Lumiracoxib 400 mg once daily is comparable to indomethacin 50 mg three times daily for the treatment of acute flares of gout

R. E. Willburger, E. Mysler¹, J. Derbot², T. Jung³, H. Thurston⁴, A. Kreiss⁵, S. Litschig⁴, G. Krammer⁴ and G. A. Tate¹

Introduction

Acute gout is characterized by the sudden onset of intense pain, erythema, swelling and tenderness of the affected joint, and these symptoms may last for several days [1]. Although pain is the primary symptom of acute gout, optimal therapy is directed at controlling inflammation. Treatments have changed little over the last 30 yrs [2]. Colchicine inhibits microtubule formation necessary for cell migration and is used for the treatment of gout [1, 3]. However, colchicine is associated with a high rate of gastrointestinal (GI) side effects and it becomes less effective as the attack of gout persists [1, 3]. Non-steroidal anti-inflammatory drugs (NSAIDs) have become standard therapy as they can suppress inflammation and provide analgesia [1, 4]. They act by inhibiting cyclooxygenase enzymes, thereby preventing the formation of prostaglandins, which mediate pain and inflammation. The NSAIDs registered for the treatment of gout in the United States are indomethacin, sulindac and naproxen [1, 4]. Indomethacin was the first NSAID used in the treatment of gout [1, 4]. Despite its poor tolerability profile when used in other conditions, indomethacin continues to be considered the ‘gold standard’ because of its demonstrated efficacy in gout. Numerous adverse events (AEs) are associated with indomethacin, with headache, vertigo and nausea appearing to be the most common [5]. Although traditional NSAIDs are effective treatments, they are associated with side effects, particularly in the GI tract, and may be poorly tolerated by many patients [6, 7]. With frequent recurrences, these side effects may decrease patients’ adherence to the treatment. The GI effects with traditional NSAIDs can vary in severity: from nausea and dyspepsia to serious complications, such as ulcers and GI bleeding, which could ultimately prove fatal. Indomethacin is considered to be one of the more GI toxic of the traditional NSAIDs [8, 9].

The need for better-tolerated NSAIDs was the driver behind the development of selective cyclooxygenase-2 (COX-2) inhibitors. These agents inhibit the predominantly inducible COX-2 enzyme that is thought to control prostaglandin production at sites of inflammation [10] while sparing cyclooxygenase-1, which is constitutively expressed in the GI tract and helps to maintain mucosal integrity [10].

Lumiracoxib is a novel selective COX-2 inhibitor that has been reported to be effective in treating acute pain, such as after dental surgery [11], arthroplasty [12] and sprains and strains [13], and in treating chronic pain associated with osteoarthritis (OA) [14]. Moreover, lumiracoxib is well tolerated. In the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), lumiracoxib 400 mg (four times the recommended dose for OA) was shown to reduce the incidence of serious GI complications by 79% compared with traditional NSAIDs in patients with OA not receiving aspirin [15]. It has recently been reported that the GI benefit with lumiracoxib compared with traditional NSAIDs can occur as early as day 32 of treatment [16]. In addition to these GI benefits, there was no increase in cardiovascular events with lumiracoxib 400 mg compared with traditional NSAIDs in TARGET [17].

The objectives of this study were to investigate the efficacy of lumiracoxib 400 mg once daily (o.d.) compared with indomethacin 50 mg three times daily (t.i.d.) in the treatment of acute gout, and to compare the safety and tolerability profiles of the two treatments.

Materials and methods

Study design

This was a 1-week, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group study (CCOX189A2426), conducted in 39 centres in Germany and

Orthopaedic University Clinic, Bochum, Germany, ¹OMI, Buenos Aires, Argentina, ²Isselburg, ³Deggingen, Germany, ⁴Novartis Pharma AG, Basel, Switzerland and ⁵Novartis Pharma GmbH, Nuremberg, Germany.

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Correspondence to: E. Mysler, University of Buenos Aires, Uruguay 725, Buenos Aires (1016), Argentina. E-mail: emysler@attglobal.net
Argentina, with the majority of the centres being located in Germany.

