Efficacy and tolerability of lumiracoxib versus placebo in patients with osteoarthritis of the hand

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Abstract

Objective

T*his multicentre, randomized, double-blind, placebo-controlled parallel-group study was undertaken to investigate the efficacy, safety and tolerability of lumiracoxib (Prexige®), a cyclooxygenase-2 selective inhibitor, in patients with primary osteoarthritis (OA) of the hand.*

Methods

The study randomized 594 patients aged ≥ 18 years with symptomatic OAof the hand. Patients underwent a 3 to 7-day washout for previous nonsteroidal anti-inflammatory drugs and those with pain intensity ≥ 40 mm on a 100 mm Visual Analogue Scale (VAS) in the target hand during the 24 hours prior to baseline and an increase in pain intensity of either ≥ 20% or ≥ 10 mm VAS since screening (whichever was greater) were randomized to lumiracoxib 200 mg once daily (od) (n=205), lumiracoxib 400 mg od (n=193) or placebo (n=196). The primary efficacy variable was overall OA pain intensity (VAS mm) in the target hand after 4 weeks of treatment. Safety and tolerability assessments were performed.

Results

After 4 weeks of treatment, overall OA pain intensity in the target hand was significantly lower for patients treated with lumiracoxib compared with patients treated with placebo (both doses $p<0.001$). There was no significant difference between lumiracoxib doses in terms of the reduction in overall OApain intensity. Lumiracoxib was well tolerated. The incidence of adverse events was similar for active treatment groups and placebo.

Conclusions

Lumiracoxib 200 and 400 mg od were effective and well tolerated treatments for OA of the hand. Lumiracoxib significantly improved overall OA pain intensity in the target hand versus placebo, with a tolerability profile similar to placebo.

Key words

Osteoarthritis, hand, non-steroidal anti-inflammatory agents, cyclooxygenase inhibitors, pain, analgesics.

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Introduction

Osteoarthritis (OA) is a highly prevalent, chronic and progressive musculoskeletal disease characterized by joint pain and stiffness (1). OA affecting the hand is a particularly disabling form of the disease as the level of joint pain and stiffness directly affects manual dexterity (2). The resulting limitations in performing activities of daily living may have a considerable impact on quality of life (QoL) and general patient well-being (3). Furthermore, the clinical manifestation of hand OA (pain, stiffness and physical function/ disability) is distinct from other types of OA such as knee or hip (3-5). As such, it is important to establish the clinical benefits of a therapeutic regimen in hand OA, in addition to separate assessment of efficacy in other types of OA.

Cyclooxygenase-2 (COX-2) selective inhibitors were developed as treatments for both acute and chronic pain, with the objective of providing efficacy similar to traditional nonsteroidal anti-inflammatory drugs (NSAIDs) combined with superior gastrointestinal (GI) tolerability. Lumiracoxib (Prexige®) is a novel COX-2 selective inhibitor that has rapid absorption and plasma clearance resulting in a short plasma half-life (3–6 hours) (6). Selectivity for COX-2 over COX-1 has been demonstrated for lumiracoxib both *in vitro* and *in vivo* (7) and at doses up to 800 mg in humans (8). Lumiracoxib lacks a sulphur-containing moiety but possesses a carboxylic acid group, which confers weakly acidic properties (pKa 4.7) (9). As a possible consequence of its distinct structure, lumiracoxib rapidly moves into (10) and persists in inflamed tissue in animal models (11), an effect not seen with other COX-2 selective inhibitors tested. In addition, lumiracoxib is associated with sustained higher concentrations in synovial fluid compared with plasma in patients with rheumatoid arthritis (12).

Lumiracoxib has demonstrated efficacy in relieving the chronic pain of OA in knee and hip models. The results of a 4-week, dose-finding study in patients with OA of the hip or knee suggested that lumiracoxib was effective in reducing joint pain intensity, and had a favourable safety profile compared with a traditional NSAID (13). Efficacy in OA was confirmed by two similarly designed 13-week studies, each involving more than 1600 patients with OAof the knee, where lumiracoxib 200 mg and 400 mg od significantly reduced OA pain intensity and improved patient's global assessments of disease activity compared with placebo from the first assessment visit at 2 weeks through to the study end (14, 15). The superior GI tolerability of lumiracoxib in comparison with NSAIDs was demonstrated in a 13-week study involving 1042 patients with OA, where lumiracoxib was found to have a GI safety profile (assessed in terms of gastroduodenal ulceration by endoscopy) superior to ibuprofen and similar to celecoxib (16).

