Valdecoxib is as effective as diclofenac in the management of rheumatoid arthritis with a lower incidence of gastroduodenal ulcers: results of a 26-week trial

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Objective. To compare the efficacy and upper gastrointestinal (GI) safety of valdecoxib 20 and 40 mg daily with those of diclofenac 75 mg slow release (SR) twice daily in treating rheumatoid arthritis (RA).

Methods. Seven hundred and twenty-two patients with adult-onset RA were enrolled into this 26-week, randomized, multicentre, double-blind, parallel-group study (246 in the valdecoxib 20 mg daily arm, 237 in the valdecoxib 40 mg daily arm and 239 in the diclofenac 75 mg SR daily arm). Acetylsalicylic acid use (≤325 mg per day) was similar across all groups: 5.4% in the diclofenac group, 5.7% in the valdecoxib 20 mg group and 5.9% in the valdecoxib 40 mg group. Efficacy was measured by the Patient’s Assessment of Arthritis Pain [visual analogue scale (VAS)] and the modified Health Assessment Questionnaire (mHAQ) at baseline and at weeks 2, 6, 8, 12, 18 and 26 of treatment, or at early termination. Upper GI safety was evaluated by endoscopy at the end of treatment, which took place no more than 2 days after the last dose of study medication or at early termination.

Results. Valdecoxib 20 and 40 mg daily were comparable to diclofenac 75 mg SR twice daily in treating the signs and symptoms of RA. No significant differences were observed between treatment groups with respect to mean changes from baseline in the Patient’s Assessment of Arthritis Pain (VAS) or mHAQ. The incidence of gastroduodenal ulcers in patients receiving valdecoxib 20 mg daily (6%) and valdecoxib 40 mg daily (4%) was significantly lower (P < 0.001) than in patients receiving diclofenac 75 mg SR twice daily (16%). Valdecoxib 20 mg daily was also associated with significantly improved GI tolerability (P = 0.035) compared with diclofenac.

Conclusions. Single daily doses of valdecoxib 20 and 40 mg provided efficacy comparable to that of diclofenac, with a superior upper GI safety profile in the long-term treatment of RA patients.

KEY WORDS: Valdecoxib, Diclofenac, Rheumatoid arthritis, Gastroduodenal ulcers.

Conventional (i.e. non-specific) non-steroidal anti-inflammatory drugs (NSAIDs) have long been used for pain relief and for the treatment of inflammatory diseases, including rheumatoid arthritis (RA). Although non-specific NSAIDs are effective therapeutic agents with analgesic, anti-inflammatory and antipyretic properties, their use is associated with a significant incidence of side-effects, including upper gastrointestinal (GI)
bleeding and ulceration and inhibition of platelet aggregation [1]. Lower GI complications are associated with NSAID use as well [2].

Both the value and the limitations of conventional NSAIDs arise from their mechanism of action, which is the non-selective inhibition of cyclooxygenase (COX). Two isoforms of COX exist, COX-1 and COX-2 [3]. Both isoforms catalyse the conversion of arachidonic acid to prostaglandins. COX-1 is constitutively expressed in most tissues and is responsible for a number of homeostatic functions, including a role in platelet function and the maintenance of upper GI mucosal integrity [3]. COX-2 is constitutively expressed in a number of tissues, including the kidney and central nervous system, but is predominantly expressed under proinflammatory or other pathophysiological conditions in response to cytokines, growth factors and tumour promoters [4]. Induction of COX-2 expression has been shown to play an important role in inflammation and pain and, conversely, inhibition of COX-2 has been shown to provide anti-inflammatory and analgesic efficacy [3–4]. Non-specific NSAIDs, such as diclofenac, naproxen and ibuprofen, inhibit both COX-1 and COX-2 at therapeutic plasma concentrations [1–5]. The result is a reduction in pain and swelling but greater potential for damage to the upper GI mucosa, resulting in a high incidence of gastroduodenal ulcers as well as clinically significant ulcer complications (perforations, gastric outlet obstruction or GI bleeding) [1]. Recent experiments in animals suggest that inhibition of both COX-1 and COX-2 (as opposed to COX-1 alone) may be required to produce GI injury [6, 7]. The incidence of gastroduodenal ulcers as detected by endoscopy is 15–40% in patients treated with NSAIDs compared with the background incidence in non-treated patients of 2–4%. Ulcer complications occur in patients receiving NSAIDs at an annual incidence of 1–2%, which represents approximately a fourfold increase above the background risk [8, 9]. Non-specific NSAID use is associated with an estimated 1200–4000 GI-related deaths in the UK [10–11].

