PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Celebrex® / Celecoxib

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00976716

PROTOCOL NO.: A3191357

PROTOCOL TITLE: An Open-Label, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of Celecoxib (YM177) in Patients with Post Traumatic Pain

Study Center(s): Twelve (12) centers in Japan

Study Initiation Date and Completion Dates: 24 September 2009 to 09 November 2009

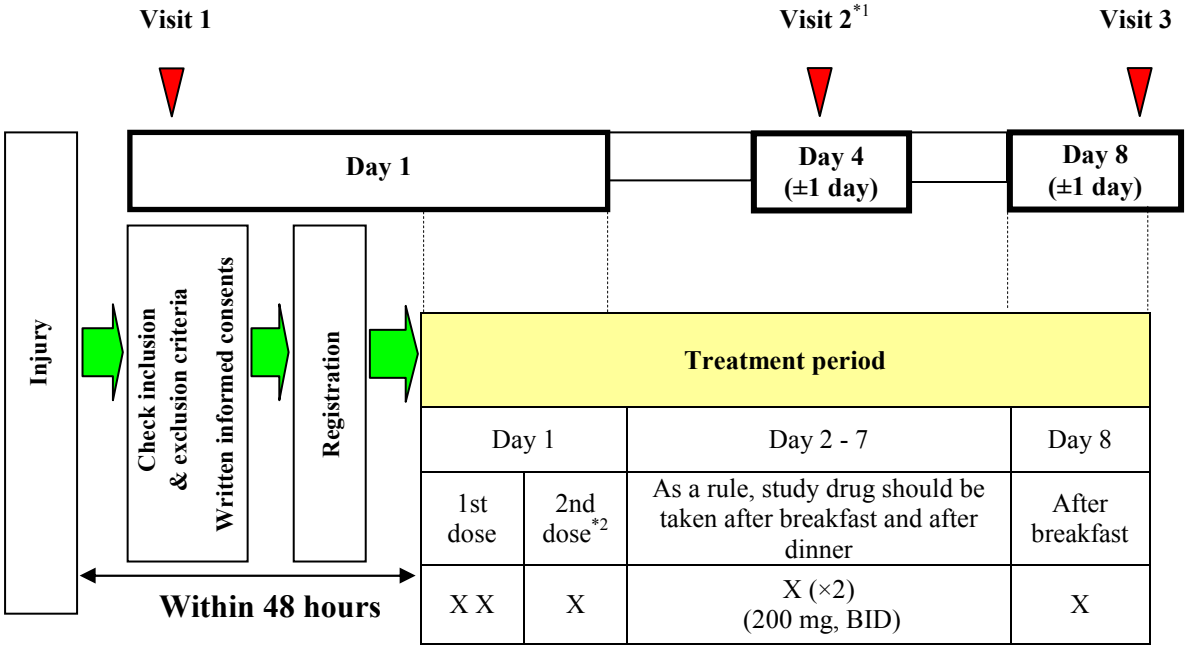
Phase of Development: Phase 3

Study Objective(s): To investigate the efficacy, safety and tolerability of celecoxib in patients with post traumatic pain.

METHODS

Study Design: This was an open-label, multicenter study in patients with post traumatic pain. The outline of the study design is shown in Figure S1.

Figure S1. Study Design



X: Celecoxib 200 mg tablet, BID: Twice daily

*1: If, at the time of evaluation/observation by the investigator/subinvestigator at Visit 2, both pain and inflammatory symptoms at the injured site had fully improved and the investigator/subinvestigator judged that no further study drug treatment was necessary, the last evaluation/observation at Visit 3 was conducted. The patient completed the study and no additional study drug was administered.

*2: The second dose of study drug (celecoxib 200 mg) was taken after 6 hours post-first dose and before bed.

Number of Subjects (Planned and Analyzed): A total of 80 subjects were planned and analyzed.

Diagnosis and Main Criteria for Inclusion: Male and female outpatients aged 20 years or older who presented, within 48 hours of injury, with post traumatic pain at rest (spontaneous pain), which was "Moderate" or "Severe" on a 4-point pain intensity (PI) scale (categorical) and a score on a Visual Analog Scale (VAS) of 45.0 mm or more, and who had at least one inflammatory symptom (swelling, redness, or localized warmth). Patients who received analgesics and anesthetics during earlier procedures for injury were excluded.

