FDA Arthritis Drug Advisory Committee Meeting

ARCOXIA™ (Etoricoxib) 30 and 60 mg
For Symptomatic Treatment of Osteoarthritis
(NDA 21-389 and NDA 21-772)

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Briefing Document (Background Package)

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TABLE OF CONTENTS

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

PAGE

LIST OF TABLES

LIST OF TABLES (CONT.)

LIST OF TABLES (CONT.)

LIST OF TABLES (CONT.)

LIST OF FIGURES

ABBREVIATIONS

AE	Adverse Experience
ALT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
APTC	Antiplatelet Trialists' Collaboration
AS	Ankylosing Spondylitis
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BID	Two times a day
BP	Blood Pressure
BUN	Blood urea nitrogen
CHF	Congestive Heart Failure
Cele	Celecoxib
CI	Confidence Interval
CLBP	Chronic Low Back Pain
Cmax	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel Test
COX	Cyclooxygenase
CRC	Case Review Committee
CRP	C-reactive protein
CV	Cardiovascular
CVA	Cerebrovascular accident
Diclo	Diclofenac
DSMB	Data Safety and Monitoring Board
EDGE	Etoricoxib Versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness study
Etori	Etoricoxib
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
GPA	Gastroprotective Agent
GPRD	General Practice Research Database
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
ICH	International Committee on Harmonization
IGADS	Investigator Global Assessment of Disease Status
INR	International Normalized Ratio
ITT	intention-to-treat
LS	Least Squared
MEDAL	Multinational Etoricoxib Versus Diclofenac Arthritis Long-Term Study
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	modified-intention-to-treat
NA	Not Applicable
NSAIDs	Non-steroidal anti-inflammatory Drugs
OA	Osteoarthritis
PBO	Placebo
PGI_2	Prostacyclin
PGADS	Patient Global Assessment of Disease Status
PGE_2	Prostaglandin E_2
PK	Pharmacokinetics

POB	Perforation, Obstruction, Bleeds
PPI	Proton Pump Inhibitor
PSUR	Periodic safety update report
PUB	Perforation, Obstructions, Ulcers, Bleeds
PYR	Patient-years at risk
QD	Every day
RA	Rheumatoid Arthritis
RR	Relative Risk
SAP	Statistical Analysis Plan
SE	Standard Error
SJS	Stevens-Johnson syndrome
SOP	Standard Operating Procedure
TXA_2	Thromboxane A_2
Tmax	Time to maximum plasma concentration
TXB_2	Thromboxane B_2
ULN	Upper limit of normal
U.S.	United States
VAS	Visual Analog Scale
VEC	Vascular Events Committee
WOMAC	Western Ontario and McMaster Osteoarthritis Index

Data Set Naming Conventions

Etoricoxib Development Program	18 Phase IIb/III chronic dosing studies (≥ 4 weeks) (Excluding MEDAL Program Studies) including studies in Osteoarthritis, Rheumatoid arthritis, Chronic low back pain, and ankylosing spondylitis (refer to Table 1).
OA Development Program	A subset of 11 studies from the Etoricoxib Development Program (refer to Table 1).
- Placebo-Controlled Population	OA Development Program - General Safety; Consists of the Placebo-Controlled portion (6-12 weeks) from 10 clinical studies (refer to Figure 3).
- 6-Month Population	OA Development Program - General Safety; 6-Month Active-Comparator-Controlled Population. Consists of 2 clinical studies comparing etoricoxib and celecoxib (refer to Figure 3).
- 1-Year Population	OA Development Program - General Safety; 1-Year Active-Comparator-Controlled Population. Consists of continuous data for 1 year from 3 clinical studies and included etoricoxib and naproxen data (refer to Figure 3).
MEDAL Program	MEDAL, EDGE II and EDGE Studies (refer to Table 1).

Executive Summary

1. Background

A variety of therapies are available for the treatment of pain in patients with osteoarthritis (OA). Despite this multitude of therapies, there is still an unmet medical need justifying new treatment options with unique profiles for patients and physicians to treat OA adequately. This unmet need is based on the variability in efficacy responses and tolerability by individual patients, and results in a large degree of dissatisfaction. Thus, there is a need for additional pharmacologic treatment options. The fact that therapies vary in their benefit-risk profiles and individual patients in their responses to these therapies, reinforces the need for careful selection of a therapy for each patient. The Unmet Needs and a summary of Existing Treatments options are provided in Sections 1.1 and 1.1.1, respectively.

Etoricoxib is a cyclooxygenase-2 (COX-2) selective inhibitor. Merck is seeking FDA approval for etoricoxib 30 and 60 mg once daily to treat the signs and symptoms of OA with 30 mg as the recommended initial dose.

Etoricoxib is currently approved in over 60 countries outside the United States with core therapeutic indications of OA (60 mg once daily), rheumatoid arthritis (RA) (90 mg), and acute gouty arthritis (120 mg). Etoricoxib is primarily marketed by Merck under the tradename ARCOXIA™. A marketing application to add a 30-mg dose for OA is currently under review in the European Union. In certain countries, indications are also approved for acute pain (120 mg), primary dysmenorrhea (120 mg), chronic low back pain (CLBP) (60 mg) and ankylosing spondylitis (AS) (90 mg). There have been an estimated 2.4 million patient-years of exposure with etoricoxib 60, 90, and 120 mg outside the United States since the product was first approved in 2001. The Regulatory Background is provided in Section 1.2.

The attached background document provides the Arthritis Advisory Committee an overview of the efficacy and safety of etoricoxib 30 and 60 mg once daily in the treatment of OA. Although this Executive Summary is prepared as a stand-alone document, it provides references to some tables/figures in the Background Package to support certain statements.

