This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC.
MK-0663
etoricoxib, Oral
acutepain

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Phase III Randomized, Double-Blind, Placebo- and Active-Comparator-Controlled, Multiple-Dose, Clinical Trial to Study the Safety and Efficacy of MK-0663/Etoricoxib and Ibuprofen in the Treatment of Postorthopedic Knee Replacement Surgery Pain #098

INVESTIGATOR(S)/STUDY CENTER(S): Sixty-three (63) centers: 13 centers in the United States, 41 centers in Europe (Bulgaria, Czech Republic, Estonia, Germany, Hungary, Lithuania, Norway, Serbia, Slovenia, South Africa, Turkey), 1 center in Latin America (Costa Rica), and 8 centers in Asia Pacific (Philippines, South Korea, Singapore, and Taiwan)

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: 30-Dec-2008 to 13-Dec-2010 **CLINICAL PHASE:** III

DURATION OF TREATMENT: Patients were treated over 7 days

OBJECTIVE(S): Co-Primary: (1) To compare the pain intensity difference measured at rest over Days 1 through 3 in patients treated with etoricoxib (120 mg, 90 mg) or placebo for the treatment of pain following total knee replacement orthopedic surgery. (2) To compare the total daily dose of morphine used over Days 1 through 3 in patients treated with etoricoxib (120 mg, 90 mg) or placebo in the treatment of pain following total knee replacement orthopedic surgery. (3) To compare the safety and tolerability of etoricoxib (120 mg, 90 mg) administered over a total 7-day time period in patients treated for pain following total knee replacement orthopedic surgery. Secondary: (1) To compare the pain intensity difference measured at rest over Days 1 through 3 in patients treated with etoricoxib (120 mg, 90 mg) or ibuprofen 1800 mg (administered as 600 mg three times daily, every 8 hours) for the treatment of pain following total knee replacement orthopedic surgery. (2) To estimate the difference in average total daily dose of morphine used over Days 1 through 3 between patients treated with etoricoxib (120 mg, 90 mg) or ibuprofen 1800 mg (administered as 600 mg three times daily, every 8 hours) in the treatment of pain following total knee replacement orthopedic surgery.

STUDY DESIGN: Double-blind, placebo- and active- comparator-controlled, parallel-group, multicenter, multiple-dose study.
Protocols 098-00 and 098-01 were finalized on 20-Jun-08 and 19-Sep-08, respectively. The study was initiated with Protocol 098-01.

SUBJECT/PATIENT DISPOSITION:

	Placebo		Etoricoxib 90 mg		Etoricoxib 120 mg		Ibuprofen 1800 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized									149	
Patients in population	98		224		230		224		776	
Study Disposition										
Completed	85	(86.7)	198	(88.4)	216	(93.9)	203	(90.6)	702	(90.5)
Discontinued	13	(13.3)	26	(11.6)	14	(6.1)	21	(9.4)	74	(9.5)
Adverse Event	5	(5.1)	15	(6.7)	8	(3.5)	10	(4.5)	38	(4.9)
Lack Of Efficacy	2	(2.0)	2	(0.9)	1	(0.4)	2	(0.9)	7	(0.9)
Physician Decision	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)	2	(0.3)
Protocol Violation	0	(0.0)	3	(1.3)	0	(0.0)	4	(1.8)	7	(0.9)
Withdrawal By Subject	6	(6.1)	6	(2.7)	4	(1.7)	4	(1.8)	20	(2.6)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.

DOSAGE/FORMULATION NOS.: The patient received 3 doses of study medications per day. The first dose of study medication was administered as 4 tablets: two 60-mg tablets of etoricoxib or placebo, one 90-mg tablet of etoricoxib or placebo, one 600 mg tablet of ibuprofen or placebo. The second and third doses of study medication were administered as one 600 mg tablet of ibuprofen or matching placebo every 8 hours on Days 1 to 3 and at 2 PM and 8 PM on Days 4 to 7.

DIAGNOSIS/INCLUSION CRITERIA: Male or female ≥ 18 years of age, who were scheduled to have a total knee replacement surgery. Women of childbearing potential demonstrated a urine β-hCG consistent with a non gravid state prior to randomization. The total knee replacement surgery was completed in ≤3 hours and the patient was able to tolerate clear liquid and had a pain intensity ≥5 (0-to-10-point numerical rating scale [NRS]) postoperatively prior to 6 PM on the day of surgery.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Primary and secondary: (1) Change from baseline in Average Pain Intensity at Rest (0-to-10-point numerical rating scale [NRS]) over Days 1 to 3. (2) Average Total Daily Dose of morphine (mg) over Days 1 to 3.

