Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind study versus placebo and celecoxib


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Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind study versus placebo and celecoxib


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Short title: Efficacy and safety of lumiracoxib in osteoarthritis

Key words: Lumiracoxib, osteoarthritis, pain relief, celecoxib
ABSTRACT

Objectives – The objective of this 13-week, multicentre, randomized, double-blind study was to compare the efficacy and safety of lumiracoxib with placebo and celecoxib for osteoarthritis (OA).

Methods – After a 3–7-day washout period for nonsteroidal anti-inflammatory drugs, 1702 patients with knee OA were randomized to lumiracoxib 200 or 400 mg once daily (od), celecoxib 200 mg od or placebo (2:2:2:1). A visual analogue scale (VAS) pain intensity ≥40 mm was required. Primary efficacy variables were OA pain intensity (VAS mm) in the target knee, patient’s global assessment of disease activity (VAS mm), and WOMAC© Pain subscale and Total scores at 13 weeks. OA pain intensity, patient’s and physician’s global assessment of disease activity, and WOMAC© (Total and all subscale scores) were analyzed by visit as secondary variables.

Results – Lumiracoxib showed significant improvements in all primary and secondary variables versus placebo. Lumiracoxib 200 mg od and celecoxib 200 mg od achieved similar improvements in OA pain intensity and functional status. Lumiracoxib 400 mg od demonstrated superior efficacy for OA pain intensity and patient’s global assessment of disease activity at Weeks 2, 4 and 8 and similar efficacy at Week 13 versus celecoxib 200 mg od. The incidence of adverse events (AEs), serious AEs and discontinuations from AEs was similar per group.

Conclusion – Lumiracoxib demonstrated significant improvement in OA pain intensity, patient’s global assessment of disease activity and the WOMAC© Pain subscale and Total scores versus placebo. Lumiracoxib was well tolerated in this study, with overall tolerability similar to placebo and celecoxib.
INTRODUCTION

Osteoarthritis (OA) is a highly prevalent, chronic condition associated with a considerable burden for patients in terms of joint pain, stiffness and inability to perform normal daily activities. As a result, this condition has a significant negative impact on quality-of-life [1].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are well established as first-line treatment for chronic moderate-severe pain in OA, providing effective relief of symptoms in most patients [2–4]. Traditional NSAIDs control the pain and inflammation associated with OA by reducing prostaglandin synthesis – a direct consequence of inhibitory effects on both isoforms of the cyclooxygenase (COX) enzyme (COX-1 and COX-2). This nonselective mechanism of action is largely responsible for the development of symptomatic ulcers and potentially serious gastrointestinal (GI) side effects [5]. The incidence of symptomatic ulcers and ulcer complications associated with traditional NSAIDs was reported to be between 2–4% per year in 1988 [6] and the management of gastropathy associated with traditional NSAID use is estimated to more than double the costs associated with the original therapy [7]. The concomitant use of gastroprotective agents with traditional NSAIDs has been reported as one possible approach to managing NSAID-related gastropathy [8]. The GI side effects are due to reduced synthesis of prostaglandins, which play a cytoprotective role in the GI tract, when COX-1 is inhibited by traditional NSAID treatment [9 10].

Lumiracoxib is a novel COX-2 selective inhibitor developed for the treatment of OA, rheumatoid arthritis (RA) and acute pain. It has demonstrated selectivity for COX-2 *in vitro* and *in vivo* [11] and in human studies [12], with selectivity maintained at doses up to 1200 mg [13]. The structure of lumiracoxib distinguishes it from other COX-2 selective inhibitors [14], which may explain its preferential distribution into inflamed tissue in animal models (an effect not observed with other COX-2 selective inhibitors), [15 16] and the sustained high concentrations of lumiracoxib observed in synovial fluid compared with plasma in patients with RA [17]. Clinical studies show that lumiracoxib is characterized by rapid absorption (T<sub>max</sub> 2–3 hours), a short plasma half-life (3–6 hours) [18] and good oral bioavailability [19]. In patients with OA, lumiracoxib demonstrates dose-proportional pharmacokinetics [20]. Once-daily lumiracoxib provides relief from the pain, stiffness and impaired physical function of OA with efficacy superior to placebo and similar to diclofenac [21–23]. Furthermore, lumiracoxib is associated with a GI tolerability profile superior to ibuprofen and similar to celecoxib in patients with OA or RA [24 25].
The aim of this study was to determine the efficacy of two doses of lumiracoxib (200 and 400 mg once daily [od]) in relieving pain and improving functional status in patients with primary knee OA, compared with placebo and celecoxib 200 mg od. The safety and tolerability profiles of all treatment groups were also assessed.
METHODS
This was a 13-week international, multicentre, randomized, double-blind, double-dummy, placebo-controlled, active-comparator study, performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (and subsequent amendments).