Efficacy data are reviewed from the placebo-controlled, Phase IIb dose-ranging study and 6 Phase III OA studies in which 30 mg (4 studies) and 60 mg (2 studies) were evaluated separately.

Safety data are organized and reviewed by domain (i.e., general safety, gastrointestinal [GI] safety, thrombotic cardiovascular [CV] safety, and renovascular safety) and are presented in the context of the following (sub)groups:

The OA Development Program consists of 11 Phase IIb/III studies that evaluated the efficacy and safety of etoricoxib in the treatment of OA. All studies were chronic dosing (≥4 weeks). Data from this set of studies are used to evaluate the general and renovascular safety of etoricoxib relative to placebo and non-steroidal anti-inflammatory

drug (NSAID) comparators in OA patients. The Etoricoxib Development Program augments the OA Development Program. It consists of the 11 studies that form the OA Development Program and 7 additional studies in either rheumatoid arthritis, ankylosing spondylitis, or chronic low back pain, all dosed chronically. Data from this set of studies are used to evaluate the upper GI and thrombotic CV safety of etoricoxib compared to placebo and traditional NSAID comparators, primarily naproxen.

The MEDAL Program consists of 3 studies: the Multinational Etoricoxib versus Diclofenac Arthritis Long-term study (MEDAL) (OA and RA patients), the Etoricoxib versus Diclofenac sodium Gastrointestinal tolerability and Effectiveness study (EDGE) (OA patients), and the EDGE II study (RA patients). This large CV outcomes study program was designed specifically to provide long-term thrombotic CV safety data for etoricoxib compared with diclofenac.

2. Pharmacokinetics, Bioavailability, and Pharmacodynamics (Section 2)

Etoricoxib has a unique bipyridine structure with a sulfone side chain and thus is not a sulfonamide. Following single oral doses, the pharmacokinetics of etoricoxib are dose proportional over the 5- to 500-mg range. Etoricoxib administered as a 120-mg tablet is well absorbed, with an estimated absolute bioavailability of 100%. Elimination occurs primarily through metabolism with the metabolites largely excreted renally. Etoricoxib is metabolized by multiple cytochrome P450 (CYP) enzymes and does not inhibit CYP3A4. The likelihood of drug-drug interactions with etoricoxib is low due to its route of elimination (see Section 2.2.5).In contrast to traditional NSAIDs, etoricoxib demonstrates no evidence of clinically relevant COX-1 inhibition in single-dose clinical studies at doses up to 500 mg or in multiple dose clinical studies up to 150 mg. In addition, at steady state and at single doses up to 500 mg as well as multiple doses up to 150 mg, etoricoxib did not affect bleeding time as measured by Ivy method indicating that etoricoxib has no effect on COX-1 mediated platelet function at therapeutic doses. Etoricoxib was shown to have no effect on the antiplatelet actions of low-dose aspirin in a clinical study described in Section 2.3.

3. Overview of Clinical Studies (Section 3)

In Section 3, Figure 1, provides a schematic of the studies included in programs outlined below and Table 1 provides a list of the studies and defines which are included in the evaluation of efficacy and in the evaluation of various safety domains. Design considerations for the Etoricoxib Development Program and the MEDAL Program are in Sections 3.2.1 and 3.2.2, respectively.

<u>OA Development Program</u>

The Phase IIb portion started with an initial dose-ranging study designed to identify the clinically effective dose range. The Phase III efficacy studies focused on etoricoxib 30 mg relative to placebo and ibuprofen 2400 mg, as well as placebo and celecoxib 200 mg, and on etoricoxib 60 mg relative to placebo and naproxen 1000 mg. General safety data,

including renovascular safety, were analyzed within 3 defined sets of data and consisted of the 6- to 12-Week Placebo-Controlled Population, and the 6-Month and 1-Year Active-Comparator-Controlled Populations (see Figure 3, Section 3.3.2.2). Altogether, there were ~2700 OA patients treated with etoricoxib in the OA Development Program.

Etoricoxib Development Program

The analyses of upper GI safety and thrombotic CV safety are based on pooled analyses of all chronic exposure studies in OA, RA, AS and CLBP (MEDAL Program studies excluded). The rationale for pooling these data is that these events are relatively rare, and therefore, the largest amount of data possible should be evaluated. The objective of the GI and thrombotic CV analyses was to compare etoricoxib (at doses of 30 to 120 mg) in Phase IIb/III chronic exposure studies with active-comparator NSAIDs (with the comparisons to naproxen being of key interest) and placebo across all indications. Upper GI safety and thrombotic CV safety were monitored (including independent adjudication of all potential events by expert panels).

MEDAL Program

The Medal Program (~17,400 patients on etoricoxib, mean study duration ~18 months) was designed to provide a non-inferiority analysis of thrombotic CV events for etoricoxib 60 or 90 mg in comparison to diclofenac 150 mg. The study design, including the choice of comparator, is justified by scientific and clinical rationales. Diclofenac is the world's most widely prescribed NSAID and thus represents a clinically relevant comparator. At the time MEDAL was designed and the choice of comparator was being made (2002), the Etoricoxib Development Program had already evaluated sufficient amounts of naproxen-controlled data to understand the emerging upper GI and thrombotic CV safety profile of etoricoxib in comparison to naproxen. It was important to gain further scientific insight into the comparison to other NSAIDs, and diclofenac was chosen for the reasons provided in Section 3.2.2.2. The enrolled OA and RA patients reflect a range of baseline thrombotic CV risk, including patients with cardiac risk factors as well as patients with known CV disease. Low-dose aspirin (LDA) for CV prophylaxis was recommended as per current treatment guidelines. Patients with a range of GI risks were included and the use of proton pump inhibitors (PPIs) or misoprostol was recommended per current guidelines in order to reduce the risk of upper GI complications. Baseline demographic for the MEDAL Program are in Table 7, Section 4.2.2.1.

