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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00139776

PROTOCOL NO.: A3191173

PROTOCOL TITLE: Double-blind, parallel-group, randomized study of the efficacy and safety of continuous use of celecoxib vs the "usual use" of celecoxib in the treatment of subjects with chronic osteoarthritis of the hip or knee who require an anti-inflammatory medication for control of their pain

Study Center(s): 111 centers in the Americas and Europe enrolled and treated subjects (2 centers in Belgium, 4 centers in Brazil, 20 centers in Canada, 5 centers in Chile, 5 centers in Columbia, 1 center in France, 15 centers in the United Kingdom, and 59 centers in the United States)

Study Initiation and Completion Dates: 13 Jul 2005 to 21 Feb 2008

Phase of Development: Phase 4

Study Objective(s):

Primary: To determine whether "continuous use" over a 6-month period of celecoxib 200 mg per day is more effective than "usual use" of celecoxib 200 mg per day in preventing spontaneous OA flares

Secondary:
- To evaluate the safety and tolerability of "continuous use" over a 6-month period of celecoxib 200 mg quaque die (QD; every day) versus "usual use" celecoxib 200 mg QD use

- To demonstrate whether disease management of OA as assessed by measures of pain and function is more effective using a regimen of celecoxib 200 mg QD "continuous use" over a 22-week period versus "usual use" celecoxib 200 mg QD

"Usual use" was used in the statement of objectives to maintain consistency with the Study Protocol. "Usual use" is hereafter referred to as "intermittent use".

METHODS

Study Design: This was a double blind, parallel group, randomized, multicenter, international study comparing treatment with celecoxib "continuous use" and celecoxib "intermittent use" in subjects with OA of the hip or knee who required non-steroidal anti-inflammatory drug (NSAIDs) to control their OA pain during the month prior to Screening. Randomization of subjects into a double-blind treatment period (Period III) allowed for a parallel-group comparison between "continuous use" celecoxib and "intermittent use" celecoxib over a 22-week period.

The study consisted of 3 periods. Visit 1 (Screening Visit) and Wash Out (Period I [14±2 days]) was focused on the OA subjects who required a continuous intake of NSAIDs for at least the past month, discontinuation of which led to an OA flare. Visit 2 (Flare Visit) and open-label run-in treatment with celecoxib (Period II [14±2 days]) allowed observation of successful treatment of an OA flare. Visit 3 (Randomization Visit) followed by a double-blind treatment period (Period III [22 weeks]) allowed investigation of "continuous use" versus "intermittent use" celecoxib. Occurrence and resolution of OA flare were defined objectively based on subject scores on the Patient's Assessment of Arthritis Pain Numerical Rating Scale and the Patient's Global Assessment of Arthritis administered by telephone through an Interactive Voice Response System (IVRS), and was confirmed based on the outcome of the Physician's Global Assessment of Arthritis administered by the investigator at each of 9 scheduled office visits.

Including Period I, individual subject participation lasted for approximately 26 weeks, with exposure to study medication lasting for 24 weeks (open-label run-in medication for 2 weeks followed by randomized, double-blind medication for 22 weeks).

Enrollment was competitive among sites, and discontinued subjects were not replaced.

Informed consent was obtained before any study-specific procedures were performed.

Number of Subjects (Planned and Analyzed):

Planned: Assuming that 25% of the subjects screened would not proceed to the Open-label Run-in Period (Period II) and that 25% of the subjects who entered the Open-label Run-in Period would not respond to celecoxib, it was considered that approximately 1445 subjects needed to be screened to ensure that 812 subjects were randomized into Period III.

Analyzed: In total, 1772 subjects were screened, 1197 subjects entered the Open-label Run-in Period (Period II), and 875 subjects were randomized into the Double-blind Treatment Period (Period III), including 17 subjects who were not treated during Period III.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18-80 years who were diagnosed according to the American College of Rheumatology (ACR) guidelines as having active and symptomatic OA of the hip and/or knee and who required oral NSAIDs to control OA pain within the past 1 month were eligible for enrollment in this study. Grounds for exclusion from the study included subjects with known sensitivity to cyclooxygenase-2

(COX-2) specific inhibitors, active gastrointestinal disease, or a body mass index (BMI) of 40 or greater.

