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**PROPRIETARY DRUG NAME/INN:** Bextra<sup>®</sup> / Valdecoxib

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** See USPI

**PROTOCOL NO.:** A3471109

**PROTOCOL TITLE:** A Multicenter, Double-Blind, Placebo-Controlled, Randomized Study of the Analgesic Efficacy and Safety of Valdecoxib 20 mg QD and Valdecoxib 20 mg BID Compared to Placebo Over Multiple Days for Management of Acute Postsurgical Pain in Patients Undergoing Anterior Cruciate Ligament Reconstruction

**Study Center(s):** Thirty-five (35) centers in the United States (US) and Canada

**Study Initiation and Completion Dates:** 17 March 2004 to 18 February 2005

**Phase of Development:** Phase 3

### **Study Objective(s):**

*Primary:* To evaluate the analgesic efficacy of valdecoxib 20 mg once a day (QD) and valdecoxib 20 mg twice a day (BID) compared with placebo in outpatients with moderate or severe pain on postoperative Days 2 to 3 after arthroscopic anterior cruciate ligament (ACL) reconstruction surgery

*Secondary:* To compare each valdecoxib dose with placebo on postoperative Days 2 to 5 on additional measures of efficacy, including measures of pain intensity, health outcomes, the use of rescue medication, and the occurrence of opioid-related symptoms, and to evaluate the safety of both doses of valdecoxib

## **METHODS**

**Study Design:** Multicenter, double-blind, randomized, placebo-controlled, multiple-dose, parallel-group study. The study consisted of a pretreatment/screening period, two treatment periods (a single-blind period lasting 1 day and a double-blind period lasting 4 days) and a post-treatment visit within 7 days of the last dose of study medication. During the single-blind phase, all eligible subjects received valdecoxib 40 mg followed by 20 mg on Day 1; during the double-blind period subjects were randomized 1:1:1 to treatment with either valdecoxib 20 mg BID, valdecoxib 20 mg QD followed by placebo QD or placebo BID.

### **Number of Patients (planned and analyzed):**

*Planned:* 450 subjects (150 subjects per treatment group)

## CLINICAL STUDY SYNOPSIS

*Analyzed:* 488 subjects (158 subjects in the valdecoxib 20 mg BID group, 163 subjects in the valdecoxib 20 mg QD group and 167 subjects in the placebo group)

**Diagnosis and Main Criteria for Inclusion:** Study included male or non-pregnant female subjects in satisfactory health (as determined by the investigator), aged 18 to 75 years, who had uncomplicated arthroscopic ACL reconstruction. Subjects were to have a Baseline pain intensity of  $\geq 50$  mm as measured on a 0 - 100mm visual analogue scale (VAS) and moderate to severe pain on a categorical scale by 23:00 hours on the day of surgery and prior to being discharged from the surgical facility. Subjects were not to have had received any medication or additional procedures that would be a confounding factor of the study. Specifically excluded after the subject was randomized were systemic corticosteroids, NSAIDs, selective Cox-2 inhibitors (other than study medication), tramadol (Ultram<sup>®</sup>), and other analgesics by any route, including a pain pump or indwelling catheter inserted during surgery for the purpose of repeated postoperative administration of anesthetics or narcotics at the index joint. The only exception was  $\leq 325$  mg of aspirin.

**Study Treatment:** Valdecoxib 20 mg capsule-shaped, white film-coated tablets, or matched placebo. All study medication was taken orally. Treatment assignment was stratified by center and according to the patient's pain intensity (PI) (categorical) at Baseline on Day 1. Following surgery on Day 1 of the study, all patients received valdecoxib 40 mg (2 valdecoxib 20-mg tablets) followed by a second dose of 20 mg valdecoxib either upon request for additional analgesia from 1 to 12 hours after the first dose or, if no additional analgesia was requested, 12 hours after the first dose, but no later than midnight on Day 1. On Days 2 to 5, subjects were randomized 1:1:1 to receive double-blind treatment with either valdecoxib 20 mg BID, valdecoxib 20 mg QD plus placebo QD or placebo BID (one tablet in the morning and one in the evening).

Rescue medication, if required, consisted of 1 to 2 tablets of Vicodin<sup>®</sup> (hydrocodone 5mg/acetaminophen 500 mg) every 4 to 6 hours as needed, open-label, not to exceed 8 tablets per day, after having taken the first 2 doses of blinded study medication.

### **Efficacy Evaluations:**

#### *Primary:*

- Summed Pain Intensity (categorical) through 24 hours (SPI 24) on Days 2 and 3
- Patient's Global Evaluation of Study Medication (PGESM) for Days 2 and 3

#### *Secondary:*

On Days 4 and 5:

- SPI 24 (categorical)
- PGESM

On Days 2 to 5, for each study day:

- Time-specific PI (categorical)
- SPI 24 (VAS)
- Time-specific PI (VAS)
- Time to first dose of rescue medication (supplemental analgesia)

## CLINICAL STUDY SYNOPSIS

- Percent of subjects who took rescue medication (supplemental analgesia)
- Amount of rescue medication taken (supplemental analgesia)
- Time between doses of study medication
- Worst Pain Intensity (derived from the Modified Brief Pain Inventory Short Form [mBPI-sf])
- Average Pain Intensity (derived from the mBPI-sf)
- Opioid-related Symptom Distress Scale Questionnaire (OR-SDS)
- Individual and Composite Pain Interference With Function score (derived from the mBPI-sf)
- Post-Discharge Recovery Experience
- Patient Satisfaction Questionnaire

**Safety Evaluations:** Evaluations included incidence of treatment-emergent adverse events (AEs), and changes in clinical laboratory values, vital signs, and physical examination from Baseline Day 1 to the Final post-treatment visit.