Patients and study design
Men and women aged ≥18 years with a confirmed diagnosis of primary OA of the knee, as confirmed by the American College of Rheumatology criteria [26], were recruited after giving written, informed consent. Patients at risk of pregnancy or those who had secondary OA, other connective tissue diseases or significant medical problems, were excluded.

Individuals meeting the initial inclusion criteria underwent a 3- to 7-day washout period, during which NSAID therapy was not permitted. At the end of the washout period, patients with pain intensity in the affected knee measuring ≥40 mm on a 100 mm visual analogue scale (VAS) (most pain) in the past 24 hours were deemed eligible for entry into the treatment phase of the study. In order to best reflect the real-life clinical situation, no increase/worsening in OA symptoms (flare) was required for study entry.

Patients were randomized to 13 weeks' once-daily treatment with lumiracoxib 200 mg, lumiracoxib 400 mg, celecoxib 200 mg or placebo. Celecoxib was administered at 200 mg od according to its label specifications. Blinding was maintained by means of a double-dummy technique. All medications were taken in the morning at least one hour before or after a meal, the first dose being taken at the clinic on Day 0 (baseline). After this, patients returned to the clinic for assessment at Weeks 2, 4, 8 and 13.

Patients were permitted to take paracetamol (≤2 g/day), supplied by the investigator, as rescue medication throughout the trial; however, they were requested to refrain from using rescue medication from midnight before each clinic visit. NSAIDs were not permitted during the course of the study, with the exception of low-dose aspirin (≤325 mg/day) for a cardiovascular indication.

Prespecified criteria for discontinuation due to notable laboratory parameter changes were established.
Outcome measures
The following primary efficacy variables were evaluated at the end of the study (Week 13):
- OA pain intensity (VAS mm) in the target knee (most pain in the previous 24 hours)
- Patient’s global assessment of disease activity (VAS mm)
- Patient’s functional status (Pain subscale and Total score of the Western Ontario and
  McMaster Universities [WOMAC©] OA Index LK3.1 questionnaire) [27].

OA pain intensity in the target knee, patient’s and physician’s global assessment of disease
activity, and WOMAC© (Total and all three subscale scores: Pain, Difficulty in Performing
Daily Activities [DPDA] and Stiffness) were analyzed by visit as secondary variables.

Safety was assessed through recording the frequency of adverse events (AEs) and serious
adverse events (SAEs) at each clinic visit. Physical examinations were performed at baseline
and at study end, vital signs were assessed at each clinic visit and standard laboratory tests
were performed at Weeks 2, 4 and 13. Electrocardiogram (ECG) measurements, analyzed
centrally, were conducted at screening, Week 4 and Week 13. A sub-population of patients,
whose post-baseline ECGs were recorded 1–4 hours after the morning dose of study
treatment to coincide with the maximum plasma concentration (C_{max}) of lumiracoxib [18],
were included into ‘peak-time’ analyses of ECG parameters.

Compliance to study treatment was monitored by pill counting and rescue medication use
was assessed at each study visit.

Statistical analyses
A minimum sample size of 432 patients in each active treatment group and 216 in the
placebo group was specified in the study protocol, i.e. a total of 1512 patients. Using a two-
group t-test with a 0.025 one-tailed significance level, this sample size would have 99%
power to reject the null hypothesis of no treatment difference over placebo, assuming a
difference of 11 mm in favour of lumiracoxib, a withdrawal rate of 15% and a common
standard deviation of 25 mm. A high power was set to enable tests of non-inferiority or
superiority of lumiracoxib to celecoxib. To this end, non-inferiority margins of 5 mm in terms
of OA pain and patient’s global assessment, and of 0.6 points in terms of the Pain subscale
of the WOMAC© questionnaire were pre-defined.
Patients were randomized in a ratio of 2:2:2:1 to 13 weeks’ once-daily treatment with lumiracoxib 200 mg, lumiracoxib 400 mg, celecoxib 200 mg or placebo.

Each primary efficacy variable was analyzed, using analysis of covariance, with baseline values as the covariate, with treatment group and study centre as the independent variables. Pairwise comparisons between treatments were performed using least square means obtained from the model. Data were analyzed by visit at a secondary level using the same model.