4. Overview of Efficacy in OA (Section 5)

Once-daily treatment of OA of the knee and hip with etoricoxib 30 and 60 mg resulted in clinically meaningful improvements in joint pain, physical function, and in patient and physician global assessments. The efficacy of etoricoxib 30 mg was comparable to ibuprofen and celecoxib (Table 10, Section 5.3.2), while etoricoxib 60 mg was comparable to naproxen (Table 9, Section 5.3.1). The efficacy comparison between 30 and 60 mg demonstrated that etoricoxib 60 mg provided significantly greater treatment effects than etoricoxib 30 mg. The onset of action with etoricoxib 30 and 60 mg was

rapid with a duration lasting over the entire dosing interval. Treatment with etoricoxib 30 and 60 mg provided sustained efficacy for treatment periods for up to 1 year. The efficacy data supports the proposed dosing recommendation that 30 mg should be the initial dose and some patients may receive additional efficacy benefit from 60 mg.

5. Overview of Safety

General Safety (Section 6)

Etoricoxib 30 and 60 mg per day was generally well tolerated. Based on an evaluation of safety data pooled across all programs, the incidence of adverse experiences observed for etoricoxib 30 mg is lower than for etoricoxib 60 mg for some adverse experiences. The rates of overall mortality were not discernibly different between etoricoxib and the active comparators (Figure 8, Section 6.3.2.1.2). In the MEDAL Program, the rates of overall mortality were very similar for etoricoxib and diclofenac (Table 21, Section 6.3.2.2.2).

Gastrointestinal Safety and Tolerability (Section 7)

The occurrence of upper GI clinical events (perforations, obstructions, ulceration and bleeds) was evaluated from pooled data across all chronic exposure studies from the Etoricoxib Development Program and separately for the pooled MEDAL Program studies.

In the Etoricoxib Development Program, a significant reduction of 47% in the rate of upper GI events was observed with etoricoxib treatment relative to combined data for traditional NSAIDs (these results were mainly driven by comparisons to naproxen). (Table 26, Section 7.1.1).

Unlike many other studies of COX-2 inhibitors, the MEDAL Program studies did not restrict the use of LDA and gastroprotective agents such as PPIs. Despite these potential confounding factors, a significant reduction of 31% in the rate of overall upper GI clinical events was still observed compared to diclofenac (driven by the difference in ulcers). No significant difference was identified in the subset of complicated events (Table 27, Section 7.1.2). Importantly, the magnitude of the reduction observed in uncomplicated events for etoricoxib was the same whether or not patients took PPIs. Although a reduction in the GI event rate was also observed whether or not patients took concomitant LDA, the magnitude of the GI benefit may be partially diminished with LDA use, consistent with what has been observed in other large GI outcomes studies.

Lower GI safety refers to lower GI clinical events (i.e., small or large bowel perforations, obstructions, or bleeds). In the MEDAL Program, these events occurred at a numerically lower rate in the etoricoxib treatment group compared with the diclofenac treatment group, although the difference was not significant (Table 32, Section 7.3.1).

Etoricoxib showed similar incidences in mean changes in liver function tests (LFTs) to naproxen, ibuprofen, and celecoxib (Etoricoxib Development Program) while LFT-related discontinuations were lower with etoricoxib than with diclofenac (MEDAL Program). Table 33 and Table 34 in Section 7.4.2 provide the data for the predefined limits of change for LFTs for the MEDAL Program.

GI tolerability is an important factor in patient compliance, and therefore, determining whether a patient derives clinical benefit and pain relief from an NSAID. Upper GI symptoms (e.g., dyspepsia, abdominal pain, and nausea) are the most common side effects of NSAID use and are one of the primary reasons for discontinuation of an NSAID. Patients treated with etoricoxib were significantly less likely to discontinue treatment due to GI adverse experiences than those treated with traditional NSAIDs, based on data from the Etoricoxib Development Program and the MEDAL Program (Table 30, Section 7.2 and Table 31, Section 7.2.2).

Thrombotic Cardiovascular Safety (Section 8)

A CV Adjudication Standard Operating Procedure (SOP) has been used for both the Etoricoxib Development and MEDAL Programs. The SOP defines the following endpoints to assess thrombotic CV safety: Confirmed Thrombotic Events and the Antiplatelet Trialists' Collaboration (APTC) combined endpoint (Table 35). In addition, the endpoint of Confirmed Arterial Events was included in the MEDAL Program as events included in this category are of clinical interest.

In the Etoricoxib Development Program, etoricoxib was compared to placebo, non-naproxen-NSAIDs (diclofenac and ibuprofen), and naproxen. In tabulations of Confirmed Thrombotic Events, no discernible difference was observed for etoricoxib versus placebo; however, due to the limited duration (≤12 weeks), the limited patient-years of exposure, and the paucity of events accrued for this data set, no definitive conclusions can be drawn. There was no discernible difference in event rates between patients taking etoricoxib and traditional NSAIDs other than naproxen. Etoricoxib was associated with a numerically higher incidence of Confirmed Thrombotic Events than naproxen with a difference achieving statistical significance for the Confirmed APTC Combined Endpoint (Table 36, Section 8.1).