To be eligible for randomization into the Double-blind Treatment Period (Period III), subjects had to experience an OA flare of the index joint upon withdrawal of their current NSAID (per definition of Screening OA Flare), resolve the flare during the Open-label Run-in Period, and have no reoccurrence of flare up to the Randomization Visit.

Study Treatment: Celecoxib was formulated in 200 mg capsules. The placebo was an opaque hard gelatin capsule identical in appearance to the celecoxib capsule, but did not contain the study drug. During Period II, all subjects received 200 mg celecoxib tablets to be taken daily until resolution of the Screening OA Flare as defined by the IVRS. During Period III, subjects in both treatment arms received a subject kit containing Bottle A (Daily Medication) and Bottle B (Flare Medication).   For "continuous use" subjects, Bottle A contained 200 mg celecoxib capsules and Bottle B contained placebo, whereas for "intermittent use" subjects, Bottle A contained placebo and Bottle B contained 200 mg celecoxib capsules. Subjects took 1 capsule from Bottle A in the morning (at approximately the same time each day). When in flare, subjects called the IVRS. If the flare was confirmed, the IVRS instructed subjects to take 1 capsule from Bottle B immediately and 1 capsule each morning without suspending intake from Bottle A. When recovered (resolution of flare), subjects again called the IVRS. If flare resolution was confirmed, the IVRS instructed subjects to stop taking medication from Bottle B and continue to take 1 capsule from Bottle A each morning.

A limited amount of oral Rescue Medication (paracetamol/acetaminophen) was permitted under strictly specified conditions.

Efficacy Evaluations:

Primary: The primary endpoint for this study was the number of flare events experienced by subjects during the Double-blind Treatment (Period III) per time of exposure, where time of exposure was defined as the period from the first dose of the randomized, double-blind study medication to the last dose of study medication in Period III. The number of flares observed during Period III and the actual time of exposure to the study drug were documented for each subject.

Secondary: The following secondary endpoints were defined and assessed during Period III:

- Patient's Assessment of Arthritis Pain Numerical Rating Scale

- Patient's Global Assessment of Arthritis

- Physician's Global Assessment of Arthritis

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

- Time (in days) from the first dose of randomized, double-blind study medication to occurrence of first OA flare

- Time (in days) that a subject was free from OA flare

- Time (in days) that a subject experienced OA flare

- Total amount of Rescue Medication (paracetamol/acetaminophen) taken

- Proportion of days on Rescue Medication

- Quantity of Flare Medication taken from Bottle B (placebo for the continuous treatment arm and celecoxib 200 mg for the "intermittent use" arm)

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:

No pharmacokinetic or pharmacodynamic evaluations were performed.

During Period III, subject quality of life was assessed using the SF-12v2™ and Medical Outcomes Study (MOS) Sleep Scale.

Safety Evaluations: Safety evaluations included physical examinations, laboratory tests, monitoring of vital signs and adverse events (AEs). Assessments of safety began upon a subject's first intake of study medication at the start of Period II through to the Final Visit at the end of Period III.

Statistical Methods:

Efficacy: The primary and secondary efficacy analyses were conducted on randomized subjects who had received at least 1 dose of double-blinded study medication (intention-to-treat [ITT] population using a 2-sided type I error rate of 0.05, as detailed in the Statistical Analysis Plan (SAP). Sensitivity analyses were also performed on ITT subjects who had no major protocol violations (Evaluable population) and on Evaluable population subjects who experienced OA flares that persisted for more than 16 days (Flare-modified ITT [FMITT].

The primary endpoint was analyzed using analysis of variance (ANOVA) with treatment as the independent variable.