All safety and efficacy evaluations were performed using the intent-to-treat (ITT) population. The safety and ITT populations were identical and included all patients randomized to treatment who had been exposed to study medication. Conventional last observation carried forward methodology was used in the event of missing data.

In addition to the analysis of AE and SAE incidence, active and placebo groups were compared with respect to the frequency of prespecified AEs 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, oesophageal 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 NOS, oedema upper limb.

- Chest pain AEs: Chest pain not elsewhere classified.

Occurrence of prespecified AEs was summarized and analyzed using a logistic regression model, including country and treatment group as variables.
RESULTS

Patient characteristics

The ITT population comprised 1702 patients, randomized to receive lumiracoxib 200 mg od (n=487), lumiracoxib 400 mg od (n=491), celecoxib 200 mg od (n=481) or placebo (n=243). The study population was predominantly female (68.5%) with a mean age of approximately 64 years. There were no significant differences between treatment groups with respect to patient demographics or baseline disease characteristics (table 1).

Table 1 Patient demographics and baseline disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Lumiracoxib</th>
<th>Lumiracoxib</th>
<th>Celecoxib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg od (n=487)</td>
<td>400 mg od (n=491)</td>
<td>200 mg od (n=481)</td>
<td></td>
</tr>
<tr>
<td>Age (years), mean ± SD (range)</td>
<td>64.1 ± 10.7 (20–93)</td>
<td>64.3 ± 10.4 (20–92)</td>
<td>64.1 ± 10.4 (30–91)</td>
<td>64.6 ± 9.9 (38–89)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>148 (30.4)</td>
<td>160 (32.6)</td>
<td>148 (30.8)</td>
<td>80 (32.9)</td>
</tr>
<tr>
<td>Female</td>
<td>339 (69.6)</td>
<td>331 (67.4)</td>
<td>333 (69.2)</td>
<td>163 (67.1)</td>
</tr>
<tr>
<td>White/Caucasian race, n (%)</td>
<td>482 (99.0)</td>
<td>485 (98.8)</td>
<td>475 (98.8)</td>
<td>242 (99.6)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean ± SD (range)</td>
<td>29.5 ± 5.8</td>
<td>29.9 ± 5.8</td>
<td>30.0 ± 5.7</td>
<td>29.6 ± 5.4</td>
</tr>
<tr>
<td>OA disease duration (years), median</td>
<td>4.2</td>
<td>5.2</td>
<td>5.3</td>
<td>4.3</td>
</tr>
<tr>
<td>OA pain intensity in target knee (mm), mean ± SD</td>
<td>65.5 ± 14.9</td>
<td>65.1 ± 14.1</td>
<td>65.1 ± 14.2</td>
<td>65.7 ± 13.3</td>
</tr>
<tr>
<td>Patient's global assessment of disease activity (mm), mean ± SD</td>
<td>62.9 ± 17.4</td>
<td>62.6 ± 17.6</td>
<td>63.6 ± 18.0</td>
<td>63.2 ± 16.5</td>
</tr>
<tr>
<td>Physician's global assessment of disease activity (mm), mean ± SD</td>
<td>58.6 ± 14.1</td>
<td>58.2 ± 14.2</td>
<td>59.2 ± 15.0</td>
<td>59.8 ± 14.3</td>
</tr>
<tr>
<td>WOMAC© Total score, mean ± SD</td>
<td>49.0 ± 14.9</td>
<td>48.1 ± 15.0</td>
<td>48.7 ± 15.4</td>
<td>49.2 ± 14.0</td>
</tr>
<tr>
<td>WOMAC© Pain subscale score, mean ± SD</td>
<td>10.1 ± 3.4</td>
<td>10.0 ± 3.3</td>
<td>10.1 ± 3.3</td>
<td>10.3 ± 3.0</td>
</tr>
<tr>
<td>WOMAC© DPDA subscale score, mean ± SD</td>
<td>34.6 ± 11.2</td>
<td>33.9 ± 11.4</td>
<td>34.4 ± 11.7</td>
<td>34.6 ± 10.4</td>
</tr>
<tr>
<td>WOMAC© Stiffness subscale score, mean ± SD</td>
<td>4.3 ± 1.7</td>
<td>4.2 ± 1.7</td>
<td>4.2 ± 1.7</td>
<td>4.3 ± 1.7</td>
</tr>
</tbody>
</table>

DPDA = Difficulty in Performing Daily Activities; OA = osteoarthritis; od = once daily; SD = standard deviation; WOMAC© = Western Ontario and McMaster Universities OA Index.
A similar number of patients discontinued from the study prematurely in each active treatment group (figure 1). The majority of discontinuations resulted from AEs; however, the proportion of patients who withdrew for this reason was similar across the four treatment groups. Overall, compliance with the treatment regimens was good, with more than 90% of patients judged to be compliant across the four treatment groups. Proportionately twice as many patients discontinued due to lack of efficacy in the placebo group than in the active treatment groups (figure 1).

