Long-term efficacy and safety of lumiracoxib 100 mg: an open-label extension of a 13-week randomized controlled trial in patients with primary osteoarthritis of the knee

E.A. Sheldon[1], A. Beaulieu[2], Z. Paster[3], S. Yu[4], R. Rebuli[5]

[1]Miami Research Associates, Miami, FL, USA; [2]Centre Hospitalier de l'Université Laval Research Centre, Ste-Foy, Canada; [3]Dean Medical Center, Oregon, WI, USA; [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [5]Novartis Pharma AG, Basel, Switzerland.

Abstract

Objective

Osteoarthritis (OA) is a chronic condition, accompanied by inflammation and pain, and it is therefore important to demonstrate long-term efficacy and safety of treatment. Here we present data from a 39-week open-label extension to a 13-week randomized, double-blind, double-dummy, parallel-group core study. The objective was to assess the long-term safety and tolerability of lumiracoxib 100 mg once daily (od).

Methods

Patients had originally received lumiracoxib 100 mg od, celecoxib 200 mg od or placebo in the core study. In the extension period, all patients received lumiracoxib 100 mg od. Efficacy variables, overall OA pain intensity (0-100 mm visual analogue scale [VAS]), patient's global assessment of disease activity and physician's global assessment of disease activity (0-100 mm VAS), were assessed at weeks 17, 26, 39 and 52. General safety and tolerability were evaluated by adverse event (AE) reporting and physical examinations and laboratory tests at each visit.

Results

Of the 1182 patients completing the core study, 834 patients entered the extension study. Improvements in the three efficacy variables after 3 months were maintained for up to 1 year with lumiracoxib treatment. Lumiracoxib was well tolerated, with most AEs being of mild-to-moderate severity and of the type expected for this patient population and duration of exposure.

Conclusion

In conclusion, these data suggest that lumiracoxib 100 mg od was effective and well tolerated when treating OA pain of the knee for periods of up to 1 year, making it a useful option for the long-term treatment of OA pain.

Key words

Anti-inflammatory agents, non-steroidal, COX-2 inhibitors, lumiracoxib, osteoarthritis, knee, visual analogue scale.

Eric A. Sheldon, MD; Andre Beaulieu, MD; Zorba Paster, MD; Shaohua Yu, PhD; Rosemary Rebuli, MD.

The study and statistical analyses were funded by Novartis Pharma AG.

Please address correspondence and reprints requests to: Eric A Sheldon MD, Medical Director, Miami Research Associates, 6141 Sunset Drive, Miami, FL 33143, USA.
E-mail: esheldon@miamiresearch.com

Received on June 20, 2007; accepted in revised form on December 14, 2007.

Conflict of interest:
Dr. E. Sheldon has previously participated as a clinical trial investigator for Novartis and has received industry-standard compensation for this work; Dr. A. Beaulieu has received clinical trial support from Roche, Amgen, Novartis and Merck; Dr. Z. Paster is a member of the Speakers' Bureau for Pfizer, Endo, Lilly and TAP, and has received research grants from Novartis, Merck, Pfizer, Endo, TAP and Sanofi-Aventis; Dr. S. Yu is an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; Dr. R. Rebuli is an employee of, and owns shares in, Novartis Pharma AG, Basel, Switzerland.

Introduction

Osteoarthritis (OA) is a highly prevalent, chronic condition where patients suffer from joint pain and stiffness, which impacts their wellbeing and their ability to perform normal activities (1, 2). Both pharmacological and non-pharmacological modalities are important for the management of OA symptoms (2, 3). Analgesics, such as acetaminophen (paracetamol), non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors form the basis of the pharmacological treatment of OA pain (2, 3). Acetaminophen is commonly used for mild-to-moderate OA pain. However, acetaminophen has the potential to cause liver toxicity in high doses or with moderate alcohol use (4), where high doses are not recommended. For many patients, acetaminophen treatment may be insufficient to provide adequate pain relief and use of NSAIDs or selective COX-2 inhibitors should be considered (2).

Although NSAIDs are well established for the relief of pain in OA (5, 6), their use is associated with gastrointestinal (GI) side effects of varying severity (7, 8). Indeed, 15-30% of patients receiving regular treatment with NSAIDs have ulcers upon examination by endoscopy (9). Symptomatic upper GI events occur with NSAID therapy in 3.0-4.5% of arthritis patients per year, and develop into serious complicated events (perforations, obstructions and bleeds) in approximately 1.5% (9). In 1999, the mortality burden from NSAID-related ulcer complications in the US was similar to that observed with AIDS (10).

Prostaglandins produced by cyclooxygenase-1 (COX-1) help to maintain GI mucosal integrity. By inhibiting these prostaglandins, traditional NSAIDs can cause gastric damage. Selective COX-2 inhibitors were developed to spare gastric COX-1 prostaglandin production and provide an analgesic agent as efficacious as traditional NSAIDs but with a more favourable GI safety profile (11). Several selective COX-2 inhibitors have been reported to be effective at reducing pain in OA (12-15).

Lumiracoxib (Prexige®) is a novel selective COX-2 inhibitor for the treatment of OA (16) and acute pain following dental surgery (17), arthroplasty (18), sprains and strains (19) and associated with gout (20), primary dysmenorrhoea (21) and episodic tension-type headache (22). Unlike other selective COX-2 inhibitors, lumiracoxib is weakly acidic and thereby distributes preferentially into inflamed tissue (23), including synovial fluid (24). The steady-state concentration of lumiracoxib in the synovial fluid of rheumatoid arthritis (RA) patients is three times the steady-state concentration in the plasma (24). Lumiracoxib also has a short mean plasma half-life (~4 hours). Consequently, concentrations of lumiracoxib in the synovial fluid persist beyond those observed in the plasma (24). This reduced systemic exposure could result in an improved safety and tolerability profile (25).

