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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

NCT NO.: 00141154

PROTOCOL NO.: A3191174

PROTOCOL TITLE: A Randomized, Double-Blind, Multicenter, Active and Placebo-Controlled Parallel Group Study to Evaluate the Efficacy and Safety of Celecoxib (YM177) 200 mg BID Compared to Loxoprofen-Na 60 mg TID in Patients with Low Back Pain

Study Center(s): Fifty-one (51) centers in Japan

Study Initiation and Completion Dates: 29 October 2004 to 08 June 2006

Phase of Development: Phase 3

Study Objective(s):

Primary Objective(s): To evaluate the superiority of celecoxib 200 mg BID to placebo and the non-inferiority of celecoxib 200 mg BID to loxoprofen-Na 60 mg TID in terms of efficacy in the treatment of low back pain

Secondary Objective(s): To evaluate the safety of celecoxib 200 mg BID in comparison with placebo and loxoprofen-Na 60 mg TID in subjects with low back pain

METHODS

Study Design: This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study designed to provide a comparative evaluation of celecoxib 200 mg BID, loxoprofen-sodium (Na) 60 mg TID, and placebo in the treatment of subjects with low back pain. Subjects who had used NSAIDs or analgesics prior to the start of the study were subjected to a washout during the screening period. The duration of treatment was 4 weeks, with visits occurring at 2 and 4 weeks after the first dose of study medication. Efficacy and safety evaluations were made at screening, baseline (Week 0), and at Weeks 2 and 4 (final visit), or at early termination. Follow-up was performed after final visit or early termination, as necessary.

Number of Subjects (Planned and Analyzed):

Planned: 1206 subjects (402 subjects in each treatment group)

Analyzed: A total of 1234 subjects were randomized as follows: 412 subjects to placebo, 411 to celecoxib and 411 to loxoprofen-Na. A total of 1227 subjects (410 each in the placebo and celecoxib treatment groups and 407 in the loxoprofen-Na treatment group) were analyzed for efficacy based on the full analysis set (FAS) and 1145 (388 in the placebo treatment group, 375 in the celecoxib treatment group and 382 in the loxoprofen-Na treatment group) based on the per protocol set (PPS).

Diagnosis and Main Criteria for Inclusion: Male or female outpatients, aged 20 years or older, who had been diagnosed with low back pain and had an X-ray/MRI or had other findings supporting the diagnosis occurring up to 3 months before the screening observation were included. In all subjects, the low back pain had to have been present for at least 2 weeks, with subjects experiencing 5 to 7 days of pain per week. Subjects had to have been expected by the investigator to receive benefit from NSAID therapy. The primary location of low back pain had to be below the 12th thoracic vertebra.

Study Treatment: Study drug administration is shown in Table S1.

- Celecoxib 200 mg tablets
- Placebo tablets matching-image for celecoxib 200 mg
- Loxoprofen-Na 60 mg tablets
- Placebo tablets matching-image for loxoprofen-Na 60 mg

Table S1 Study Drugs Administration

Treatment group	After Breakfast	After Lunch	After Dinner
Celecoxib 200 mg BID	● + □	○ + □	● + □
Placebo	○ + □	○ + □	○ + □
Loxoprofen-Na 60 mg TID	○ + ■	○ + ■	○ + ■

●Celecoxib 200 mg tablet; ○Placebo tablet matched-image for celecoxib 200 mg tablet; ■Loxoprofen-Na 60 mg tablet; □Placebo tablet matched-image for loxoprofen-Na 60 mg tablet

Total duration of the study was 4 weeks.

Efficacy Evaluations:

Primary Endpoint: Patient’s Assessment of Pain (Visual Analog Scale: VAS)

Secondary Endpoints:

- Patient’s Global Assessment of Condition (VAS)
- Physician’s Global Assessment of Patient’s Condition (VAS)
- Roland Morris Disability Questionnaire (RDQ)

Safety Evaluations: Adverse events (AEs), laboratory tests, vital signs and 12-lead electrocardiogram (ECG)

Statistical Methods:

Efficacy: The full analysis set (FAS) was the primary analysis population. A subject was included in the FAS if he or she took at least 1 dose of study medication and had at least 1 primary efficacy endpoint evaluation.

- Change from Baseline in Patient’s Assessment of Pain (VAS) at Week 4 (based on the last observation carried forward [LOCF] approach) was analyzed using analysis of covariance (ANCOVA) with treatment, center and duration of current episode of low back pain as factors, and the baseline value as a covariate, and adjusted mean for each treatment group and a two-sided 95% confidence interval (CI) were calculated. The difference in adjusted means between celecoxib and placebo was tested at a two-sided 5% significance level to evaluate the superiority of celecoxib to placebo. If the superiority of celecoxib to placebo was demonstrated, then the non-inferiority of celecoxib to loxoprofen-Na was evaluated in a step-wise fashion. The non-inferiority of celecoxib to loxoprofen was assessed by a confidence interval approach. When the upper limit of two-sided 95% confidence interval for the difference in adjusted means between celecoxib and loxoprofen-Na was less than or equal to a non-inferiority margin of 5.0 mm, celecoxib was declared non-inferior to loxoprofen-Na. Changes from baseline to Week 2 and Week 4 (without LOCF) were also analyzed using ANCOVA.
- Changes from Baseline at each visit were analyzed for Patient’s Global Assessment of Condition (VAS), Physician’s Global Assessment of Patient’s Condition (VAS), and RDQ, using ANCOVA with treatment, center and duration of low back pain as factors and the baseline value as a covariate.