Efficacy

PRIMARY VARIABLES

All active treatments were statistically significantly superior to placebo with respect to each of the primary variables at 13 weeks.

For OA pain intensity (VAS mm) in the target knee at Week 13, the estimated least square mean differences from placebo in favour of active treatment were 6.33 mm (p<0.001) in the lumiracoxib 200 mg od group, 7.94 mm (p<0.001) in the lumiracoxib 400 mg od group and 5.75 mm (p=0.001) in the celecoxib 200 mg od group (figure 2). The mean change from baseline in OA pain intensity at Week 13 was similar for all active treatments (−26.0 mm for lumiracoxib 200 mg od, −27.4 mm for lumiracoxib 400 mg od and −25.2 mm for celecoxib 200 mg od) compared with −19.8 mm for placebo (table 2), and non-inferiority of lumiracoxib 200 and 400 mg od to celecoxib 200 mg od was demonstrated.

Significant improvement in patient’s global assessment of disease activity was observed in all active treatment groups at Week 13 compared with placebo (all p<0.001 v placebo; figure 3, table 2). All active treatments were similar and non-inferiority of lumiracoxib 200 and 400 mg od to celecoxib 200 mg od was demonstrated.

The WOMAC© Pain subscale and Total scores at Week 13 were significantly better with lumiracoxib and celecoxib than with placebo (all p<0.01 v placebo for the Pain subscale and all p<0.001 for the Total score). Mean changes from baseline are shown in figure 4 and table 3.

SECONDARY VARIABLES

Significant improvements were seen in OA pain intensity (VAS mm) in the target knee from Week 2 onwards in all active treatment groups compared with placebo (table 2, figure 2). The
reduction in pain intensity with lumiracoxib 200 mg od was of similar magnitude to that of celecoxib 200 mg od at all timepoints. At Weeks 2, 4 and 8, lumiracoxib 400 mg od provided significantly greater reductions in OA pain intensity in the target knee than celecoxib 200 mg od.

The patient’s global assessment of disease activity (VAS mm) was significantly improved from Week 2 onwards in all active treatment groups compared with placebo (table 2, figure 3). In the lumiracoxib 400 mg od group, the reduction in the mean score was significantly greater than in the celecoxib 200 mg od group at Weeks 2, 4 and 8 (figure 3). In addition, all active treatment groups were significantly more efficacious than placebo at Weeks 2, 4, 8 and 13 according to the physician’s global assessment of disease activity (table 2).

Table 2 Change from baseline in OA pain intensity in the target joint, and patient’s and physician’s global assessments of disease activity at Weeks 2 and 13

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Week 2</th>
<th>Week 13</th>
<th>Week 2</th>
<th>Week 13</th>
<th>Week 2</th>
<th>Week 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumiracoxib 200 mg od (n=487)</td>
<td>–19.2 ± 21.7</td>
<td>–26.0 ± 26.3</td>
<td>–14.9 ± 22.4</td>
<td>–23.2 ± 26.9</td>
<td>–14.6 ± 18.4</td>
<td>–23.0 ± 22.4</td>
</tr>
<tr>
<td>Lumiracoxib 400 mg od (n=491)</td>
<td>–20.2 ± 21.0</td>
<td>–27.4 ± 24.5</td>
<td>–16.4 ± 20.8</td>
<td>–24.1 ± 25.0</td>
<td>–14.3 ± 17.0</td>
<td>–23.6 ± 21.4</td>
</tr>
<tr>
<td>Celecoxib 200 mg od (n=481)</td>
<td>–17.5 ± 20.5</td>
<td>–25.2 ± 24.7</td>
<td>–14.3 ± 20.6</td>
<td>–22.4 ± 25.7</td>
<td>–14.0 ± 16.9</td>
<td>–22.4 ± 22.0</td>
</tr>
<tr>
<td>Placebo (n=243)</td>
<td>–9.1 ± 19.3</td>
<td>–19.8 ± 26.1</td>
<td>–7.9 ± 19.2</td>
<td>–15.7 ± 26.1</td>
<td>–8.3 ± 17.3</td>
<td>–18.0 ± 24.3</td>
</tr>
</tbody>
</table>

OA = osteoarthritis; od = once daily; SD = standard deviation; VAS = visual analogue scale.
Significant improvements were observed in WOMAC© Total and all three subscale scores for all active treatment groups versus placebo at Week 2 (all \( p<0.01 \) \( \text{v} \) placebo; table 3). At Week 13, all active treatments were associated with significant improvements according to the DPDA and Stiffness subscales (all \( p<0.01 \) \( \text{v} \) placebo; table 3).