In the MEDAL Program, the primary noninferiority hypothesis was met. The point estimate for the relative risk (and 95% confidence intervals) of etoricoxib (60 and 90 mg) to diclofenac for thrombotic CV events was 0.95 (0.81, 1.11) (Table 40, Section 8.2.1). The thrombotic CV safety for etoricoxib and diclofenac was comparable across different statistical approaches, endpoints, studies, vascular beds (cardiovascular, cerebrovascular, and peripheral vascular), and patient populations (men and women, younger and older, with or without prior histories of symptomatic CV disease or risk factors, with or without LDA use, OA and RA patients). Results for subgroups of key interest are in Table 43, Section 8.2.3. The results are also consistent with the results of previous etoricoxib studies. Most importantly, the MEDAL Program analysis is based on far more data and is, therefore, more robust than previous datasets.

Renovascular Safety (Section 9)

To evaluate the renovascular safety of etoricoxib, the known mechanism-based adverse effects of NSAIDs were evaluated. The clinical impact of potential renovascular effects with etoricoxib was evaluated using prespecified composites of investigator-reported edema-related adverse experiences, congestive heart failure (CHF), and hypertension-related adverse

experiences. An SOP for adjudication of serious CHF adverse experiences has been used for the MEDAL Program only. The MEDAL Program also prespecified renal-related adverse experiences, a composite of clinical and laboratory adverse experiences.

The incidence of edema- and CHF for etoricoxib 30 mg was similar or less than the comparator NSAIDs, this incidence was similar for etoricoxib 60 mg and comparator NSAIDs. The incidence of discontinuations due to edema-related adverse experiences (a potential indicator of more severe adverse experiences) and CHF was low and generally similar across treatment groups. In the MEDAL Program, the absolute incidence of CHF was less than 1.1% in any treatment group. Data on edema-related and CHF adverse experiences for the Etoricoxib Development Program are in Table 45 and Table 46, Section 9.1.1 and for the MEDAL Program studies are in Table 47-Table 49, Section 9.1.2.

In the OA Development Program and the MEDAL Program, hypertension was a common baseline comorbidity; 36 to 52% and approximately 50% of the patients had a history of hypertension at baseline in each program, respectively. Etoricoxib is associated with a dose-related trend in hypertension-related adverse experiences with an incidence greater than placebo (Section 9.2.1, Table 50). For etoricoxib 30 mg, the incidence in hypertension-related adverse experiences was numerically lower than ibuprofen, similar to naproxen, and significantly higher than celecoxib. For etoricoxib 60 mg, this incidence was numerically lower than ibuprofen, numerically higher than naproxen, and significantly higher than diclofenac (Table 53 and Table 54, Section 9.2.2). Predefined limits of change for blood pressure were generally reflective of hypertension–related adverse experience findings and these data are in Table 51 and Table 52, Section 9.2.1 for the Etoricoxib Development Program and Table 55, Section 9.2.2 for the MEDAL Program studies.

In the MEDAL Program, the effects of etoricoxib 60 mg on systolic blood pressure were generally small across the study populations (maximum increase in mean systolic blood pressure of 1 to 2 mmHg versus screening values). Hypertension-related serious adverse experiences were rare. The incidence of discontinuations due to hypertension-related adverse experiences was <3% in any treatment group (<1% in the OA Development Program).

Evaluation of renal function based on predefined limits of change in serum creatinine indicated similar, generally small changes, similar to the comparator NSAIDs (Table 56 and Table 58, Section 9.3). Discontinuations due to renal-related adverse experiences, evaluated in the MEDAL Program studies were similarly low for etoricoxib and diclofenac (Table 57, Section 9.3.2).

Published Observational Data (Section 10)

The limited amount of published observational data for etoricoxib (3 studies) are outlined.

Post-Marketing Experience (Section 11)

Information regarding the use of etoricoxib from countries in which etoricoxib is approved is provided. Estimates of patient exposures by dose are included. No notable findings were observed.

Risk Management Plan (Section 12)

The risk management plan for etoricoxib is outlined. This plan includes aspects of risk assessment, communication, and management as well as continuous evaluation of risk. The risk management plan starts with a product circular consistent with the NSAID class template and with findings from clinical trials and postmarketing surveillance. The proposed product circular will restrict the use of the drug to the appropriate patient population. Postmarketing reports will be continuously monitored via our routine pharmacovigilance program with continued characterization of the safety profile in the postmarketing environment. An observational study of etoricoxib users has been conducted utilizing the General Practice Research Database (GPRD) database. In addition, a pregnancy registry will be operational in the United States. Plans are outlined for a drug utilization study or studies in the U.S. after product approval to understand the patient population for whom etoricoxib is being prescribed and how the 30 mg and 60 mg doses are being used in clinical practice. This approach will provide a surveillance mechanism to help ensure that dosing recommendations are being followed (i.e., the initial dose of etoricoxib of 30 mg). Merck intends to work closely with the FDA to finalize a risk management plan.

6. Benefit and Risk Assessment (Section 13)

6.1 Benefits

Efficacy

Etoricoxib is an effective COX-2 selective NSAID that would provide patients and physicians an additional treatment option in the management of OA. The efficacy of etoricoxib 30 mg is comparable to ibuprofen 2400 mg and celecoxib 200 mg. The efficacy of etoricoxib 60 mg has been shown to be greater than 30 mg in a study directly comparing the two doses. In other studies, etoricoxib 60 mg is comparable to naproxen. These data support the dosing recommendation of 30 mg as the initial dose, while some patients may receive additional efficacy benefit from 60 mg.

Improved GI Safety and Tolerability

Etoricoxib has a GI safety and tolerability profile consistent with COX-2 selective NSAIDs. This profile was established versus naproxen in the Etoricoxib Development Program based on upper GI clinical events, including a benefit in complicated clinical events. The MEDAL Program results support an upper GI safety advantage for etoricoxib versus another NSAID, diclofenac, based on a reduction in ulcers. The MEDAL program contains the first OA/RA studies with GI outcomes to allow PPI use. The fact that a benefit was maintained in patients on PPIs is an important finding given

the outstanding question of whether in high risk patients on a PPI who require NSAID therapy, there is additional benefit attained with the use of a COX-2 selective NSAID. The MEDAL data suggests the lowest GI risk strategy is a COX-2 selective inhibitor plus PPI rather than NSAID plus PPI.