Study Treatment: Celecoxib 200 mg tablet was used. Subjects took the first dose of study drug (celecoxib 400 mg) within 48 hours after injury. During a period after 6 hours post-first dose and before bed on Day 1, subjects took the second dose of study drug (celecoxib 200 mg). From Day 2 to Day 7, study drug (celecoxib 200 mg) was taken twice a day (as a rule, after breakfast and after dinner). On Day 8 (Visit 3), study drug was taken only after breakfast. Besides the scheduled doses after breakfast and after dinner, study drug could be taken when the subject thought it was necessary. However, at least a 6-hour interval was

required between study drug administrations, and study drug was taken no more than twice a day.

Efficacy Evaluations:

Primary endpoint: Efficacy rate based on patient impression from the first study drug administration on Day 1 until Final Visit (Visit 3 or last observation/discontinuation).

Secondary endpoints: Efficacy rate based on patient impression from the first study drug administration on Day 1 until each time point; PI of pain at rest (spontaneous pain) and pain on active movement assessed on the VAS; Pain intensity difference (PID) between baseline and the first post-dosing time point for PI; Sum of PID (SPID) up to 6 hours after the first study drug administration; Peak PID (PPID) up to 6 hours after the first study drug administration; Severity of inflammatory symptoms (swelling, redness, and localized warmth) assessed by the investigator; and withdrawal due to lack of efficacy.

Safety Evaluations: Safety endpoints were adverse events, clinical laboratory test results, and vital signs (blood pressure and pulse rates).

Statistical Methods:

Efficacy analysis was performed on the full analysis set (FAS), consisting of all subjects who had received at least one dose of study drug and had at least one post-baseline efficacy endpoint measurement regardless of the primary or secondary endpoints. For the primary endpoint, the efficacy rate based on patient impression from the first study drug administration on Day 1 until Final Visit (Visit 3 or last observation/discontinuation) and its two-sided 95% confidence interval (CI) were calculated. Missing values of the primary endpoint were replaced by the method of the last observation carried forward (LOCF). For the secondary endpoints, summary statistics and two-sided 95% CIs for the efficacy rate based on patient impression from the first study drug administration on Day 1 until each time point, the PIs (assessed on the VAS), PIDs, SPIDs, and PPIDs were calculated using a normal distribution approximation. The severity of inflammatory symptoms for swelling, redness and localized warmth at each time point was summarized using frequency and percentage, respectively. With the withdrawal due to lack of efficacy as an outcome measure, cumulative incidence using the Kaplan-Meier method and two-sided 95% CI were to be calculated. The proportion of subjects who withdrew due to lack of efficacy was also to be calculated. The method of the LOCF was used to summarize the secondary endpoints at last observation/discontinuation. At other time points, the observed values were used for the secondary endpoints except the SPID. If a subject withdrew from the study before 6 hours after the first study drug administration on Day 1 and the measurement of the PI at 6 hours on Day 1 was missing, the method of the LOCF was used for the PI at 6 hours on Day 1 to derive the SPID.

The safety analysis set consisted of all subjects who had received at least one dose of study drug. The safety analysis was primarily performed in accordance with Pfizer Data Standards, which defined the standard procedures of collecting and reporting safety data.

RESULTS

Subject Disposition and Demography: The disposition of subjects is summarized in Table S1. A total of 80 subjects were enrolled in this study. All subjects received the study drug, and 79 subjects (98.8%) completed the study. All subjects were included in the FAS and safety analysis set. One subject discontinued the study due to a treatment-related adverse event (mild eczema).

Table S1. Subject Disposition

Subject Disposition	N (%)
Enrolled	80
Treated with the Study Drug	80
Analyzed for Efficacy (FAS)	80 (100)
Analyzed for Safety	80 (100)
Completed	79 (98.8)
Discontinued	1 (1.3)
Treatment-related adverse event	1 (1.3)

The mean age of the subjects was 37.1 years (range, 20 to 79 years), with over 70% of subjects falling between the age of 18 and 44 years. Only a small proportion of subjects (3.8%) were 65 years or older. The male and female ratio was balanced. The mean height was 164.4 cm, the mean weight was 63.8 kg, and the mean body-mass index (BMI) was 23.4. At baseline, approximately 90% of subjects rated PI of pain at rest (spontaneous pain) as "Moderate" on a 4-point scale (categorical), and the remaining 10% rated it as "Severe." The mean PIs for pain at rest and pain on active movement assessed on the VAS at baseline were 59.9 mm and 75.5 mm, respectively. The traumas that subjects had experienced consisted of contusion (32 subjects), joint sprain (31 subjects), fracture (12 subjects), wound (4 subjects), and muscle rupture (1 subject).