### Statistical Methods:

*Efficacy:* All statistical analyses for efficacy were performed on the modified intent-to-treat (MITT) cohort, defined as all randomized patients who took at least 1 dose of study medication on Day 2. All statistical tests were performed at a 0.05 significance level. No multiple comparison adjustments were made.

Daily time-interval weighted SPI, on days 2 - 5, was calculated by weighting the pain intensity scores by the time interval between successive scheduled assessments and summing over the total time period assessed.

SPI 24 and time specific PI were analyzed using a general linear model with treatment and center as factors, and baseline pain intensity as covariate. A similar method, omitting the covariate, was used to analyze the total number of tablets of rescue analgesia taken on each day.

PGESM and Patient Satisfaction Questionnaire scores were analyzed using the Cochran-Mantel-Haenszel (CMH) method, controlling for center. Missing results were imputed using the last observation carried forward (LOCF) technique.

Daily responses to the mBPI-sf pain-intensity questions were analyzed using analysis of variance (ANOVA) with treatment and center as factors and baseline pain intensity as a covariate. Exploratory mBPI-sf calculations and analyses were similarly conducted and included summation of assessments taken on Days 3 to 6 or early termination of the worst and average pain items. Each of the eight items of the mBPI-sf designed to assess pain interference with function was individually analyzed as well as a pain interference composite score being calculated from all 8 items combined. Additionally, a 5-item pain interference composite score (consisting of the items general activity, walking ability, mood, sleep and relations with others) was calculated. Missing components of the mBPI-sf were imputed using LOCF.

Median times to first dose of rescue medication and to second dose of study medication, with corresponding 95% confidence intervals, were determined using the Kaplan-Meier estimator.

## CLINICAL STUDY SYNOPSIS

The distributions of times were analyzed using a log-rank test. The time between doses of study medication was summarized.

Analysis of OR-SDS scores was based on observed data only. Mean scores were calculated for each symptom for each of the three symptom dimensions (frequency, severity, and level of bother); averaging these three dimensions by item and across all items resulted in Multidimensional Averages and the overall Multidimensional Average, respectively. Mean values were compared across treatment groups. Composite 10-item average scores were also calculated for each dimension. Exploratory summed average scores were calculated by area-under-the-curve (AUC) methods to estimate the overall Multidimensional Average across Days 2 to 5.

Summary statistics were presented for the number of patient-days, by treatment group, with episodes of each OR-SDS symptom and by days with any OR-SDS symptom. The percentages of patients in each treatment group reporting clinically meaningful events (CMEs) were tabulated. CMEs were defined as a patient-reported symptom judged to be on the upper end of the distress continuum for frequency, bother, or severity. A symptom episode/event was classified as a CME if any of the following criteria were met:

- Subjects rated the frequency dimension as “frequently” or “almost constantly”
- Subjects rated the severity dimension as “moderate”, “severe”, or “very severe”
- Subjects rated the bother dimension as “quite a bit” or “very much”.

Treatment groups were compared using Fisher’s exact test as well as Poisson and logistic regression methods. The number of days a patient experienced specific CMEs was tested using the Mantel-Haenszel Chi-square test for trend; relative risks were calculated using Poisson regression.

*Safety:* Analyses for safety measures included all randomized patients who received at least 1 dose of study medication. All AEs, serious AEs and AEs leading to discontinuation were summarized by treatment group and compared between treatment groups using a Fisher’s exact test.

Clinical laboratory data and changes in vital signs from Baseline to Final were compared between treatment groups using analysis of covariance (ANCOVA) using pairwise treatment comparisons with treatment group as a factor and Baseline value as a covariate.

## RESULTS

**Subject Disposition and Demography:** A summary of subject disposition is presented in Table S1.

## CLINICAL STUDY SYNOPSIS

**Table S1 Subject Disposition**

	Placebo	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID
	Number (%) subjects		
Randomized	170	167	162
Treated	169 (99.4)	166 (99.4)	162 (100.0)
Completed	158 (93.5)	161 (96.4)	151 (93.2)
Discontinued	11 (6.5)	5 (3.0)	11 (6.8)

A summary of demographic characteristics is given in Table S2.

**Table S2 Baseline Demographic Characteristics: All Randomized Patients**

	Placebo N = 170	Valdecoxib 20 mg QD N = 167	Valdecoxib 20 mg BID N = 162
Age (Years), mean (SD)	32.5 (10.29)	32.0 (9.93)	32.8 (9.67)
Gender			
Male, N (%)	112 (65.9)	106 (63.5)	116 (71.6)
Female, N (%)	58 (34.1)	61 (36.5)	46 (28.4)
Race/Ethnic Origin, N (%)			
White	150 (88.2)	147 (88.0)	134 (82.7)
Black	14 (8.2)	14 (8.4)	16 (9.9)
Other	6 (3.5)	6 (3.6)	12 (7.4)
Height (cm), mean (SD)	174.1 (10.12)	174.8 (10.14)	175.1 (9.99)
Weight (kg), mean (SD)	82.33 (17.62)	85.40 (18.23)	84.5 (18.72)

### Efficacy Results:

#### *Primary Efficacy Measures*

Results of the evaluations of SPI (categorical) over 24 hours and PGESM on Days 2 and 3 are presented in Tables S3 and S4, respectively.