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), the largest study to date (18 325 patients with OA) that primarily evaluated GI safety of a selective COX-2 inhibitor, reported a 79% reduction in GI ulcer complications with lumiracoxib 400 mg once daily (od) (four times the recommended dose in OA) compared with NSAIDs (ibuprofen and naproxen) in the non-aspirin population (26).

Lumiracoxib 100 mg od has already been shown to be effective at reducing pain intensity in patients with OA, and two 13-week studies have shown it to be comparable to celecoxib 200 mg od (16, 27). However, patients with OA may require treatment for extended periods and, therefore, data on long-term safety and efficacy are required. This paper reports results from a 39-week extension of a 13-week core study (16). The objective was to assess the long-term efficacy, safety and tolerability (up to 1 year) of lumiracoxib 100 mg od in patients with knee OA.

Materials and methods

This was a 39-week, open-label extension to a 13-week, multicentre, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study. The combined duration of the core and extension study was 52 weeks. The 13-week (core) study was conducted at 137

centres in the USA and 38 centres in Canada (16). The extension phase was conducted at 117 centres in the US and 36 centres in Canada.

The study received Ethics Committee approvals and was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (1964 and subsequent revisions). All patients provided written informed consent prior to entering both study phases (core and extension).

Patients and study design

Core study. The design of the core study has been reported previously (16). Briefly, the core study recruited male and female patients aged ≥18 years with a diagnosis of symptomatic primary knee OA according to American College of Rheumatology (ACR) criteria (28). Patients were also required to have OA pain intensity in the target knee ≥40 mm on a 100 mm visual analogue scale (VAS) and needed NSAID or other analgesic therapy for ≥3 months.

The exclusion criteria for the core study have been published previously. Briefly, patients with a known hypersensitivity to NSAIDs, secondary OA, recent knee surgery within the past year, other connective tissue disease, or significant medical problems, such as peptic ulceration, GI bleeding, or a history of malignancy within the past 5 years, were excluded. Women who were pregnant, lactating or of childbearing potential and not using a reliable method of contraception were also excluded.

Following a screening period, during which prior NSAID therapy was washed out (with the exception of rescue acetaminophen or low-dose aspirin for prophylaxis against a cardiovascular [CV] or cerebrovascular event), eligible patients were randomized (1:1:1:1) to receive lumiracoxib 100 mg od, lumiracoxib 100 mg od with an initial dose of lumiracoxib 200 mg od for the first 2 weeks (referred to as lumiracoxib 100 mg od with a 200 mg od initial dose), celecoxib 200 mg od or placebo for 13 weeks in the core study. Lumiracoxib 100 mg od with a 200 mg initial dose was used in the core study to evaluate whether the initial dose-response rate or onset of action could be further improved.

Extension study. The extension study population consisted of patients who had successfully completed the 13-week core study without a major protocol violation and who consented to participate in the extension phase. Patients who demonstrated poor compliance during the core study or were considered inappropriate for continued participation by the study physician were excluded from the extension period.

All patients in the extension period received treatment with lumiracoxib 100 mg od, regardless of their treatment in the core study, and patients were switched without a washout period. Compliance with study drug was monitored by counting tablets returned by the patient at each visit. Compliance was defined as patients taking at least 75% of the full daily doses (a dose was considered to be fully taken if all tablets for that day were taken).

Patients were allowed to take up to 2 g/day of acetaminophen as rescue medication. No rescue medication was to be taken in the 24 hours before a visit. Use of rescue medication was tracked by counting tablets returned at each visit and by the completion of a diary by the patients. Patients taking >2 g of rescue medication for two-thirds of the days between consecutive visits were discontinued from the study for an unsatisfactory therapeutic effect.

Concomitant NSAID therapy was not allowed during the study (including the screening period), with the exception of aspirin (≤325 mg/day) for prophylaxis against a CV event. Other permitted concomitant medications included H_2-receptor antagonists, proton pump inhibitors, antacids and cytoprotective agents (taken at usual labelled doses).

The primary objective of the extension period was to assess the long-term safety and tolerability of lumiracoxib in patients who completed the core study. Secondary objectives were to assess the long-term efficacy of lumiracoxib with regard to overall pain intensity in the target knee, the patient's and physician's global assessment of disease activity at each visit, and the rate of discontinuation due to unsatisfactory therapeutic effect.

Outcome measures

Study assessments were performed in the clinic at screening, baseline and at weeks 2, 4, 8 and 13 (end of core study). After the final core study visit at week 13, patients attended visits at weeks 17, 26, 39 and 52 for evaluation. Two weeks after the end of the extension study (week 54), patients were followed up by telephone to evaluate the incidence of serious adverse events (SAEs) and GI events.

The efficacy variables, overall OA pain intensity (VAS [0-100 mm]) in the target knee, and the patient's and physician's global assessments of disease activity (VAS [0-100 mm]) were assessed at each visit in the extension study.

General safety and tolerability was evaluated by recording adverse events (AEs) and SAEs at each visit. Physical examinations were performed at weeks 0, 13, 26 and 52. Vital signs were assessed and laboratory tests (haematology, serum chemistry and urinalysis) were performed at each clinic visit. Investigators were required to report all suspected occurrences of a series of GI, CV, and hepatobiliary events. These events were forwarded to independent safety committees and adjudicated, blinded to treatment, according to prespecified criteria. AEs in five categories (GI events excluding ulcers [abdominal pain, constipation, diarrhoea, nausea, vomiting, dyspepsia, dysphagia and loose stools], GI ulcers, oedema, chest pain and CV events [angina pectoris, cerebrovascular accidents, myocardial infarction, transient ischemic attack, syncope and phlebitis]) were prespecified for analysis.

