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


Objectives: To compare the efficacy and safety of lumiracoxib with placebo and celecoxib for osteoarthritis (OA) in a 13 week, multicentre, randomised, double blind study.

Methods: After a 3–7 day washout period for non-steroidal anti-inflammatory drugs, 1702 patients with knee OA were randomised 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 analysed by visit as secondary variables.

Results: Lumiracoxib showed significant improvements in all primary and secondary variables compared with 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 better 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 compared with celecoxib 200 mg od. The incidence of adverse events (AEs), serious AEs, and discontinuations due to AEs was similar in each 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 compared with placebo. Lumiracoxib was well tolerated in this study, with overall tolerability similar to that of placebo and celecoxib.

Osteoarthritis (OA) is a highly prevalent, chronic condition associated with a considerable burden for patients due to joint pain, stiffness, and inability to perform normal daily activities. As a result, this condition has a significant negative impact on quality of life. Non-steroidal 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. 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 cyclo-oxygenase (COX) enzymes (COX-1 and COX-2). This non-selective mechanism of action is largely responsible for the development of symptomatic ulcers and potentially serious gastrointestinal (GI) side effects. The incidence of symptomatic ulcers and ulcer complications associated with traditional NSAIDs was reported to be between 2 and 4% a year in 1988, and the management of gastropathy associated with traditional NSAID use is estimated to more than double the costs associated with the original treatment. The concomitant use of gastroprotective agents with traditional NSAIDs has been reported as one possible approach to managing NSAID related gastropathy. The GI side effects are due to reduced synthesis of prostaglandins, which have a cytoprotective role in the GI tract, when COX-1 is inhibited by traditional NSAID treatment.

Lumiracoxib is a new 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 and in human studies, with selectivity maintained at doses up to 1200 mg. The structure of lumiracoxib distinguishes it from other COX-2 selective inhibitors, which may explain its preferential distribution into inflamed tissue in animal models (an effect not observed with other COX-2 selective inhibitors), and the sustained high concentrations of lumiracoxib seen in synovial fluid compared with plasma in patients with RA. Clinical studies show that lumiracoxib is characterised by rapid absorption (Tmax 2–3 hours), a short plasma half life (3–6 hours), and good oral bioavailability. In patients with OA, lumiracoxib demonstrates dose proportional pharmacokinetics. Once daily lumiracoxib provides relief from the pain, stiffness, and impaired physical function of OA with efficacy better than placebo and similar to diclofenac. Furthermore, lumiracoxib is associated with a GI tolerability profile better than ibuprofen and similar to celecoxib in patients with OA or RA.

This study aimed at determining 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.

Abbreviations: AE, adverse event; COX, cyclo-oxygenase; DPDA, difficulty in performing daily activities; ECG, electrocardiogram; GI, gastrointestinal; ITT, intention to treat; NOS, not otherwise specified; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; od, once daily; RA, rheumatoid arthritis; SAE, serious adverse event; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
PATIENTS AND METHODS

This 13 week international, multicentre, randomised, double blind, double dummy, placebo controlled, active comparator study, was 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, according to the American College of Rheumatology criteria, 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.

People meeting the initial inclusion criteria underwent a 3–7 day washout period, during which NSAID treatment 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. To best reflect the “real life” clinical situation, no increase/worsening in OA symptoms (flare) was required for study entry.

Table 1  Patient demographics and baseline disease characteristics

<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>Age (years), mean (SD)</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, No (%)</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>399 (69.6)</td>
<td>331 (67.4)</td>
<td>333 (69.2)</td>
<td>163 (67.1)</td>
</tr>
<tr>
<td>White, No (%)</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)</td>
<td>29.5 (5.8) [17.1–62.1]</td>
<td>29.9 (5.8) [16.0–56.6]</td>
<td>30.0 (5.7) [18.4–63.6]</td>
<td>29.6 (5.4) [16.8–64.1]</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)</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)</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)</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</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</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>
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<tr>
<td>WOMAC DPDA subscale score</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</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>

Results are given as mean (SD) unless stated otherwise.

DPDA, difficulty in performing daily activities; OA, osteoarthritis; od, once daily; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 1  Patient flow diagram. *Other includes protocol violation, withdrawal of consent, and condition no longer requiring the study drug.
Lumiracoxib in the treatment of OA of the knee

Figure 2  Osteoarthritis pain intensity (VAS mm) in the target knee at weeks 2, 4, 8, and 13 with lumiracoxib (200 mg and 400 mg od), celecoxib (200 mg od), and placebo. Values are least square means, except for baseline, which are means. **p < 0.001 all active treatment groups vs placebo; †p < 0.05 lumiracoxib 400 mg od vs celecoxib 200 mg od; ‡p < 0.05 lumiracoxib 400 mg od vs lumiracoxib 200 mg od.