## CLINICAL STUDY SYNOPSIS

**Table S3 Sum of Pain Intensity (Categorical Scale) Over 24 Hours on Days 2 and 3**

	Placebo	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID
<b>Day 2</b>	N=164	N=160	N=154
Mean (standard deviation)	40.90 (14.28)	42.09 (15.66)	40.69 (16.22)
LS Mean	39.94 A	41.62 A	39.82 A
<b>Day 3</b>	N=161	N=159	N=153
Mean (standard deviation)	40.11 (16.06)	36.28 (15.94)	34.31 (16.63)
LS Mean	39.79 B	36.27 A	34.14 A

SPI 24 ranges from 0 to 72; larger number indicates more pain.

Treatments with same letter are not significantly different from each other.

**Table S4 Patient's Global Evaluation of Study Medication on Days 2 and 3**

	Placebo	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID	p-Values <sup>a</sup>		
				Valdecoxib 20 mg QD vs Placebo	Valdecoxib 20 mg BID vs Placebo	Valdecoxib 20 mg QD vs Valdecoxib 20 mg BID
<b>Day 2 (%)</b>				0.541	0.470	0.880
Excellent	7	13	12			
Good	40	37	39			
Fair	45	39	38			
Poor	8	11	10			
<b>Day 3 (%)</b>				0.006	0.002	0.945
Excellent	7	19	18			
Good	40	40	46			
Fair	40	32	25			
Poor	13	9	11			

<sup>a</sup>Compared with placebo using Cochran-Mantel-Haenszel test adjusted by center using modified ridit as score.

### *Secondary Efficacy Measures:*

Results of SPI (categorical) over 24 hours on Days 4 and 5 are presented in Table S5, below.

**Table S5 Sum of Pain Intensity (Categorical Scale) Over 24 Hours on Days 4 and 5**

	Placebo	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID
<b>Day 4</b>	N=159	N=158	N=151
Mean (standard deviation)	35.31 (15.96)	31.71 (17.21)	29.34 (16.50)
LS Mean	34.58 B	31.30 AB	28.56 A
<b>Day 5</b>	N=157	N=157	N=148
Mean (standard deviation)	35.96 (14.90)	30.44 (16.74)	28.24 (17.28)
LS Mean	34.66 B	29.67 A	27.10 A

SPI 24 ranges from 0 to 72; larger number indicates more pain.

Treatments with same letter are not significantly different from each other.

Results for PGESM on Days 4 and 5 are summarized in Table S6.

## CLINICAL STUDY SYNOPSIS

**Table S6 Patient's Global Evaluation of Study Medication on Days 4 and 5**

	Placebo	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID	p-Values <sup>a</sup>		
				Valdecoxib 20 mg QD vs Placebo	Valdecoxib 20 mg BID vs Placebo	Valdecoxib 20 mg QD vs Valdecoxib 20 mg BID
<b>Day 4 (%)</b>				<0.001	0.007	0.289
Excellent	11	22	19			
Good	40	47	46			
Fair	35	25	26			
Poor	14	7	9			
<b>Day 5 (%)</b>				<0.001	0.009	0.183
Excellent	11	28	22			
Good	42	40	43			
Fair	33	23	25			
Poor	14	9	10			

<sup>a</sup>Compared with placebo using Cochran-Mantel-Haenszel test adjusted by center using modified ridit as score.

Results of SPI (VAS) over 24 hours on Days 2 to 5 are summarized in Table S7.

**Table S7 Summed Pain Intensity (VAS) Over 24 Hours on Days 2 - 5**

	Placebo	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID
<b>Day 2</b>	N=164	N=160	N=155
Mean (standard deviation)	1201.9 (529.27)	1222.8 (544.22)	1127.2 (563.45)
LS Mean	1171.6 AB	1203.6 B	1089.2 A
<b>Day 3</b>	N=159	N=160	N=153
Mean (standard deviation)	1172.1 (558.15)	993.3 (560.00)	913.8 (578.95)
LS Mean	1175.2 B	1001.7 A	906.8 A
<b>Day 4</b>	N=158	N=158	N=151
Mean (standard deviation)	1005.0 (560.14)	837.9 (563.37)	757.76 (571.56)
LS Mean	985.5 B	826.0 A	724.7 A
<b>Day 5</b>	N=157	N=156	N=148
Mean (standard deviation)	1030.5 (553.33)	767.4 (565.92)	708.6 (570.93)
LS Mean	991.3 B	737.7 A	659.3 A

The summed pain intensity (visual analogue score) over 24 hours ranged from 0 to 2400; larger number indicates more pain.

Treatments with same letter are not significantly different from each other.

Results of time between doses of study medication on Days 2 to 5 are summarized in Table S8, below.