Sulfonamide-Allergic Patients

As a non-sulfonamide agent, etoricoxib can be used safely in patients with sulfonamide allergies. Many hypersensitivity reactions, previously thought to be of immunologic origin, are now thought to be of non-immunologic origin and may be related to COX-1 inhibition suggesting a potential advantage to using COX-2 selective inhibitors such as etoricoxib as a safe treatment alternative in patients who cannot tolerate traditional non-selective NSAIDs.

Platelet Effects

Etoricoxib has no effect on COX-1 at therapeutic doses, providing analgesic and anti-inflammatory benefit without increasing the risk of bleedings due to inhibition of platelet COX-1. Thus therapy with etoricoxib, unlike traditional NSAIDs, does not need to be stopped prior to surgery due to potential bleeding risks. It should be noted that all NSAIDs are contraindicated for use immediately post-operatively for coronary artery bypass (CABG) surgery.

Metabolism

With a half-life of ~21 hours, etoricoxib can effectively be administered on a once-daily basis. The onset of efficacy was observed within the first 24 hours in patients with OA. Etoricoxib does not inhibit CYP3A4 and its metabolism is not affected by the genetic polymorphism associated with CYP2C9 unlike celecoxib, which is primarily metabolized by CYP2C9. The risk of etoricoxib interacting with other drugs is low.

6.2 Potential Risks

Thrombotic Cardiovascular Events

In the Etoricoxib Development Program, the use of naproxen 1000 mg was associated with an incidence of thrombotic CV events which was lower than with etoricoxib, whereas no discernible difference was observed between etoricoxib and non-naproxen NSAIDs (diclofenac, ibuprofen). The MEDAL Program showed comparable rates of thrombotic CV events for etoricoxib and diclofenac. When viewed in the context of published randomized clinical trials data for all COX-2 selective and traditional NSAIDs, these results are consistent with the current understanding of the thrombotic CV safety profile of traditional and COX-2 selective NSAIDs.

Renovascular Events

All NSAIDs are associated with dose-dependent, mechanism-based renovascular effects. Data from the OA Development Program indicate that etoricoxib use is associated with a dose-related trend in hypertension-related adverse experiences with an incidence greater

than placebo, but within the range of that observed for comparator NSAIDs, depending on the etoricoxib dose and the comparator studied. A difference was observed between etoricoxib 30 mg and celecoxib 200 mg but not between etoricoxib 30, 60 mg and naproxen 1000 mg or ibuprofen 2400 mg.

In the MEDAL Program studies, treatment with etoricoxib 60 mg was associated with a significantly higher incidence of discontinuations due to hypertension-related adverse experiences compared with diclofenac 150 mg. At the 60-mg dose, the incidence of edema-related adverse experiences or discontinuations due to these events and the incidence of CHF were similar for etoricoxib and diclofenac.

Blood pressure effects can be observed with all NSAIDs, including etoricoxib as the data show. These should be monitored for, as they can be managed clinically. Importantly, these effects are reversible upon cessation of therapy.

7. Summary

In clinical practice, the selection of an anti-inflammatory agent for a specific patient with OA, needs to take into consideration the individual's prior treatment history, their risk for GI and thrombotic CV events, as well as potential renovascular effects, GI tolerability profile, and the need for symptomatic relief. The MEDAL Program provides a robust amount of information to address the safety aspects of etoricoxib relative to diclofenac, and combined with the large amount of efficacy and safety data from the Etoricoxib Development Program, provides patients and practitioners information to help make informed decisions about their choice of treatment. Etoricoxib, at doses of 30 and 60 mg, provides a treatment option for OA with 1) comparable efficacy to traditional and COX-2 selective NSAIDs, 2) a superior GI safety and tolerability profile compared with traditional NSAIDs that is maintained with PPI use, and 3) an otherwise safety and tolerability profile that is consistent with that of traditional and COX-2 selective NSAIDs, providing an overall favorable benefit/risk relationship. The thrombotic CV safety profile is comparable to diclofenac, a widely used traditional NSAID. The renovascular effects of edema, CHF, and hypertension are dose related and, at the doses recommended for OA (30 and 60 mg), within the range of other NSAIDs. Finally, etoricoxib is dosed once daily, its efficacy is maintained throughout the dosing period and can be used safely in patients with sulfonamide allergies. Therefore, with appropriate labeling etoricoxib should be an option for the treatment of OA.

1. Introduction

Etoricoxib is a cyclooxygenase-2 (COX-2) selective inhibitor under review by the Food and Drug Administration (FDA). Merck is currently seeking approval for etoricoxib 30 mg and 60 mg once daily for the treatment of the signs and symptoms of osteoarthritis (OA). This background document provides the Arthritis Advisory Committee an overview of the efficacy and safety of etoricoxib in the treatment of OA. The data presented include comparisons to commonly used NSAIDs and placebo. Safety data from studies performed in chronic conditions other than osteoarthritis are included where appropriate. These additional data are primarily the rheumatoid arthritis (RA) safety data from the MEDAL Program. In total, the data presented provide a comprehensive evaluation of efficacy and safety for etoricoxib with significant long-term treatment exposure.