Safety: All subjects who took at least 1 dose of the study medication and had any safety evaluation were included in the safety data set. Safety was analyzed using tabulations and descriptive statistics.

RESULTS

Subject Disposition and Demography:

A summary of subject disposition is presented in Table S2.

Table S2 Subject Disposition

	Placebo	Celecoxib 200 mg BID	Loxoprofen-Na 60 mg TID
Number of subjects randomized	412	411	411
Number of subjects treated	411 (99.8%)	410 (99.8%)	410 (99.8%)
Number of subjects completed	381 (92.5%)	382 (92.9%)	369 (89.8%)
Number of subjects discontinued	30 (7.3%)	28 (6.8%)	41 (10.0%)
Adverse event	11 (2.7%)	12 (2.9%)	25 (6.1%)
Protocol violation	1 (0.2%)	0 (0.0%)	4 (1.0%)
Consent withdrawn	5 (1.2%)	4 (1.0%)	3 (0.7%)
Lost to follow-up	0 (0.0%)	1 (0.2%)	1 (0.2%)
Lack of efficacy	3 (0.7%)	2 (0.5%)	2 (0.5%)
Investigator's judgment based on safety information	10 (2.4%)	9 (2.2%)	6 (1.5%)

Note: Denominator for percentage calculation is randomized subject number in each treatment group.

The mean age of subjects was similar across treatment groups (40.9 – 42.1 years), with the majority of subjects (91.7% – 92.2%) being below 65 years of age. The male/female ratio, body weight and height were also similar across treatment groups. The mean duration of low back pain for each group was 6.76 – 8.38 years, with almost half of the subjects having suffered from low back pain for at least 5 years. More than 60% of subjects in each treatment group had a recurring episode of low back pain, and in more than 70% of subjects, the current episode of back pain had lasted for at least 3 months at the time of the entry. Demographic characteristics and low back pain history were similar across treatment groups.

Efficacy Results:

The results of the efficacy analysis (both primary and secondary endpoints) at Week 4 (LOCF) are presented in Table S3.

Table S3 Results for Primary and Secondary Endpoints at Week 4 (LOCF): FAS

Treatment Group	Placebo	Celecoxib	Loxoprofen-Na*
		200 mg BID	60 mg TID
<i>Primary Endpoint: Patient's Assessment of Pain, VAS, mm</i>			
Adjusted mean change ± SE	-26.2 ± 1.09	-31.7 ± 1.09	-29.3 ± 1.09
Differences between groups ± SE [†]	-5.4 ± 1.44	–	-2.4 ± 1.45
95% CI	-8.3, -2.6	–	-5.2, 0.4
P-value	<0.001	–	NA
<i>Secondary Endpoints</i>			
Patient's Global Assessment, VAS, mm			
Adjusted mean change ± SE	-18.5 ± 1.02	-22.8 ± 1.02	-21.6 ± 1.02
Differences between groups ± SE [†]	-4.3 ± 1.35	–	-1.2 ± 1.35
95% CI	-7.0, -1.7	–	-3.8, 1.5
P-value	0.001	–	NA
Physician's Global Assessment, VAS, mm			
Adjusted mean change ± SE	-26.4 ± 1.02	-31.6 ± 1.01	-28.8 ± 1.02
Differences between groups ± SE [†]	-5.2 ± 1.34	–	-2.8 ± 1.35
95% CI	-7.9, -2.6	–	-5.5, -0.2
P-value	<0.001	–	NA
Roland Morris Disability Questionnaire Score			
Adjusted mean change ± SE	-3.0 ± 0.15	-3.7 ± 0.15	-3.3 ± 0.15
Differences between groups ± SE [†]	-0.7 ± 0.20	–	-0.4 ± 0.20
95% CI	-1.1, -0.3	–	-0.8, 0.0
P-value	<0.001	–	NA

*Loxoprofen-Na and placebo were not compared. [†]Celecoxib group – placebo group or loxoprofen group. Adjusted mean was calculated from ANCOVA with treatment, centers, and duration of current episode of low back pain (<3 months or ≥ 3 months) as factors and Baseline value as a covariate
 CI= Confidence interval, FAS= Full analysis set, LOCF= Last observation carried forward, VAS= Visual analogue scale

Safety Results:

All causality AEs were reported in 189 subjects (46.0%), 210 subjects (51.2%), and 204 subjects (49.8%) in the placebo, celecoxib, and loxoprofen-Na treatment groups, respectively. The most commonly observed all causality AEs (those occurring at ≥ 2.0%) are summarized in Table S4.