The following secondary endpoints were also analyzed using ANOVA: proportion of days in OA flare/free from OA flare (with treatment as a factor), mean total milligrams of Rescue Medication (with treatment as a fixed effect), the proportion of days on Rescue Medication (with treatment as a factor), and days on Flare Medication. The following secondary endpoints were analyzed using analysis of covariance (ANCOVA): AUC of Patient's Assessment of Arthritis Pain Numerical Rating Scale and Patient's Global Assessment of Arthritis scores (both with treatment as a fixed effect and baseline value as a covariate), change in total WOMAC, Pain, Stiffness, and Physical Function subscale scores (with treatment as a fixed effect and Randomization Visit baseline value as a covariate), and AUCs

of total WOMAC, Pain, Stiffness, and Physical Function subscale (with treatment as a fixed effect and Randomization Visit baseline value as a covariate). Time (in days) from first dose of randomized, double-blind study medication to occurrence of first OA flare was analyzed using Kaplan-Meier (KM) methods, and Physician's Global Assessment of Arthritis at the Final Visit was analyzed with a Cochran-Mantel-Haenszel (CMH) test using modified ridit scores. Additional ANCOVA analyses were performed post-hoc for the Patient's Global Assessment of Arthritis and the Patient's Assessment of Arthritis Pain Numerical Rating Scales using treatment as a fixed effect and baseline value as a covariate. Also, an additional summary table regarding new-onset and exacerbation of hypertension during the Double-blind Treatment Period (Period III) was generated post-hoc.

Safety: All subjects who took at least 1 dose of study medication were analyzed for safety (Safety population). All safety data were subject to clinical review and summarized by descriptive statistics with no formal statistical analyses. Safety assessments (eg, AEs, laboratory tests, vital signs, physical examinations) were performed according to the format and algorithms described in Pfizer Data Standards documentation.

RESULTS

The data are presented below by the weeks from Day 0 (Flare Visit), generally 2 weeks before randomization. The weeks post-randomization are different from the study weeks.

Subject Disposition and Demography: Subject disposition is summarized in Table S1.

Table S1. Subject Disposition (Period III)

	Celecoxib 200 mg QD "Continuous Use"[a]		Celecoxib 200 mg QD "Intermittent Use"[a]	
	N	%[b]	N	%[b]
Subjects randomized into Period III	440	-	435	-
Treated (ITT population)	431	98.0	427	98.2
Completed	355	80.7	321	73.8
Discontinued	76	17.3	106	24.4
Analyzed for Safety (Safety population)	431	98.0	427	98.2
Adverse events	431	98.0	427	98.2
Laboratory data	390	88.6	393	90.3

[a]Subjects took celecoxib 200 mg (Bottle B) only during flare.
[b]Based on the number of subjects randomized into Period III.
ITT = intention-to-treat, N = the number of subjects in the respective treatment group,
Period III = Double-blind Treatment Period, QD = quaque die (every day).

Subjects in the 2 treatment groups were well comparable in all baseline demographic characteristics. Those randomized and treated during the Double-blind Treatment Period (Period III) were predominantly female (73.5% "continuous use" subjects and 71.0% "intermittent use subjects) and white (78.4% "continuous use" subjects and 78.0% "intermittent use" subjects). The mean age in both treatment groups was approximately 59 years.

Concomitant use of acetylsalicylic acid occurred in 19.5% of "continuous use" subjects and 20.6% of "intermittent use" subjects.

Efficacy Results:

Primary: Subjects in the "continuous use" group experienced 2.0 fewer OA flares during the 22-week duration of Period III (5.1 months) compared with their counterparts who took 200 mg celecoxib QD on a "intermittent use" basis (p-value: <0.0001).

Among subjects included in the Evaluable and FMITT populations, the "continuous use" group experienced 1.7 and 2.3 fewer OA flares in 5.1 months, respectively, compared with subjects in the "intermittent use" group (p-values: <0.0001).

Secondary:

Time to Occurrence of First OA Flare During Period III

In the "continuous use" group, the median time to occurrence of first OA flare was 16 days among the 314 subjects who had flare in the ITT population (77.1 %). Among subjects in the "intermittent use" group, the median time to occurrence of first OA flare was 8 days (354 subjects with flare, 89.4% of the ITT Population). This difference was statistically significant between the celecoxib treatment groups (log-rank p-value: <0.0001).