The unmet medical need for anti-inflammatory analgesics without deleterious side-effects prompted the development of drugs with COX-2 specificity. Indeed, celecoxib and rofecoxib, which are COX-1-sparing at therapeutic doses, appear to provide the therapeutic benefits of non-specific NSAIDs, while obviating the concurrent adverse events associated with COX-1 inhibition [12, 13]. Valdecoxib is a novel COX-2-specific inhibitor [14] recently approved by the United States Food and Drug Administration for the treatment of the signs and symptoms of RA, osteoarthritis and primary dysmenorrhea. Valdecoxib has also been shown to be an effective analgesic in the treatment of postoperative pain [15, 16].

This randomized, multicentre, double-blind, parallel-group study compared the efficacy and GI safety of once-daily (q.d.) doses of valdecoxib 20 mg and valdecoxib 40 mg with twice-daily (b.i.d.) doses of diclofenac 75 mg slow release (SR), administered for 26 weeks, in treating the signs and symptoms of RA. Efficacy was measured using the Patient’s Assessment of Arthritis Pain on a visual analogue scale (VAS) and the modified Health Assessment Questionnaire (mHAQ). Upper GI safety was measured by endoscopy at week 26 or at early termination.

Methods

Patients, at least 18 yr old, who had been diagnosed with adult-onset RA of at least 6 months’ duration satisfying the American College of Rheumatology (ACR) criteria [17], and who required continuous treatment with anti-inflammatory drugs to control arthritis symptoms, were eligible for entry into the study. At baseline, patients were required to have a Functional Capacity Classification of I–III and a Global Assessment of Arthritis rated as fair, poor or very poor [17].

Patients were excluded if they had any other inflammatory arthritis or secondary, non-inflammatory arthritis that was symptomatic enough to interfere with the evaluation of the study medications or if they had been diagnosed or treated for oesophageal, gastric, pyloric channel or duodenal ulceration within 30 days prior to receiving the first dose of study medication. Additionally, patients who had started taking or changed the dosing regimen of one or more of the following medications within a specified period prior to the first dose of study medication were ineligible: gold salts, antimalarials, azathioprine, penicillamine, etanercept, leflunomide, glucosamine chondroitin, diacerein, hyaluronic acid, infliximab, cyclosporin, tacrolimus or other biologicals, anti-CD4s, prosorba, sulphasalazine (doses of up to 3 g/day were allowed), methotrexate (doses of up to 25 mg/week were allowed), antibiotics used in treating RA (e.g. minocycline or doxycycline), warfarin, or corticosteroids (oral or intramuscular, intra-articular, intravenous or soft-tissue injections). Patients who had taken any NSAIDs or analgesics within 48 h (except for paracetamol within 24 h) prior to baseline assessments were excluded. Acetylsalicylic acid (ASA) ≤325 mg/day was allowed if the dosing regimen was stable for at least 30 days prior to the first dose of study medication.

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The study protocol was approved by the appropriate Independent Ethics Committee for each participating site. Written informed consent was obtained from all patients at the screening visit and before any study procedures were initiated.

Study design

The study was a 26-week, randomized, multicentre, double-blind, parallel-group trial designed to evaluate the arthritis efficacy and GI safety of valdecoxib 20 and 40 mg q.d. compared with diclofenac 75 mg SR b.i.d. in treating the signs and symptoms of RA. This study was conducted at 133 sites in 26 countries throughout Europe, Australia, South America and Africa. Written informed consent was obtained from all patients at the screening visit and before any study procedures were initiated.

The study period was preceded by a screening visit, and a minimum washout period of 2–4 days from prior NSAIDs (depending on the patient’s baseline drug therapy) before the baseline visit. Patients were randomly assigned based on a computer-generated sequence upon enrolment to the valdecoxib 20 mg q.d., valdecoxib 40 mg q.d. or diclofenac 75 mg SR b.i.d. treatment group. All study medications were identical in
Efficacy and upper GI safety of valdecoxib

Efficacy assessments

Efficacy was assessed by Patient’s Assessment of Arthritis Pain (VAS) and by the modified Health Assessment Questionnaire (mHAQ). The mHAQ was based on an evaluation of eight areas of daily function by the patient. Patients graded their ability to perform these activities on a four-point scale (0 = without difficulty, 3 = unable to perform) [18] at baseline and at weeks 2, 6, 12, 18 and 26. The Patient’s Assessment of Arthritis Pain (VAS) was a 100 mm visual analogue scale from 0 (no pain) to 100 (most severe pain) [19].