Table 3 Change from baseline in WOMAC© Total and subscale scores at Weeks 2 and 13

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Week 2</th>
<th>Week 13</th>
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<th>Week 13</th>
<th>Week 2</th>
<th>Week 13</th>
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</thead>
<tbody>
<tr>
<td>Lumiracoxib 200 mg od</td>
<td>-10.6 ± 13.2</td>
<td>-14.1 ± 16.8</td>
<td>-2.6 ± 3.3</td>
<td>-3.2 ± 4.3</td>
<td>-6.9 ± 9.6</td>
<td>-9.8 ± 12.1</td>
<td>-1.0 ± 1.7</td>
<td>-1.2 ± 1.8</td>
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<tr>
<td>(n=487)</td>
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</tr>
<tr>
<td>Lumiracoxib 400 mg od</td>
<td>-9.8 ± 13.9</td>
<td>-14.1 ± 16.9</td>
<td>-2.6 ± 3.4</td>
<td>-3.2 ± 3.8</td>
<td>-6.4 ± 10.3</td>
<td>-9.7 ± 12.6</td>
<td>-0.9 ± 1.6</td>
<td>-1.2 ± 1.8</td>
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<tr>
<td>(n=491)</td>
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<tr>
<td>Celecoxib 200 mg od</td>
<td>-8.6 ± 13.1</td>
<td>-13.4 ± 15.8</td>
<td>-2.4 ± 3.1</td>
<td>-3.1 ± 3.8</td>
<td>-5.5 ± 9.9</td>
<td>-9.2 ± 11.6</td>
<td>-0.8 ± 1.6</td>
<td>-1.2 ± 1.7</td>
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<tr>
<td>(n=481)</td>
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</tr>
<tr>
<td>Placebo (n=243)</td>
<td>-4.3 ± 12.4</td>
<td>-9.4 ± 16.1</td>
<td>-1.4 ± 3.3</td>
<td>-2.4 ± 3.8</td>
<td>-2.4 ± 8.8</td>
<td>-6.2 ± 11.8</td>
<td>-0.5 ± 1.5</td>
<td>-0.9 ± 1.6</td>
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</tbody>
</table>

DPDA = Difficulty in Performing Daily Activities; od = once daily; SD = standard deviation; WOMAC© = Western Ontario and McMaster Universities OA Index.

The mean number of rescue medication tablets consumed was significantly greater in the placebo group (0.8 tablets/day) compared with any active treatment group throughout the study (0.5 tablets/day for both lumiracoxib groups and 0.6 tablets/day for celecoxib 200 mg od; all \( p<0.05 \) \( \text{v} \) placebo). Between–treatment analyses showed that at Week 4, the number of rescue medication tablets taken was significantly
higher in the celecoxib 200 mg od group compared with the lumiracoxib 400 mg od; no other between–treatment differences were observed (data not shown).

Safety
Lumiracoxib was well tolerated. There were no deaths during the study and the incidence of SAEs was similar in all active treatment groups and the placebo group (2.5% of patients on lumiracoxib 200 mg od, 2.9% on lumiracoxib 400 mg od, 2.9% on celecoxib 200 mg od and 3.3% on placebo; table 4). The proportion of patients reporting at least one AE was 57.5% and 58.7% in the lumiracoxib 200 mg od and 400 mg od groups, respectively, compared with 51.0% for the placebo group and 53.2% for the celecoxib 200 mg od group. AEs led to discontinuation from the study in a similar proportion of patients in each treatment group. In all treatment groups the most common AEs leading to discontinuation were those affecting the GI system; 18 patients (3.7%) in the lumiracoxib 200 mg od group, 22 patients (4.5%) in the lumiracoxib 400 mg od group, 19 patients (3.9%) in the celecoxib 200 mg od group and six patients (2.5%) in the placebo group (table 4). In a post-hoc analysis, no statistically significant differences were detected in discontinuation rates for GI AEs between any active treatments compared with placebo.