1.1 Unmet Medical Need

Osteoarthritis (OA) is broadly described as an age-related, dynamic reaction of a joint to insult or injury [3]. OA represents a heterogeneous group of conditions sharing common pathogenic, diagnostic, and radiologic features, and has acute and chronic components with variable triggers. As the most common joint disorder, OA is a worldwide public health concern, estimated to affect ~21 million people in the United States in 1998 [4] and to be steadily increasing in prevalence. OA is second only to ischemic heart disease as a cause of disability in men over 50 years of age [3]. Given the large population affected by OA, the economic burden of this disease is great, both from direct medical expenses as well as through indirect effects such as lost wages, which can account for ~75% of the total cost of the disease [5]. Pharmacologic agents to treat the symptoms of OA include acetaminophen, opioids (including the synthetic opioid tramadol), NSAIDs (including COX-2 selective inhibitors), and intra-articular injections (e.g., glucocorticoids and hyaluronates) [6; 7; 8; 9]. Despite the widespread use of nutriceuticals (chondroitin and glucosamine), there is controversy about the ability of these agents to improve pain and swelling. Treatment in extreme cases can require surgery including joint lavage, osteotomy, and total joint arthroplasty [8]. As the elderly population continues to grow in the United States and other developed countries, OA is, and will continue to be, an increasingly prominent health care issue [10; 11; 12]. The chronic joint destruction in OA leads to chronic pain, and there are currently no therapies proven to induce remission of OA. Successful management of pain, the most frequent and prominent symptom, is the primary goal of drug therapy [13].

1.1.1 Summary of Treatments

Existing Treatments

Nonpharmacologic therapy is viewed as an important component of OA management and includes patient education, physical or occupational therapy as well as weight loss programs for overweight individuals [14; 15; 7]. Pharmacologic therapy, however, is used by most patients who do not achieve adequate results with only nonpharmacologic methods [16]. Current American College of Rheumatology guidelines for the management of OA

pain propose a step-wise approach beginning with nonpharmacologic therapy [17]. Acetaminophen is recommended as the initial pharmacologic therapy for mild symptoms, followed by a traditional or COX-2 selective NSAID. Opiates can be used with patients in whom NSAIDs are either contraindicated, not effective and/or poorly tolerated. In patients with increased gastrointestinal (GI) risk for whom an NSAID is recommended, use of a COX-2 selective inhibitor or a traditional NSAID plus a gastroprotective agent (proton pump inhibitor or misoprostol) is currently recommended [17]. Below is a discussion of key safety issues relevant to the existing pharmacologic therapies for the treatment of symptomatic OA.

1.1.1.1 Non-NSAID Treatments

Acetaminophen, at doses as high as 3000 mg per day, is effective for some patients and is generally well tolerated. For many patients with more than mild OA pain, acetaminophen may not provide adequate symptom relief [18; 19; 20; 21]. High doses of acetaminophen are associated with liver failure [22], and guidelines recommend ≤ 4 gm/day if used [17]. Data suggest that acetaminophen use may be associated with other GI side effects such as dyspepsia symptoms [23; 24; 25] and epidemiologic data suggest that use of acetaminophen is associated with an increased incidence of hypertension [26; 27]. Acetaminophen use, like NSAID use, has also been associated with inhibition of prostacyclin [25], a prostanoid involved in hemostasis and thought to play a role in gastric protection as well as renal function. Clinical data describing the long-term thrombotic CV safety of acetaminophen are not available.

Opiates (including centrally acting synthetic opioid agents such as tramadol) are indicated for short-term pain management, however, their use to treat chronic pain, including OA pain, has increased over the past several years [28] (IMS Health, LRX May 2004 - Nov 2006). Some of this increased opioid use is likely due to the availability of controlled release formulations that lessen side effects such as sedation. The observed increase in opioid use may also be due to rising safety concerns with other OA therapies, including the NSAID class of traditional and COX-2 selective agents. Opiate use is associated with GI and central nervous system (CNS) side effects such as constipation, nausea, vomiting, and sedation. The addictive potential of opiates is of great concern. In addition, the increased use of opiates has been associated with an increase in overdoses and deaths, even when these agents are used at prescribed doses [28]. Tolerance is also a problem experienced by many patients requiring chronic opiate therapy and can limit the course of treatment [29].

1.1.1.2 NSAID Treatments Including COX-2 Selective Inhibitors

NSAIDs are the therapies of choice for many OA patients suffering from daily moderate to severe pain [19; 20], and have been estimated to be used by ~13 million patients in the U.S. for the treatment of OA and RA on a regular basis [30]. For some patients, other available pharmacologic options offer either insufficient efficacy [18] or, unacceptable safety and tolerability [28]. A recent review of clinical data shows that better symptomatic relief, especially in patients with moderate to severe OA pain, is achieved with NSAIDs versus analgesics such as acetaminophen [21].

GI Safety and Tolerability

Although widely used, traditional NSAIDs are commonly associated with GI toxicity [31] ranging from GI symptoms that cause patients to discontinue therapy (e.g., dyspepsia, abdominal pain, and nausea) to more serious upper GI clinical events (perforation, obstruction, bleeding, or ulcer; PUBs) that require additional medical attention [32]. Dyspepsia is the most common adverse experience that results in discontinuation of NSAID use [33], while serious GI complications were estimated to be responsible for over 100,000 hospitalizations and 16,500 deaths in the United States based on a 1999 study [30]. Inhibition of prostaglandin synthesis within the GI mucosa plays a predominant role in the pathogenesis of NSAID-induced GI gastropathy [34; 35; 36; 37], particularly upper GI clinical events (i.e., GI ulceration, obstruction, perforation and/or bleeding). NSAID gastropathy is considered one of the most common serious (and life threatening) adverse drug events among patients in industrialized nations [30; 38].