Table S4 Incidence of Adverse Events Occurring in $\geq 2\%$ of Subjects in Any Treatment Group (Safety Population)

	Placebo n (%)	Celecoxib 200 mg BID n (%)	Loxoprofen-Na 60 mg TID n (%)
Number of subjects analyzed	411	410	410
Number of subjects with AEs	189 (46.0)	210 (51.2)	204 (49.8)
Number of AEs	319	360	404
Adverse Event:			
Occult blood positive	49 (11.9)	48 (11.7)	62 (15.1)
Nasopharyngitis	17 (4.1)	37 (9.0)	36 (8.8)
Urinary β_2 microglobulin Increased	13 (3.2)	30 (7.3)	24 (5.9)
NAG increased	6 (1.5)	20 (4.9)	10 (2.4)
Abdominal pain upper	12 (2.9)	15 (3.7)	11 (2.7)
Blood creatine phosphokinase increased	15 (3.6)	15 (3.7)	9 (2.2)
Diarrhea	10 (2.4)	10 (2.4)	17 (4.1)
Stomach discomfort	16 (3.9)	10 (2.4)	13 (3.2)
Stomatitis	4 (1.0)	8 (2.0)	14 (3.4)
Blood urine present	12 (2.9)	6 (1.5)	10 (2.4)
Constipation	7 (1.7)	3 (0.7)	9 (2.2)
ALT (GPT) increased	7 (1.7)	2 (0.5)	8 (2.0)
γ -GTP increased	4 (1.0)	0 (0.0)	9 (2.2)

Note: Table sorted in descending order by incidence of AEs in celecoxib treatment group.

AE= Adverse event, ALT= Alanine aminotrasferase, GTP= Glutamyl transpeptidase, NAG= Narrow angle glaucoma

There were no deaths in the study. Serious adverse events (SAEs) were reported in 4 subjects in the placebo group (cholelithiasis, cerebral hemorrhage, meniscus lesion and intervertebral disc protrusion), 2 subjects in the celecoxib group (diverticulitis and intervertebral disc protrusion) and 1 subject in the loxoprofen-Na group (cholelithiasis). Furthermore, an SAE of rectal polyp (benign) was reported in 1 placebo-treated subject 29 days after the last treatment. None of these events were considered to be related to treatment.

Treatment discontinuations due to AEs were reported in 11 subjects (2.7%), 12 subjects (2.9%), and 25 subjects (6.1%) in the placebo, celecoxib, and loxoprofen-Na treatment groups, respectively. Adverse events that led to the discontinuation of more than 1 subject in any treatment group are presented in Table S5.

Table S5 Discontinuations Due to Adverse Events Occurring in More Than 1 Subject in Any Treatment Group

	Placebo n (%)	Celecoxib 200 mg BID n (%)	Loxoprofen-Na 60 mg TID n (%)
Number of subjects analyzed	411	410	410
Subjects with any AE Causing Withdrawal	11 (2.7)	12 (2.9)	25 (6.1%)
Adverse Event :			
Rash	0 (0.0)	3 (0.7)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	3 (0.7)
Face edema	0 (0.0)	0 (0.0)	3 (0.7)
Diarrhea	1 (0.2)	0 (0.0)	2 (0.5)
Gastritis	1 (0.2)	0 (0.0)	2 (0.5)
Gastric ulcer	0 (0.0)	0 (0.0)	2 (0.5)
Generalized edema	0 (0.0)	0 (0.0)	2 (0.5)
Peripheral edema	0 (0.0)	0 (0.0)	2 (0.5)
Headache	0 (0.0)	0 (0.0)	2 (0.5)
Eczema	0 (0.0)	0 (0.0)	2 (0.5)
Gastroenteritis	2 (0.5)	0 (0.0)	0 (0.0)

Note: Table sorted in descending order by incidence of AEs in celecoxib or loxoprofen-Na treatment group.

In terms of mean changes in laboratory values from Baseline, differences between groups were generally small and not clinically significant. No clinically relevant changes from Baseline were observed in any of the vital sign parameters or ECG results.

CONCLUSION(S):

In this multicenter, randomized, double-blind, parallel-group, placebo-controlled study in subjects with low back pain that was present for at least 2 weeks, subjects were treated with celecoxib 200 mg BID, loxoprofen-Na 60 mg TID, or placebo for 4 weeks. The conclusions were:

- Celecoxib 200 mg BID was statistically superior to placebo (p-value < 0.001) in alleviating pain as determined by Patient's Pain Assessment (primary endpoint) and the following secondary endpoints: Patient's Global Assessment, Physician's Global Assessment and Roland Morris Disability Questionnaire Score.
- Celecoxib 200 mg BID was non-inferior to loxoprofen-Na 60 mg TID in alleviating pain as demonstrated by the primary efficacy endpoint 95% CI of loxoprofen-Na 60 mg TID compared with that of celecoxib 200 mg BID was -5.2 to 0.4. Thus, 0.4 was less than the pre-defined non-inferiority margin of 5.0 mm.
- Celecoxib 200 mg BID was generally safe and well tolerated in subjects with low back pain.