Proportion of Days in OA Flare/Free From OA Flare During Period III

For the ITT population, subjects in the "continuous use" group had 15.4 more flare-free days than "intermittent use" subjects over the 22 weeks of treatment during Period III (5.1 months; p-value: <0.0001). Subjects in the "continuous use" group also had 15.4 fewer days in flare compared with subjects in the "intermittent use" group (p-value: <0.0001). The difference in favor of "continuous use" between the 2 celecoxib treatment groups was also significant in analyses of these secondary endpoints based on the Evaluable and FMITT populations.

Patient's Assessment of Arthritis Pain Numerical Rating Scale

These results are shown in Table S2.

Table S2. Patient's Assessment of Arthritis Pain Numerical Rating Scale Analyzed Using Area Under the Curve (AUC) during Period III (ITT Population)

Subject population Assessment time points[b]	Celecoxib 200 mg QD "Continuous Use"[a]		Celecoxib 200 mg QD "Intermittent Use"[a]		p-value[d]
	n[c]	LSMean AUC (SE)	n[c]	LSMean AUC (SE)	
ITT population		N = 431		N =427	
Week 4	415	81.7 (1.1)	414	90.5 (1.1)	<0.001
Week 8	401	148.8 (2.6)	395	167.0 (2.6)	<0.001
Week 12	383	212.6 (4.1)	363	234.3 (4.1)	<0.001
Week 16	373	272.7 (5.9)	339	297.6 (5.9)	0.003
Week 20	362	335.9 (7.8)	323	361.1 (7.8)	0.022
Week 24	350	378.1 (9.1)	309	403.9 (9.2)	0.047

[a]Subjects took celecoxib 200 mg (Bottle B) only during flare.
[b]Last value carried forward approach was applied for missing values.
[c]n = number of subjects with data available at the respective time point.
[d]Based on analysis of variance with treatment as fixed effect and baseline (Randomization Visit) as a covariate.
ITT = intention-to-treat, LSMean = least square of the mean, N = number of subjects in the respective treatment group, QD = quaque die (every day), SE = standard error.

Patient's Global Assessment of Arthritis

These results are shown in Table S3.

Table S3. Patient's Global Assessment of Arthritis Analyzed Using Area Under the Curve (AUC) during Period III (ITT Population)

Subject population Assessment time points[b]	Celecoxib 200 mg QD "Continuous Use"[a]		Celecoxib 200 mg QD "Intermittent Use"[a]		p-value[d]
	n[c]	LSMean AUC (SE)	n[c]	LSMean AUC (SE)	
ITT population		N = 431		N = 427	
Week 4	415	67.9 (0.68)	414	71.7 (0.69)	<0.001
Week 8	401	126.0 (1.55)	395	133.2 (1.56)	0.001
Week 12	383	182.8 (2.48)	363	188.7 (2.48)	0.096
Week 16	373	236.3 (3.59)	339	241.2 (3.59)	0.338
Week 20	362	292.4 (4.83)	323	293.8 (4.84)	0.832
Week 24	350	329.2 (5.75)	309	328.9 (5.76)	0.972

[a]Subjects took celecoxib 200 mg (Bottle B) only during flare.
[b]Last value carried forward approach was applied for missing values.
[c]n = number of subjects with data available at the respective time point.
[d]Based on analysis of variance with treatment as fixed effect and baseline (Randomization Visit) as a covariate.
ITT = intention-to-treat, LSMean = least square of the mean, N = number of subjects in the respective treatment group, QD = quaque die (every day), SE = standard error.

Physician's Global Assessment of Arthritis at the Final Visit

These results are shown in Table S4.