Efficacy was also assessed at weeks 2, 6, 8, 12, 18 and 26 by the number of patients responding to treatment according to the ACR Responder’s Index (ACR-20) [20]. A responder was defined as a patient with at least 20% improvement from baseline in the number of tender/painful joints and in the number of swollen joints, as well as at least a 20% improvement from baseline in at least three of the following assessments: Physician’s Global Assessment of Arthritis, Patient’s Global Assessment of Arthritis, Patient’s Assessment of Arthritis Pain, C-reactive protein (CRP) levels and mHAQ. The Patient’s Global Assessment of Arthritis and the Physician’s Global Assessment of Arthritis were based on the following five-point scale: 1 = very good, 2 = good, 3 = fair, 4 = poor, 5 = very poor. Physician’s Assessments of Joint Tenderness/Pain and Swelling were conducted on 68 joints as previously described [21–23]. Duration of morning stiffness [19] and CRP levels were also determined at all study visits. The incidence of withdrawal due to treatment failure was monitored throughout the study.

GI safety assessments

GI safety was evaluated by endoscopy, which took place no more than 2 days after the last dose of study medication at week 26 or at early termination. Based on a modification of the criteria reported by Lanza et al. [24], the mucosa of the stomach and duodenum were assigned a separate score from 0 to 7 as follows: 0 = normal mucosa, 1 = 1–10 petechiae, 2 = >10 petechiae, 3 = 1–5 erosions, 4 = 6–10 erosions, 5 = 11–25 erosions, 6 = >25 erosions, and 7 = ulcer. Erosions were defined as any break in the mucosa without obvious depth. Ulcers were defined as any break in the mucosa of at least 3 mm in diameter with unequivocal depth. Helicobacter pylori status was assessed by serology.

Safety/tolerability assessments

General clinical safety and tolerability were monitored throughout the study via the monitoring of adverse events and changes in laboratory and vital sign measurements. Adverse events were graded as mild, moderate or severe by the investigator.

Statistical methods

The sample size was calculated based on the mean changes from baseline in arthritis pain as measured on a 100 mm VAS scale. The objective of the study was to show that the valdecoxib test treatments (T) were not inferior to the diclofenac reference treatment (R). The null hypothesis, testing inferiority, was $H_0: \mu_T - \mu_R \geq 15 \text{ mm}$, i.e. the true mean change from baseline in the reference group was at least 15 mm larger than the true mean change in the test group. The alternative hypothesis, testing non-inferiority, was $H_1: \mu_T - \mu_R < 15 \text{ mm}$, i.e. the true mean change in the reference group was less than 15 mm larger than the true mean change in the test group. The inferiority and non-inferiority hypotheses were tested by calculating 95% two-sided confidence intervals for the differences in mean changes from baseline for the test and reference treatments. The power of this test (assuming a one-sided test with $\alpha = 0.025$, a sample size of 230 patients per treatment arm, a standard deviation of 25 mm, and a true difference between the two treatment mean changes of no more than 5 mm) is at least 90%. The choice of 15 mm as an appropriate difference in this measure was based on a Delphi exercise conducted by Bellamy et al. [25] to consider the minimum clinically important difference for a number of different parameters used in RA clinical trials.

Efficacy and safety analyses were carried out on the intent-to-treat (ITT) cohort using the Last Observation Carried Forward method. The ITT cohort consisted of all patients who were randomized to treatment and who received at least one dose of study medication. Changes from baseline at each visit were analysed for each primary and secondary outcome measure. These analyses were carried out using analysis of covariance with investigational site and treatment group as factors and baseline as the covariate. Pairwise comparisons were carried out to compare the efficacy of treatments. The results of the pairwise comparisons were interpreted using Hochberg’s [26] procedure to control for type-1 error associated with multiple treatment-group comparisons. The Hochberg procedure improves the traditional Bonferroni procedure for pairwise comparisons by comparing the sequentially ordered observed $P$ values with the corresponding sequentially ordered critical $P$ values for significance that are obtained by dividing the overall $\alpha$ level (e.g. 0.05) by the increasing number of pairwise comparisons. When a specific observed $P$ value is less than the corresponding ranked critical $P$ value, all observed $P$ values that are smaller than or equal to the specific $P$ value are considered significant by the Hochberg procedure. The ACR-20 Responders’ analyses were done using the Cochran–Mantel–Haenszel (CMH) test, controlling for investigational site.