Statistical analysis

All efficacy variables were analysed descriptively using the extension efficacy population, which included all patients in the extension period who received at least one dose of study medication and who provided efficacy data. Last observation carried forward (LOCF) techniques were used in the event of missing data. The baseline used for the extension efficacy population was week 0 for patients randomized to lumiracoxib in the core study, and week 13 for patients who completed the core phase on

celecoxib or placebo. A post hoc analysis of the primary efficacy variables was conducted for patients switching from placebo to lumiracoxib.

Safety data were analysed descriptively using the extension safety population (39 weeks), which included all patients from the core study who consented to enter the extension phase, and the total safety population (all patients who received lumiracoxib 100 mg od during the core and/or extension study periods [52 weeks]).

A post hoc analysis was also conducted to calculate Kaplan-Meier estimates for patients discontinuing treatment due to unsatisfactory therapeutic effect and AEs.

Results

Efficacy, safety and tolerability results for the 13-week core study have been published previously (16). A total of 1551 patients were randomized into the core study (Fig. 1). Of these, 1182 patients completed the core study and the total safety population comprised 1181 patients. The extension safety population (*i.e.*, those patients entering the extension study) comprised 834 patients and efficacy data were available on 827 patients (extension efficacy population). Of the patients entering the extension study, 67% (n=559) completed the study. The mean (standard deviation [SD]) duration of exposure to lumiracoxib in the extension study safety population was 261.9 (101.1) days. Baseline demographics and disease characteristics for patients entering the extension study are presented in Table I.

Efficacy results

The overall OA pain intensity (VAS mm), patient's global assessment of disease activity and physician's global assessment of disease activity decreased after 3 months of treatment with lumiracoxib, and these decreases were all maintained for the entire duration of the extension phase (Fig. 2; Table II). A post hoc analysis demonstrated that, after switching from placebo to lumiracoxib 100 mg od at week 13, OA pain intensity decreased by 6.6-7.2 mm, the patient's global assessment of disease

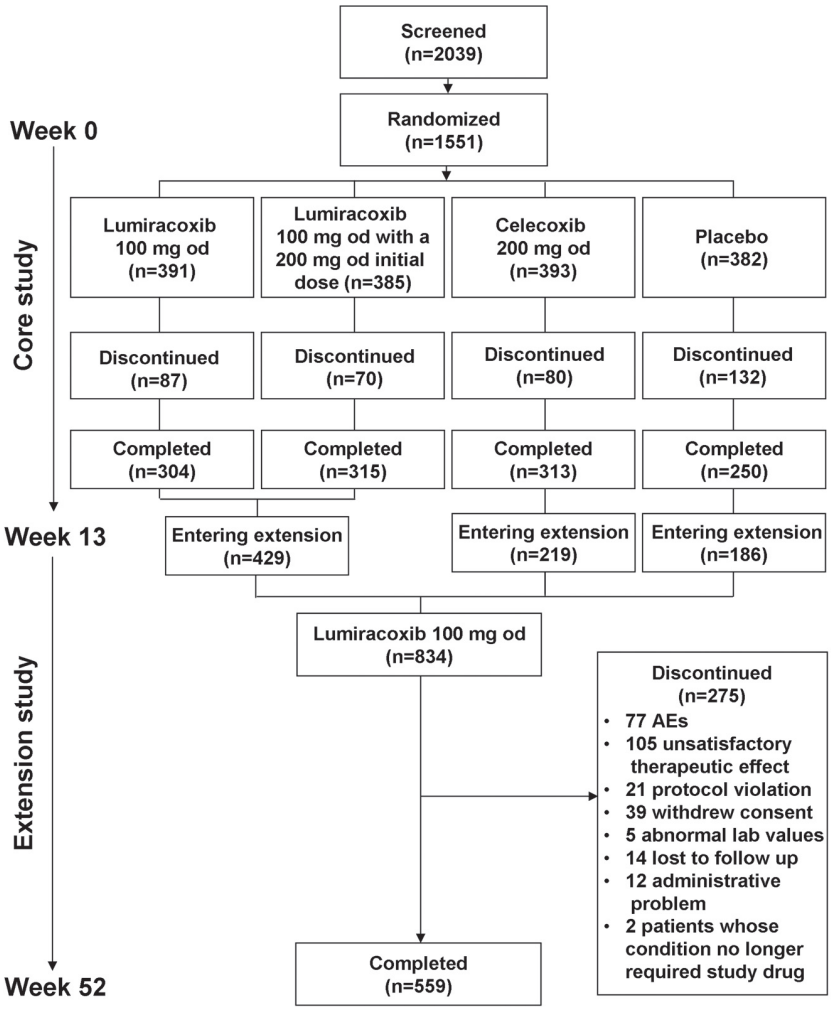

Fig. 1. Patient flow during the core study and extension period.

Table I. Baseline demographic and disease characteristics.

	Lumiracoxib 100 mg od Extension safety population (n=834)
Age (years), mean ± SD	60.7 ± 10.5
Females, n (%)	516 (61.9)
BMI (kg/m^2), mean ± SD	32.2 ± 6.9
Race, n (%)	
White/Caucasian	749 (89.8)
Black/African American	41 (4.9)
Japanese	1 (0.1)
Other Asian or Pacific Islander	1 (0.1)
Hispanic	30 (3.6)
Other	12 (1.4)
Disease duration (years), mean ± SD	7.0 ± 8.0
	Efficacy population (n=827)
OA pain (VAS, mm), mean ± SD	52.4 ± 23.1
Patient's global assessment of disease activity (VAS, mm), mean ± SD	51.3 ± 24.0
Physician's global assessment of disease activity (VAS, mm), mean ± SD	49.6 ± 22.5

BMI: body mass index; od: once daily; SD: standard deviation; VAS: visual analogue scale.
Baseline values were performed at week 0 for patients treated with lumiracoxib and at week 13 for patients who switched therapy.

