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**PROPRIETARY DRUG NAME/GENERIC DRUG NAME:** Celebrex<sup>®</sup> / Celecoxib

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

**NCT NO.:** 00163241

**PROTOCOL NO.:** A3191068

**PROTOCOL TITLE:** A double-blind, placebo-controlled, randomized 24-month study, assessing the effect of celecoxib long term treatment on hip osteoarthritis (OA) progression

**Study Centers:** Investigators at one (1) study center in Canada and 16 centers in France enrolled subjects in this study.

**Study Initiation and Completion Dates:** 30 June 2004 to 19 January 2006

The study was terminated prematurely as a result of low enrollment.

**Phase of Development:** Phase 3

**Study Objectives:** The *primary* objective of this study was to assess the ability of continuous treatment with celecoxib 200 mg versus placebo administered once daily (QD) for 24 months in slowing disease progression in subjects with OA of the hip as assessed radiographically.

The *secondary* objectives of this study were to:

1. Assess the ability of a continuous treatment of celecoxib 200 mg versus placebo administered QD for 24 months in treating disease signs and symptoms in subjects with OA of the hip
2. Evaluate the ability of a continuous 24-month intake of celecoxib 200 mg QD versus placebo to reduce number of subjects requiring hip replacement according to the investigator
3. Evaluate the tolerability and safety of continuous 24-month intake of celecoxib 200 mg QD versus placebo in subjects with OA of the hip

## METHODS

### Study Design:

This prospective, multicenter, randomized, double-blind, placebo-controlled, 24-month, parallel-group study was designed to evaluate the efficacy, tolerability and safety of continuous treatment with celecoxib 200 mg QD versus placebo, in slowing disease progression in subjects with OA of the hip, as assessed radiographically at baseline, Month 12 and Month 24. An exit radiograph was also taken, in this case, when the study was prematurely terminated. There was a period of 2 to 4 weeks between the Screening Visit and the Randomization Visit to ensure satisfactory washout of previous medication and adequate time for centralized review of screening radiographs. The maximum and expected duration of the study for an individual subject, including washout, treatment, and follow-ups was not to exceed 25 months. The estimated length of time needed to complete the entire study (from enrollment of the first subject to completion of the last subject) was 49 months.

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

*Planned:* It was planned to randomize 666 subjects in a 1:1 ratio into celecoxib and placebo treatment groups.

*Analyzed:* Twenty-three (23) subjects were enrolled, all of whom were treated (17 celecoxib and 6 placebo) and analyzed for safety.

**Diagnosis and Main Criteria for Inclusion:** Subjects were males and females aged  $\geq 50$  years old who had a diagnosis of OA of the hip as defined by the American College of Rheumatology criteria and symptomatic OA, as defined by the presence of daily hip pain for at least 1 month (not necessarily continuously) during the 2 months prior to screening visit. The subject had to have hip baseline pain of  $\geq 3$  and  $\leq 9$  on a 10-point Visual Numerical Scale in the index hip.

**Study Treatment:** A celecoxib 200 mg capsule or matched placebo capsule was taken orally once daily at the same time each day (e.g., morning), with food, throughout the 24-month treatment period.

**Efficacy Evaluations:** The primary efficacy endpoint was the change in the minimal joint space width of the index hip during the 24-month follow up, compared with baseline.

Secondary efficacy endpoints included the number of days with rescue medication usage by drug category (paracetamol/paracetamol combination products, opioid/opioid combination products, celecoxib and other [e.g., propoxyphene]); the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), subscales pain and function, compared with baseline; the subject global assessment of OA; and the proportion of subjects who were felt by investigator to require hip replacement.

**Safety Evaluations:** Safety evaluations included vital signs and physical examination at all visits, adverse events (AEs) at all visits (except screening), and safety laboratory tests at the screening and randomization visit, as well as at Months 1, 3, 9, 15, and 21.

## Statistical Methods:

*Efficacy:* The primary efficacy endpoint was the change in the minimal joint space width of the index hip during the 24-month follow up, compared with baseline. This endpoint was to be expressed as the proportion of subjects achieving a 0.5 mm decrease in joint space width on a radiograph and confirmed on a successive radiograph, if any, during the 24-month follow up. The proportion of subjects achieving a decrease in joint space width of at least 0.5 mm (threshold value) in each group during the study period was to be compared using Kaplan-Meier estimates of the survival curves of subjects not reaching the threshold value and using log-rank test for comparisons of the survival curves. Efficacy analyses were not performed.