The overall and pairwise incidence rates of gastroduodenal, gastric and duodenal ulcers and erosions and/or ulcers were compared using CMH controlling for investigational sites. The incidence rates of gastroduodenal, gastric and duodenal ulcers were also analysed using CMH controlling for the subjects’ H. pylori status, ASA use status, gender, age <65 yr vs >65 yr, presence or absence of cardiovascular disease, previous NSAID GI intolerance, history of gastroduodenal ulcer and history of GI bleeding.

Results

Patient disposition

Patient disposition is summarized in Fig. 1. All patients who received at least one dose of study medication were included in the efficacy and safety analyses. Two patients who had been randomized to diclofenac were withdrawn from the study before receiving study medication due to a baseline adverse event or protocol non-compliance. Treatment groups were similar with respect to baseline and demographic variables, with the exception of a statistically significant difference in duration of morning stiffness ($P = 0.047$) (Table 1).
Efficacy outcomes

Single daily doses of valdecoxib (20 and 40 mg) were as efficacious as twice-daily diclofenac 75 mg SR in treating the signs and symptoms of RA over the 26-week study period. Patients' arthritis pain and functional disability were significantly improved at each assessment for each treatment group. Improvements in arthritis pain, indicated by a reduction in mean VAS scores relative to baseline, were observed at each assessment. The mean reduction from baseline at week 26 was 11.3 mm for the valdecoxib 20 mg q.d. group, 12.3 mm for the valdecoxib 40 mg q.d. group, and 13.0 mm for the diclofenac 75 mg SR b.i.d. group (Fig. 2). There were no significant differences in the magnitude of change in VAS scores from baseline between the three treatment groups at any time point (P > 0.359).

No significant differences were observed at week 26 between valdecoxib 20 or 40 mg q.d. and diclofenac 75 mg SR b.i.d., or between the two doses of valdecoxib, in any of the other efficacy assessments (Table 2). Across weeks 2, 6, 12, 18 and 26, the range of ACR-20 responder rates were 17–32% in the valdecoxib groups.

**Table 1. Patient baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Valdecoxib 20 mg q.d. (n = 246)</th>
<th>Valdecoxib 40 mg q.d. (n = 237)</th>
<th>Diclofenac 75 mg b.i.d. SR (n = 239)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr): mean (s.d.)</td>
<td>55.7 (12.6)</td>
<td>54.8 (11.9)</td>
<td>56.4 (11.7)</td>
<td>0.239</td>
</tr>
<tr>
<td>Weight (kg): mean (s.d.)</td>
<td>70.0 (13.8)</td>
<td>69.9 (14.4)</td>
<td>69.8 (14.4)</td>
<td>0.978</td>
</tr>
<tr>
<td>Race/ethnic origin</td>
<td></td>
<td></td>
<td></td>
<td>0.956</td>
</tr>
<tr>
<td>Caucasian</td>
<td>86%</td>
<td>86%</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10%</td>
<td>11%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Gender (% males)</td>
<td>27%</td>
<td>29%</td>
<td>20%</td>
<td>0.057</td>
</tr>
<tr>
<td>Disease duration (yr): mean (s.d.)</td>
<td>9.9 (8.7)</td>
<td>10.6 (8.4)</td>
<td>10.0 (8.5)</td>
<td>0.829</td>
</tr>
<tr>
<td>Aspirin use&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 (5.7%)</td>
<td>14 (5.9%)</td>
<td>13 (5.4%)</td>
<td>0.976</td>
</tr>
<tr>
<td>History of upper GI bleeding</td>
<td>2.4%</td>
<td>1.3%</td>
<td>1.3%</td>
<td>0.502</td>
</tr>
<tr>
<td>History of gastroduodenal ulcer</td>
<td>10.6%</td>
<td>5.9%</td>
<td>5.9%</td>
<td>0.076</td>
</tr>
<tr>
<td>H. pylori status (% positive)</td>
<td>38.6%</td>
<td>37.1%</td>
<td>36.0%</td>
<td>0.944</td>
</tr>
<tr>
<td>VAS score: mean (s.d.)</td>
<td>56.5 (18.6)</td>
<td>55.8 (18.0)</td>
<td>56.8 (18.2)</td>
<td>0.935</td>
</tr>
<tr>
<td>mHAQ Functional Disability Score: mean (s.d.)</td>
<td>1.4 (0.7)</td>
<td>1.3 (0.6)</td>
<td>1.3 (0.7)</td>
<td>0.742</td>
</tr>
<tr>
<td>Physician’s Global Assessment of Arthritis</td>
<td></td>
<td></td>
<td></td>
<td>0.361</td>
</tr>
<tr>
<td>Fair</td>
<td>69%</td>
<td>71%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>28%</td>
<td>24%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Tender/painful joint score: mean (s.d.)</td>
<td>40.6 (27.8)</td>
<td>38.4 (27.6)</td>
<td>38.6 (29.3)</td>
<td>0.489</td>
</tr>
<tr>
<td>Tender/painful joint count: mean (s.d.)</td>
<td>28.5 (16.5)</td>
<td>26.6 (15.7)</td>
<td>26.2 (15.8)</td>
<td>0.066</td>
</tr>
<tr>
<td>Swollen joint score: mean (s.d.)</td>
<td>25.7 (21.0)</td>
<td>24.2 (20.7)</td>
<td>23.6 (20.7)</td>
<td>0.178</td>
</tr>
<tr>
<td>Swollen joint count: mean (s.d.)</td>
<td>18.7 (13.2)</td>
<td>17.2 (12.9)</td>
<td>17.2 (13.0)</td>
<td>0.057</td>
</tr>
<tr>
<td>Duration of morning stiffness (min)</td>
<td>111.4 (121.5)</td>
<td>145.6 (245.2)</td>
<td>160.1 (282.0)</td>
<td>0.047&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>CRP (mg/l): mean (s.d.)</td>
<td>13.6 (15.9)</td>
<td>13.9 (18.2)</td>
<td>13.0 (19.9)</td>
<td>0.839</td>
</tr>
</tbody>
</table>