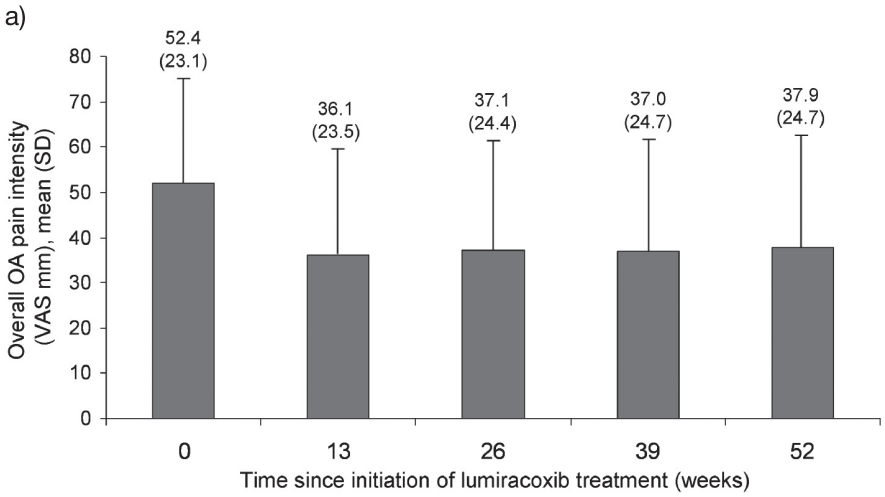

Fig. 2a. The reduction in overall OA pain intensity with lumiracoxib 100 mg od is maintained for 12 months.

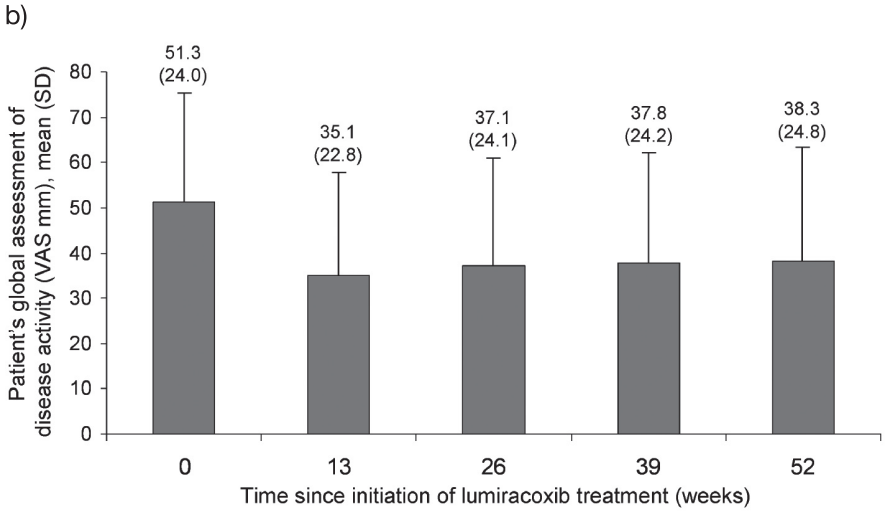

Fig. 2b. The reduction in patient's global assessment of disease activity with lumiracoxib 100 mg od is maintained for 12 months.

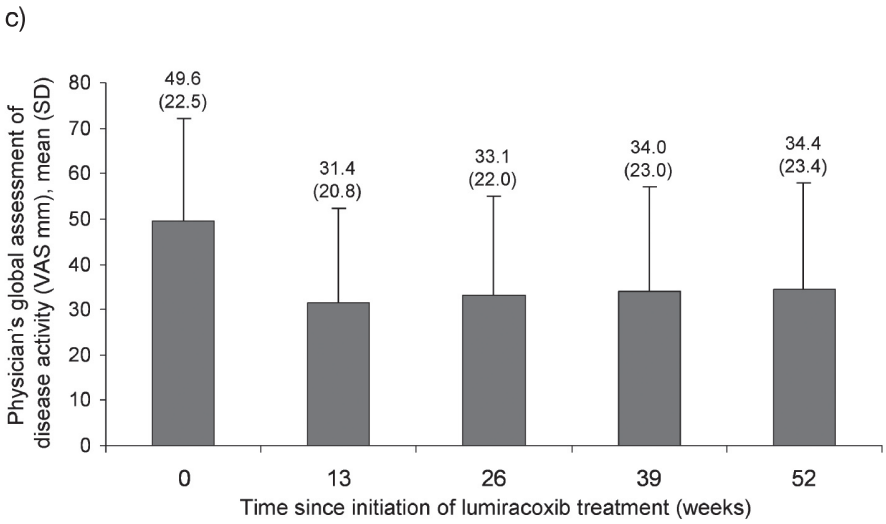

Fig. 2c. The reduction in physician's global assessment of disease activity with lumiracoxib 100 mg od is maintained for 12 months.

activity was reduced by 7.3-8.4 mm, and the physician's global assessment of disease activity decreased by 7.8-9.2 mm during the 13 to 39 weeks of lumiracoxib treatment in the extension period.

The overall rate of discontinuations due to an unsatisfactory therapeutic response was 12.6% in the extension period. Kaplan-Meier estimates for discontinuations due to an unsatisfactory therapeutic effect relative to the total exposure to lumiracoxib during the whole study (core + extension) are presented in Table III.