The aim of this study was to compare the efficacy of lumiracoxib (200 or 400 mg od) with placebo in patients with OAof the hand. Safety and tolerability were assessed as secondary objectives.

Methods

This was a randomized, double-blind, placebo-controlled, parallel-group study, conducted at 52 centres in four countries (Germany, Canada, France and Italy). The study 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 any study procedure.

Patients and study design

Patients aged ≥ 18 years with a diagnosis of symptomatic primary OA of the hand, as confirmed by the American College of Rheumatology classification criteria (4), who had symptoms for at least 3 months were eligible for inclusion. Female patients were required to be post-menopausal, surgically sterile or practising an acceptable method of birth control. Patients with evidence of active peptic ulceration within the previous 12 months, secondary OA, other types of disease in the target hand or other significant medical problems were excluded.

Patients meeting the inclusion criteria

underwent a washout period of 3–7 days for NSAIDs and/or other analgesic therapy. Physical examinations, evaluation of vital signs and assessment of baseline disease activity were performed before randomization. Patients were required to have pain intensity ≥ 40 mm on a 100 mm Visual Analogue Scale (VAS) (most pain) in the target hand during the 24 hours prior to baseline. An increase in pain intensity in the target hand of either ≥ 20% or ≥ 10 mm VAS at the baseline visit compared with screening values (whichever was greater) was required to assess those patients who required analgesia. Patients were randomized in a 1:1:1 ratio to receive lumiracoxib 200 mg od, 400 mg od or placebo for 4 weeks. Rescue medication (paracetamol ≤ 2 g/day) was permitted during the screening and treatment periods, except from midnight directly before a scheduled study visit. Patients were asked to return all unused medication at the end of the study and were considered to be compliant if they had taken at least 80% of the daily doses.

During treatment, efficacy and safety were assessed during study visits at Weeks 2 and 4, and a follow-up telephone call was made at Week 6 to check for serious adverse events (SAEs). All randomized patients prematurely discontinuing were followed-up by telephone up to 2 weeks after their last known dose of medication in order to request information on the possible occurrence of a complicated ulcer and to ensure a complete dataset.

Prespecified criteria for discontinuation due to notable laboratory parameter changes were established.

Efficacy measures

The primary efficacy variable was overall OApain intensity (VAS mm) in the target hand, assessed after 4 weeks of treatment. This was determined by asking patients to indicate the most pain they had from their OA over the previous 24 hours. Secondary efficacy variables were overall OA pain intensity (VAS mm) in the target hand in the previous 24 hours, assessed after 2 weeks of treatment, physician's and patient's global assessments of disease activity (VAS mm) at each visit, patient's functional status measured by the Australian/Canadian OA Hand Index (AUSCAN) categorical score at Week 4, and patient's QoL measured by the Health Assessment Questionnaire (HAQ©) disability dimension at Week 4. Patient's grip strength was measured by a dynamometer at Week 4 and the use of rescue medication was monitored at Weeks 2 and 4.

The AUSCAN is a validated, self-administered questionnaire developed to assess the functional status of the hand during the previous 48 hours (17). It is based on five-point Likert scales, where numerical values are allocated to each of 5 possible responses (none = 0; mild = 1; moderate = 2; severe = 3; extreme = 4). The AUSCAN questionnaire consists of 15 questions grouped into three sections (Pain = 5 questions; Difficulty Performing Daily Activities [DPDA] = 9 questions; Stiffness = 1 question). The AUSCAN Total score is derived by summation of the scores for the 15 individual questions.

The HAQ© questionnaire disability dimension consists of 22 questions grouped into 12 sections and focuses on the patient's ability to perform common activities of daily living over the previous 7 days (18). The study nurse or investigator was advised to check patients'questionnaires for completeness. The dynamometer procedure allowed the patient to make three sequential attempts to measure his or her maximum grip strength. The patient was allowed to rest and recover from the previous attempt before starting the next one.

Tolerability and safety measures

All adverse events (AEs) were recorded and assessed in terms of severity (mild, moderate and severe) and suspected relationship to study drug. Safety and tolerability was also evaluated through regular assessment of haematology, blood chemistry and urinalysis. Vital signs and physical examinations were performed at baseline and at Weeks 2 and 4; electrocardiograms (ECGs) were performed at baseline and at Week 4.