<sup>a</sup>C20 mg for cardiovascular prophylaxis.

<sup>7</sup>Statistically significant.
and 18–36% in the diclofenac treatment group. An improvement in the mHAQ Functional Disability Index scores relative to baseline was also observed at each assessment. Comparable improvements in the Patient’s and Physician’s Global Assessment of Arthritis were recorded for the valdecoxib and diclofenac groups. The number of tender/painful joints and the tender/painful joint score were also improved relative to baseline in each treatment group.

The incidence of withdrawal due to treatment failure was 9% for the valdecoxib 20 and 40 mg q.d. treatment groups and 10% for the diclofenac group. Pairwise comparisons showed no statistically significant differences between either of the valdecoxib treatment groups and the diclofenac group, or between the valdecoxib groups.

**GI safety outcomes**

Significantly fewer gastroduodenal ulcers were observed in patients assigned to the valdecoxib treatment groups compared with patients assigned to the diclofenac group ($P < 0.001$) (Fig. 3). No statistically significant differences were noted between the valdecoxib treatment groups. Significantly fewer gastric ulcers were detected in patients taking valdecoxib 20 or 40 mg q.d. (2%) than in patients taking diclofenac 75 mg SR b.i.d. (13%) ($P < 0.001$). Duodenal ulcers were detected in 4% of patients taking valdecoxib 20 mg, 1% of patients taking valdecoxib 40 mg and 6% of patients taking diclofenac 75 mg SR. Patients receiving valdecoxib 40 mg developed significantly fewer duodenal ulcers than those taking diclofenac 75 mg SR ($P < 0.01$). No treatment differences with respect to the incidence of duodenal ulcers were evident between valdecoxib 20 mg and diclofenac. *H. pylori* status, ASA use and age had no significant effect on gastroduodenal ulcer rates among treatment groups ($P \geq 0.51$).

Ulcers or erosions were present in 21% of patients receiving valdecoxib 20 mg, 26% of those receiving valdecoxib 40 mg and 48% of those receiving diclofenac 75 mg ($P < 0.001$ for valdecoxib groups vs diclofenac). Significantly fewer gastric ulcers/erosions were detected in patients taking valdecoxib 20 and 40 mg than in patients taking diclofenac 75 mg SR b.i.d. ($P < 0.001$). Significantly fewer duodenal ulcers/erosions were detected in patients taking valdecoxib 40 mg q.d. than diclofenac 75 SR b.i.d. ($P < 0.01$). No treatment differences with respect to the incidence of duodenal ulcers/erosions were evident between valdecoxib 20 mg and diclofenac. No statistically significant differences were noted between the valdecoxib treatment groups.