Following screening, eligible patients were randomized (1:1) to receive lumiracoxib 400 mg o.d. or indomethacin 50 mg t.i.d. for 7 days. Patients were assigned a unique patient number and randomized to one of the treatment groups stratified by centre. The Drug Supply department within Novartis Pharma AG produced a computer-generated randomization list using a validated system that automates the random assignment of treatment groups to randomization numbers in a block formation, in order to have treatment groups balanced within centres. Patients, investigators and personnel involved in monitoring the study, handling data or conducting the trial were all blinded to treatment. A double-dummy design was used to blind the identity of the study drugs, which could not be disguised due to their different forms, and their different regimens (o.d. vs t.i.d.).

Ethics Committee approval was obtained from all relevant institutional review boards, in accordance with the Declaration of Helsinki (1964 and subsequent revisions). The study was performed according to Good Clinical Practice guidelines, and all patients provided written informed consent before entering the study.

Study population
Men and women (≥18 yrs of age) with a clinical diagnosis of gout according to the 1977 American College of Rheumatology classification criteria [18] were recruited into the study. Patients were to have had an acute attack of gout in four or fewer joints with onset within the 48 h prior to evaluation, and at least moderate pain intensity (3 on a 5-point Likert scale) in the target joint at baseline. Pain intensity at baseline was assessed in the absence of analgesia (i.e. 4 h after ≤400 mg ibuprofen, ≤1 g paracetamol, ≤600 mg aspirin, or two or less tablets of other over-the-counter aspirin-based or paracetamol-based medications; or 8 h after >400 mg ibuprofen or ≤50 mg diclofenac; or 12 h after >500 mg naproxen).

Patients were excluded if they had: an acute attack of gout with onset before the last 48 h prior to evaluation; polyarticular gout involving more than four joints; rheumatoid arthritis, infectious arthritis, pseudo-gout or other acute forms of inflammatory arthritis; clinically significant hepatic or renal disease, previous or active peptic ulceration or GI bleeding, a history of cardiac or cerebral thrombotic/ischaemic disease, or other significant medical problems; used NSAIDs other than those listed earlier in the previous 4 weeks; allergic-type reactions after taking aspirin, paracetamol or any NSAIDs (including selective COX-2 inhibitors). Women who were pregnant, lactating or, if pre-menopausal, not using an contraceptive method (such as oral contraceptives, the patch or injection) were not eligible for inclusion.

Study assessments
Patients recorded pain intensity of the affected study joint [using a 5-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme)] in a diary at baseline [before start of treatment on day 1 (h 0)], and 4 h (h 4) after treatment with the first dose of study medication on each day of the study. Patients also recorded their global assessment of response to treatment (patient’s global assessment) on a 5-point Likert scale (0 = very good, 1 = good, 2 = fair, 3 = poor, 4 = very poor) 4 h after the first intake of study medication on each day. Intake of rescue medication (paracetamol ≥3 g/day permitted) was also recorded in the diary when it was taken. Quality of life and functional status was assessed by SF-36 and EuroQol (EQ)-5D questionnaires completed by patients at baseline and at the end of treatment.

At baseline, days 2 and 5 and at the end of the study, the study physician assessed: joint tenderness on palpation or passive movement of the affected study joint (4-point Likert scale: 0 = no pain, 1 = patient states ‘there is pain’, 2 = patient states ‘there is pain’ and winces, 3 = patient states ‘there is pain’ and winces and withdraws); joint swelling (4-point Likert scale: 0 = no swelling, 1 = palpable, 2 = visible, 3 = bulging beyond the joint margins); and erythema (present, absent or not assessable). At days 2 and 5, and at the end of study, physicians also assessed the global response to treatment on a 5-point Likert scale (0 = very good, 1 = good, 2 = fair, 3 = poor, 4 = very poor).

Physical examination and measurements of haematological and blood chemistry parameters and vital signs were also performed at baseline and end of study. All AEs and serious AEs (SAEs) were examined.

The end of study visit occurred at day 7 (+1 day, if necessary) in patients completing the study or at the early termination visit for patients discontinuing treatment.