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## CLINICAL STUDY SYNOPSIS

**Table S8 Patients Who Received 2 Doses of Study Medication and Time Between Doses on Days 2-5**

	<b>Placebo</b>	<b>Valdecoxib 20 mg QD</b>	<b>Valdecoxib 20 mg BID</b>
<b>Day 2, N (%)</b>	N=167	N=163	N=158
Number (%) subjects receiving 2 doses of study medication	163 (97.6)	163 (100.0)	150 (94.9)
Time Between Doses (Hours)			
Mean (standard deviation) [Median]	4.9 (3.67) [3.8]	5.8 (4.09) [4.7]	5.5 (3.99) [4.3]
Range	0.9 – 12.3	0.9 – 17.5	1.0 – 12.3
<b>Day 3, N (%)</b>	N=163	N=162	N=154
Number (%) subjects receiving 2 doses of study medication	158 (96.9)	162 (100.0)	151 (98.1)
Time Between Doses (Hours)			
Mean (standard deviation) [Median]	5.6 (3.74) [4.7]	6.8 (4.28) [6.8]	6.5 (3.94) [6.3]
Range	0.3 – 12.3	1.0 – 16.3	1.0 – 12.3
<b>Day 4, N (%)</b>	N=159	N=161	N=153
Number (%) subjects receiving 2 doses of study medication	156 (98.1)	156 (96.9)	147 (96.1)
Time Between Doses (Hours)			
Mean (standard deviation) [Median]	6.6 (4.14) [5.9]	7.3 (4.22) [8.3]	7.6 (3.90) [8.3]
Range	0.8 – 14.8	0.8 – 16.7	1.0 – 13.7
<b>Day 5, N (%)</b>	N=158	N=161	N=151
Number (%) subjects receiving 2 doses of study medication	155 (98.1)	158 (98.1)	145 (96.0)
Time Between Doses (Hours)			
Mean (standard deviation) [Median]	6.3 (4.06) [5.8]	7.7 (4.12) [8.6]	7.5 (4.11) [8.2]
Range	0.5 – 12.5	0.8 – 15.2	1.0 – 14.0

Results for the number of subjects who took rescue medication and time to first dose of rescue medication on Days 2 to 5 are presented in Table S9.

## CLINICAL STUDY SYNOPSIS

**Table S9 Percent Subjects Taking Rescue Medication and Time to First Dose of Rescue Medication on Days 2 to 5**

	Placebo	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID
<b>Day 2</b>	N=167	N=163	N=158
Number (%) taking rescue medication	144 (86.2)	135 (82.8)	131 (82.9)
Median time, HH:MM	07:25 A	07:16 A	08:40 A
95% Confidence Interval	05:43, 09:05	05:38, 09:42	06:55, 10:00
<b>Day 3</b>	N=163	N=162	N=154
Number (%) taking rescue medication	126 (77.3)	115 (71.0)	108 (70.1)
Median time, HH:MM	08:11 A	10:30 A	11:00 A
95% Confidence Interval	06:45, 09:53	07:15, 13:45	08:51, 14:20
<b>Day 4</b>	N=159	N=161	N=153
Number (%) taking rescue medication	113 (71.1)	102 (63.4)	89 (58.2)
Median time, HH:MM	11:04 B	13:17 AB	15:55 A
95% Confidence Interval	08:05, 13:12	10:47, 15:25	12:54, 20:40
<b>Day 5</b>	N=158	N=161	N=151
Number (%) taking rescue medication	118 (74.7)	98 (60.9)	84 (55.6)
Median time, HH:MM	10:22 B	15:59 A	16:25 A
95% Confidence Interval	08:29, 12:20	14:01, 16:50	12:47, >24:00

HH:MM= hours:minutes.

Treatments with same letter are not significantly different from each other.

Table S10 summarizes the amount of rescue medication taken on Days 2 to 5

**Table S10 Number of Tablets of Rescue Medication Taken on Days 2 to 5**

	Placebo N=167	Valdecoxib 20 mg QD N=163	Valdecoxib 20 mg BID N=158
<b>Day 2, N</b>	167	163	158
Mean (standard deviation)	3.44 (2.86)	3.56 (3.03)	3.16 (2.69)
LS Mean	3.08 A	3.27 A	2.80 A
<b>Day 3, N</b>	163	162	155
Mean (standard deviation)	3.19 (2.82)	2.86 (2.09)	2.54 (2.72)
LS Mean	2.99 B	2.73 AB	2.35 A
<b>Day 4, N</b>	159	161	153
Mean (standard deviation)	2.70 (2.52)	2.16 (2.41)	1.98 (2.41)
LS Mean	2.56 B	2.06 AB	1.80 A
<b>Day 5, N</b>	158	161	151
Mean (standard deviation)	2.70 (2.51)	2.02 (2.38)	1.73 (2.29)
LS Mean	2.55 B	1.94 A	1.57 A

Treatments with same letter are not significantly different from each other.

Results on time-specific PI on Days 2 to 5 are presented in Table S11, below.

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**Table S11 Mean Time-Specific Pain Intensity on Days 2 to 5**