**Safety outcomes**

Of the 720 patients in the ITT population, a total of 490 patients reported at least one adverse event during the course of the study: 67% of patients in the valdecoxib 20 mg treatment group, 65% of patients in the valdecoxib 40 mg treatment group and 73% of patients in the

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**Table 2. Secondary outcome measures at week 26**

<table>
<thead>
<tr>
<th></th>
<th>Valdecoxib 20 mg q.d.</th>
<th>Valdecoxib 40 mg q.d.</th>
<th>Diclofenac 75 mg b.i.d. SR</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACR-20</strong></td>
<td>73 (32%)</td>
<td>70 (32%)</td>
<td>79 (36%)</td>
<td>0.665</td>
</tr>
<tr>
<td><strong>mHAQ: mean change from baseline at week 26</strong></td>
<td>–0.17</td>
<td>–0.25</td>
<td>–0.26</td>
<td></td>
</tr>
<tr>
<td><strong>Global Assessment of Disease Activity: no. (%) improved</strong></td>
<td>41 (17%)</td>
<td>40 (17%)</td>
<td>47 (20%)</td>
<td>0.571</td>
</tr>
<tr>
<td>Patient’s</td>
<td>38 (15%)</td>
<td>44 (19%)</td>
<td>43 (18%)</td>
<td>0.365</td>
</tr>
<tr>
<td>Physician’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal due to treatment failure</td>
<td>23 (9%)</td>
<td>22 (9%)</td>
<td>24 (10%)</td>
<td>0.796</td>
</tr>
<tr>
<td>No. (%) withdrawn</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician’s assessment: mean change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender/painful joint count</td>
<td>–9.9</td>
<td>–9.4</td>
<td>–9.2</td>
<td>0.834</td>
</tr>
<tr>
<td>Tender/painful joint score</td>
<td>–16.5</td>
<td>–16.2</td>
<td>–15.9</td>
<td>0.734</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>–6.5</td>
<td>–5.0</td>
<td>–5.6</td>
<td>0.103</td>
</tr>
<tr>
<td>Swollen joint score</td>
<td>–9.8</td>
<td>–8.0</td>
<td>–8.9</td>
<td>0.295</td>
</tr>
<tr>
<td>CRP (mg/l): mean change</td>
<td>1.9</td>
<td>–0.04</td>
<td>2.2</td>
<td>0.419</td>
</tr>
<tr>
<td>Duration of morning stiffness (min): mean change</td>
<td>–32.2</td>
<td>–21.3</td>
<td>–38.7</td>
<td>0.522</td>
</tr>
</tbody>
</table>

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**Fig. 2.** Mean ($\pm$ S.E.) Patient’s Assessment of Arthritis Pain (VAS) scores at baseline and weeks 2, 6, 12, 18 and 26.
The majority of adverse events were mild or moderate in severity. No apparent dose-dependent effect was observed for adverse events occurring in the valdecoxib 20 and 40 mg q.d. treatment groups. The overall incidence of adverse events was not significantly different between the treatment groups. The incidence of withdrawal due to any adverse events was 9.8 and 10.5% in the valdecoxib 20 and 40 mg q.d. treatment groups respectively, and 15.2% in the diclofenac 75 mg SR b.i.d. group. Significantly more patients taking diclofenac (11.8%) withdrew due to GI adverse events compared with patients taking either valdecoxib 20 mg q.d. (4.5%) or valdecoxib 40 mg q.d. (5.5%) ($P \leq 0.021$).

The incidence of GI-related adverse events was 39.4% in patients assigned to the valdecoxib 20 mg q.d. treatment group, 40.1% in the valdecoxib 40 mg q.d. group and 49.4% in the diclofenac 75 mg SR b.i.d. group. The incidence of GI-related adverse events within the valdecoxib 20 mg group was significantly lower ($P = 0.035$) than in the diclofenac treatment group. The most common GI-related adverse events were abdominal pain, diarrhoea, dyspepsia and nausea.

### Discussion

This study demonstrated that valdecoxib 20 or 40 mg, administered once daily, provides sustained analgesic and anti-inflammatory efficacy in RA patients over a 26-week period, as assessed by the primary efficacy measures (VAS and mHAQ). All primary and secondary efficacy measures support the conclusion that valdecoxib 20 and 40 mg once daily are comparable to diclofenac 75 mg twice daily in treating the signs and symptoms of RA. Moreover, patients taking valdecoxib 20 and 40 mg experienced a significantly lower incidence of gastroduodenal ulcers. Valdecoxib 20 mg also provided better GI tolerability than diclofenac. The 40 mg dose of valdecoxib provided no additional therapeutic benefit over that of the 20 mg dose in treating the signs and symptoms of RA.