Safety results

AEs were observed in 69.5% of patients (Table IV). Most AEs were of mild-to-moderate severity and the most frequently occurring AEs were headache, arthralgia, nasopharyngitis and back pain (Table V). AEs leading to discontinuation occurred in 77 (9.2%) patients during the extension period and in 115 (9.7%) patients in the total safety population (Table III). Treatment-related AEs were observed in 12.4% (n=103) of patients in the extension safety population and 17.4% (n=206) in the total safety population. The GI system was the most commonly affected organ class in both the extension (4.8% [n=40]) and total safety populations (8.3% [n=98]). Dyspepsia was the most frequently reported treatment-related AE in the extension safety population (1.4% [n=12]) and the total safety population (2.3% [n=27]). Kaplan-Meier estimates for discontinuations due to AEs relative to the total exposure to lumiracoxib during the whole study (core + extension) are presented in Table III.

There were 31 patients (3.7%) with SAEs during the extension period and three of these events were suspected to be related to study drug by the investigator (haemorrhagic enterocolitis, pulmonary embolism and a decrease in creatinine clearance). In the total safety population, 41 patients (3.5%) experienced SAEs. In addition to the one death (myocardial infarction in a patient with a history of coronary heart disease, hypertension and hypercholesterolemia) reported in the core study

Table II. Mean (SD) change from baseline* in efficacy variables (extension efficacy population [n=827], last observation carried forward).

Time since lumiracoxib treatment was initiated†	Overall OA pain intensity (VAS, mm), mean (SD)	Patient's global assessment of disease activity (VAS, mm), mean (SD)	Physician's global assessment of disease activity (VAS, mm), mean (SD)
13 weeks	-16.3 (28.7)	-16.1 (27.7)	-18.3 (28.0)
26 weeks	-15.4 (29.7)	-14.2 (28.6)	-16.6 (28.8)
39 weeks	-15.4 (29.3)	-13.5 (28.1)	-15.6 (28.6)
52 weeks	-14.5 (28.7)	-13.0 (28.3)	-15.3 (28.8)

SD: standard deviation; VAS: visual analogue scale.
*Baseline was at week 0 for patients who continued on lumiracoxib 100 mg od and week 13 for patients who switched from celecoxib 200 mg od or placebo; †either in the core or extension phase, depending upon initial treatment allocation.

Table III. Number of patients who completed the study and Kaplan-Meier estimates for discontinuations due to unsatisfactory therapeutic effect or adverse events.

Interval days	Patients at risk*, n (%)	Patients who completed the study, n (cumulative n, %)	Cumulative Kaplan-Meier estimates discontinuations due to	
			UTE (%)	AE (%)
1–14	1181 (100.00)	43 (43, 3.64)	1.6278	0.5108
15–28	1138 (96.36)	54 (97, 8.21)	4.6756	0.7808
29–56	1084 (91.79)	73 (170, 14.39)	7.7076	2.6568
57–91	1011 (93.52)	131 (301, 25.49)	10.0337	4.1414
92–119	880 (74.51)	150 (451, 38.19)	11.7921	5.5837
120–182	730 (61.81)	72 (523, 44.28)	15.0514	8.2585
183–273	658 (55.72)	222 (745, 63.08)	17.5874	11.8864
274–364	436 (36.92)	270 (1015, 85.94)	18.6993	15.3383

UTE: unsatisfactory therapeutic effect; AE: adverse event.
*Subjects at risk are those continuing in the study without an event before the start of the specified time interval.
†Cumulative KM estimate of the % discontinued to UTE/AE at the end of the specified time interval.

Table IV. The number and incidence of AEs and SAEs in the extension study.

Number (%) of patients	Extension safety population (39 weeks) (n=834)	Total safety population (52 weeks) (n=1181)
With AEs	580 (69.5)	886 (73.3)
Prespecified	126 (15.1)	231 (19.6)
Leading to discontinuation*	77 (9.2)	115 (9.7)
With SAEs	31 (3.7)	41 (3.5)
Related to study drug†	3 (0.4)	4 (0.3)
Deaths	1 (0.1)	2 (0.2)

AEs: adverse events; SAEs: serious adverse events.
*Including SAEs; †according to investigator's opinion.

(16), one death occurred during the extension period (adjudicated by the independent CV safety committee as a confirmed CV death occurring 8 days after hospitalization for a confirmed ischaemic stroke). Neither death was considered to be treatment related.

The incidence of prespecified AEs in the safety population of the extension period was 15.1% (n=126), and the majority of these events (11.4% [n=95] of patients) were GI events (excluding ulcers). In the extension period, oedema occurred in 19 patients (2.3%) and chest pain in 12 patients (1.4%). CV events were rare (n=6 [0.7%]). For the total safety population the incidences of prespecified AEs during the entire study period (52 weeks) were: GI events (excluding ulcers), 16.0% (n=189); GI events (perforations, ulcers and bleeds), 0.17% (n=2); oedema, 3.0% (n=35); and CV events, 0.8% (n=10). The Kaplan-Meier estimates at one year are 20.3%, 4.6% and 1.7% for predefined GI events (excluding ulcers), oedemas and CV events, respectively.

Newly occurring or worsening increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to >3 x the upper limit of normal (ULN) occurred in 1.0% (n=8) and 0.5% (n=4) of patients, respectively, in the extension period. In the total safety population, 0.8% (n=9) and 0.3% (n=4) of patients had an increase >3 x ULN in ALT or AST, respectively. Newly occurring or worsening increases in serum creatinine >1.5 x ULN occurred in one patient (0.1%) in the total safety population and this occurred during the extension period. Increases in serum creatinine to >35.36 μmol/L from baseline occurred in 36 (4.3%) patients during the extension period and 42 (3.6%) patients in the total safety population.