Statistical analyses

The planned total sample of 498 gave a power of over 80% to detect a significant difference between lumiracoxib 400 mg od and placebo at a 5% level. If this were achieved, significance of lumiracoxib 200 mg od would also be tested at the 5% level without the need to adjust for multiple testing.

The primary efficacy analysis was performed on the intent-to-treat (ITT) population, comprising all randomized patients exposed to study drug. Last observation carried forward (LOCF) was performed in the event of missing observations. The primary efficacy variable was analyzed using an analysis of covariance model fitting baseline value, centre and treatment group. Between–treatment pairwise comparisons were performed using least square means (LSMs) obtained from the model.

The analysis of all secondary efficacy variables was also performed on the ITT population (LOCF). For the analysis of the number of paracetamol rescue tablets taken during the study, treatment groups were compared with respect to the proportion of patients having taken rescue medication using a multiple logistic regression model with country, treatment group and baseline OA pain (VAS mm) as explanatory variables. Odds ratios and 95% confidence intervals were determined. For each of the other secondary efficacy variables, between–treatment pairwise comparisons were performed using LSMs obtained from an analysis of covariance model. The safety and ITT populations were identical. The occurrence of prespecified AEs was summarized and any differences between treatments analyzed using Fisher's exact test. Prespecified AEs were defined using medical terms as coded by a standard medical dictionary:

- Prespecified GI AEs and ulcers: Abdominal pain not otherwise specified (NOS), abdominal pain lower, abdominal pain upper, abdominal pain aggravated, constipation, constipation aggravated, diarrhoea NOS, diarrhoea aggravated, nausea, nausea aggravated, vomiting NOS, vomiting aggravated, dyspepsia, dyspepsia aggravated, dysphagia, dysphagia aggravated, loose stools, oe-

sophageal ulcer, peptic ulcer, peptic ulcer aggravated, gastric ulcer, duodenal ulcer, duodenal ulcer aggravated, gastroduodenal ulcer, GI ulcer, pyloric ulcer.
- Peripheral oedema AEs: Oedema peripheral, oedema lower limb, oedema upper limb, oedema NOS.
- Chest pain AEs: Chest pain not elsewhere classified.

Results

Patients and treatment

Of 669 patients screened, 594 were randomized to receive lumiracoxib 200 mg od (n=205), lumiracoxib 400 mg od (n=193) or placebo (n=196) (Fig. 1). Patient demographics and baseline disease characteristics were comparable between treatment groups (Table I). A slightly smaller proportion of patients in the lumiracoxib 400 mg od group had received prior treatment with NSAIDs compared with the other treatment groups, although this difference was not significant.

Compliance rates were high, with ≥ 99% of patients in each group achieving >80% compliance over the treatment period. During the course of treatment, 10, 11 and 14 patients withdrew prematurely from the lumiracoxib 200 mg od, lumiracoxib 400 mg od, and placebo groups respectively. Figure 1 illustrates the breakdown of patients screened, randomized, withdrawn and completing the study.

Efficacy

Primary variables. Lumiracoxib 200 mg od and 400 mg od reduced overall OA pain intensity in the target hand compared with placebo at Week 4 (Fig. 2; Table II). Between-treatment comparisons of LSMs showed that lumiracoxib 200 mg od and lumiracoxib 400 mg od were statistically superior to placebo (treatment-placebo differences: -9.9 mm and -10.2 mm for lumiracoxib 200 and 400 mg od, respectively; both $p < 0.001$). No significant difference was observed between the two doses of lumiracoxib in terms of the reduction in overall OApain intensity.

Secondary variables. Lumiracoxib was significantly more effective than placebo with respect to overall OA pain intensity in the target hand at Week 2 (treatment-placebo LSM differences: -9.6 mm and -8.4 mm for lumiracoxib 200 and 400 mg od, respectively; both $p < 0.001$). No significant difference was observed between the two doses of lumiracoxib in terms of the reduction in overall OA pain intensity at Week 2. Mean changes from baseline in overall OA pain intensity in the target hand at Weeks 2 and 4 are shown in Table II.