Table S4. Physician's Global Assessment of Arthritis at the Final Visit (Period III; ITT Population)

Subject population PhGAA score	Celecoxib 200 mg QD "Continuous Use"[a] Visit 9 Score[b] n[c] (%)[d]	Celecoxib 200 mg QD "Intermittent Use"[a] Visit 9 Score[b] n[c] (%)[d]	p-value[e]
ITT population	N = 431	N = 427	
Very Good	68 (16.0)	39 (9.2)	0.0046
Good	242 (56.8)	244 (57.4)	
Fair	91 (21.4)	113 (26.6)	
Poor	23 (5.4)	27 (6.4)	
Very Poor	2 (0.5)	2 (0.5)	

[a]Subjects took celecoxib 200 mg (Bottle B) only during flare.
[b]Missing scores were not included.
[c]n = number of subjects with respective score.
[d]Percentages were calculated using the non-missing data at that month's visit.
[e]Treatment effect was tested by Cochran-Mantel-Haenszel test using modified ridit scores based on total for each visit; missing scores were not included.
ITT = intention-to-treat, N = number of subjects in the respective treatment group, PhGAA = Physician's Global Assessment of Arthritis, QD = quaque die (every day), Visit 9 = Final Visit.

Total Amount of Rescue Medication Taken During Period III

These results are shown in Table S5.

Table S5. Total Rescue Medication Taken (Period III; ITT Population)

Subject population Total Rescue Medication taken per month per subject (mg)[a]	Celecoxib 200 mg QD "Continuous Use"[b]	Celecoxib 200 mg QD "Intermittent Use"[b]	p-value[c]
ITT population	N = 431; n =220[d]	N = 427; n = 239[d]	
Mean (SD)	1566 (4840)	2428 (4974)	0.0102
Median	89	397	
Range	0 – 70517	0 – 41386	

[a]Subjects who did not take Rescue Medication were assumed to have taken 0 mg. Mean, SD, median, range, and p-value calculations included these subjects.
[b]Subjects took celecoxib 200 mg (Bottle B) only during flare.
[c]Based on analysis of variance with treatment as fixed effect.
[d]n = number of subjects in the respective treatment group who took Rescue Medication.
ITT = intention-to-treat, N = number of subjects in the respective treatment group, QD = quaque die (every day), SD = standard deviation.

Proportion of Days on Rescue Medication and the Number of Days on Flare Medication During Period III

These results are shown in Table S6 and Table S7, respectively.

Table S6.   Proportion of Days on Rescue Medication (Period III; ITT Population)

Subject population Proportion of days on Rescue Medication[a, b]	Celecoxib 200 mg QD "Continuous Use"[c]	Celecoxib 200 mg QD "Intermittent Use"[c]	p-value[d]
ITT population	N = 431; n =220[e]	N = 427; n = 239[e]	
Mean (SD)	0.044 (0.102)	0.069 (0.121)	0.0012
Median	0.006	0.013	
Range	0.000 – 0.902	0.000 – 0.814	

[a]Calculated for each subject as the number of days on Rescue Medication divided by the number of days on the study medication during Period III.
[b]Subjects who did not take Rescue Medication were calculated as 0. Mean, SD, median, range, and p-value calculations included these subjects.
[c]Subjects took celecoxib 200 mg (Bottle B) only during flare.
[d]Based on analysis of variance with treatment as fixed effect.
[e]n = number of subjects in the treatment group who took Rescue Medication.
ITT = intention-to-treat, N = number of subjects in the respective treatment group, QD = quaque die (every day), SD = standard deviation.

Table S7.   Number of Days on Flare Medication (Period III; ITT Population)

Subject population Number of days on Flare Medication per month per subject[a]	Celecoxib 200 mg QD "Continuous Use"[b]	Celecoxib 200 mg QD "Intermittent Use"[b]	p-value[c]
ITT population	N = 431; n = 282[d]	N = 427; n = 339[d]	
Mean (SD)	6.589 (8.589)	9.793 (9.253)	<0.0001
Median	2.393	7.250	
Range	0.00 – 30.000	0.00 – 29.273	

[a]Subjects who did not take Flare Medication were calculated as 0. Mean, SD, median, range, and p-value calculations included these subjects.
[b]Subjects took celecoxib 200 mg (Bottle B) only during flare.
[c]Based on analysis of variance with treatment as fixed effect.
[d]n = number of subjects in the treatment group who took Flare Medication.
ITT = intention-to-treat, N = number of subjects in the respective treatment group, QD = quaque die (every day), SD = standard deviation.