Table 4 Summary of adverse events, serious adverse events and discontinuations due to adverse events

<table>
<thead>
<tr>
<th></th>
<th>Lumiracoxib 200 mg od (n=487)</th>
<th>Lumiracoxib 400 mg od (n=491)</th>
<th>Celecoxib 200 mg od (n=481)</th>
<th>Placebo (n=243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with SAEs, n (%)</td>
<td>12 (2.5)</td>
<td>14 (2.9)</td>
<td>14 (2.9)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td>Patients with AEs, n (%)</td>
<td>280 (57.5)</td>
<td>288 (58.7)</td>
<td>256 (53.2)</td>
<td>124 (51.0)</td>
</tr>
<tr>
<td>Discontinuations due to AEs, n (%)</td>
<td>42 (8.6)</td>
<td>43 (8.8)</td>
<td>47 (9.8)</td>
<td>21 (8.6)</td>
</tr>
<tr>
<td>Discontinuations due to GI AEs, n (%)</td>
<td>18 (3.7)</td>
<td>22 (4.5)</td>
<td>19 (3.9)</td>
<td>6 (2.5)</td>
</tr>
</tbody>
</table>

AE = adverse event; GI = gastrointestinal; od = once daily; SAE = serious adverse event.
The majority of AEs were mild or moderate in severity. The frequency and nature of AEs were similar in both lumiracoxib groups and the celecoxib group; overall, nasopharyngitis, headache and upper abdominal pain, were the most commonly reported AEs in all treatment groups (table 5).

**Table 5 Incidence of most frequently reported adverse events (>3%) and prespecified adverse events**

<table>
<thead>
<tr>
<th></th>
<th>Lumiracoxib 200 mg od (n=487)</th>
<th>Lumiracoxib 400 mg od (n=491)</th>
<th>Celecoxib 200 mg od (n=481)</th>
<th>Placebo (n=243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most frequently reported AEs, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>34 (7.0)</td>
<td>28 (5.7)</td>
<td>23 (4.8)</td>
<td>12 (4.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (3.9)</td>
<td>29 (5.9)</td>
<td>27 (5.6)</td>
<td>9 (3.7)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>23 (4.7)</td>
<td>25 (5.1)</td>
<td>25 (5.2)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15 (3.1)</td>
<td>11 (2.2)</td>
<td>14 (2.9)</td>
<td>11 (4.5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>19 (3.9)</td>
<td>21 (4.3)</td>
<td>17 (3.5)</td>
<td>9 (3.7)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>13 (2.7)</td>
<td>18 (3.7)</td>
<td>11 (2.3)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (1.6)</td>
<td>14 (2.9)</td>
<td>17 (3.5)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td>Hypertension NOS</td>
<td>8 (1.6)</td>
<td>17 (3.5)</td>
<td>12 (2.5)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Influenza</td>
<td>11 (2.3)</td>
<td>16 (3.3)</td>
<td>11 (2.3)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>Prespecified AEs, n (%)</td>
<td>94 (19.3)</td>
<td>101 (20.6)</td>
<td>77 (16.0)</td>
<td>30 (12.3)</td>
</tr>
<tr>
<td>GI events</td>
<td>85 (17.5)</td>
<td>96 (19.6)</td>
<td>72 (15.0)</td>
<td>25 (10.3)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>6 (1.2)</td>
<td>4 (0.8)</td>
<td>6 (1.2)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (0.6)</td>
<td>4 (0.8)</td>
<td>2 (0.4)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

AE = adverse event; GI = gastrointestinal; NOS = not otherwise specified; od = once daily.

Multiple regression analyses of the incidence of prespecified AEs revealed no significant differences between lumiracoxib and celecoxib (table 5). The proportion of patients reporting prespecified GI events was similar in each active treatment group. The incidence of prespecified peripheral oedema and chest pain was low and no clinically relevant pattern was observed between treatment groups.

Clinically relevant laboratory abnormalities were uncommon in all treatment groups; however, four patients were withdrawn from the study because of abnormal values. As required by study protocol, one patient in the lumiracoxib 400 mg od group discontinued because of an elevated creatinine level (>2 x upper limit of normal [ULN]). In total, nine patients experienced elevations in liver function parameters (alanine aminotransferase /aspartate...
aminotransferase) >3 x ULN (two patients in the lumiracoxib 200 mg od group; three patients in the lumiracoxib 400 mg od group; four patients in the celecoxib 200 mg od group). Of these nine patients, three were discontinued from the study (one patient in each of the lumiracoxib 200 mg od, lumiracoxib 400 mg od and celecoxib 200 mg od groups). All cases of elevated liver function parameters resolved either while on study medication or following treatment cessation and none were accompanied by clinical symptoms.