Study efficacy endpoints
The primary efficacy endpoint was the mean change in pain intensity from baseline over days 2–5 (calculated as baseline—mean pain intensity on days 2, 3, 4 and 5). Secondary efficacy variables were: the mean change in pain intensity from baseline over days 2–7; the average patient’s global assessment of response to therapy over days 2–5 and days 2–7; the average physician’s global assessment of response to therapy over days 2 and 5 and days 2, 5 and end of study; the average physician’s assessment of tenderness, swelling and erythema of the study joint over days 2 and 5 and days 2, 5 and end of study; the use of rescue medication; and health-related quality of life, as assessed by the SF-36 and EQ-5D questionnaires at the end of study. The level of C-reactive protein (CRP) at the end of the study was also a secondary efficacy variable.

Statistical analysis
The sample size was calculated using NQuery Advisor 4.0. It was estimated that a total of 210 patients would be required (105 patients in each treatment group) for a one-sided t-test at a significance level of 2.5% to show non-inferiority of lumiracoxib to indomethacin with respect to the primary efficacy variable with 95% power. Assumptions were made that the non-inferiority margin is 0.5, the expected true difference between lumiracoxib and indomethacin is 0.1 in favour of indomethacin and the common standard deviation (s.d.) is 0.8. To allow for dropouts, it was planned to enrol 117 patients in each treatment arm.

Study endpoints were analysed primarily for the per protocol population and repeated, for sensitivity reasons, for the intention-to-treat (ITT) population. For most efficacy endpoints, a confidence interval (CI) approach was used on an analysis of covariance (ANCOVA) model, with a two-sided 5% level of significance. A multiple logistic model was used to analyse the use of rescue medication. For the ANCOVA models, treatment group and centre were fixed effects and baseline value (if assessed) and common standard deviation (S.D.) is 0.8. To allow for dropouts, it was planned to enrol 117 patients in each treatment arm.

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One of the participating centres was closed following a health authority inspection. Since the database had been locked including data from the eight patients from this centre, a post-hoc sensitivity analysis was performed to investigate whether there...
would be any significant changes in some of the key parameters in this study.

**Results**

**Patient characteristics and disposition**

A total of 236 patients were screened and 235 patients were randomized to treatment with lumiracoxib 400 mg o.d. (n = 118) or indomethacin 50 mg t.i.d. (n = 117) (Fig. 1). Major protocol violations resulting in exclusion from the per protocol population occurred in six patients receiving lumiracoxib and seven patients receiving indomethacin (Fig. 1). The per protocol population comprised 112 patients receiving lumiracoxib and 110 patients receiving indomethacin. More patients completed the study in the lumiracoxib group (98.3%) than in the indomethacin group (91.5%).

At baseline, treatment groups were comparable in terms of demographic and disease characteristics (Table 1). Relevant medical histories were generally similar. Of note, there was a high incidence of hypertension (50% in each treatment group) (Table 1). Mean systolic and diastolic blood pressures for treatment groups at baseline are presented in Table 1. Although a history of cardiac disorders was observed more frequently at baseline in patients randomized to lumiracoxib (15.3%) compared with indomethacin (7.7%), this difference was not attributable to any specific condition and was due to single different events.

**Efficacy**

The primary efficacy endpoint, the mean change in pain intensity from baseline over days 2–5 in the per protocol population, demonstrated that lumiracoxib 400 mg o.d. had comparable efficacy to indomethacin 50 mg t.i.d. (Fig. 2). The estimated difference between treatments for the change from baseline in pain intensity over days 2–5 was -0.004 (95% CI -0.207 to 0.199). Similar results were observed for the ITT population.

Reduction in pain was similar in both treatment groups throughout the study. Indeed, the mean change in pain intensity from baseline over days 2–7 in the per protocol population demonstrated that lumiracoxib was not statistically significantly different to indomethacin (P > 0.05) (Fig. 2). On average, the pain intensity improved to a similar extent between treatment groups during the course of the study (Fig. 3).

Both drugs showed clinically relevant improvement by the first pain assessment, 4 h after the first intake of study drug on day 1. The number of patients (per protocol population) who reported severe or extreme pain at baseline (lumiracoxib, 52.7%; indomethacin, 50.0%) was reduced by half at the first assessment (4 h after start of treatment) with lumiracoxib (26.8%) and to a similar extent with indomethacin (29.1%).