NSAID-induced adverse events in the GI tract are a cause for concern in the treatment of RA. The relative risk of ulcers and serious GI complications for users of NSAIDs ranges from 1 to 30 times greater than for non-users [1, 10, 27]. Of the NSAIDs in common use, diclofenac appears to be associated with a comparatively low relative risk of GI toxicity [28]. With long-term use, ulcers develop most frequently in the stomach and to a lesser extent in the duodenum. Less serious but more frequently, patients experience dyspepsia, nausea, vomiting, diarrhoea or constipation and abdominal pain with NSAID use, which may affect patient compliance and ultimately the clinical utility of these agents.

In this study, upper GI endoscopic evaluation revealed that long-term treatment with valdecoxib, at either the 20 mg or 40 mg dose, resulted in a significantly lower incidence of gastroduodenal ulcers, compared with diclofenac 75 mg. Our results with valdecoxib are similar to those of endoscopic studies with other COX-2-specific inhibitors such as celecoxib and rofecoxib, which also demonstrated a GI safety advantage when compared with conventional NSAIDs [29–33]. Moreover, for both celecoxib and rofecoxib, endoscopic findings appear to predict a GI safety benefit with respect to a more

### Table 3. Adverse events with an incidence of ≥5%

<table>
<thead>
<tr>
<th>Event</th>
<th>Valdecoxib 20mg q.d.</th>
<th>Valdecoxib 40mg q.d.</th>
<th>Diclofenac 75mg b.i.d. SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any adverse event</td>
<td>164 (66%)</td>
<td>154 (65%)</td>
<td>172 (73%)</td>
</tr>
<tr>
<td>CNS and PNS disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22 (9%)</td>
<td>15 (6%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>GI system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23 (9%)</td>
<td>26 (11%)</td>
<td>36 (15%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>14 (6%)</td>
<td>24 (10%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>3 (1%)</td>
<td>4 (2%)</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>Gastritis (dyspepsia)</td>
<td>9 (4%)</td>
<td>11 (5%)</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (8%)</td>
<td>17 (7%)</td>
<td>23 (10%)</td>
</tr>
<tr>
<td>Respiratory system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>10 (4%)</td>
<td>15 (6%)</td>
<td>12 (5%)</td>
</tr>
</tbody>
</table>

CNS, central nervous system; PNS, peripheral nervous system.
Efficacy and upper GI safety of valdecoxib

clinically relevant outcome of ulcer complications vs conventional NSAIDs [34–37]. Valdecoxib was associated with an improved GI tolerability profile in this study. The overall incidence of GI-related adverse events within the valdecoxib 20 mg treatment group was consistently lower than that in the diclofenac treatment group. Kivitz et al. [38] and Sikes et al. [39] also observed lower rates of GI symptoms such as dyspepsia and constipation in patients treated with valdecoxib than in patients treated with naproxen, ibuprofen or diclofenac.

For patients with RA, valdecoxib in single daily doses of 10–40 mg has provided effective pain relief and improvements in physical function comparable to those given by naproxen 500 mg b.i.d. [40]. Overall, our study suggests that single daily doses of valdecoxib 20 mg are as effective as diclofenac for the treatment of RA and that no additional benefit is derived from the 40 mg dose. In addition, valdecoxib offers improved GI safety and tolerability compared with diclofenac, as evidenced by the reduction in gastroduodenal ulcers and improved GI tolerability. Thus, valdecoxib appears to be a potent, effective, safe, once-daily alternative to non-specific NSAIDs, with a significantly better GI safety profile, and may be a valuable new option for the treatment of RA.