Figure 3  Patient’s global assessment of disease activity (VAS mm) at weeks 2, 4, 8, and 13 with lumiracoxib (200 mg and 400 mg od), celecoxib (200 mg od), and placebo. Values are least square means, except for baseline, which are means. **p < 0.001 all active treatment groups vs placebo; †p < 0.05 lumiracoxib 400 mg od vs celecoxib 200 mg od.

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

Results are shown as mean (SD)
non-inferiority margins of 5 mm for OA pain and patient’s global assessment, and of 0.6 points for the pain subscale of the WOMAC questionnaire were predefined.

Patients were randomised 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 analysed, 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 analysed by visit at a secondary level using the same model.

All safety and efficacy evaluations were performed using the intention to treat (ITT) population. The safety and ITT populations were identical and included all patients randomised to treatment who had been exposed to the study drug. Conventional last observation carried forward methodology was used when data were missing.

In addition to the analysis of AE and SAE incidence, the incidence of prespecified AEs was compared in treated and placebo groups 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, gastro duodenal ulcer, GI ulcer, pyloric ulcer


- Peripheral oedema AEs: oedema, oedema lower limb, oedema upper limb
- Chest pain AEs: chest pain not elsewhere classified.

Occurrence of prespecified AEs was summarised and analysed using a logistic regression model, including country and treatment group as variables.

RESULTS

Patient characteristics

The ITT population comprised 1702 patients, randomised 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 group was predominantly female (68.5%) with a mean age of approximately 64 years. There were no significant differences in patient demographics or baseline disease characteristics between the treatment groups (table 1).

A similar number of patients discontinued the study prematurely in each active treatment group (fig 1). Most 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 owing to a lack of efficacy in the placebo group as in the active treatment groups (fig 1).

Efficacy

Primary variables

All active treatments were statistically significantly better than placebo for 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 (fig 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 the 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 seen in all active treatment groups at week 13 compared with placebo (all p<0.001 v placebo; fig 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). Figure 4 and table 3 show the mean changes from baseline.

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, fig 2). The reduction in pain intensity with lumiracoxib 200 mg od was of similar magnitude to that of celecoxib 200 mg od at all times. 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,
fig 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 (fig 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).

Significant improvements were seen in WOMAC total and all three subscale scores for all active treatment groups compared with placebo at week 2 (all p < 0.01 vs 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 vs placebo; table 3).

The mean number of rescue drug tablets consumed was significantly greater in the placebo group (0.8 tablets/day) than in 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 vs placebo). Between-treatment analyses showed that at week 4, the number of rescue drug tablets taken was significantly higher in the celecoxib 200 mg od group than in the lumiracoxib 400 mg od group; no other between-treatment differences were seen (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 receiving lumiracoxib 200 mg od, 2.9% receiving lumiracoxib 400 mg od, 2.9% receiving celecoxib 200 mg od, and 3.3% receiving 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 (3.7%) patients in the lumiracoxib 200 mg od group, 22 (4.5%) patients in the lumiracoxib 400 mg od group, 19 (4.0%) patients in the celecoxib 200 mg od group, and 6 (2.5%) patients 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.

The majority of AEs were mild or moderately severe. The incidence 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).

Multiple regression analyses of the incidence of prespecified AEs showed 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 seen 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 a raised creatinine level (>2 × the upper limit of normal). In total, nine patients had increases in liver function parameters (alanine aminotransferase/aspartate aminotransferase) >3 × the upper limit of normal (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 withdrawn 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 raised liver function parameters resolved either while receiving the study drug or after treatment had stopped 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, randomised, double blind, placebo controlled, active comparator study demonstrate the clinical efficacy and tolerability of lumiracoxib, a new COX-2 selective inhibitor, at doses of 200 or 400 mg od, in patients with OA of the knee. After 13 weeks of treatment, patients

**Table 3** Change from baseline in WOMAC total and subscale scores at weeks 2 and 13

<table>
<thead>
<tr>
<th>Treatment</th>
<th>WOMAC total score</th>
<th>WOMAC pain subscale score</th>
<th>WOMAC DPDA subscale score</th>
<th>WOMAC stiffness subscale score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumiracoxib 200 mg od (n = 487)</td>
<td>10.6 (13.2)</td>
<td>-2.6 (3.3)</td>
<td>-6.9 (9.6)</td>
<td>-1.0 (1.7)</td>
</tr>
<tr>
<td>Lumiracoxib 400 mg od (n = 491)</td>
<td>9.8 (13.9)</td>
<td>-2.6 (3.4)</td>
<td>-6.4 (10.3)</td>
<td>-0.9 (1.6)</td>
</tr>
<tr>
<td>Celecoxib 200 mg od (n = 481)</td>
<td>8.6 (13.3)</td>
<td>-2.4 (3.1)</td>
<td>-5.5 (9.9)</td>
<td>-0.8 (1.6)</td>
</tr>
<tr>
<td>Placebo (n = 243)</td>
<td>4.3 (12.4)</td>
<td>-1.4 (3.3)</td>
<td>-2.4 (8.8)</td>
<td>-0.5 (1.5)</td>
</tr>
</tbody>
</table>