The patient's global assessment of response to therapy revealed that lumiracoxib was as effective as indomethacin in the per protocol population. Least squares mean scores for lumiracoxib were similar to those observed with indomethacin over days 2–5 (2.33 vs 2.36, respectively; P = 0.81) and days 2–7
between treatments over days 2–5 was −0.023 (95% CI −0.219 to 0.173, \( P > 0.05 \)), and over days 2–7 was −0.033 (95% CI −0.221 to 0.156, \( P > 0.05 \) (Table 2). In addition, the proportions of ‘good’ or ‘very good’ ratings on the patient’s global assessment of response to therapy scale were similar for both study drugs and increased during the study (4 h after intake of study drug on Day 1: lumiracoxib ‘good’ = 16.1%, ‘very good’ = 1.8%; indomethacin ‘good’ = 16.4%, ‘very good’ = 2.7%; Day 7: lumiracoxib ‘good’ = 42.0%, ‘very good’ = 33.0%; indomethacin ‘good’ = 40.0%, ‘very good’ = 35.5%). No statistically significant difference was observed between treatments for the physician’s global response to therapy or the physician’s assessments of study joint swelling, tenderness and erythema (Table 2). Similarly, health-related quality of life scores (SF-36 and EQ-5D) were not statistically significantly different between treatment groups (Table 2). There was no statistically significant difference between the treatment groups in the number of patients taking rescue medication.

Mean (s.d.) CRP levels at baseline were 10.3 (16.87) mg/l with lumiracoxib and 7.3 (11.7) mg/l with indomethacin. At study end, the least square mean CRP levels were 6.74 mg/l with lumiracoxib and 4.13 mg/l with indomethacin (difference not statistically significant, \( P > 0.05 \)).

Also, for all secondary efficacy endpoints, results in the ITT population were comparable with those observed in the per protocol population.

The post-hoc sensitivity analyses, which were performed without the eight patients from the centre that was closed, did not change the efficacy results of the study substantially and therefore do not affect any conclusions drawn.

Safety and tolerability

AEs were reported by 10.2% of patients treated with lumiracoxib and 22.2% of patients receiving indomethacin (safety population). The incidences of individual AEs were comparable between groups, with the exceptions of upper abdominal pain, headache and vertigo, which occurred in fewer patients treated with lumiracoxib than indomethacin (Table 3). The study investigators attributed AEs to study medication more frequently with lumiracoxib than indomethacin (Table 3). The study investigators attributed AEs to study medication more frequently with lumiracoxib and 7.3 (11.7) mg/l with indomethacin. At study end, the least square mean CRP levels were 6.74 mg/l with lumiracoxib and 4.13 mg/l with indomethacin (difference not statistically significant, \( P > 0.05 \)).

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pain and was hospitalized for the same. The patient was diagnosed as having subacute abdomen, which resolved spontaneously.

Lumiracoxib had a positive effect on blood pressure compared with indomethacin. The change from baseline for mean systolic blood pressure was a reduction of 1.0 mmHg in lumiracoxib-treated patients compared with a mean increase of 2.5 mmHg in indomethacin-treated patients \( (P = 0.009) \). In addition, the change from baseline for mean diastolic blood pressure was a reduction of 1.3 mmHg compared with an increase of 0.5 mmHg in indomethacin-treated patients \( (P = 0.028) \).

To reflect routine clinical practice when treating gout, elevations in alanine aminotransferase/aspartate aminotransferase (ALT/AST) were not an exclusion criterion of this study. Therefore, some patients with elevated ALT/AST levels at baseline were enrolled in the study. Newly occurring ALT/AST levels \( > 3 \times \) upper limit of normal (ULN) were noted in three patients receiving indomethacin. For one of these patients, no baseline values were obtained and the first measurement, which showed an elevation in AST of \( > 3 \times \) ULN, was performed on day 2 of the study. One case of newly occurring ALT levels \( > 3 \times \) ULN compared with baseline was adjudicated as being possibly related to study medication by the independent liver safety committee. In the lumiracoxib group, no patients with newly occurring ALT/AST elevations to \( > 3 \times \) ULN were observed. Two patients with ALT levels \( > 3 \times \) ULN at baseline were enrolled in the lumiracoxib arm and in both patients ALT levels had decreased to \(< 3 \times \) ULN after 7 days of treatment. No patient had ALT/AST levels \( > 5 \times \) ULN.