Both doses of lumiracoxib were significantly superior to placebo for patient's and physician's global assessments of

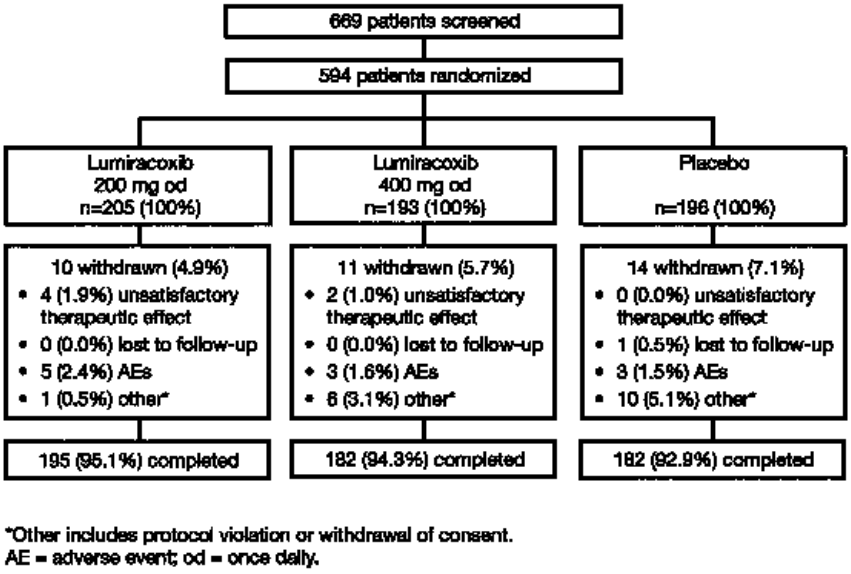

Fig. 1. Patient flow diagram.

Table I. Patient demographics and baseline disease characteristics.

	Lumiracoxib 200 mg od (n=205)	Lumiracoxib 400 mg od (n=193)	Placebo (n=196)
Age (years), mean ± SD	62.0 ± 12.1	61.0 ± 12.4	62.7 ± 11.7
Sex, no. (%)			
Male	37 (18.0)	33 (17.1)	34 (17.3)
Female	168 (82.0)	160 (82.9)	162 (82.7)
Ethnicity, no. (%)			
Caucasian	203 (99.0)	187 (96.9)	196 (100.0)
Black/African American	1 (0.5)	0 (0)	0 (0)
Asian/Pacific Islander	1 (0.5)	2 (1.0)	0 (0)
Other*	0 (0)	4 (2.1)	0 (0)
BMI (kg/m^2), mean ± SD	26.6 ± 4.6	27.2 ± 4.9	27.0 ± 4.8
Disease duration (years), mean ± SD	4.9 ± 4.8	5.4 ± 5.3	5.7 ± 6.0
Prior NSAID therapy, n (%)	181 (88.3)	160 (82.9)	167 (85.2)
Overall OApain intensity in the target hand (VAS mm), mean ± SD	70.9 ± 12.9	72.2 ± 13.1	71.2 ± 12.6
Patient's global assessment of disease activity (VAS mm), mean ± SD	60.5 ± 18.0	63.7 ± 15.7	62.1 ± 16.0
Physician's global assessment of disease activity (VAS mm), mean ± SD	59.7 ± 14.6 (n=201)	60.0 ± 13.2 (n=191)	62.1 ± 13.3 (n=191)
AUSCAN Total score, mean ± SD	33.4 ± 11.0	34.9 ± 10.7	34.9 ± 11.7

AUSCAN: Australian/Canadian osteoarthritis hand index; BMI: body mass index; NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis; od: once daily; SD: standard deviation; VAS: visual analogue scale.
*Other: non-Caucasian, non-Black, non-Asian.