COX-2 selective inhibitors were developed to provide efficacy comparable to traditional NSAIDs but with an improved GI safety profile. GI outcomes trials have compared rates of upper GI clinical events on COX-2 selective inhibitors versus traditional NSAIDs [39; 40; 41; 42] with a clear benefit shown for COX-2 selective inhibitors in two of these trials, and results consistent with this demonstrated benefit in a third trial of 12-weeks duration. These data are supported by an extensive amount of endoscopy data comparing COX-2 selective NSAIDs to traditional NSAIDs. Data also suggest that the magnitude of GI risk for individual COX-2 selective inhibitors (and thus the risk reduction versus traditional NSAIDs) will vary somewhat between agents and by dose.

An important clinical question is what the relative effect of a COX-2 selective inhibitor is versus a traditional NSAID in the setting of GPA use (i.e., PPIs). Prior to the MEDAL Program, no clinical trial has addressed the relative risk of GI clinical events with COX-2 selective inhibitors versus traditional NSAIDs in the setting of GI co-therapy. Specifically, none of the large GI outcomes studies has allowed the use of PPIs and therefore no prospectively collected data exist for GI safety in the context of PPI use.

Another important clinical question is whether concomitant low-dose aspirin mitigates the GI benefit of COX-2 selective inhibitors. Data from endoscopic trials indicate that a COX-2 selective inhibitor plus low-dose aspirin has a mucosal injury incidence and an ulcer incidence that is lower than with a traditional NSAID plus low-dose aspirin [43; 44]. An observational cohort study also reported a significantly lower rate of upper GI complications with COX-2 selective NSAIDs than with traditional NSAIDs among low-dose aspirin users [45]. However, subgroup analyses from randomized outcomes trials of COX-2 selective inhibitors (lumiracoxib and celecoxib) versus traditional NSAIDs have not identified significant reductions in upper GI clinical events in patients taking low-dose aspirin [46; 47; 42].

GI tolerability is a measure of GI symptoms (e.g., abdominal pain, dyspepsia, and nausea), which may be sufficiently severe to result in discontinuation of treatment. In addition to frequently necessitating discontinuation of NSAID therapy, GI intolerance

can trigger expensive evaluations and treatments. In an elderly population studied, upper GI symptoms and prescriptions for GI protective drugs were higher in users of traditional NSAIDs than users of COX-2 selective inhibitors [48]. Although symptoms like dyspepsia are often dismissed as being of less clinical significance than GI bleeds, they are responsible for a significant portion of the clinical burden (and associated health care resource utilization) of non-selective NSAIDs [49; 50]. Dyspepsia symptoms, for example, were reported weekly in up to ~30% of patients who were regular users of NSAIDs [51] and these symptoms are the most common reason for discontinuation of NSAID therapy [33].

Lower GI clinical events associated with NSAID use have also become an area of interest. However, to date no studies (including epidemiologic) have been conducted to show that non-selective NSAIDs are associated with an increased risk over COX-2 selective inhibitors for lower GI events including bleeding, perforation, obstruction, ulcerations, and symptomatic diverticular disease. The benefit of a COX-2 selective inhibitor over a traditional NSAID was shown in a post-hoc analysis of a large GI outcomes study [52], but has not been shown in a prospectively designed trial.

Thrombotic CV Safety

COX-2 inhibitors were developed to decrease the risk of GI injury of traditional NSAIDs due to their lack of inhibition of COX-1. However, safety concerns have emerged for COX-2 selective inhibitors due to an increased risk of thrombotic CV events observed in placebo-controlled trials for 3 different COX-2 selective inhibitors [53; 54; 55]. Long-term, placebo-controlled trials in patients with arthritis assessing the thrombotic CV risk of traditional NSAIDs are not available. In addition, clinical trials directly comparing the risk of thrombotic CV events of traditional NSAIDs to COX-2 selective inhibitors have been limited to approximately one year of drug exposure [47]. Thus, the risk of traditional NSAIDs is not clearly understood. Several lines of evidence suggest that most traditional NSAIDs are associated with increased thrombotic CV risk compared with placebo. Recently, a meta-analysis of all randomized controlled trials of COX-2 inhibitors and traditional NSAIDs or placebo showed that a difference in thrombotic CV risk between traditional NSAIDs and COX-2 selective inhibitors could not be distinguished, with the exception of naproxen [56]. Two meta-analyses of observational studies and a recent observational cohort study have also shown an increased risk associated with both traditional NSAIDs and COX-2 selective inhibitors compared with non-use [57; 58; 59]. These data indicate that any thrombotic CV risk observed versus placebo for several COX-2 selective inhibitors also likely extends to some commonly used traditional NSAIDs.

In 2005, following a review of currently available data from long-term controlled clinical trials, the U.S. Food and Drug Administration concluded that the data “do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than traditional NSAIDs” [60]. In addition, they concluded that all non-selective NSAIDs, except aspirin, may carry an increased risk of cardiovascular events

following long-term use and that this should be stated in their product labels [61]. Product labeling for COX-2 inhibitors and non-selective NSAIDs now includes boxed warnings regarding CV and GI risk [61].

The etiology for the increased thrombotic CV risk seen in the long-term clinical trials involving COX-2 selective inhibitors versus placebo is not fully understood. Cyclooxygenase and its prostanoid products have important roles in both inflammation and hemostasis. It is thought that COX-mediated hemostatic effects are primarily mediated by 2 prostanoids, thromboxane A2 (TXA2) and prostacyclin (PGI2). The biology of thromboxane and prostacyclin is complex, and the thrombotic CV effects of NSAIDS (both COX-2 selective and traditional) and aspirin are areas of ongoing scientific investigation. Prostacyclin is a prostanoid that acts as a restraint on mediators of platelet activation, hypertension, and atherogenesis [62]. Mediators include thromboxane A2 which is generated by COX-1 in the platelet. Suppression of prostacyclin represents one explanation for the CV hazard from NSAIDs that has been offered [62]. Alternative hypotheses have been suggested [63; 64; 65; 66; 67]; however, to date, the underlying mechanism has not been determined.