Mean systolic and mean diastolic blood pressure tended to decrease slightly during the extension period (Table VI).

Discussion

Given that treatments for OA pain may be administered for extended periods of time, it is important to demonstrate long-term efficacy and safety of treatments. Open-label extensions to randomized trials can therefore be useful to obtain long-term data. Here we report efficacy and safety data from an open-label extension to a previously reported study (16).

The original core study reported that lumiracoxib 100 mg od reduced pain intensity in the target knee by 25.1 mm (VAS) from baseline, which was comparable to reductions in pain with celecoxib 200 mg od (24.1 mm VAS) and significantly greater than placebo (18.1 mm VAS) ($p<0.001$) (16). Moreover, lumiracoxib 100 mg od with a 200 mg od initial dose did not improve efficacy more than the lumiracoxib 100 mg od in the core study. A direct comparison of efficacy data between the core study and the extension period is

Table V. The 10 most frequent AEs* during the extension study.

AE preferred term	Extension safety population (39 weeks) (n=834)	Total safety population (52 weeks) (n=1181)
Headache, n (%)	107 (12.8)	170 (14.4)
Nasopharyngitis, n (%)	54 (6.5)	115 (9.7)
Arthralgia, n (%)	72 (8.6)	102 (8.6)
Upper respiratory tract infection, n (%)	46 (5.5)	84 (7.1)
Back pain, n (%)	51 (6.1)	80 (6.8)
Diarrhoea, n (%)	35 (4.2)	64 (5.4)
Urinary tract infection, n (%)	33 (4.0)	59 (5.0)
Sinusitis, n (%)	28 (3.4)	54 (4.6)
Pain in extremity, n (%)	39 (4.7)	49 (4.1)
Dyspepsia, n (%)	18 (2.2)	40 (3.4)

AEs: adverse events.
*Ranked by the frequency for the total safety population.

Table VI. Mean (SD) change from baseline in systolic and diastolic blood pressure.

n	Week 3 797	Week 26 714	Week 36 630	Week 52 294
Systolic blood pressure				
Mean (SD) baseline, mmHg	128.3 (13.6)	128.6 (13.7)	128.3 (13.9)	128.4 (13.7)
Mean (SD) change from baseline, mmHg	-0.8 (12.3)	-1.5 (13.4)	-0.3 (13.3)	-0.1 (14.3)
Diastolic blood pressure				
Mean (SD) baseline, mmHg	77.9 (8.5)	77.9 (8.5)	77.9 (8.7)	78.0 (8.5)
Mean (SD) change from baseline, mmHg	-1.1 (8.7)	-1.6 (8.6)	-0.8 (8.7)	-1.5 (9.7)

SD: standard deviation.
At each time point, only those patients with a measurement at baseline and at that time point were included.

difficult. Since patients switched treatment for the extension period, baseline data were obtained at the visit when the first dose of lumiracoxib 100 mg od was received. Consequently, baseline was considered to be at week 13 for patients who received celecoxib or placebo and week 0 for those treated with lumiracoxib. Since pain intensity and other efficacy assessments had already been decreased at week 13 with celecoxib or placebo treatment, this reduced the mean baseline efficacy measurements for the extension period such that they were not comparable to the core study. A post hoc analysis of patients switching from placebo at week 13 was conducted and demonstrated further improvement in efficacy upon exposure to lumiracoxib for the remainder of the 39-week extension period. The difference in baseline efficacy variable levels means that changes from baseline could not be compared directly between the core and extension studies. However, it was notable that the reduction in OA pain intensity and patient's and physician's global assessment of disease activity observed 13 weeks after the initiation of lumiracoxib was maintained for the entire extension period (*i.e.*, up to 52 weeks). This is consistent with the findings from an extension of a 13-week study by Lehmann *et al*. (27), which also reported that reductions in OA pain intensity and patient's and physician's global assessment of disease activity were maintained for up to 52 weeks with lumiracoxib 100 mg od or celecoxib 200 mg od (29). The magnitude of changes reported in the current core study (16) was similar to that reported in the 13-week study described by Lehmann *et al*. (27).

In the 13-week core study, discontinuations due to an unsatisfactory therapeutic response occurred in 18.3% of patients treated with placebo and 9.7% of patients receiving lumiracoxib 100 mg (16). Of note, despite the longer duration of treatment in this extension study, the overall rate of discontinuations due to an unsatisfactory therapeutic response was 12.6%. Comparable rates of discontinuation due to unsatisfactory therapeutic response have been reported previously in 1-year studies with other COX-2 inhibitors and NSAIDs (30, 31). These data provide further support for the maintenance of the efficacy of lumiracoxib in the long term.

Lumiracoxib was well tolerated in the core study, with the overall incidence of AEs similar to that observed with celecoxib 200 mg od or placebo. The extension period has demonstrated that lumiracoxib is well tolerated with a favourable safety profile over 1 year. The incidence and type of AEs were as expected given the duration of the study and the population studied.