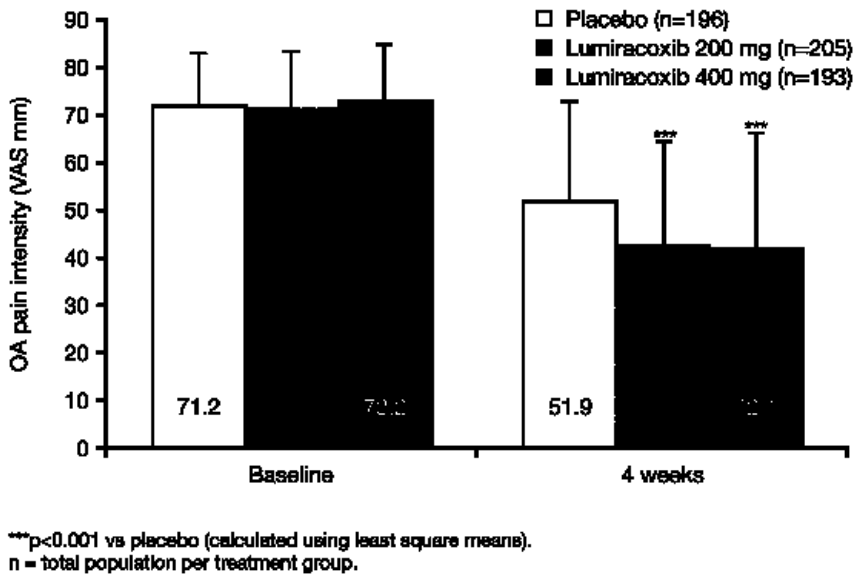

Fig. 2. Osteoarthritis (OA) pain intensity (mean + SD) in the target hand after 4 weeks of treatment with lumiracoxib 200 mg od, 400 mg od or placebo.

disease activity at Weeks 2 and 4 (all $p < 0.001$). Mean changes from baseline are shown in Table II.

Analysis of AUSCAN Total score LSMs at Week 4 showed that lumiracoxib 200 mg and 400 mg od were significantly superior to placebo in terms of patient's functional status ($p=0.003$ and $p<0.001$, respectively) (Fig. 3; Table III). Both doses of lumiracoxib were significantly superior to placebo with respect to all of the AUSCAN subscale scores (Pain, DPDA and Stiffness) after 4 weeks of treatment (all $p < 0.01$) (mean change from baseline shown in Table III).

Both doses of lumiracoxib were significantly superior to placebo in terms of overall rescue medication use: 52.2% of patients in the lumiracoxib 200 mg od group ($p=0.035$ vs placebo), 43.3% of patients in the lumiracoxib 400 mg od group ($p<0.001$ vs placebo) and 61.9% of patients in the placebo group required rescue medication. In addition to overall intake, comparison of rescue medication use from baseline to Week 2 and from Week 2 to Week 4 showed a significant difference for both doses of lumiracoxib versus placebo (data not shown). In addition, mean rescue tablet consumption per day was higher in the placebo group than in the active treatment groups. No significant differences were observed between the two doses of lumiracoxib with respect to the amount of rescue medication consumed.

No significant differences were seen between treatment groups in terms of QoL (HAQ© disability dimension) or patient's grip strength at Week 4.

Safety

The overall frequency of AEs was similar in the lumiracoxib 200 mg od and placebo groups (24.9% and 21.4%, respectively) and lower in the lumiracoxib 400 mg od group (16.6%) (Table IV). The majority of AEs were mild or moderate in intensity. No deaths or SAEs were reported during the course of the study, including the 2-week follow-up period.

The number of patients discontinuing treatment because of AEs was five (2.4%) in the lumiracoxib 200 mg od group, three (1.6%) in the lumiracoxib 400 mg od group and three (1.5%) in the placebo group (Table IV).

Nausea and headache were the most common AEs: nausea was reported by 4.9% of patients in the lumiracoxib 200 mg od group and in 1.6% and 1.5% of the lumiracoxib 400 mg od and placebo groups, respectively; headache was reported by 2.9%, 2.1% and 3.1% of the three groups, respectively. The GI tract was the most commonly affected system overall, with the most frequent GI AEs being nausea, diarrhoea and upper abdominal pain. No statistical differences between treatment groups were observed in terms of the incidence of prespecified GI AEs in any study group (Table IV). There were no GI ulcers in any treatment group. Overall, 42 patients had AEs suspected to be related to study drug, including 22 (10.7%) in the lumiracoxib 200 mg od group, 9 (4.7%) in the lumiracoxib 400 mg od group and 11 (5.6%) in the placebo group. There was no dose–response relationship between lumiracoxib 200 mg and 400 mg in terms of the incidence of AEs.

Table II. Change from baseline in overall OApain intensity in the target hand and patient's and physician's global assessments of disease activity at Weeks 2 and 4

	Change from baseline (VAS mm), mean ± SD					
	Overall OApain intensity in the target joint		Patient's global assessment of disease activity		Physician's global assessment of disease activity	
Treatment group	Week 2	Week 4	Week 2	Week 4	Week 2	Week 4
Lumiracoxib 200 mg od (n=205)	–21.3 ± 19.2	–28.0 ± 23.2	–11.9 ± 19.7	–16.3 ± 24.3	–13.6 ± 17.5	–17.8 ± 21.4
Lumiracoxib 400 mg od (n=193)	–21.1 ± 21.9	–30.0 ± 24.3	–13.3 ± 20.1	–20.9 ± 22.9	–12.3 ± 17.5	–18.7 ± 20.1
Placebo (n=196)	–12.5 ± 16.8	–19.3 ± 20.0	–5.3 ± 17.4	–9.4 ± 20.0	–7.8 ± 15.6	–12.5 ± 19.6

OA: osteoarthritis; od: once daily; SD: standard deviation; VAS: visual analogue scale.