SAFETY MEASUREMENTS: Frequency of clinical and laboratory adverse events, vital signs, physical exams, and laboratory tests (serum creatinine, estimated glomerular filtration rate [eGFR], serum blood urea nitrogen [BUN], haemoglobin, and haematocrit)

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The Full-Analysis-Set population was the primary analysis population for all efficacy endpoints. The primary analyses for change from baseline in Average Pain intensity at Rest over Days 1 to 3 was performed using the longitudinal data analysis (LDA) method with the terms for baseline pain intensity (moderate or severe), type of anesthesia (spinal or general), treatment, day, and the interaction of day by treatment, and the primary analyses for Average total daily dose of morphine over Days 1 to 3 was performed using a longitudinal analysis of variance (ANOVA) model that included terms baseline pain intensity (moderate or severe), type of anesthesia (spinal or general), treatment, day, and the interaction of day by treatment. Both LDA model and longitudinal ANOVA model assume that data are missing at random (MAR). Missing data were imputed implicitly by the model when they occurred. The least-squares (LS) mean differences in change from baseline in Average Pain Intensity at Rest (0-to-10-point NRS) over Days 1 to 3 were estimated from the LDA model. Log-transformation was applied to the total daily dose of morphine to bring them to a relative scale. The LS geometric mean was estimated from the model for Average Total Daily Dose of Morphine (mg) over Days 1 to 3 by treatment group, and the percent reduction relative to placebo in morphine consumption was estimated by the ratio of the LS geometric means for an etoricoxib dose group to that of the placebo group. To preserve the experimental-wise type-I error rate for the co-primary and secondary hypotheses, the comparisons of the 2 etoricoxib doses to placebo were conducted in a step-down manner; that is, etoricoxib 120 mg was compared to placebo with the co-primary endpoints first, and only if it was shown to be superior to placebo at the 5% critical level (2-sided) for each of the 2 co-primary endpoints would the 90-mg dose be compared with placebo, also at the 5% critical level for each of the co-primary endpoints (2-sided).

SAFETY: The All-Patients-as-Treated (APaT) population was employed for safety and tolerability analyses. The safety and tolerability analyses followed a tiered approach. For this study, the adverse events (AEs) prespecified as events of clinical interest (Tier 1 events) were edema-related AEs, hypertension-related AEs, AEs of congestive heart failure, pulmonary edema, or cardiac failure, and opioid-related AEs. For these Tier-1 AEs, p-values and 95% confidence intervals were provided for between-treatment differences in the percentage of patients with events using the Miettinen and Nurminen method (1985).

RESULTS:

EFFICACY: Both of the etoricoxib (120 mg and 90 mg) dose groups were superior to placebo in the 2 co-primary endpoints, change from baseline in Average Pain Intensity at Rest (0-to-10-point NRS) over Days 1-3 (p= 0.018, p= 0.009, respectively) and Average Total Daily Dose of Morphine (mg) over Days 1 to 3 (p<0.001). Both of the etoricoxib (120 mg and 90 mg) dose groups were non-inferior to ibuprofen 1800 mg with regard to the change from baseline in Average Pain Intensity at Rest (0-to-10-point NRS) over Days 1-3. Results from the Per-Protocol analysis of the primary endpoints were consistent with those of the Full Analysis Set population.

Key results are summarized in the tables below:

Primary Analysis: Pain Intensity at Rest (0- to 10-point NRS)
Average Change from Baseline Over Days 1 to 3
(Full Analysis Set Population)

Treatment	N [†]	Baseline Mean (SD)	Days 1-3 Mean (SD)	Change from Baseline over Days 1-3 Mean (SD)	Change from Baseline over Days 1-3 LS Mean (95% CI) [†]
Placebo	96	7.06 (1.78)	3.73 (1.68)	-3.33 (2.27)	-3.39 (-3.74, -3.04)
Etoricoxib 90 mg	211	7.01 (1.76)	3.14 (1.40)	-3.87 (2.00)	-3.93 (-4.17, -3.69)
Etoricoxib 120 mg	224	7.13 (1.81)	3.19 (1.57)	-3.94 (2.11)	-3.87 (-4.11, -3.64)
Ibuprofen 1800 mg	216	6.93 (1.70)	3.18 (1.53)	-3.75 (1.99)	-3.83 (-4.07, -3.59)