Studies of the long-term treatment of some COX-2 inhibitors, such as rofecoxib and celecoxib, have reported an increased risk of CV events compared with placebo with these agents (32-34). The incidence of CV events in this extension study was low (0.7%). A recent meta-analysis has reported that the risk of CV events with selective COX-2 inhibitors is similar to that observed with most NSAIDs (35). In TARGET, the incidence of non-fatal and silent myocardial infarction, stroke, or CV death with lumiracoxib was comparable to that observed with the traditional NSAIDs, naproxen and ibuprofen (36). In the present study, lumiracoxib 100 mg did not increase systolic or diastolic blood pressure from baseline. This is in keeping with studies showing that lumiracoxib has a blood pressure profile similar to placebo (37) and superior to traditional NSAIDs, such as naproxen and ibuprofen (36, 38). Moreover, in a meta-analysis of nearly 35 000 patients, it has been shown that the rate of confirmed or probable CV events (Antiplatelet Trialists' Collaboration [APTC] endpoint) with lumiracoxib was comparable to those reported with naproxen, non-naproxen NSAIDs and placebo (39).

There was no incidence of GI ulcers during the 39-week extension period. This would add further support to a beneficial GI profile for lumiracoxib. Indeed, in TARGET, lumiracoxib 400 mg od (four times the recommended dose in OA) was associated with a

79% reduction in GI ulcer complications compared with NSAIDs (ibuprofen and naproxen) in patients with OA not receiving low-dose aspirin (26). Moreover, lumiracoxib 200 mg and 400 mg has been reported to reduce the incidence of gastroduodenal ulcers compared with ibuprofen (40).

Increases in ALT >3 x ULN were observed in 0.8% of the total safety population. This incidence rate is similar to the 1% incidence rate reported in the prescribing information for many NSAIDs, such as naproxen and ibuprofen (41, 42). Newly occurring elevations in AST >3 x ULN were observed in 0.3% of patients. Worsening or newly occurring increases in serum creatinine of >1.5 x ULN occurred in one patient (0.1%). The favourable long-term safety and tolerability profile with lumiracoxib may be a result of its pharmacokinetics. Lumiracoxib has a short plasma half-life (24), which may limit its systemic exposure and improve its safety profile. However, lumiracoxib is also weakly acidic and distributes preferentially into inflamed/synovial tissue, where concentrations persist after levels in the plasma have fallen (23, 24). This pharmacokinetic profile means that efficacy of lumiracoxib is retained with once-daily dosing whilst also limiting its systemic exposure.

In conclusion, these data suggest that lumiracoxib 100 mg od was both well tolerated and maintained effective pain relief in patients with OA of the knee for up to 1 year. These data also suggest that lumiracoxib is a useful option for the long-term treatment of pain associated with OA.

Acknowledgements

We thank the investigators of the study, the staff of the centres involved in this work, the clinical trial team for their expert collaboration and the patients who participated in the study. The authors would like to thank Dr. Graham Allcock, a professional medical writer with ACUMED®, for his assistance with drafting the manuscript and incorporating subsequent revisions. The authors would also like to thank Kirstin Stricker for her critical review of the manuscript.

References

1. REGINSTER JY: The prevalence and burden of arthritis. *Rheumatology* 2002; 41 (Suppl. 1): 3-6.
2. JORDAN KM, ARDEN NK, DOHERTY M *et al.*: EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003; 62: 1145-55.
3. AMERICAN COLLEGE OF RHEUMATOLOGY: Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum* 2000; 43: 1905-15.
4. FDA: Label changes to OTC analgesics. Available at: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01533.html (accessed 4 April 2007).
5. DOUGADOS M: The role of anti-inflammatory drugs in the treatment of osteoarthritis: a European viewpoint. *Clin Exp Rheumatol* 2001; 19 (Suppl. 25): S9-14.
6. MOSKOWITZ RW: The role of anti-inflammatory drugs in the treatment of osteoarthritis: a United States viewpoint. *Clin Exp Rheumatol* 2001; 19 (Suppl. 25): S3-8.
7. LANGMAN MJ, WEIL J, WAINWRIGHT P *et al.*: Risk of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; 343: 1075-8.
8. WOLFE MM, LICHTENSTEIN DR, SINGH G: Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1999; 340: 1888-99.
9. LAINE L: Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001; 120: 594-606.
10. SINGH G, TRIADAFILOPOULOS G: Epidemiology of NSAID-induced GI complications. *J Rheumatol* 1999; 26 (Suppl. 56): 18-24.
11. HAWKEY CJ: COX-2 inhibitors. *Lancet* 1999; 353: 307-14.
12. DETORA LM, KRUPA D, BOLOGNESE J, SPERLING RS, EHRICH EW: Rofecoxib shows consistent efficacy in osteoarthritis clinical trials, regardless of specific patient demographic and disease factors. *J Rheumatol* 2001; 28: 2494-503.
13. EDWARDS JE, MCQUAY HJ, MOORE RA: Efficacy and safety of valdecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *Pain* 2004; 111: 286-96.
14. PINCUS T, KOCH G, LEI H *et al.*: Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis* 2004; 63: 9319.
15. BERENBAUM F, GRIFKA J, BROWN JP *et al.*: Efficacy of lumiracoxib in osteoarthritis: a review of nine studies. *J Int Med Res* 2005; 33: 21-41.
16. SHELDON E, BEAULIEU A, PASTER Z, DUTTA D, YU S, SLOAN VS: Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: A 13-week, randomized, double-blind comparison with celecoxib and placebo. *Clin Ther* 2005; 27: 64-77.
17. FRICKE J, DAVIS N, YU V, KRAMMER G: An evaluation of the efficacy of lumiracoxib 400 mg, celecoxib 400 mg or placebo for treating pain following dental surgery. *Reg Anesth Pain Med* 2006; 30: A-12.
18. CHAN VW, CLARK AJ, DAVIS JC, WOLF RS, KELLSTEIN D, JAYAWARDENE S: The postoperative analgesic efficacy and tolerability of lumiracoxib compared with placebo and naproxen after total knee or hip arthroplasty. *Acta Anaesthesiol Scand* 2005; 49: 1491-500.
19. KYLE C, ZACHARIAH J, KASANGRA M, ANDREWS C, ELLIS G, KINCH H: Lumiracoxib 400 mg once daily is comparable to naproxen 500 mg twice daily for treatment of acute muscular pain following soft tissue injury. *Ann Rheum Dis* 2006; 65 (Suppl. II): 241 (Abstract THU0415).
20. WILLBURGER RE, MYSLER E, DERBOT J *et al.*: Lumiracoxib 400 mg once daily is comparable to indomethacin 50 mg three times daily for the treatment of acute flares of gout. *Ann Rheum Dis* 2006; 65 (Suppl II): 566 (Abstract SAT0383).
21. GITTON X, ZHOU W, JAYAWARDENE S, DANIELS S, BARTON S, MATCHABA P: Lumiracoxib 200 mg od is an effective and well-tolerated treatment for primary dysmenorrhoea. British Pain Society (BPS) 2006 *Book of Abstracts*, 24-27 April, Harrogate, UK (Abstract 7).
22. PACKMAN E, PACKMAN B, THURSTON H, TSENG L: Lumiracoxib is effective in the treatment of episodic tension-type headache. *Headache* 2005; 45: 1163-70.
23. WEAVER ML, FLOOD DJ, KIMBLE EF, FUJIMOTO RA: Lumiracoxib demonstrates preferential distribution to inflamed tissue in the rat following a single oral dose: an effect not seen with other cyclooxygenase-2 inhibitors. *Ann Rheum Dis* 2003; 62 (Suppl. I): 378 (Abstract AB0044).
24. SCOTT G, RORDORF C, REYNOLDS C *et al.*: Pharmacokinetics of lumiracoxib in plasma and synovial fluid. *Clin Pharmacokinet* 2004; 43: 467-78.
25. DAY RO: Pharmacokinetic and pharmacodynamic aspects of the ideal COX-2 inhibitor: a rheumatologist's perspective. *Clin Exp Rheumatol* 2001; 19 (Suppl. 25): S59–S62.
26. SCHNITZER TJ, BURMESTER GR, MYSLER E *et al.*: TARGET Study Group: Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; 364: 665-74.
27. LEHMANN R, BRZOSKO M, KOPSA P *et al.*: Efficacy and tolerability of lumiracoxib 100 mg once daily in knee osteoarthritis: a 13-week, randomized, double-blind study vs. placebo and celecoxib. *Curr Med Res Opin* 2005; 21: 517-26.
28. ALTMAN R, ASCH E, BLOCH D *et al.*: Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986; 29: 1039-49.

