemoglobin, hematocrit, and RBCs) and thus none of these changes were considered to be clinically meaningful.

There was 1 subject who had a clinically significant abnormal laboratory finding that was considered to be related to the study treatment. One subject from the parecoxib 40/20 mg arm had mild hypokalemia during the study. The potassium level was 3.8 mmol/L on Day 0, 3.1 mmol/L on Day 2, and 3.2 mmol/L on Day 3 (normal range=3.5 to 5.1 mmol/L). The hypokalemia was still ongoing at the time of study completion.

Other clinically significant abnormal laboratory findings that were not considered to be related to the study treatment included: anemia (6 subjects in the parecoxib 40/20 mg arm and 4 subjects in the placebo arm), thrombocytosis, activated partial thromboplastin time abnormal, and RBC count decreased (1 subject each in the parecoxib 40/20 mg arm), and blood potassium decreased (2 subjects in the parecoxib 40/20 mg arm).

CONCLUSIONS:

- The cumulative amount of morphine (bolus plus PCA) used in the parecoxib 40/20 mg group was statistically significantly lower than that used by subjects in the placebo group (LS means difference 7.58 mL, p-value=0.035) thus demonstrating the opioid-sparing effect of parecoxib 20 mg. Similar findings were observed using the ANOVA model for the mITT population, however, the differences were not significant (p-value=0.059).

- Parecoxib 40/20 mg was safe and well tolerated in this subject population. One subject from each group had 1 unit of blood transfused within the first 48 hours after surgery. Four subjects from the parecoxib 40/20 mg group and 1 subject from the placebo group had 2 units of blood transfused within the first 48 hours after surgery.