Pairwise Comparison [‡]	Difference in LS Means (95% CI)[‡]	p-Value[§]
Etoricoxib 120 mg vs. Placebo	-0.49 (-0.89, -0.08)	0.018
Etoricoxib 90 mg vs. Placebo	-0.54 (-0.95, -0.14)	0.009
Etoricoxib 120 mg vs. Ibuprofen 1800 mg[‖]	-0.04 (-0.36, 0.27)	
Etoricoxib 90 mg vs. Ibuprofen 1800 mg [‖]	-0.10 (-0.42, 0.22)	

Estimated Difference	Difference in LS Means (95% CI)
Etoricoxib 120 mg vs. Etoricoxib 90 mg	0.06 (-0.26, 0.37)
Ibuprofen 1800 mg vs. Placebo	-0.45 (-0.85, -0.04)

Pooled SD [¶] = 1.66

Note:

[†] Pain Intensity at Rest (0- to 10-point NRS): 0=no pain, to 10=pain as bad as you can imagine

[‡] Least-squares mean; Estimate obtained from LDA model with terms for baseline pain intensity (moderate or severe), type of anesthesia (spinal or general), treatment, day, and the interaction of day by treatment. N reflects the number of patients included in the LDA model.

[§] A negative difference indicates a beneficial effect of Etoricoxib.

[‖] Comparison to placebo and Ibuprofen were conducted in a step-down manner; the 90-mg dose was evaluated only if 120 mg is demonstrated to be superior to placebo with respect to both co-primary endpoints (PID and Morphine).

[¶] Non-inferiority reached if the upper bound of the 95% confidence interval of the between-treatment difference (Etoricoxib minus Ibuprofen) in LS means is no greater than 1.

Primary Analysis: Postoperative Morphine Consumption (mg)
Average Total Daily Dose Over Days 1 to 3
(Full Analysis Set Population)

Treatment	N[†]	Geometric Mean	LS Geometric Mean[†]	SE in log scale	95% CI for LS Geometric Mean[†]
Placebo	96	6.47	13.4	0.09	(11.2, 16.0)
Etoricoxib 90 mg	215	3.57	8.87	0.06	(7.88, 9.97)
Etoricoxib 120 mg	225	3.57	9.25	0.06	(8.26, 10.4)
Ibuprofen 1800 mg	217	3.93	8.82	0.06	(7.85, 9.91)

Pairwise Comparison	Between-Treatment Ratio [‡] (95% CI)	p-Value for Treatment Difference[§]
Etoricoxib 120 mg vs. Placebo	0.69 (0.56, 0.85)	<0.001
Etoricoxib 90 mg vs. Placebo	0.66 (0.54, 0.82)	<0.001

Estimated Difference	Between-Treatment Ratio (95% CI)
Etoricoxib 120 mg vs. Ibuprofen 1800 mg	1.05 (0.89, 1.23)
Etoricoxib 90 mg vs. Ibuprofen 1800 mg	1.01 (0.85, 1.18)
Etoricoxib 120 mg vs. Etoricoxib 90 mg	1.04 (0.89, 1.23)
Ibuprofen 1800 mg vs. Placebo	0.66 (0.53, 0.81)

Pooled SD in log(dose) = 0.86

Note: Opioids taken were converted to mg morphine equivalents according to the following conventions:1 mg morphine sulphate=1 mg morphine,1 mg morphine hydrochloride=1.17 mg morphine.A 5 mg oxycodone tablet=2.5 mg morphine,12.5 mg meperidine (DEMEROL™) = 1.67 mg morphine.[redacted]

[†] Least-squares mean back-transformed; estimate obtained from longitudinal ANOVA model on log-transformed morphine dose with terms for baseline pain intensity(moderate or severe),type of anesthesia (spinal, general),treatment ,day, and the interaction of day by treatment. N reflects the number of patients included in the longitudinal ANOVA model.

[‡] A ratio <1 indicates a beneficial effect of Etoricoxib.

[§] Comparison to placebo and Ibuprofen were conducted in a step-down manner (the 90-mg dose was evaluated only if the null hypotheses for co-primary endpoints (PID and Morphine) 120-mg doses were rejected).