Western Ontario and McMaster Universities Osteoarthritis Index

The LSMean change in the total WOMAC score and each analyzed WOMAC subscale showed an increase (worsening) from Visit 3 (Randomization Visit; Week 2) to Visit 9 (Final Visit; Week 24) for subjects in both the "continuous use" and "intermittent use" groups, with the lower bound of the 95% confidence interval greater than zero for all LSMean change scores except stiffness in the "continuous use" group. However, the "intermittent use" group demonstrated greater increases in pain, stiffness, and problems with physical function between Visit 3 and Visit 9 than did the "continuous use" group (ITT population, p-value <0.005).

Similar results were observed for the Evaluable population. The FMITT population excluded those subjects with prolonged flares (>16 days); analysis based on this population indicated improvement in total WOMAC and Physical Function subscale for "continuous use" subjects

from the Randomization Visit to the Final Visit. There was a significant worsening in the "intermittent use" group for total WOMAC, Pain, Stiffness and Physical Function subscales.

At Visit 3 (Randomization Visit) mean WOMAC Total, Pain, Stiffness, and Physical Function scores were comparable in both treatment groups in the ITT population, without statistically significant differences. The WOMAC AUC increased throughout the study, but the increase was more pronounced in the "intermittent use" group, with statistically significant differences between the treatment groups in favor of "continuous use" (p-value <0.001).

SF-12v2^{TM}

SF-12v2^{TM} results showed greater improvements in the Physical Function, Role Physical, Bodily Pain, and Vitality subscales from 0-6 months for subjects in the "continuous use" group than for subjects in the "intermittent use" group. These results were consistent with WOMAC (Physical Function subscale) data, as well as with AE data that indicated fatigue to be less prevalent among "continuous use" subjects (documented in 1.4% of "continuous use" subjects versus 2.1% of "intermittent use").

MOS-Sleep

There were no significant differences between the 2 treatment groups regarding the MOS-Sleep Scale.

Safety Results:

All Causality Treatment-emergent Adverse Events

All Causality treatment-emergent AEs are shown by System Organ Class in Table S8.

Table S8. All Causality Adverse Events By System Organ Class (Period III; Safety Population)

MedDRA System Organ Class	Celecoxib 200 mg QD "Continuous Use"[a] (N = 431)		Celecoxib 200 mg QD "Intermittent Use" [a] (N = 427)	
	n[b]	%	n[b]	%
Blood and lymphatic system disorders	2	0.5	2	0.5
Cardiac disorders	4	0.9	2	0.5
Ear and labyrinth disorders	11	2.6	7	1.6
Endocrine disorders	1	0.2	1	0.2
Eye disorders	10	2.3	5	1.2
Gastrointestinal disorders	70	16.2	64	15.0
General disorders and administration site conditions	23	5.3	43	10.1
Hepatobiliary disorders	1	0.2	0	0
Immune system disorders	2	0.5	2	0.5
Infections and infestations	83	19.3	93	21.8
Injury, poisoning, and procedural complications	29	6.7	23	5.4
Investigations	4	0.9	13	3.0
Metabolism and nutritional disorders	6	1.4	8	1.9
Musculoskeletal and connective tissue disorders	82	19.0	89	20.8
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	3	0.7	5	1.2
Nervous system disorders	77	17.9	80	18.7
Psychiatric disorders	26	6.0	16	3.7
Renal and urinary disorders	7	1.6	7	1.6
Reproductive system and breast disorders	5	1.2	8	1.9
Respiratory, thoracic, and mediastinal disorders	32	7.4	23	5.4
Skin and subcutaneous tissue disorders	12	2.8	20	4.7
Surgical and medical procedures	1	0.2	4	0.9
Vascular disorders	12	2.8	16	3.7

[a]Subjects took Flare Medication (Bottle B) only during flare.
[b]n = number of subjects with at least 1 specified adverse event.
MedDRA = Medicinal Dictionary for Regulatory Activities, version 11.0, N = number of patients in the respective treatment group, QD = quaque die (every day).