29. PAVELKA K, ZAMANI O, ALTEN R, YU S, LITSCHIG S, SLOAN VS: Lumiracoxib is effective and well tolerated in the long-term treatment of knee osteoarthritis. *Ann Rheum Dis* 2005; 64 (Suppl. 3): 353 (Abstract FRI0319).
30. CANNON GW, CALDWELL JR, HOLT P *et al.*: Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib Phase III Protocol 035 Study Group. *Arthritis Rheum* 2000; 43: 978-87.
31. SAAG K, VAN DER HEIJDE D, FISHER C *et al.*: Rofecoxib, a new cyclooxygenase 2 inhibitor, shows sustained efficacy, comparable with other nonsteroidal anti-inflammatory drugs: a 6-week and a 1-year trial in patients with osteoarthritis. Osteoarthritis Studies Group. *Arch Fam Med* 2000; 9: 1124-34.
32. BRESALIER RS, SANDLER RS, QUAN H *et al.*: Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators: Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; 352: 1092-102.
33. SOLOMON SD, MCMURRAY JJ, PFEFFER MA *et al.*: Adenoma Prevention with Celecoxib (APC) Study Investigators: Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; 352: 1071-80.
34. ZARRAGA IG, SCHWARZ ER: Coxibs and heart disease: what we have learned and what else we need to know. *J Am Coll Cardiol* 2007; 49: 1-14.
35. KEARNEY PM, BAIGENT C, GODWIN J, HALLS H, EMBERSON JR, PATRONO C: Do selective COX-2 inhibitors and traditional NSAIDs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; 332: 1302-8.
36. FARKOUH ME, KIRSHNER H, HARRINGTON RA *et al.*: TARGET STUDY GROUP: Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004; 364: 675-84.
37. WHITEHEAD A, SIMMONDS M, MELLEIN B, FRIEDE T, GITTON X, SALLSTIG P: Blood pressure profile of lumiracoxib is similar to placebo in arthritis patients. *Osteoarthritis Cartilage* 2006; 14 (Suppl. 2): S168-9 (Abstract P309).
38. FARKOUH ME, VERHEUGT FWA, KIRSHNER H *et al.*: Lumiracoxib provides superior blood pressure profile compared to NSAIDs after 4 weeks of treatment. *Arthritis Rheum* 2006; 54 (Suppl. 1): S678 (Abstract 1692).
39. MATCHABA P, GITTON X, KRAMMER G *et al.*: Cardiovascular safety of lumiracoxib: a meta-analysis of all randomized controlled trials ≥1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. *Clin Ther* 2005; 27: 1196-214.
40. HAWKEY CJ, SVOBODA P, FIEDOROWICZ-FABRYCY IF *et al.*: Gastroduodenal safety and tolerability of lumiracoxib compared with ibuprofen and celecoxib in patients with osteoarthritis. *J Rheumatol* 2004; 31: 1804-10.
41. MOTRIN: Prescribing information. Available at: http://www.pfizer.com/pfizer/download/uspi_motrin.pdf (accessed October 2006).
42. NAPROSYN: Product information. Available at: http://www.rocheusa.com/products/naprosyn/pi.pdf (accessed October 2006).