SAFETY: Administration of etoricoxib (120 mg, 90 mg) and ibuprofen 1800 mg (600 mg three times daily) in the postoperative period was well tolerated. There were no significant differences among the etoricoxib (120 mg, 90 mg), placebo, and ibuprofen groups with respect to the proportions of patients who reported prespecified Tier 1 adverse events. Key results of the prespecified Tier 1 adverse events are summarized in the table below.

Analysis of Patients With Prespecified Adverse Events
(Incidence >0 Patients in One or More Treatment Groups)
All Patients as Treated

			Difference in % vs Placebo		Difference in % vs Ibuprofen 1800 mg		Difference in % vs Etoricoxib 90 mg	
Treatment	n	(%)	Estimate (95% CI)[†]	p-value[†]	Estimate (95% CI)[†]	p-value[†]	Estimate (95% CI)[†]	p-value[†]
Patients in population								
Placebo	98							
Etoricoxib 90 mg	222							
Etoricoxib 120 mg	230							
Ibuprofen 1800 mg	223							
Adverse experiences of congestive heart failure, pulmonary edema, or cardiac failure								
Placebo	0	(0.0)			0.0 (-1.7, 3.8)	>0.999		
Etoricoxib 90 mg	1	(0.5)	0.5 (-3.3, 2.5)	0.506	0.5 (-1.3, 2.5)	0.316		
Etoricoxib 120 mg	0	(0.0)	0.0 (-3.8, 1.7)	>0.999	0.0 (-1.7, 1.7)	>0.999	-0.5 (-2.5, 1.2)	0.309
Ibuprofen 1800 mg	0	(0.0)	0.0 (-3.8, 1.7)	>0.999				
Edema-related adverse experiences								
Placebo	4	(4.1)			2.3 (-1.3, 8.4)	0.227		
Etoricoxib 90 mg	2	(0.9)	-3.2 (-9.2, 0.1)	0.054	-0.9 (-3.7, 1.6)	0.415		
Etoricoxib 120 mg	4	(1.7)	-2.3 (-8.4, 1.2)	0.209	-0.1 (-3.0, 2.8)	0.965	0.8 (-1.7, 3.6)	0.437
Ibuprofen 1800 mg	4	(1.8)	-2.3 (-8.4, 1.3)	0.227				
Hypertension-related adverse experiences								
Placebo	7	(3.1)			-0.1 (-3.9, 5.7)	0.971		
Etoricoxib 90 mg	8	(3.6)	0.5 (-5.3, 4.5)	0.806	0.5 (-3.2, 4.2)	0.786		
Etoricoxib 120 mg	3	(1.3)	-1.8 (-7.4, 1.4)	0.278	-1.8 (-5.2, 1.0)	0.184	-2.3 (-5.8, 0.6)	0.113
Ibuprofen 1800 mg	7	(3.1)	0.1 (-5.7, 3.9)	0.971				
Opioid-related adverse experiences								
Placebo	41	(41.8)			5.5 (-5.9, 17.2)	0.349		
Etoricoxib 90 mg	77	(34.7)	-7.2 (-18.8, 4.2)	0.222	-1.6 (-10.5, 7.3)	0.718		
Etoricoxib 120 mg	84	(36.5)	-5.3 (-17.0, 6.0)	0.365	0.2 (-8.7, 9.0)	0.965	1.8 (-7.0, 10.6)	0.684
Ibuprofen 1800 mg	81	(36.3)	-5.5 (-17.2, 5.9)	0.349				

[†] Based on Miettinen & Nurminen method.

Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.

CONCLUSIONS: In the treatment of pain following total knee replacement surgery, etoricoxib (120 mg, 90 mg) administered post-operatively and then daily for the 6-days:

1. Resulted in greater pain control in the treatment of postorthopedic knee replacement surgery pain compared to placebo, as evidenced by improvements in pain intensity at rest and opioid use.
2. The 2 etoricoxib dose groups (120 mg, 90 mg) demonstrated similar efficacy as compared to ibuprofen 1800 mg with regard to efficacy endpoints described above.
3. Administration of etoricoxib (120 mg, 90 mg) in the postoperative period was well tolerated when administered post-operatively and over 6 days in patients that underwent a total knee replacement surgery. There were no significant differences between etoricoxib (120 mg, 90 mg) compared to placebo and ibuprofen in terms of overall safety.

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