No AEs, SAEs or elevated liver function tests were reported for the eight patients from the centre that was closed due to the audit. Following the post-hoc sensitivity analysis, the only notable change in safety variables was that the difference in diastolic blood pressure between treatment groups was no longer statistically significant (change from baseline: lumiracoxib, \(-1.2 \) mmHg; indomethacin, \(0.5 \) mmHg; \( P = 0.057\)). However, the statistical significance of the difference between lumiracoxib and indomethacin was maintained for the systolic blood pressure \( (P = 0.017) \).

Discussion

Gout is an intensely painful condition and strategies for providing analgesia are a very important part of treatment. There is a high level of variability in individual responses and tolerability to different pain relief strategies and, therefore, a wide variety of options are essential for effective management. The current study has compared the efficacy of indomethacin, the current gold standard of treatment for gout, with lumiracoxib, a new selective COX-2 inhibitor. The study demonstrated that lumiracoxib 400 mg o.d. provides effective and well-tolerated analgesia in patients with acute gout. Indeed, lumiracoxib 400 mg o.d. was shown to have comparable efficacy to indomethacin 50 mg t.i.d. for the primary efficacy variable: the mean change in pain intensity over days 2–5. In addition, all secondary efficacy variables, including the change in pain intensity over 7 days’ treatment, the patient’s and physician’s global assessment and health-related quality of life, were similar for patients receiving lumiracoxib 400 mg o.d. compared with those receiving indomethacin 50 mg t.i.d. Moreover, an assessment of pain severity 4 h after the start of treatment indicates that lumiracoxib was as rapidly acting as indomethacin. The findings of this study were consistent with observations that lumiracoxib is effective at minimizing other forms of acute pain, such as following arthroplasty [12], dental surgery [11] and soft tissue injuries [13].

Controlling inflammation is also an important aspect of gout treatment. After treatment, levels of CRP, an acute phase marker has increased.

### Table 2. Treatment comparisons \(^*\) for secondary efficacy variables (per protocol population)

<table>
<thead>
<tr>
<th></th>
<th>Lumiracoxib 400 mg</th>
<th>Indomethacin 50 mg</th>
<th>Estimated difference ((95% \ CI))</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s global assessment of response to therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 2–5</td>
<td>2.333</td>
<td>2.357</td>
<td>(-0.023) ((-0.219, 0.173))</td>
<td>(0.814)</td>
</tr>
<tr>
<td>Days 2–7</td>
<td>2.173</td>
<td>2.205</td>
<td>(-0.053) ((-0.221, 0.156))</td>
<td>(0.733)</td>
</tr>
<tr>
<td>Physician’s global assessment of response to therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 2 and 5</td>
<td>2.464</td>
<td>2.465</td>
<td>(-0.001) ((-0.203, 0.202))</td>
<td>(0.994)</td>
</tr>
<tr>
<td>Days 2, 5 and end of study</td>
<td>2.215</td>
<td>2.231</td>
<td>(-0.016) ((-0.202, 0.170))</td>
<td>(0.866)</td>
</tr>
<tr>
<td>Physician’s assessment of tenderness (^*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 2 and 5</td>
<td>0.960</td>
<td>0.888</td>
<td>(-0.072) ((-0.065, 0.209))</td>
<td>(0.303)</td>
</tr>
<tr>
<td>Days 2, 5 and end of study</td>
<td>0.738</td>
<td>0.703</td>
<td>(-0.035) ((-0.088, 0.159))</td>
<td>(0.575)</td>
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<tr>
<td>Physician’s assessment of swelling (^*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Days 2 and 5</td>
<td>0.982</td>
<td>0.926</td>
<td>(-0.056) ((-0.082, 0.194))</td>
<td>(0.421)</td>
</tr>
<tr>
<td>Days 2, 5 and end of study</td>
<td>0.733</td>
<td>0.677</td>
<td>(-0.056) ((-0.060, 0.171))</td>
<td>(0.343)</td>
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<tr>
<td>Physician’s assessment of erythema (^*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 2 and 5</td>
<td>0.373</td>
<td>0.398</td>
<td>(-0.025) ((-0.122, 0.072))</td>
<td>(0.608)</td>
</tr>
<tr>
<td>Days 2, 5 and end of study</td>
<td>0.269</td>
<td>0.293</td>
<td>(-0.024) ((-0.096, 0.049))</td>
<td>(0.515)</td>
</tr>
<tr>
<td>SF-36 at end of study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component</td>
<td>40.485</td>
<td>40.978</td>
<td>(-0.493) ((-2.524, 1.538))</td>
<td>(0.633)</td>
</tr>
<tr>
<td>Mental component</td>
<td>51.099</td>
<td>50.928</td>
<td>(0.171) ((-1.808, 2.150))</td>
<td>(0.865)</td>
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<tr>
<td>EQ-5D health status at end of study</td>
<td>0.873</td>
<td>0.888</td>
<td>(-0.016) ((-0.058, 0.027))</td>
<td>(0.470)</td>
</tr>
</tbody>
</table>