ECG analyses showed that lumiracoxib was not associated with QT interval prolongation or any form of arrhythmia. There was no evidence of drug- or dose-related changes in ECG recordings or increase in qualitative ECG abnormalities in any treatment group.
DISCUSSION

The results of this large, randomized, double-blind, placebo-controlled, active-comparator study demonstrate the clinical efficacy and tolerability of lumiracoxib, a novel COX-2 selective inhibitor, at doses of 200 or 400 mg od, in patients with OA of the knee. After 13 weeks of treatment, lumiracoxib 200 and 400 mg od were significantly superior to the placebo group in terms of OA pain intensity in the target knee, patient’s global assessment of disease activity and patient’s functional status.

Analyses of OA pain intensity in the target knee and patient’s global assessment of disease activity by clinic visit (secondary variables), showed that both doses of lumiracoxib provided statistically significant improvements over placebo from the first clinic visit after treatment commenced (Week 2), an effect sustained throughout the length of the study. The magnitude of improvement was similar for lumiracoxib 200 mg od and celecoxib 200 mg od at all timepoints. Lumiracoxib 400 mg od was significantly more effective than celecoxib 200 mg od at Weeks 2, 4 and 8, but no significant differences were observed by study end (Week 13). With regard to the other secondary efficacy variables, physician’s global assessment of disease activity and WOMAC© Difficulty in Performing Daily Activities (DPDA) and Stiffness subscales, both lumiracoxib groups and the celecoxib group were significantly superior to placebo throughout the study.

Celecoxib has been shown to provide sustained analgesic effects and improvements in physical function in patients with OA, with efficacy superior to placebo and similar to the traditional NSAIDs, naproxen and diclofenac [28 29]. Celecoxib was therefore chosen as a reference therapy for this study, and was used at the recommended dose for the treatment of OA [30]. Thus, it is notable that in this study lumiracoxib 200 mg od was found to be similar to celecoxib in all clinical efficacy parameters examined.

This study recruited patients without OA flare with the intention of replicating the real-life clinical situation for patients with OA. In previously-reported celecoxib studies in OA, a flare design was used, whereby patients were required to demonstrate a worsening in OA symptoms during an NSAID washout period between screening and baseline [28 31]. In both these studies, a marked placebo effect was observed in terms of mean change from baseline in OA pain intensity (VAS mm) and celecoxib was associated with mean changes from baseline of up to –30.0 mm and differences versus placebo of up to –15.0 mm after 2 weeks of treatment [28 31]. In this study, the lack of a requirement for OA flare would be expected to
provide an overall less dramatic treatment effect and consequently a smaller difference versus placebo.

In addition, it has recently been suggested that the concept of a minimal clinically perceptible difference is applicable to the WOMAC© DPDA subscale, whereby the minimal difference perceived by 75% of patients (MDP75) is considered to represent a clinically meaningful difference. In a study sample of 1354 patients with hip and knee OA, the MDP75 for the WOMAC© DPDA subscale was found to be 5.2 [32]. It is notable that in the study reported here, mean changes in WOMAC© DPDA subscale scores were >6 for both doses of lumiracoxib at Week 2, rising to >9 at Week 13.

In terms of safety and tolerability, celecoxib and rofecoxib are associated with a lower incidence of ulcers and GI events than traditional nonselective NSAIDs [33–35]. Although the results of the celecoxib outcomes study (CLASS) were not positive for celecoxib compared with traditional nonselective NSAIDs in terms of ulcer-related complications at 12 months [36 37], a recent systematic review of a wide range of celecoxib studies found that it does offer significantly improved GI safety and tolerability (including ulcers and serious upper GI events) compared with traditional NSAIDs [38]. In this study, both doses of lumiracoxib and celecoxib were associated with a similar incidence of AEs, including GI disorders, suggesting no dose-relationship. In addition, the number of patients who withdrew from the study because of AEs or GI-specific AEs was similar across all active treatment groups. Furthermore, lumiracoxib was not associated with an increase in overall renal AEs or associated symptoms of oedema compared with placebo, and did not result in QT interval prolongation or any form of arrhythmia.