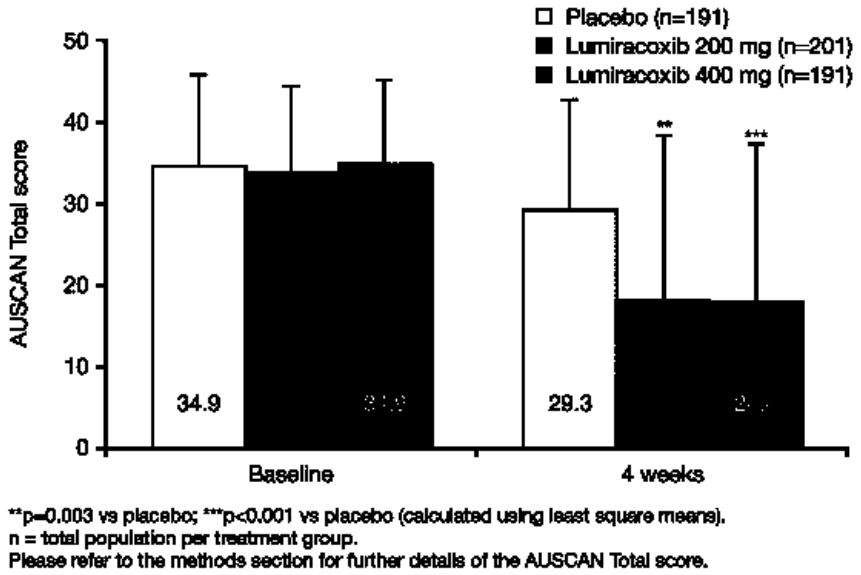

Fig. 3. AUSCAN Total score (mean + SD) after 4 weeks of treatment with lumiracoxib 200 mg od, 400 mg od or placebo.

Table III. Change from baseline in the AUSCAN total and subscale scores at Week 4.

	AUSCAN, Change from baseline, mean ± SD			
	Total score	Pain subscale score	DPDAsubscale score	Stiffness subscale score
Treatment group	Week 4	Week 4	Week 4	Week 4
Lumiracoxib 200 mg od (n=205)	–7.7 ± 11.5	–3.0 ± 4.2	–4.3 ± 7.3	–0.6 ± 1.0
Lumiracoxib 400 mg od (n=193)	–10.5 ± 12.0	–3.9 ± 4.5	–6.0 ± 7.5	–0.7 ± 1.0
Placebo (n=196)	–5.6 ± 11.3	–2.1 ± 4.1	–3.1 ± 7.0	–0.4 ± 0.9

AUSCAN: Australian/Canadian osteoarthritis hand index; DPDA: difficulty in performing daily activities; od: once daily; SD: standard deviation.
Please refer to the Methods section for further details regarding the AUSCAN Total score.

Table IV. Summary of adverse events.

Number of patients with	Lumiracoxib 200 mg od (n=205)	Lumiracoxib 400 mg od (n=193)	Placebo (n=196)
Any AE, no. (%)	51 (24.9)	32 (16.6)	42 (21.4)
GI disorders, no. (%)	25 (12.2)	15 (7.8)	13 (6.6)
Discontinuation due to any AE, no. (%)	5 (2.4)*	3 (1.6)	3 (1.5)
Prespecified AEs, no. (%)	21 (10.2)	12 (6.2)	13 (6.6)
GI events	20 (9.8)	11 (5.7)	12 (6.1)
Peripheral oedema	1 (0.5)	0 (0.0)	0 (0.0)
CVevents (including chest pain)	0 (0.0)	1 (0.5)	1 (0.5)

AE: adverse event; CV: cardiovascular; GI:gastrointestinal; od:once daily.
*Includes one patient in whom treatment with the study drug was temporarily interrupted because of nausea and vertigo; this discontinuation then became permanent.

