Two isoforms of cyclooxygenase (COX), COX-1 and COX-2,1-4 catalyze human prostaglandin synthesis. Almost all currently available nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both COX isoforms.5 COX-1 is constitutively expressed and generates prostaglandins believed to be involved in gastrointestinal (GI) mucosal protection,6 while COX-2 is induced at sites of inflammation throughout the body and generates prostaglandins that mediate inflammation and pain.7 Therefore, the anti-inflammatory effects of NSAIDs appear to be mediated via inhibition of COX-2,8 while the deleterious GI effects, a significant source of morbidity and mortality, are believed to occur primarily via inhibition of COX-1.3 These GI-related adverse effects (AEs)9-11 are estimated to be responsible for 107 000 hospitalizations and 16 500 deaths annually in the United States alone.12

Rofecoxib (Vioxx, Merck & Co, Inc, Whitehouse Station, NJ) specifically inhibits COX-213,14; at dosages of up to 375 mg/d for 12 days15 and up to 1000 mg in single doses,13 it had no effect on COX-1 isoenzyme activity. In vitro studies of rofecoxib showed no significant effect on prostaglandin synthesis in human gastric biopsies.16 In addition, rofecoxib demonstrated low potential for GI injury (at dosages of 25 and 50 mg/d) as measured by intestinal permeability17 and fecal red blood cell loss,18 and by assessment of endoscopic gastroduodenal mucosal injury in both healthy volunteers (at 250
mg/d) and patients with osteoarthritis (at 25 and 50 mg/d).

This study was a planned, blinded, combined analysis of 8 randomized, double-blind, phase 2b/3 clinical trials performed from December 1996 through March 1998 of rofecoxib in patients with osteoarthritis to examine the incidence of upper GI perforations, symptomatic gastroduodenal ulcers, and upper GI bleeding (PUBs). We hypothesized that the incidence of PUBs would be lower with rofecoxib (12.5-, 25-, and 50-mg combined treatment groups) than with NSAIDs (ibuprofen, diclofenac, and nabumetone combined treatment groups).

**METHODS**

The plan used to analyze the incidence of PUBs with rofecoxib compared with NSAIDs was prespecified. PUBs are rare and large numbers of patients are necessary to evaluate the rate of incidence with precision; therefore, in this analysis, we pooled patients from all 8 phase 2b/3 osteoarthritis trials of rofecoxib and their blinded extensions (Table 1). All patients gave signed informed consent and an institutional review board approved each study.

The analysis plan prespecified that patients with asymptomatic ulcers diagnosed within a 7-day window surrounding the scheduled procedure dates in the 2 surveillance endoscopy studies would be excluded from the analysis. Eleven additional patients with asymptomatic ulcers confirmed by investigators to have been detected at surveillance endoscopies scheduled outside the 7-day window for a variety of reasons were also excluded.

Investigators were instructed to report all laboratory and clinical AEs, including upper GI dyspepsia and PUBs, that occurred during treatment and within 14 days of study drug discontinuation. In all the studies, a final patient contact and/or evaluation was scheduled for the 14th day following study completion or study drug discontinuation. Patients were followed up in each study until final evaluation after completion of study therapy or after early discontinuation for any reason (eg, diagnosis of PUB, other AE, lack of treatment efficacy, withdrawal of consent), death, or loss to follow-up.

Clinical source documentation for suspected PUBs was reviewed by a blinded, external adjudication committee. Only PUBs judged as confirmed, according to prespecified definitions (Table 2), were analyzed. PUBs that occurred more than 14 days after the last dose of study drug were not included in the analysis (as prespecified).

Adverse events, including PUBs, were coded blind to treatment with a standard automated dictionary that classified AEs into broader categories grouped by body system. We also compared discontinuations due to any GI AE and discontinuations due to a prespecified subset of GI AEs typical of upper GI symptoms associated with NSAIDs. The latter category (hereafter referred to as “dyspeptic-type GI AEs”) consists of all AEs mapped by the dictionary to the categories of acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea, or vomiting.