Treatment-related Adverse Events

The most frequent investigator-assessed, treatment-related AEs that occurred during the Double-blind Treatment Period (Period III) are summarized by System Organ Class in Table S9.

Table S9. Treatment-related Adverse Events By System Organ Class (Period III; Safety Population)

MedDRA System Organ Class	Celecoxib 200 mg QD "Continuous Use"[a] (N = 431)		Celecoxib 200 mg QD "Intermittent Use" [a] (N = 427)	
	n[b]	%	n[b]	%
Blood and lymphatic system disorders	1	0.2	0	0
Cardiac disorders	1	0.2	1	0.2
Ear and labyrinth disorders	2	0.5	0	0
Eye disorders	5	1.2	0	0
Gastrointestinal disorders	42	9.7	29	6.8
General disorders and administration site conditions	11	2.6	9	2.1
Infections and infestations	4	0.9	2	0.5
Investigations	3	0.7	2	0.5
Metabolism and nutritional disorders	2	0.5	2	0.5
Musculoskeletal and connective tissue disorders	9	2.1	4	0.9
Nervous system disorders	28	6.5	27	6.3
Psychiatric disorders	8	1.9	3	0.7
Renal and urinary disorders	3	0.7	2	0.5
Respiratory, thoracic, and mediastinal disorders	4	0.9	4	0.9
Skin and subcutaneous tissue disorders	6	1.4	7	1.6
Vascular disorders	7	1.6	11	2.6

[a]Subjects took celecoxib 200 mg (Bottle B) only during flare.
[b]n = number of subjects with at least 1 specified treatment-related adverse event.
MedDRA = Medicinal Dictionary for Regulatory Activities, version 11.0, N = number of patients in the respective treatment group, QD = quaque die (every day).

Adverse Events of Special Interest

Cardiac disorders, gastrointestinal, psychiatric disorders, and vascular disorders are particularly relevant in risk-benefit assessments. The vast majority of the AEs in these System Organ Classes experienced by subjects in both treatment groups were mild or moderate in severity. Gastrointestinal disorders were attributed to the study medication by the investigator in 9.7% of "continuous use" subjects and 6.8% of "intermittent use" subjects, whereas vascular disorders were attributed to the study medication in 1.6% of "continuous use" subjects and 2.6% of "intermittent use" subjects. Few cases of cardiac disorders (0.2% for both treatment groups) and psychiatric disorders (1.9% of the "continuous use" treatment group and 0.7% in the "intermittent use" treatment group) were judged to be related to the study medication.

In a post-hoc analysis, approximately 45% of subjects in each treatment group had hypertension at baseline (Randomization Visit), based on a diagnosis of hypertension, and/or receiving anti-hypertension concomitant medication, and/or having a systolic blood pressure (BP) ≥140 and diastolic BP ≥90 mm Hg. In the "continuous use" and "intermittent use" treatment groups, 11.8 % and 10.5% of subjects, respectively, experienced an exacerbation of hypertension during Period III (defined as having existing baseline hypertension and having either systolic BP ≥140 and diastolic BP ≥90 mm Hg documented during at least 1 post-randomization visit or a hypertension AE). New Period III cases of hypertension (defined as having no baseline hypertension and having either systolic BP ≥140 and diastolic

BP ≥90 mm Hg documented during at least 2 post-randomization visits or a hypertension AE) were documented in 2.3% of "continuous use" subjects and 3.0% of "intermittent use" subjects.

Adverse Events that led to Discontinuation

Subject discontinuations during Period III due to AE were few (less than 6% of each treatment group). The most common treatment-related AE that led to subject discontinuation among "continuous use" subjects was headache which occurred in 2 subjects. That among "intermittent use" subjects was abdominal pain which occurred in 3 subjects.