Day/Time Post First Dose (hours)	Categorical Scale <sup>a</sup>						Visual Analogue Scale <sup>b</sup>						
	Placebo		Valdecoxib 20 mg QD		Valdecoxib 20 mg BID		Placebo		Valdecoxib 20 mg QD		Valdecoxib 20 mg BID		
<b>Day 2</b>	0	1.38	A	1.46	A	1.36	A	38.73	A	40.28	A	37.21	A
	2	1.33	A	1.40	A	1.35	A	37.76	A	39.37	A	36.81	A
	4	1.47	A	1.52	A	1.52	A	41.79	A	43.57	A	40.58	A
	8	1.66	A	1.70	A	1.68	A	48.38	A	48.55	A	45.80	A
	12	1.78	A	1.83	A	1.79	A	52.83	A	53.32	A	50.06	A
	16	1.85	A	1.91	A	1.81	A	55.11	AB	56.47	B	50.71	A
	24	1.89	A	1.91	A	1.84	A	56.70	B	56.69	B	51.74	A
<b>Day 3</b>	0	1.44	AB	1.52	B	1.33	A	41.67	B	40.88	B	35.67	A
	2	1.33	A	1.26	A	1.19	A	38.01	B	32.92	AB	30.82	A
	4	1.51	B	1.30	A	1.27	A	43.17	B	35.51	A	33.06	A
	8	1.66	B	1.46	A	1.42	A	48.55	B	40.25	A	37.36	A
	12	1.74	B	1.54	A	1.48	A	51.19	B	41.61	A	39.81	A
	16	1.77	B	1.62	AB	1.51	A	52.01	B	44.82	A	40.74	A
	24	1.82	B	1.64	AB	1.52	A	53.47	B	45.91	A	41.05	A
<b>Day 4</b>	0	1.28	A	1.26	A	1.13	A	36.65	B	32.31	AB	28.31	A
	2	1.21	B	1.11	B	0.93	A	32.62	B	27.97	AB	23.61	A
	4	1.26	B	1.12	AB	1.02	A	34.49	B	28.35	A	24.76	A
	8	1.48	B	1.26	A	1.16	A	42.10	B	32.05	A	29.49	A
	12	1.52	B	1.34	AB	1.27	A	44.10	B	35.72	A	32.86	A
	16	1.57	B	1.42	AB	1.33	A	45.14	B	39.07	A	35.40	A
	24	1.60	B	1.49	AB	1.38	A	46.02	B	39.77	A	36.54	A
<b>Day 5</b>	0	1.27	A	1.24	A	1.09	A	35.47	B	31.05	AB	26.27	A
	2	1.24	B	1.02	A	1.01	A	33.16	B	24.56	A	23.78	A
	4	1.28	B	1.10	A	1.03	A	36.40	B	26.85	A	25.00	A
	8	1.42	B	1.22	A	1.12	A	40.30	B	29.53	A	27.32	A
	12	1.57	B	1.29	A	1.21	A	45.48	B	32.59	A	30.80	A
	16	1.64	B	1.36	A	1.26	A	47.60	B	34.96	A	32.59	A
	24	1.66	B	1.42	A	1.29	A	47.70	B	36.68	A	32.93	A

<sup>a</sup>Categorical scale: 0= None; 1= Mild; 2= Moderate; 3= Severe; <sup>b</sup>VAS ranges from 0 (no pain) to 100 (pain as bad as you can imagine)

Treatments with same letter are not significantly different from each other.

Modified Brief Pain Inventory– Short Form.

Results for PI and pain interference with function derived from mBPI-sf are presented in Tables S12 and S13, respectively.

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## CLINICAL STUDY SYNOPSIS

**Table S12 Worst and Average Pain Intensity (From mBPI-sf) on Days 2 to 5**

		Placebo		Valdecoxib 20 mg QD		Valdecoxib 20 mg BID	
<b>Day 2</b>	Worst Pain Intensity (Mean)	5.75	A	6.01	A	5.78	A
	Average Pain Intensity (Mean)	3.83	A	3.89	A	3.76	A
<b>Day 3</b>	Worst Pain Intensity (Mean)	5.19	A	5.09	A	4.80	A
	Average Pain Intensity (Mean)	3.37	A	3.12	A	2.92	A
<b>Day 4</b>	Worst Pain Intensity (Mean)	4.94	B	4.50	AB	4.06	A
	Average Pain Intensity (Mean)	3.18	B	2.81	AB	2.56	A
<b>Day 5</b>	Worst Pain Intensity (Mean)	4.89	B	4.23	AB	4.12	A
	Average Pain Intensity (Mean)	3.15	B	2.52	A	2.44	A

Pain intensity scale ranges from 0 (no pain) through 10 (pain as bad as you can imagine).  
Treatments with same letter are not significantly different from each other.

**Table S13 Pain Interference With Function (mBPI-sf) on Days 2 to 5**

Treatment Group Comparison	Study Day			
	2	3	4	5
<b>Valdecoxib 20 mg QD Versus Placebo</b>				
5-Item Composite <sup>a</sup>				X
8-Item Composite <sup>b</sup>			X	X
General Activity				
Mood				X
Walking Ability				
Relations With Others			X	
Sleep			X	X
Coughing				X
Breathing				X
Concentration				
<b>Valdecoxib 20 mg BID Versus Placebo</b>				
5-Item Composite <sup>a</sup>			X	
8-Item Composite <sup>b</sup>			X	X
General Activity				
Mood				
Walking Ability				
Relations With Others			X	
Sleep			X	X
Coughing				
Breathing				
Concentration			X	X

Note: "X" denotes significance at p= 0.05 comparing each valdecoxib dose with placebo.

<sup>a</sup>The Average of Mood, Walking Ability, Relations with Others, Sleep, and Concentration for 5-item composite.

<sup>b</sup>The Average of General Activity, Mood, Walking Ability, Relations with Others, Sleep, Coughing, Deep Breathing, and Concentration for 8-item composite.

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A summary of OR-SDS results is presented in Table S14.

**Table S14 Significant Reductions in Frequency, Severity, Bother, and Overall Scores for Individual Opioid-Related Symptoms**

Symptom	Day 2				Day 3				Day 4				Day 5			
	F <sup>†</sup>	S <sup>†</sup>	B <sup>†</sup>	O <sup>†</sup>	F <sup>†</sup>	S <sup>†</sup>	B <sup>†</sup>	O <sup>†</sup>	F <sup>†</sup>	S <sup>†</sup>	B <sup>†</sup>	O <sup>†</sup>	F <sup>†</sup>	S <sup>†</sup>	B <sup>†</sup>	O <sup>†</sup>
<b>Valdecoxib 20 mg QD versus Placebo</b>																
Fatigue											X			X	X	
Drowsiness																
Concentration																
Nausea																
Dizziness													X	X	X	X
Constipation													X	X	X	X
Itching																
Urination																
Confusion																
Retching/Vomiting																
<b>Valdecoxib 20 mg BID versus Placebo</b>																
Fatigue									X	X	X	X		X	X	
Drowsiness			X						X	X	X	X				
Concentration																
Nausea			X													
Dizziness													X	X	X	X
Constipation									X	X	X	X	X	X	X	X
Itching																
Urination																
Confusion									X	X	X	X				
Retching/Vomiting																

X= Significant at P= 0.05.