Analyses were based on all patients treated in the 8 trials, with exceptions as follows. Patients from the placebo and 5-mg rofecoxib groups of Protocol 029 (Table 1) were switched after 6 weeks to diclofenac, 12.5 mg of rofecoxib, or 25 mg of rofecoxib in an extension phase. Similarly, patients from the placebo group of Protocol 058 were switched after 6 weeks to nabumetone, 12.5 mg of rofecoxib, or 25 mg of rofecoxib in an extension phase. To avoid double-counting patients in the analyses, it was prespecified that the data from patients randomized to the placebo or 5-mg rofecoxib groups in the 6-week placebo-

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**Table 1. Features of Studies Included in the Combined Analysis**

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Design</th>
<th>Duration*</th>
<th>Treatments Assessed</th>
<th>Total No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>029</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group, dose range in patients with knee or hip osteoarthritis</td>
<td>6 Weeks plus extensions up to 2 years</td>
<td>Placebo (first 6 weeks) Rofecoxib (plus diclofenac in extensions)</td>
<td>571†</td>
</tr>
<tr>
<td>033/040</td>
<td>Twin US and multinational studies: randomized, double-blind, active- and placebo-controlled, parallel-group, safety and efficacy in patients with knee or hip osteoarthritis</td>
<td>6 Weeks</td>
<td>Placebo Rofecoxib Ibuprofen</td>
<td>1545</td>
</tr>
<tr>
<td>034/035</td>
<td>Twin US and multinational studies: randomized, double-blind, active comparator-controlled, parallel-group, safety and efficacy in patients with knee or hip osteoarthritis</td>
<td>1 Year plus extension of 1 year</td>
<td>Rofecoxib Diclofenac</td>
<td>1477</td>
</tr>
<tr>
<td>044/045</td>
<td>Twin US and multinational studies: randomized, double-blind, active- and placebo-controlled, parallel-group, endoscopic surveillance in patients with osteoarthritis</td>
<td>6 Months (placebo treatment stopped at 4 months)</td>
<td>Placebo Rofecoxib Ibuprofen</td>
<td>1517</td>
</tr>
<tr>
<td>058</td>
<td>Randomized, double-blind, active- and placebo-controlled, parallel-group, efficacy, safety and tolerability in patients aged 80 years and older with knee and hip osteoarthritis</td>
<td>6 Weeks with extension of 6 months</td>
<td>Placebo (first 6 weeks) Rofecoxib Nabumetone</td>
<td>325‡</td>
</tr>
</tbody>
</table>

*Patients were eligible to voluntarily continue treatment in extensions on completion of study.
†There were 101 patients (54 receiving placebo and 47 receiving 5-mg rofecoxib) enrolled in this study who did not continue into extensions and were excluded from the analysis (see “Methods”). No upper gastrointestinal perforations, symptomatic gastroduodenal ulcers, and upper gastrointestinal bleeding (PUBs) occurred in these patients.
‡Sixteen placebo patients who did not continue into extensions were excluded from the analysis (see “Methods”). No PUBs occurred in these patients.
controlled phase of both studies would be excluded from analyses, while the data from these patients’ extension phase would be included. However, 117 such patients (2.1% of the total population) did not continue into extensions or did not have extension data at the time of the analysis and were therefore excluded.

A survival analysis of the time to first PUB diagnosis date was used for between-treatment comparisons. This method is appropriate because it takes into account the varying lengths of treatment in the 8 studies. For PUBs diagnosed in inpatients, the hospital admission date was used as the diagnosis date. For PUBs diagnosed in outpatients, the date of the diagnostic procedure or clinical observation was used. The log-rank test was the primary method used to compare time-to-first-event distributions between groups. The cumulative incidence difference between rofecoxib and NSAIDs was assessed at 6 weeks and at 4, 6, 12, and 24 months, using the method of Breslow and Crowley. Results are reported at 4 months (maximum duration of placebo) and 12 months (no PUBs occurred beyond 12 months). Differences between groups were considered significant when \( P < .05 \). The Cox proportional hazards model was used to estimate overall relative risks (RRs) and 95% confidence intervals (CIs) of rofecoxib vs NSAIDs. Treatment by type of protocol interactions were evaluated in the Cox model. Analyses stratified by type of protocol and analyses in which each type of protocol was removed from the analysis were therefore excluded.

**RESULTS**

The analysis included 5435 patients. Of these, 3357 patients were treated with rofecoxib (1209, 1603, and 545 patients received 12.5, 25, and 50 mg, respectively, once daily), 1564 patients were treated with NSAIDs (847 received ibuprofen, 800 mg 3 times daily; 590 received diclofenac, 50 mg 3 times daily; and 127 received nabumetone, 1500 mg once daily) and 514 patients were treated with placebo. Total patient-years of exposure were 1428, 615, and 112, in the rofecoxib, NSAID, and placebo groups, respectively. The average dosage of rofecoxib was 24.7 mg once daily.