Acknowledgements

This study was supported by G. D. Searle & Co. The investigators who participated in this study are Michael Ahern (Australia), Jose J. Orozco Alcala (Mexico), Juan M. Anaya (Colombia), Seva Augustinovich (Czech Republic), Geza Balint (Hungary), Carol M. Black (UK), Per Blilchfeldt (Norway), Ladislav Bortlik (Czech Republic), Marco Brogini (Italy), Russell Buchanan (Australia), Daniele Cammelli (Italy), Alain Cantagrel (France), Patricia Carreira Delgado (Spain), Luis Carreno Perez (Spain), Monique Chalem (Colombia), Gerard Chales (France), Laure Chapuis (France), Kjeld Christensen (Denmark), Eduardo Collantes Estevez (Spain), Laszlo Czirjak (Hungary), Hans-Gerd Dammann (Germany), Richard Day (Australia), Luc K. C. De Clercq (Belgium), Jean-Pierre Devogelaer (Belgium), Lief Ejstrup (Denmark), Geza Eszenyi (Hungary), Clodoveo Ferri (Italy), Anna Filipowicz-Sosnowska (Poland), Oliver FitzGerald (Ireland), P. Singh Gagragh (New Zealand), Janos Gal (Hungary), Gyorgy Gentl (Hungary), Emmanuel George (UK), Piet P. M. M. Geusens (Belgium), Juan Gomez Reino (Spain), David Gotlieb (South Africa), Andrew K. Gough (UK), Leslie Green (Israel), Erika Gromnica-Ihle (Germany), Anthony Hammond (UK), Birthe Lund Hansen (Denmark), Holm Hantschel (Germany), Joel Hautin (France), Per-Johan Hedin (Sweden), Clinton L. J. Herd (Australia), Marco Hirsch (Belgium), Jesus Ibanez Ruan (Spain), Antione Jallut (Switzerland), Maria J. Jannaut (Colombia), T.L.T.A Jansen (The Netherlands), M. Janssen (The Netherlands), Penti Jarvinen (Finland), Peter B. Jones (New Zealand), Joachim P. Kaltwasser (Germany), Zdenko Killinger (Slovakia), Andrew P. Kirk (UK), John R. Kirwan (UK), Michaela Kulhava (Czech Republic), Rubem Lederman (Brazil), Ennio Leggieri (Italy), Olivier Leloire (France), Jan L. A. Lenaerts (Belgium), Marc Leon (Belgium), Ulla Lindqvist (Sweden), Jean-Marie Loix (Belgium), Karel Macek (Czech Republic), Katarina Machova (Slovakia), Michel Malaise (Belgium), Nicholas Manolios (Australia), David A. Marshall (UK), Jane Matthesen (Denmark), Conor McCarthy (Ireland), Iain B. McInnes (UK), Frank McKenna (UK), Manfred Meyer-Owen (Germany), Knut Mikkelsen (Norway), Emilio Martin Mola (Spain), Michael G. Molloy (Ireland), Jose Munoz Gomez (Spain), Peter T. Nash (Australia), Savithree Nayaiger (South Africa), Hubert Nusslein (Germany), Fedra Irazoqui Palazuelos (Mexico), Karel Pavelka (Czech Republic), Michel Pellaton (Switzerland), Anne Peretz (Belgium), Henrik Peterhoff (Sweden), Kevin D. Pile (Australia), Domingos Pinto De Araujo (Portugal), Gyula Pokorny (Hungary), Armando L. Porto (Portugal), Ana M. Posada (Colombia), Sebastiao C. Radominski (Brazil), Kari A. Raji (Finland), Maria Rell-Bakalaraska (Poland), Monika Reuss-Borst (Germany), Vicente Rodriguez Valverde (Spain), Itzhak A. Rosner (Israel), Isabel Rotes (Spain), Guido Rotveta (Italy), Jorge Rueda (Brazil), Claudio Rugarli (Italy), Ivan Rybar (Slovakia), Juan Sanchez Burson (Spain), Rui Andre Santos (Portugal), Thierry Schaeverbeke (France), Peter Schlapbach (Switzerland), Les Schrieber (Australia), Thomas P. G. Sheeran (UK), Timothy Spector (UK), Jacques Stalder (Switzerland), Leszek Szczepanski (Poland), Jacek Szechinski (Poland), Zoltan Szekanecz (Hungary), Laszlo Tamasi (Hungary), Philippe Taueron (France), Andrew Taylor (Australia), Jacques S. Tebib (France), Elke L. Theander (Sweden), Mohammed Tikly (South Africa), Thomas Tinture Eguren (Spain), Witold Tlustochowicz (Poland), Niels Tveite (Denmark), Ivan Ujvari (Slovakia), Heikki Valcleala (Finland), Wilfried G. Verdick (Belgium), Javier Vidal Fuentes (Spain), Elisabeth Waldorf-Bolten (Germany), David J. Walker (UK), Richard B. Williams (UK), Wolf-Dieter Worth (Germany), Neville D. Yeomans (Australia) and Henning Zeidler (Germany).

Conflict of interest

Both D. Recker and K. Verburg are employees of Pharmacia and own shares of company stock. K. Pavelka is an investigator in the trial and has no conflicts of interest to declare.

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