Efficacy Results: The results of efficacy rate based on patient impression are shown in Table S2. The efficacy rate based on patient impression from the first study drug administration on Day 1 until Final Visit (the primary endpoint) was 87.5% (70 of 80 subjects). The efficacy rate based on patient impression from the first study drug administration on Day 1 until 6 hours after the first dose was 55.0%, indicating that more than half of the subjects rated the study drug as "good" or "excellent" at 6 hours after the first dose. The efficacy rates at Visit 2 and at Visit 3 were 75.0% and 88.2%, respectively.

Table S2. Efficacy Rate Based on Patient Impression (FAS)

	N	Poor	Fair	Good	Excellent	Efficacy Rate (%)*[1]	95% CI
		n (%)	n (%)	n (%)	n (%)		
Day 1: Up to 6 hours after the first study drug administration	80	7 (8.8)	29 (36.3)	35 (43.8)	9 (11.3)	55.0	(44.1, 65.9)
Day 1: Before bed	80	6 (7.5)	26 (32.5)	31 (38.8)	17 (21.3)	60.0	(49.3, 70.7)
Day 2: Before bed	80	4 (5.0)	21 (26.3)	35 (43.8)	20 (25.0)	68.8	(58.6, 78.9)
Visit 2	80	2 (2.5)	18 (22.5)	39 (48.8)	21 (26.3)	75.0	(65.5, 84.5)
Visit 3	68	1 (1.5)	7 (10.3)	27 (39.7)	33 (48.5)	88.2	(80.6, 95.9)
Final Visit (LOCF)	80	1 (1.3)	9 (11.3)	33 (41.3)	37 (46.3)	87.5	(80.3, 94.7)

*1: The proportion of subjects who rated the study drug as "good" or "excellent"

In secondary endpoints assessed on the VAS, the PIs and PIDs for pain at rest (spontaneous pain) and pain on active movement showed decreases in VAS scores from baseline at 2 hours after the first dose (a mean decrease of 12.6 mm and 14.3 mm, respectively) and further decreases from baseline at 6 hours after the first dose (a mean decrease of 19.6 mm and 24.3 mm, respectively). The alleviation of pain was also confirmed by the SPIDs and PPIDs up to 6 hours after the first dose. The inflammatory symptoms (swelling, redness, and localized warmth) assessed by the investigator either resolved or improved during the study. No subjects discontinued the study due to lack of efficacy.

Safety Results: The adverse events reported in the study are summarized in Table S3. Of 80 subjects, 10 subjects (12.5%) experienced a total of 20 all-causality adverse events, and 8 subjects (10.0%) experienced a total of 16 treatment-related adverse events.

Table S3. Summary of Adverse Events

	All-Causality	Treatment-Related
Subjects evaluable for safety	80	80
Subjects with adverse events (%)	10 (12.5)	8 (10.0)
Number of adverse events	20	16
Subjects who discontinued the study due to adverse events (%)	1 (1.3)	1 (1.3)
Subjects with dose or temporary discontinuation due to adverse events	0	0

The incidence of all treatment-emergent adverse events is shown in Table S4. All of the adverse events reported in this study were mild in severity.

Table S4. Treatment-Emergent Adverse Events

System Organ Class and MedDRA (version 12.1) Preferred Term	All-Causality
Subjects evaluable for safety	80
Number of adverse events	20
Subjects with adverse events (%)	10 (12.5)
Gastrointestinal disorders	
Diarrhoea	1 (1.3)
Injury, poisoning and procedural complications	
Muscle strain	1 (1.3)
Investigations	
Alanine aminotransferase increased	1 (1.3)
Aspartate aminotransferase increased	1 (1.3)
Beta 2 microglobulin urine increased	5 (6.3)
Beta-N-acetyl-D-glucosaminidase increased	3 (3.8)
Blood bilirubin increased	1 (1.3)
Blood creatine phosphokinase increased	3 (3.8)
Blood lactate dehydrogenase increased	2 (2.5)
Urobilin urine present	1 (1.3)
Skin and subcutaneous tissue disorders	
Eczema	1 (1.3)

One subject discontinued the study due to a treatment-related adverse event (mild eczema), but the event resolved without any treatment. No deaths or serious adverse events were reported in this study.

The results of laboratory tests, blood pressure and pulse rates indicated no clinically significant findings.

CONCLUSION(S): This was an open-label, multicenter study in patients with post traumatic pain, in which the first dose of celecoxib 400 mg and the second dose of celecoxib 200 mg at least 6 hours apart were given on Day 1, followed by celecoxib 200 mg BID for up to 7 days from Day 2. The following conclusions were obtained from the results.

- Celecoxib was effective in improving pain at rest (spontaneous+ pain) and pain on active movement in patients with post traumatic pain.

- All adverse events were mild in severity. Celecoxib was safe and well tolerated in patients with post traumatic pain.