DPDA, difficulty in performing daily activities; od, once daily; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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

<table>
<thead>
<tr>
<th>Treatment</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</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</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</td>
<td>42 (8.6)</td>
<td>47 (9.6)</td>
<td>47 (9.6)</td>
<td>21 (8.6)</td>
</tr>
<tr>
<td>Discontinuations due to GI AEs</td>
<td>18 (3.7)</td>
<td>22 (4.5)</td>
<td>19 (4.0)</td>
<td>6 (2.5)</td>
</tr>
</tbody>
</table>

Results are shown as No (%). AE, adverse event; GI, gastrointestinal; od, once daily; SAE, serious adverse event.
who had received lumiracoxib 200 and 400 mg od had significantly less OA pain intensity in the target knee, and better patient’s global assessment of disease activity and patient’s functional status than the placebo group.

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 the start of treatment (week 2), an effect sustained throughout the study. The magnitude of improvement was similar for lumiracoxib 200 mg od and celecoxib 200 mg od at all times. Lumiracoxib 400 mg od was significantly more effective than celecoxib 200 mg od at weeks 2, 4, and 8, but no significant differences were seen by the study end (week 13). For the other secondary efficacy variables, physician’s global assessment of disease activity, and WOMAC DPDA and stiffness subscales, both lumiracoxib groups and the celecoxib group were significantly better than placebo throughout the study.

Celecoxib has been shown to provide sustained analgesic effects and improvements in physical function in patients with OA, with efficacy better than placebo and similar to that of the traditional NSAIDs, naproxen and diclofenac. Celecoxib was therefore chosen as a reference treatment for the treatment of OA. In this study both doses of culcoxib were associated with a reduced incidence of ulcers and GI events than traditional non-selective NSAIDs. Although the results of the Celecoxib Outcomes Study (CLASS) were not positive for celecoxib compared with traditional non-selective NSAIDs for ulcer related complications at 12 months, 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. 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 seen in this study confirm findings of earlier studies in patients with OA. In a 4 week study of 583 patients with primary OA of the hip and knee, lumiracoxib demonstrated efficacy comparable with the traditional NSAID, diclofenac, for pain relief, improved functional status, and response to treatment. 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 gastro-duodenal ulcers than ibuprofen. In addition, it was notable that lumiracoxib and celecoxib demonstrated a similar GI tolerability profile. 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. Similarly, in healthy volunteers, lumiracoxib was associated with a reduced incidence of gastroduodenal erosions compared with the traditional NSAID, naproxen.

In summary, our study shows that lumiracoxib at a dose of 200 or 400 mg od provides sustained relief from the painful

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Incidence of most frequently reported adverse events (&gt;3%) and prespecified adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lumiracoxib 200 mg od (n = 487)</td>
</tr>
<tr>
<td>Most frequently reported AEs</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>28 (5.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>27 (5.5)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>25 (5.1)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>12 (2.5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Hypertension NOS</td>
<td>16 (3.3)</td>
</tr>
<tr>
<td>Influenza</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>Prespecified AEs</td>
<td></td>
</tr>
<tr>
<td>GI events</td>
<td>94 (19.3)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>85 (17.5)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Most frequently reported AEs</td>
<td></td>
</tr>
<tr>
<td>AE, adverse event; GI, gastrointestinal; NOS, not otherwise specified; od, once daily.</td>
<td></td>
</tr>
</tbody>
</table>

<p>| Results are shown as No (%) | | | | |</p>
<table>
<thead>
<tr>
<th>Lumiracoxib 200 mg od</th>
<th>Lumiracoxib 400 mg od</th>
<th>Celecoxib 200 mg od</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>34 (7.0)</td>
<td>28 (5.7)</td>
<td>23 (4.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (3.9)</td>
<td>27 (5.6)</td>
<td>10 (3.0)</td>
</tr>
<tr>
<td>Shoulder pain upper</td>
<td>23 (4.7)</td>
<td>25 (5.1)</td>
<td>25 (5.2)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>15 (3.1)</td>
<td>11 (2.2)</td>
<td>14 (2.9)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>19 (3.9)</td>
<td>21 (4.3)</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>13 (2.7)</td>
<td>18 (3.7)</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (1.6)</td>
<td>14 (2.9)</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>Hypertension NOS</td>
<td>8 (1.6)</td>
<td>17 (3.5)</td>
<td>12 (2.5)</td>
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<td>16 (3.3)</td>
<td>11 (2.3)</td>
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</tbody>
</table>

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symptoms of OA of the knee and improves functional status with significantly better efficacy than 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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