\(LS\) mean = least square mean.

\(^*\)ANCOVA with treatment group and centre as fixed effects and baseline value (if assessed) and mono/polyarticular gout as covariates.

\(^{\text{a}}\)Study joint.
of inflammation, decreased by a similar degree in both treatment groups. It was also noted that comparable effects were observed between lumiracoxib and indomethacin on symptoms of inflammation, such as the physician’s assessment of erythema, tenderness and swelling. These data would indicate that lumiracoxib had, in addition to its analgesic effects, anti-inflammatory properties similar to indomethacin.

Despite its efficacy, indomethacin, like many non-selective NSAIDs, is known for its poor GI tolerability [1, 9]. These adverse GI events vary in severity, from dyspepsia to ulcers and potentially life-threatening GI ulcers and bleeds [7–9]. Therefore, alternative treatment options that are efficacious but better tolerated are desirable. This study demonstrates that lumiracoxib is well tolerated, resulting in fewer AEs and changes in laboratory values than indomethacin when treating acute gout for 7 days.

In this study, there was no screening to exclude patients with elevated hepatic enzymes. There were no new instances of elevations (>3 × ULN) in ALT with lumiracoxib and three instances of newly occurring ALT elevations >3 × ULN with indomethacin.

In this study, approximately one half of patients had hypertension at baseline. Given that hypertension is a risk factor for hyperuricaemia and gout [22, 23], a high prevalence of hypertension was not unexpected. Indeed, a greater prevalence of hypertension has been previously observed in gout patients (43%) compared with controls (18%) [24]. Hypertension is a major cardiovascular risk factor that promotes the development of atherosclerosis among hyperuricaemic subjects [25]. Indeed, elevated serum uric acid levels and hypertension appear to have a synergistic effect on cardiovascular risk [25]. Therefore, the effect of gout treatments on blood pressure may be important for these patients.

Traditional NSAIDs have been reported to increase blood pressure compared with placebo [26]. Indomethacin has also been shown to increase blood pressure [27–29]. An association between the use of traditional NSAIDs and hypertension has been noted [29, 30]. It was noteworthy that in this study, blood pressure increased with indomethacin but decreased with lumiracoxib. This is consistent with the TARGET study, where traditional NSAIDs increased systolic and diastolic blood pressure significantly more than lumiracoxib [17]. It may be that these small differences in blood pressure could be clinically relevant in the long term. Indeed, even relatively small changes in blood pressure can have a significant effect on cardiovascular risk and its resulting morbidity and mortality [31–33].

In summary, the current study has demonstrated that lumiracoxib 400 mg o.d. has comparable efficacy to indomethacin 50 mg t.i.d., the current ‘gold standard’ NSAID for the management of acute gout. In addition, lumiracoxib was well tolerated and had numerically fewer AEs and a better blood pressure profile as compared with indomethacin. This and previous studies would suggest that lumiracoxib represents an alternative option for the management of gout that also minimizes the potential for GI ulcer complications.

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References

25 Lin KC, Tsao HM, Chen CH, Chou P. Hypertension was the major risk factor leading to development of cardiovascular disease among men with hyperuricemia. J Rheumatol 2004;31:1152–8.