The efficacy and tolerability of lumiracoxib observed in this study confirm findings of earlier studies in patients with OA. In a 4-week study involving 583 patients with primary OA of the hip and knee, lumiracoxib demonstrated efficacy comparable with the traditional NSAID, diclofenac, in terms of pain relief, improved functional status and response to treatment [21]. In a 13-week study comparing the GI effects of lumiracoxib with ibuprofen and celecoxib in 1042 patients with primary OA of the hip, knee, hand or spine, lumiracoxib was associated with significantly fewer gastroduodenal ulcers than ibuprofen. In addition, it was notable that lumiracoxib and celecoxib demonstrated a similar GI tolerability profile [24]. Lumiracoxib resulted in significantly lower rates of gastroduodenal ulceration than ibuprofen in a separate study of 893 patients with RA; the incidence of gastroduodenal ulcers was also similar for lumiracoxib and celecoxib in this study [25]. Similarly, in healthy volunteers, lumiracoxib was
associated with a reduced incidence of gastroduodenal erosions versus the traditional NSAID, naproxen [12 39].

In summary, the present study shows that lumiracoxib at a dose of 200 or 400 mg od provides sustained relief from the painful symptoms of OA of the knee and improves functional status with significantly superior efficacy to placebo. In addition, lumiracoxib was found to be as effective and well tolerated as the recommended dose of the established COX-2 selective inhibitor, celecoxib.
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Figure legends

Figure 1. Patient flow diagram.

Figure 2. Osteoarthritis pain intensity (visual analogue scale mm) in the target knee at Weeks 2, 4, 8 and 13 with lumiracoxib (200 mg and 400 mg once daily [od]), celecoxib (200 mg od) and placebo.

Figure 3. Patient’s global assessment of disease activity (visual analogue scale mm) at Weeks 2, 4, 8 and 13 with lumiracoxib (200 mg and 400 mg once daily [od]), celecoxib (200 mg od) and placebo.

Figure 4. Mean (SEM) change from baseline in WOMAC© Pain subscale (a) and Total (b) scores at Week 13 with lumiracoxib (200 mg and 400 mg once daily [od]), celecoxib (200 mg od) and placebo.
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tolerability of lumiracoxib vs placebo and naproxen: A pilot endoscopic study in healthy
Figure 1

2052 patients screened

1702 patients randomized

Lumiracoxib
200 mg od
n=487 (100%)

- 79 withdrawn (16.2%)
  - 13 (2.7%) unsatisfactory therapeutic effect
  - 3 (0.6%) lost to follow-up
  - 42 (8.6%) AEs
  - 21 (4.3%) other*

408 (83.8%)
completed trial

Lumiracoxib
400 mg od
n=491 (100%)

- 77 withdrawn (15.7%)
  - 14 (2.8%) unsatisfactory therapeutic effect
  - 2 (0.4%) lost to follow-up
  - 43 (8.8%) AEs
  - 18 (3.7%) other*

414 (84.3%)
completed trial

Celecoxib
200 mg od
n=481 (100%)

- 80 withdrawn (16.6%)
  - 15 (3.1%) unsatisfactory therapeutic effect
  - 1 (0.2%) lost to follow-up
  - 47 (9.8%) AEs
  - 17 (3.5%) other*

401 (83.4%)
completed trial

Placebo
n=243 (100%)

- 43 withdrawn (17.7%)
  - 15 (6.2%) unsatisfactory therapeutic effect
  - 3 (1.2%) lost to follow-up
  - 21 (8.6%) AEs
  - 4 (1.7%) other*

200 (82.3%)
completed trial

*Other includes protocol violation, withdrawal of consent and condition no longer requiring study drug
AE = adverse event; od = once daily
Figure 2

Values are least square means except baseline = means

*** p<0.001 all active treatment groups v placebo
* p<0.05 lumiracoxib 400 mg od v celecoxib 200 mg od
† p<0.05 lumiracoxib 400 mg od v lumiracoxib 200 mg od
Figure 3

Values are least square means
except baseline = means

***p<0.001 all active treatment groups v placebo
*p<0.05 lumirocsoxib 400 mg od v celecoxib 200 mg od
Figure 4

A

Lumiracoxib 200 mg od (n=487)
Lumiracoxib 400 mg od (n=491)
Celecoxib 200 mg od (n=481)
Placebo (n=243)

WOMAC Pain mean change from baseline
(SD at Week 13)

**
***
**

B

Lumiracoxib 200 mg od (n=487)
Lumiracoxib 400 mg od (n=491)
Celecoxib 200 mg od (n=481)
Placebo (n=243)

WOMAC Total mean change from baseline
(SD at Week 13)

***
***
***

Statistical analyses performed using least square means

**p<0.01 v placebo; ***p<0.001 v placebo