<sup>†</sup>F, S, B, O= Frequency, Severity, Bother, and Overall (the average of frequency, severity, and bother), respectively. Unlike the other 9 symptoms rated by a 5-point scale (0= no symptom through 4= almost constantly), the frequency of Retching/Vomiting was recorded as a number of episodes and is hence excluded from the analyses in this table.

A summary of the relative risk of experiencing a study day with an opioid-related clinically meaningful event is presented in Table S15 for the comparison of valdecoxib 20 mg QD with placebo and Table S16 for the comparison of valdecoxib 20 mg BID with placebo.

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**Table S15 Relative Risk of Experiencing a Study Day With an Opioid-Related Clinically Meaningful Event (CME): Valdecoxib 20 mg QD Versus Placebo Across Study Days 2 to 5**

	Placebo		Valdecoxib 20 mg QD		Relative Risk RR (95% CI)	% CME Prevented/Attributed	
	Total CME Days/Total Days	Incidence Rate	Total CME Days/Total Days	Incidence Rate		% (95% CI) <sup>a, b</sup>	p- Value <sup>c</sup>
Days with at least 1 CME	314/647	0.49	301/647	0.47	0.96	4.1 (18.4, -11.2)	0.600
Days with at least 2 CMEs	204/647	0.32	173/647	0.27	0.85	15.2 (31.2, -4.2)	0.111
Days with at least 3 CMEs	112/647	0.17	92/647	0.14	0.82	17.9 (38.3, -8.4)	0.162
Clinically Meaningful Events							
Fatigue	162/647	0.25	128/647	0.20	0.79	21.0 (0.00, 37.8)	0.046*
Drowsiness	163/647	0.25	164/647	0.25	1.01	0.61 (20.5, -19.5)	0.956
Inability to concentrate	74/647	0.11	79/647	0.12	1.07	6.3 (32.7, -23.2)	0.686
Nausea	46/647	0.07	40/647	0.06	0.87	13.0 (44.5, -26.4)	0.518
Dizziness	37/647	0.06	32/647	0.05	0.86	13.5 (47.8, -29.9)	0.548
Constipation	113/647	0.17	85/647	0.13	0.75	24.8 (0.00, 43.9)	0.047*
Itching	82/647	0.13	83/647	0.13	1.01	1.2 (28.1, -26.3)	0.938
Difficulty with urination	20/647	0.03	18/647	0.03	0.90	10.0 (55.1, -44.2)	0.746
Confusion	16/647	0.02	18/647	0.03	1.13	11.1 (57.6, -45.9)	0.732
Retching/Vomiting	5/647	0.01	8/647	0.01	1.60	37.5 (83.9, -53.8)	0.410

CME= Clinically Meaningful Event: Patient-reported opioid-related symptom judged to be on the upper distress continuum for frequency, severity, or bothersomeness.

<sup>a</sup>For RR <1, the prevented percent among the exposed is calculated as  $100 \times (1 - RR)$ . For RR  $\geq 1$ , the attributable percent among the exposed is calculated as  $100 \times (RR - 1)/RR$ . The confidence interval is obtained by similarly transforming the interval values for RR.

<sup>b</sup>A negative value indicates a change in interpretation, compared with the point estimate, from/to prevented percent to/from attributable percent (e.g., if RR < 1 and an interval % CME prevented is negative, the interval interpretation changes from prevented to attributable percentage).

<sup>c</sup>\*Statistically significant at p=0.05. p-Values shown are from Poisson regression, adjusted for total days exposed to study medication.

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**Table S16 Relative Risk of Experiencing a Study Day With an Opioid-Related Clinically Meaningful Event (CME): Valdecoxib 20 mg BID Versus Placebo Across Study Days 2 to 5**

	Placebo		Valdecoxib 20 mg BID		Relative Risk RR (95% CI)	% CME Prevented/Attributed	
	Total CME Days/Total Days	Incidence Rate	Total CME Days/Total Days	Incidence Rate		% (95% CI) <sup>a, b</sup>	p- Value <sup>c</sup>
Days with at least 1 CME	314/647	0.49	255/616	0.41	0.85	14.7 (28.0, -0.9)	0.059
Days with at least 2 CMEs	204/647	0.32	150/616	0.24	0.77	22.8 (4.2, 37.9)	0.016*
Days with at least 3 CMEs	112/647	0.17	77/616	0.13	0.72	27.8 (2.6, 46.7)	0.028*
Clinically Meaningful Events							
Fatigue	162/647	0.25	123/616	0.20	0.80	20.3 (37.4, -1.4)	0.058
Drowsiness	163/647	0.25	127/616	0.21	0.82	18.2 (35.6, -3.7)	0.090
Inability to Concentrate	74/647	0.11	64/616	0.10	0.91	9.2 (36.0, -22.3)	0.574
Nausea	46/647	0.07	35/616	0.06	0.80	20.1 (50.0, -21.1)	0.318
Dizziness	37/647	0.06	23/616	0.04	0.65	34.7 (63.0, -11.4)	0.108
Constipation	113/647	0.17	77/616	0.13	0.72	28.4 (3.5, 47.1)	0.024*
Itching	82/647	0.13	69/616	0.11	0.88	11.6 (36.8, -18.9)	0.450
Difficulty With Urination	20/647	0.03	28/616	0.05	1.47	32.0 (63.7, -20.1)	0.188
Confusion	16/647	0.02	7/616	0.01	0.46	54.0 (84.0, -15.3)	0.086
Retching/Vomiting	5/647	0.01	8/616	0.01	1.68	40.5 (84.7, -51.5)	0.363

CME= Clinically Meaningful Event: Patient-reported opioid-related symptom judged to be on the upper distress continuum for frequency, severity, or bothersomeness.