Serious Adverse Events

There were no deaths reported.

Treatment-emergent, non-fatal SAEs are summarized in Table S10.

Table S10. Treatment-emergent, Non-fatal Serious Adverse Events (Safety Population)

Treatment Subject ID	SAE (MedDRA Preferred Term)	Onset (Day)[a]	Resolution (Day)[a]	Severity	Outcome	Study Disc.?	Causality[b]
Open-label Run-in Period (Period II)							
11651029	Anaemia	-2	>8	Severe	Still present	Yes	Other
11121011	Vitreous haemorrhage	16	20	Moderate	Resolved	No	Other
Double-blind Treatment Period (Period III)							
Celecoxib 200 mg QD "Continuous Use"[c]							
11141003	Metastases to the central nervous system	131	>151	Severe	Still present	Yes	Other
11181016	Rectal haemorrhage	133	139	Moderate	Resolved	Yes	Other
	Melaena	145	154	Moderate	Resolved	Yes	SM
11291004	Atrial fibrillation	101	108	Severe	Resolved	Yes	Other
	Pulmonary oedema	101	108	Severe	Resolved	Yes	Other
	Acute respiratory failure	101	108	Severe	Resolved	Yes	Other
10431019	Chest pain	19	27	Moderate	Recovered	Yes	Other
10291007	Nephrolithiasis	58	97	Severe	Recovered	Yes	Other
11891017	Coronary artery disease	43	82	Severe	Recovered	No	Other
Celecoxib 200 mg QD "Intermittent Use"[c]							
10271028	Squamous cell carcinoma	52	>129	Severe	Still present	Yes	Other
10021042	Knee arthroplasty	155	139	Severe	Resolved	Yes	DUS
11201025	Abdominal pain	42	45	Severe	Resolved	Yes	SM
11121005	Pancreatitis	30	112	Severe	Resolved	Yes	Other
11381022	Transient ischaemic attack	47	48	Severe	Resolved	Yes	SM
10361008	Osteoarthritis	91	99	Moderate	Resolved	Yes	DUS
11261008	Bipolar disorder	25	32	Moderate	Resolved	Yes	Other
	Osteoarthritis	53	101	Moderate	Resolved	Yes	DUS
	Hypertensive crisis	56	58	Severe	Resolved	No	Other
10631004	Non-cardiac chest pain	72	75	Mild	Resolved	No	Other
10741019	Gastritis	92	94	Severe	Resolved	No	Other
	Chest pain	92	94	Severe	Resolved	No	Other
10041035	Skin laceration	46	94	Moderate	Resolved	No	Other

[a]Day relative to first day of each treatment period. First day of each treatment period = Day 1.
[a]Relative to the Flare Visit on Day 0.
[b]As assessed by the investigator.
[c]Subjects took Flare Medication (Bottle B) only during flare.
DUS = disease under study, ID = identification number, disc. = discontinued, MedDRA = Medicinal Dictionary for Regulatory Activities (version 11.0), QD = quaque die (every day), SAE = serious adverse event, SM = study medication.

Other Safety Assessments

With the exception of glucose level greater than 1.5 times the upper limit of normal that was documented in 5% of "continuous use" subjects and in 13% of "intermittent use" subjects, laboratory abnormalities were documented in less that 3% of total subjects in either treatment group. At the final observation (Final Visit or Early Termination Visit), there were very small changes from baseline (Randomization Visit) in laboratory test data, physical examinations, and vital signs of any subjects enrolled in this study, including those that were treated during the Open-label Run-in Period, but not randomized into Period III.

CONCLUSION(S): This study demonstrated that "continuous use" of celecoxib 200 mg QD for subjects with osteoarthritis of the knee or hip was more effective than "intermittent use" in treating spontaneous OA flares, leading to significantly less OA flares, less arthritis pain, and better patient function as measured by the WOMAC, without an increase in adverse events (including gastrointestinal events), during the 5.1-month double-blind treatment period, suggesting "continuous use" is an appropriate and beneficial treatment regimen for patients requiring regular NSAIDs to control their OA.