There were no clinically meaningful differences in baseline characteristics between groups (Table 3). Mean age overall was 63 years (range, 38-94 years); 45% of patients were 65 years or older, and 73% were women. Most (90%) patients had previously used NSAIDs for their osteoarthritis. Approximately 10% of the patients in each group had a prior medical history of PUB.

Rofecoxib was generally well tolerated and fewer patients overall discontinued rofecoxib compared with the NSAIDs (Table 4): 9.4% of rofecoxib patients vs 10.7% of NSAID patients discontinued the study drug because of any clinical AE, and 3.5% of the rofecoxib patients discontinued the study drug due to a GI AE, compared with 4.8% of NSAID patients (Table 4). The cumulative incidence of dyspeptic-type GI AEs up to 6 months was significantly lower for rofecoxib than with NSAIDs (23.5% vs 25.5%; \( P = .02 \)), after which the incidence rates converged. The 12-month cumulative incidences of study drug discontinuation due to GI AEs were 5.7% vs 7.8% for the rofecoxib and NSAID groups. The difference was significantly lower (\( P = .02 \)) in the rofe-
coxib group compared with the NSAID group over 12 months (8.2 vs 12.0 per 100 patient-years, respectively; RR = 0.70; 95% CI, 0.52-0.94).

Forty-nine potential PUBs were submitted by investigators and adjudicated; 5 (3 in the rofecoxib and 2 in the NSAID group) did not meet the prespecified case definition because they occurred more than 14 days after study drug discontinuation. Of the remaining 44 cases, 38 (19 in the rofecoxib, 16 in the NSAID, 3 in the placebo group) were adjudicated as having at least 1 confirmed PUB, and 6 (all in the NSAID group) were adjudicated as having unconfirmed PUBs. Nine patients had more than 1 PUB (2, 3, and 4 in the placebo, rofecoxib, and NSAID groups respectively); all of these patients had 2 PUBs each, except for 1 patient (NSAID group) with 3 PUBs. Only the first PUB in a given patient was included in the analysis. There were no PUBs during the small amount of patient exposure (25 patient-years) to nabumetone in the 1 study that included this treatment.

The cumulative incidence of confirmed PUBs over 12 months with rofecoxib was significantly lower (1.3% vs 1.8%, P = .046) than with NSAIDs (FIGURE). The rates per 100 patient-years over 12 months were 1.33 and 2.60 for rofecoxib and NSAIDs, respectively. The overall RR over 12 months for rofecoxib vs NSAIDs was 0.51 (95% CI, 0.26-1.00). Analyses stratified by type of protocol yielded very similar results to the unstratified analyses (RR = 0.53; 95% CI, 0.27-1.03; P = .06), and analyses that sequentially removed each protocol type also yielded consistent results, demonstrating a lack of confounding by type of protocol. No statistically significant treatment by type of protocol interaction was present (P > .10) in the unstratified Cox model. The difference between rofecoxib and NSAIDs in the incidence of confirmed PUBs became statistically significant as early as 6 weeks (RR for rofecoxib vs NSAIDs, 0.21; 95% CI, 0.06-0.67; P = .004), and remained so up to 12 months.

In analyses confined to placebo-controlled protocols, which were up to 4 months in duration, the cumulative incidence rates of confirmed PUBs were 0.9%, 0.9%, and 1.6% for placebo, rofecoxib, and NSAIDs, respectively. The corresponding rates per 100 patient-years over 4 months were 2.68, 2.50, and 7.21. The RR over 4 months for NSAIDs vs placebo was 2.50 (95% CI, 0.68-9.24), while that for rofecoxib vs placebo was 0.94 (95% CI, 0.25-3.60).

**COMMENT**

Because PUBs are rare, we carried out a prespecified analysis of data obtained from 8 randomized, double-blind phase 2b/3 osteoarthritis trials with rofecoxib to determine whether COX-2 specific inhibition would be associated with a lower incidence of PUBs than nonspecific COX inhibition. The combined population included patients at high risk of PUBs (eg, those with a history of PUB and/or age ≥ 65 years), as reported previously. The analysis demonstrated a significantly lower incidence of confirmed PUBs with rofecoxib than with NSAIDs over 12 months. In addition, the total rate of study drug discontinuations due to GI AEs was significantly lower in the group receiving rofecoxib than in the group receiving NSAIDs.