<sup>a</sup>For RR <1, the prevented percent among the exposed is calculated as  $100 \times (1 - RR)$ . For RR  $\geq 1$ , the attributable percent among the exposed is calculated as  $100 \times (RR - 1)/RR$ . The confidence interval is obtained by similarly transforming the interval values for RR.

<sup>b</sup>A negative value indicates a change in interpretation, compared with the point estimate, from/to prevented percent to/from attributable percent (e.g., if RR < 1 and an interval % CME prevented is negative, the interval interpretation changes from prevented to attributable percentage).

<sup>c</sup>\*Statistically significant at p= 0.05. p-Values shown are from Poisson regression, adjusted for total days exposed to study medication.

### Post-discharge recovery experience for Days 2 to 5

The Post-Discharge Recovery Experience Questionnaire surveyed patients with regard to the percentage of normal activities they performed and whether they contacted a health care professional for anything related to their ACL surgery during the four days immediately following surgery. The results are summarized in Table S17, below.

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**Table S17 Percentage of Normal Activities on Days 2 to 5**

Percentage of normal activities	Placebo	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID	P-value
Day 2	16.7	21.6	21.6	0.034
Day 3	23.4	30.0	30.7	0.005
Day 4	27.6	36.5	37.2	<0.001
Day 5	31.5	40.1	39.7	0.001

Treatment groups did not differ significantly for the percentage of patients contacting a health care professional on any postoperative day. Across all study days, the mean percentage of patients ranged from 84.0-92.5% for patients receiving placebo, 80.1-91.8% for patients receiving valdecoxib 20 mg QD, and 80.4-93.5% for patients receiving valdecoxib 20 mg BID.

A summary of patient satisfaction with pain relief questionnaire results (categorical ratings) is given in Table S18.

**Table S18 Summary of Patient Satisfaction With Pain Relief Questionnaire Results (Categorical Ratings) on Days 2 to 5**

	Placebo	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID
Day 2 Percentage of subjects somewhat or very satisfied with treatment	58% A	64% A	67% A
Day 3 Percentage of subjects somewhat or very satisfied with treatment	61% A	71% B	67% AB
Day 4 Percentage of subjects somewhat or very satisfied with treatment	61% A	77% B	72% B
Day 5 Percentage of subjects somewhat or very satisfied with treatment	60% A	72% B	71% B

Treatments with same letter are not significantly different from each other.

A similar pattern of results was observed for patient satisfaction with overall performance of study drug: differences in the distribution of categorical ratings were significant on Day 3 for the valdecoxib 20 mg QD treatment group (59% of placebo patients and 69% of valdecoxib 20 mg QD patients were Somewhat Satisfied or Very Satisfied), and on Day 4 (60% of placebo patients, 76% of valdecoxib 20 mg QD patients, and 71% of valdecoxib 20 mg BID patients were Somewhat Satisfied or Very Satisfied) and Day 5 (59% of placebo patients, 73% of valdecoxib 20 mg QD patients, and 72% of valdecoxib 20 mg BID patients were Somewhat Satisfied or Very Satisfied for both valdecoxib treatment groups, compared with placebo).

**Safety Results:** A summary of all AEs reported in  $\geq 2\%$  subjects in any treatment group is presented in Table S19, below.

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**Table S19 Summary of Treatment-Emergent Adverse Events in  $\geq 2\%$  of Patients in Any Treatment Group**

Body System Adverse Event <sup>a</sup>	Single-Blind Phase	Double-Blind Phase			p-Value Versus Placebo <sup>b</sup>	
	Valdecoxib 40mg/20 mg BID N (%)	Placebo N (%)	Valdecoxib 20 mg QD N (%)	Valdecoxib 20 mg BID N (%)	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID
Treated Patients	497	167	163	158	—	—
Any Event	109 (21.9)	62 (37.1)	64 (39.3)	49 (31.0)	—	—
<b>Body as a Whole</b>						
Edema Peripheral	0	6 (3.6)	9 (5.5)	7 (4.4)	—	—
Fatigue	0	9 (5.4)	6 (3.7)	8 (5.1)	—	—
Fever	0	7 (4.2)	4 (2.5)	1 (0.6)	—	0.068
<b>Nervous System Disorders</b>						
Dizziness	0	7 (4.2)	5 (3.1)	5 (3.2)	—	—
Headache	10 (2.0)	10 (6.0)	11 (6.7)	4 (2.5)	—	0.172
<b>Gastrointestinal System Disorders</b>						
Constipation	0	11 (6.6)	16 (9.8)	6 (3.8)	—	—
Nausea	54 (10.9)	14 (8.4)	15 (9.2)	11 (7.0)	—	—
Vomiting	26 (5.2)	4 (2.4)	4 (2.5)	3 (1.9)	—	—
<b>Psychiatric Disorders</b>						
Concentration Impaired	0	4 (2.4)	5 (3.1)	5 (3.2)	—	—
Insomnia	0	2 (1.2)	3 (1.8)	4 (2.5)	—	—
Somnolence	0	8 (4.8)	9 (5.5)	8 (5.1)	—	—
<b>Skin and Appendages</b>						
Pruritus	12 (2.4)	11 (6.6)	8 (4.9)	7 (4.4)	—	—
<b>Urinary System Disorders</b>						
Micturition Disorders	0	4 (2.4)	5 (3.1)	3 (1.9)	—	—

—Indicates p-value  $>0.20$ .