*Safety:* Due to the premature termination of the trial, only safety analyses were conducted. The safety population was defined as subjects who took at least 1 dose of assigned treatment. Safety reporting included demographic characteristics, AEs and subject discontinuations.

## RESULTS

**Subject Disposition and Demography:** Of the 62 subjects screened, 23 subjects (including 8 males and 15 females) were assigned to study treatment, 17 to celecoxib and 6 to placebo. All 23 subjects received at least 1 dose of study drug. However, none of the subjects completed this prematurely terminated study. Eight (8) subjects discontinued for reasons unrelated to study termination (see Table S1). Twenty-three (23) subjects were included in the safety analysis.

**Table S1 Discontinuations from Study**

	<b>Celecoxib (n=17)</b>	<b>Placebo (n=6)</b>
<b>Related to study drug</b>	13	5
Adverse event	0	1
Lack of efficacy	5	0
Other*	8	4
<b>Not related to study drug</b>	4	1
Other*	3	0
Subject defaulted†	1	1

\*Premature termination of the study

†Consent withdrawn or subject lost to follow-up

Table S2 presents the demographic characteristics for the subjects.

**Table S2 Demographic Characteristics**

<b>Number of subjects</b>	23
<b>Age (years)</b>	
Mean, SD	63.0, 5.9
Min-Max	54 – 74
<b>Weight (kg)</b>	
Mean, SD	72.4, 12.6
Min-Max	47 – 97
<b>Height (cm)</b>	
Mean, SD	166.1, 6.6
Min-Max	154 – 180

SD= Standard deviation

**Efficacy Results:** Efficacy evaluations were not performed because the study was terminated prematurely as a result of low enrollment.

**Safety Results:** Given the premature termination of this study, only the core safety data collected were reported.

*Deaths and Serious Adverse Events:* There were no deaths during the study.

There was 1 serious adverse event (SAE) during the study in the placebo group. The subject was a 61-year-old male patient who experienced arrhythmia approximately 8 months after the last study treatment. The investigator assessed the causality as underlying heart disease and not related to study treatment. The subject recovered from the event approximately 5 weeks following its onset.

*Discontinuations Due to an Adverse Event:* One subject in the placebo group discontinued as a result of an AE. The AE reported was moderate upper abdominal pain that was considered by the investigator to be related to study drug. The AE subsequently resolved.

*Treatment-emergent Adverse Events:* Table S3 shows the incidence of treatment-emergent AEs.

**Table S3 Incidence of Treatment-emergent Adverse Events, All Causality  
 (Treatment-related)**

Numbers of evaluable subjects for AEs	Celecoxib N= 17	Placebo N= 6
<b>Gastrointestinal disorders</b>		
Abdominal pain upper	1	1
Dry mouth	1	0
Gastric disorder	0	1
Toothache	1	0
<b>General disorders and administration site conditions</b>		
Pain	1	0
<b>Infections and infestations</b>		
Upper respiratory tract infection	0	1
Vulvovaginal mycotic infection	1	0
<b>Metabolism and nutrition disorders</b>		
Diabetes mellitus	1	0
<b>Musculoskeletal and connective tissue disorders</b>		
Back pain	1	0
Groin pain	1	0
Muscle spasms	1	0
Neck pain	1	0
Periarthritis	1	0
<b>Nervous system disorders</b>		
Headache	2	0
Neuralgia	1	0
Sciatica	0	1
<b>Psychiatric disorders</b>		
Depression	0	1
<b>Respiratory, thoracic and mediastinal disorders</b>		
Allergic bronchitis	1	0
Pulmonary fibrosis	0	1
<b>Total preferred term events</b>	<b>15</b>	<b>6</b>

Includes data up to 30 days after last dose of study drug.

**CONCLUSION:**

No conclusions can be drawn from this study as it was prematurely terminated due to poor enrollment. There were no deaths in this study and no unexpected safety findings.