### Table 4. Exposure to Study Drug and Number of Patients Who Completed and Who Were Discontinued From the Study Populations

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 514)</th>
<th>Rofecoxib (n = 3357)</th>
<th>NSAID (n = 1564)</th>
<th>Total (N = 5435)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patient-years of exposure</td>
<td>112</td>
<td>1428</td>
<td>615</td>
<td>. . .</td>
</tr>
<tr>
<td>Mean patient-years of exposure per patient</td>
<td>0.22</td>
<td>0.43</td>
<td>0.39</td>
<td>. . .</td>
</tr>
<tr>
<td>Completed</td>
<td>383 (74.5)</td>
<td>2323 (69.2)</td>
<td>984 (62.9)</td>
<td>3690 (67.9)</td>
</tr>
<tr>
<td>Discontinued, total</td>
<td>131 (25.5)</td>
<td>1034 (30.8)</td>
<td>580 (37.1)</td>
<td>1745 (32.1)</td>
</tr>
<tr>
<td>Clinical adverse experience</td>
<td>24 (4.7)</td>
<td>317 (9.4)</td>
<td>168 (10.7)</td>
<td>509 (9.4)</td>
</tr>
<tr>
<td>Digestive system clinical adverse experience</td>
<td>8 (1.6)</td>
<td>118 (3.5)</td>
<td>75 (4.8)</td>
<td>201 (3.7)</td>
</tr>
<tr>
<td>Laboratory adverse experience</td>
<td>2 (0.4)</td>
<td>20 (0.6)</td>
<td>41 (2.6)</td>
<td>63 (1.2)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>45 (8.8)</td>
<td>296 (8.8)</td>
<td>113 (7.2)</td>
<td>454 (8.4)</td>
</tr>
<tr>
<td>Study end point in endoscopy trials†</td>
<td>15 (2.9)</td>
<td>64 (1.9)</td>
<td>127 (8.1)</td>
<td>206 (3.8)</td>
</tr>
<tr>
<td>Other‡</td>
<td>45 (8.8)</td>
<td>337 (10)</td>
<td>131 (8.4)</td>
<td>513 (9.4)</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) unless otherwise indicated. NSAID indicates nonsteroidal anti-inflammatory drug.

†End point was development of gastroduodenal ulcer during surveillance; category also includes 19 patients who discontinued the study due to development of gastrointestinal erosions.

‡Includes patients who were lost to follow-up, moved, withdrew consent, or deviated from protocol.

**Figure. 12-Month Survival Analysis of Confirmed Upper Gastrointestinal (GI) Perforations, Symptomatic Ulcers, and Upper GI Bleeding by Combined Treatment Groups**

Relative risk with rofecoxib vs nonsteroidal anti-inflammatory drugs (NSAIDs) is 0.51 (95% confidence interval, 0.26-1.00; P = .046 by log-rank test).
The analysis has particular strengths. It was prospectively designed and used prespecified adjudication criteria, hypotheses, and data analysis plans, and an external, blinded committee adjudicated all reported PUBs. It included all phase 2b/3 osteoarthritis trials of rofecoxib and a broad range of patients, including those with prior PUB history. The primary hypothesis involved a biologically meaningful comparison of GI safety with COX-2 specific inhibition vs non-specific COX-1/COX-2 inhibition, and the doses of NSAID comparators for the included studies were chosen to be within the clinical dose range for treatment of osteoarthritis. The average dosage of rofecoxib in this study was 24.7 mg/d, which corresponds to the highest recommended daily dose (25 mg) for osteoarthritis. The average dosage in the study was 24.7 mg/d, which corresponds to the highest recommended daily dose (25 mg) for osteoarthritis. The average dosage in the study was 24.7 mg/d, which corresponds to the highest recommended daily dose (25 mg) for osteoarthritis.

Our analysis shows that COX-2 specific inhibition with rofecoxib was associated with a significantly lower risk of PUBs relative to NSAIDs. These findings are consistent with the results of studies of intestinal permeability, with upper GI endoscopy with rofecoxib and indicate that risks of GI toxic effects as associated with NSAIDs can be reduced by COX-2 specific inhibition.

Funding/Support: This work was supported by Merck & Co Inc, Whitehouse Station, NJ.

Acknowledgment: We thank Marie R. Griffin, MD, Department of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, Tenn, for her leadership as chair of the Clinical Event Case Review Committee and for her thoughtful review and critique of the manuscript. We also thank Maryanne Plesher, MS, and Carrie Schmidt, BA, for their assistance in conducting the study.

REFERENCES


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