No clinically significant treatment-related abnormalities were observed during the study in vital signs, ECG parameters or clinical laboratory measures and no patients discontinued because of abnormal laboratory values.

Discussion

The current findings indicate that lumiracoxib is effective and well tolerated for the treatment of OAof the hand. Both doses of lumiracoxib demonstrated significant superiority to placebo in terms of overall OA pain intensity in the target hand after 4 weeks of treatment. No significant difference was observed between lumiracoxib 200 mg and 400 mg od for this variable. These results are consistent with those observed in previous studies, in both a 4-week study involving patients with OA of the hip or knee (13) and two 13-week studies in patients with OAof the knee (14,15), where lumiracoxib demonstrated significantly superior efficacy compared with placebo in terms of reducing joint pain intensity.

Both doses of lumiracoxib demonstrated significantly superior efficacy compared with placebo in terms of patient's and physician's global assessments of disease activity. Use of the validated AUSCAN questionnaire, which has been specifically designed to assess functional improvements in hand OA, demonstrated that treatment with lumiracoxib 200 mg and 400 mg od resulted in significantly superior AUSCAN Total scores compared with placebo at study end. The effect of treatment on aspects of patients' daily lives relating to their condition, including pain, stiffness and the ability to perform daily activities, were assessed by evaluation of the AUSCAN subscales. Overall, both doses of lumiracoxib were associated with significantly lower Pain, DPDA and Stiffness subscale scores versus placebo at the end of the study. The maintenance of pain relief and improvements in stiffness and manual dexterity is particularly important in patients with OA of the hand, which is considered to be an important indicator of a systemic tendency to OAinvolving weight-bearing joints, notably the hip and knee (3). Rescue medication use was significantly greater in the placebo group compared with either active treatment group, which may help to explain the reductions in pain intensity and the lack of patients discontinuing due to unsatisfactory therapeutic effect in the placebo group.

No significant differences could be found between treatment groups in terms of patient's grip strength at Week 4. Of note, it has previously been observed that the results of grip strength assessments may not correlate with

functional consequences, reducing the value of this measurement (19); an observation confirmed by the findings of this study.

Analysis of QoL was included as an exploratory measure in the study; however, a significant improvement in QoL versus placebo was not observed. Although the HAQ© is a validated tool for measurement of health status (18-20), improvements in QoL are not always evident with NSAIDs which have demonstrated efficacy in other measures of clinical activity (21, 22).

Overall, lumiracoxib 200 mg and 400 mg od were well tolerated with a safety and tolerability profile similar to that of placebo. No dose–response relationship was observed between lumiracoxib 200 mg and 400 mg od for the incidence of AEs. The results provide further support for the good GI tolerability of lumiracoxib as observed previously in an endoscopy study in more than 1000 patients with OAof the hip, knee, hand or spine, which indicated that lumiracoxib causes less gastroduodenal ulceration and fewer GI AEs compared with the traditional NSAID ibuprofen (16).

The results of the current study indicate that lumiracoxib 200 mg or 400 mg od is an effective and well-tolerated treatment option for the management of primary OA of the hand, providing effective pain relief, and improving joint stiffness and overall function. To our knowledge, this is the first clinical study conducted specifically with the primary objective of evaluating the efficacy of a COX-2 selective inhibitor in patients with OA of the hand. The reduction in joint pain and improvements in joint stiffness and functional ability following treatment with lumiracoxib may help to improve dexterity and limit disability in patients with OAaffecting the hands (2) and, consequently, could in the long-term, have a positive impact on patients' QoL and overall well-being.