<sup>a</sup>A patient could have had more than 1 adverse event.

<sup>b</sup>p-Value from Fisher's exact test, double-blind phase only.

There were no deaths reported in this study.

There were two serious AEs reported during the study, one in the valdecoxib 20 mg QD group (thrombophlebitis deep) and one in the valdecoxib 20 mg BID group (bone disorder). Neither event was considered related to treatment.

Five subjects (1%) withdrew from the study on Day 1 (valdecoxib 40 mg followed by valdecoxib 20 mg) due to an AE. These AEs were nausea in three subjects and hypertonia, vomiting and bone disorder in one patient each. None of these events were considered to be related to study drug.

Withdrawal rates due to adverse events during the double-blind phase were 2% in the placebo treatment group, 1% in the valdecoxib 20 mg QD treatment group, and  $< 1\%$  in the valdecoxib 20 mg BID treatment group. Placebo-treated subjects withdrew due to hypertonia, myalgia, nausea and vomiting (one patient each). In the valdecoxib treatment groups, adverse events leading to withdrawal included dyspepsia and vomiting in the 20 mg QD treatment group and diarrhea in the 20 mg BID treatment group (one subject each). Nausea and vomiting in the placebo treatment group and dyspepsia and diarrhea in the valdecoxib treatment groups were attributed to study treatment. All of the events in the valdecoxib-treated subjects resolved.

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Significant differences between the valdecoxib 20 mg QD or BID treatment group and the placebo treatment group in mean change from Baseline to Final Visit were detected for the following clinical laboratory parameters: Eosinophil counts (QD and BID), calcium (QD and BID), and lactate dehydrogenase (LDH) (BID) (Table S20). All mean changes were increases from Baseline, and all had higher mean increases in the valdecoxib treatment groups than in the placebo treatment group.

**Table S20 Summary of Clinical Laboratory Parameters With Significant Differences Between Placebo and Valdecoxib Treatment in Mean Changes From Baseline**

Laboratory Parameter	Mean Change From Baseline (standard error)			p-Value versus Placebo	
	Placebo	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID	Valdecoxib 20 mg QD	Valdecoxib 20 mg BID
Eosinophil count (×10 <sup>6</sup> /L)	24.6 (7.04)	57.3 (9.49)	63.1 (8.86)	0.005	<0.001
LDH (U/L)	22.7 (2.49)	24.5 (3.19)	29.2 (2.67)	—	0.035
Calcium (mmol/L)	0.156 (0.0116)	0.180 (0.0109)	0.172 (0.0103)	0.038	0.044

LDH= Lactate dehydrogenase.

—Indicates p-value >0.20.

### **CONCLUSION(S):**

In this multicenter, double-blind, randomized, placebo-controlled, multiple-dose, parallel-group study consisting of two treatment periods (a single-blind period when all eligible subjects received valdecoxib 40 mg followed by 20 mg on Day 1; and a double-blind period lasting 4 days when subjects received either valdecoxib 20 mg BID, valdecoxib 20 mg QD followed by placebo QD or placebo BID for the treatment of pain following ACL reconstruction surgery), the conclusions are:

- For primary endpoints, SPI (categorical) over 24 hours and PGESM on Days 2 and 3: Valdecoxib 20 mg QD and BID were significantly improved compared with placebo for Day 3, but not Day 2.
- For the secondary endpoints: Valdecoxib 20 mg BID showed significant improvement compared with placebo on Days 4 and 5, with the exception of pain interference with function (m-BPI-sf) for general activity, mood, walking ability, coughing, breathing on Days 4 and 5, relations with others on Day 5 and mean Time-Specific Pain Intensity at time 0 post-first dose on Day 5; Valdecoxib 20 mg QD showed significant improvement compared with placebo on Days 4 and 5 with the exception of: SPI 24 (categorical) on Day 4, Time to First Dose of Rescue Medication on Day 4, number of tablets of Rescue Medication on Day 4, Mean Time-Specific Pain Intensity (categorical) at 0, 2, 4, 12, 16, 24 hours post first dose on Day 4 and 0 hours post first dose on Day 5, Mean Time-Specific Pain Intensity (VAS) at 0 and 2 hours post first dose on Day 4 and 0 hours post first dose on Day 5, worst pain intensity on Days 4 and 5, average pain intensity on Day 4 and for pain interference with function (m-BPI-sf) for general activity, walking ability and concentration on

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Days 4 and 5; mood, coughing and breathing on Day 4; and relations with others on Day 5.

- The relative risk of experiencing an opioid-related CME for valdecoxib 20 mg BID versus placebo Days 2 to 5 was significantly less for Days with at least 2 CMEs and 3 CMEs and constipation. For the valdecoxib 20 mg QD, there was a significant improvement for fatigue and constipation over Days 2 to 5.
- Patient Satisfaction with pain relief (categorical) was significant compared with placebo for valdecoxib 20 mg BID and valdecoxib 20 mg QD for both Day 4 and 5.
- Valdecoxib 20 mg QD and 20 mg BID were safe and well tolerated; the adverse events were similar across both active treatment groups and placebo. No patient had a serious cutaneous adverse reaction and no valdecoxib-treated patient had a thrombotic cardiovascular or cerebrovascular event.

**Based on a report completed on: 11 July 2005**