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References

1. TODD C: Meeting the therapeutic challenge of the patient with osteoarthritis. *J Am Pharm Assoc* 2002; 42: 74–82.
2. BELLAMY N, SOTHERN RB, CAMPBELL J, BUCHANAN WW: Rhythmic variations in pain, stiffness, and manual dexterity in hand osteoarthritis. *Ann Rheum Dis* 2002; 61: 1075–80.
3. HART DJ, SPECTOR TD: Definition and epidemiology of osteoarthritis of the hand: a review. *Osteoarthritis Cartilage* 2000; 8 (Suppl. A): S2–7.
4. ALTMAN R, ALARCON G, APPELROUTH D *et al.*: The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990; 33: 1601–10.
5. LEQUESNE MG, MAHEU E: Methodology of clinical trials in hand osteoarthritis: conventional and proposed tools. *Osteoarthritis Cartilage* 2000; 8 (Suppl. A): S64–9.
6. SCOTT G, RORDORF C, BLOOD P *et al.*: Dose escalation study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of COX189 in healthy subjects. *Ann Rheum Dis* 2002; 61 (Suppl. 1): 242 (Abstract FRI 0300).
7. MARSHALL PJ, BERRY C, WASVARY J *et al.*: The *in vitro* and *in vivo* selectivity of lumiracoxib, a new and highly selective inhibitor of COX-2. *Ann Rheum Dis* 2002; 61 (Suppl. 1): 259 (Abstract SAT0013).
8. SCOTT G, RORDORF C, MILOSAVLJEV S *et al.*: Multiple-dose lumiracoxib shows rapid absorption and COX-2 selectivity without accumulation in patients with rheumatoid arthritis. *In* TULUNAY FC and ORME M (Eds.): *Proceedings of the Sixth Congress of the European Association for Clinical Pharmacology and Therapeutics.* Berlin, Springer-Verlag, 2003: 124.
9. MANGOLD JB, GU H, RODRIGUEZ LC, BONNER J, DICKSON J, RORDORF C: Pharmacokinetics and metabolism of lumiracoxib in healthy male subjects. *Drug Metab Dispos* 2004; 32: 566–71.
10. 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. 1): 378 (Abstract AB0044).
11. DAWSON J, JAGHER B, TOSCANO KT, FUJIMOTO RA, QUADROS E: Lumiracoxib shows rapid distribution to inflamed sites in a rat tissue chamber model compared with rofecoxib and celecoxib. *Ann Rheum Dis* 2003; 62 (Suppl. 1): 377 (AB0042).
12. REYNOLDS C, SCOTT G, LOOBY M *et al.*: Pharmacokinetics of lumiracoxib in plasma and synovial fluid. *Clin Pharmacokinet* 2004; 43: 467-78.
13. SCHNITZER TJ, GEUSENS P, HASLER P *et al.*: Efficacy and safety of four doses of lumiracoxib versus diclofenac in patients with knee or hip primary osteoarthritis: A phase II, four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Care Res* 2004; 51: 549-57.
14. TANNENBAUM H, BERENBAUM F, REGINSTER J-Y *et al.*: Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind study versus placebo and celecoxib. *Ann Rheum Dis* Published Online First 27 February 2004. doi: 10.1136/ard.2003.015974.
15. FLEISCHMANN R, SHELDONE, MALDONADO COCCO J, YU S, DUTTA D, USISKIN K: A prospective randomized 13-week study evaluating the efficacy of lumiracoxib in patients with osteoarthritis of the knee. *Ann Rheum Dis* 2003; 62 (Suppl. 1): 266 (Abstract FRI0233).
16. HAWKEY CJ AND THE PUCCINI (PREVENTION OF ULCERS WITH COX189 COMPARED WITH IBUPROFEN IN NSAID INVESTIGATION) STUDY GROUP: Reduced cumulative incidence of gastroduodenal ulcers with two doses of a new coxib, COX189 compared with standard therapeutic doses of ibuprofen in osteoarthritis patients. *Gastroenterology* 2002; 122 (Suppl. 1): A-345 (Abstract M1732).
17. BELLAMY N, CAMPBELL J, HARAOUI B *et al.*: Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. *Osteoarthritis Cartilage* 2002; 10: 855–62.
18. FRIES JF, SPITZ P, KRAINES R, HOLMAN H: Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23: 137–45.
19. BELLAMY N: Osteoarthritis clinical trials: candidate variables and clinimetric properties. *J Rheumatol* 1997; 24: 768–78.

20. BRUCE B, FRIES JF: The Stanford Health Assessment Questionnaire: A review of its history, issues, progress, and documentation. *J Rheumatol* 2003; 30: 167–78.
21. COLBERG K, HETTICH M, SIGMUND R, DEGNERFL: The efficacy and tolerability of an 8-day administration of intravenous and oral meloxicam: a comparison with intramuscular and oral diclofenac in patients with acute lumbago. German Meloxicam Ampoule Study Group. *Curr Med Res Opin* 1996; 13: 363–77.
22. GRACE D, ROGERS J, SKEITH K, ANDERSON K: Topical diclofenac versus placebo: a double-blind, randomized clinical trial in patients with osteoarthritis of the knee. *J Rheumatol* 1999; 26: 2659–63.