Renovascular Safety

Both traditional NSAIDs and COX-2 selective inhibitors can be associated with mechanism-based, dose-related, renovascular effects. These include salt and fluid retention leading to edema and CHF as well as increases in blood pressure and worsening renal function [68; 69; 65]. These renovascular effects can often occur within a week of initiating therapy, but can also develop later during the course of therapy and can persist while the patient remains on NSAID treatment [68]. These effects, on average, are small and are reversible but may be significant for certain patients, for example, those with pre-existing hypertension. These dose-related effects appear to be generally similar for non-selective NSAIDs and COX-2 selective inhibitors. Some differences between agents have been reported, but the data have been difficult to interpret, as equipotent doses have not always been compared [70].

In rare cases, traditional NSAIDs and COX-2 selective inhibitors may also be associated with renal toxicity such as renal failure or interstitial nephritis. Susceptible patients include those with compromised effective intravascular volume, as occurs in volume depletion, congestive heart failure, or cirrhosis, as well as patients with renal insufficiency who depend on high angiotensin levels for maintenance of glomerular filtration.

Hypersensitivity Reactions

All NSAIDs have been shown to induce hypersensitivity reactions, and cross reactivity with other members of the NSAID class has been observed [71; 72; 73; 74; 75; 76]. The pathogenesis of hypersensitivity reactions is poorly understood but is generally categorized as immunologic versus non-immunologic reactions. However, there are cutaneous reactions, such as urticaria and angioedema, which can be due to an anaphylactic (immunologic) as well as an anaphylactoid (non-immunologic) reaction. Recent studies have provided evidence that COX-2 selective inhibitors are generally

well tolerated in individuals who exhibit cutaneous reactions to traditional NSAIDs, although a small percentage of patients who have cutaneous reactions with traditional NSAIDs may still be at risk for experiencing cutaneous reactions with COX-2 selective inhibitors [77; 71; 76]. While it has been shown that the inhibition of COX-1 may play an important role in non-immunologic hypersensitivity to traditional NSAIDs, it should be noted that the reactions due to immunologic mechanisms may still occur independent of COX-1 inhibition.

Serious skin reactions including Stevens-Johnson-Syndrome (SJS) are known side effects of traditional NSAIDs and have been observed with selective COX-2 inhibitors [78]. Drug-related serious skin reactions are thought to be the result from immune-mediated tissue injury, not to inhibition of cyclooxygenases. Differences in the rates are more closely associated with the structural class of the NSAIDs than with functional class. The differences between molecules appear to reflect different immunogenicity which, in turn is likely due to differences in chemical structures and/or differences in propensity for chemical reactivity with host proteins.

Inhibition of COX-1 has also been shown to be involved in the pathogenesis of aspirin-induced asthma. In some asthma patients, aspirin and non-selective NSAIDs can trigger bronchoconstriction that may lead to exacerbation of asthma. Several studies have demonstrated that asthmatic patients with aspirin intolerance who were administered different COX-2 selective inhibitors exhibited no pulmonary clinical symptoms [72; 79; 80]. The suspected mechanism is non-immunologic and appears to be related to a COX-1 mechanism.

Hepatic Reactions

NSAIDs have been associated with hepatic side effects ranging from mild, asymptomatic elevations in aminotransferases to more significant parenchymal disease. Hepatic effects appear to be associated with certain agents within the class rather than considered as a class-wide effect. Most notable are the elevations in aminotransferases associated with diclofenac [81; 82].

Patient Response and Switching with NSAIDs

It is a well known clinical observation that individual patient responses to NSAIDs (both traditional and COX-2 selective) are variable. This may be related to individual variability in plasma drug concentrations or pharmacodynamic responses [83], although the reasons are not well understood. Nonetheless, patients commonly switch between NSAID therapies due to inconsistent efficacy at the individual patient level [84; 85]. This is highlighted by data showing that within the NSAID class approximately 40% of patients are dissatisfied with the treatment options (Data extracted from: Consumer Health Sciences.NATIONAL HEALTH AND WELLNESS SURVEY, 2005 [USA]. Princeton, NJ.); inadequate efficacy is cited as the primary reason for dissatisfaction [86; 87].

Switching from COX-2 selective inhibitors is observed less frequently than with traditional NSAIDs [88; 89; 90; 91; 92; 93]. It is unclear whether this reflects improved tolerability, efficacy, or the lack of alternative therapies that provide similar benefit-to-risk considerations. It has been suggested that the decrease in switching from COX-2 selective inhibitors may be related to greater patient satisfaction, improved efficacy [91], and GI tolerability [51; 94]. The primary benefit of the class of COX-2 selective inhibitors over traditional NSAIDs is their improved GI safety and tolerability profile [40; 95; 96; 97; 98]. Thus, switching patterns may likely reflect this benefit. Decreased switching rates for COX-2 selective inhibitors translates into an increased effectiveness and underscores the need for additional agents in this class as currently celecoxib is the only COX-2 selective inhibitor approved for use in the United States. Although switching was found to be less frequent with this class of agents it still occurred [88; 89; 90] and clinical trials data indicate that, similar to traditional NSAIDs, not all patients achieve adequate efficacy or acceptable tolerability with celecoxib [99]. These data highlight the importance not only to have a variety of nonselective NSAIDs available, but also COX-2 selective agents for patients who are in need of efficacious therapies with improved GI safety. In fact, data show that patients who were previously taking the two COX-2 inhibitors that were taken off the market were twice as likely to switch to opiates after those products were withdrawn as patients taking traditional NSAIDs who switched their medications. These data may suggest that limited choices in the COX-2 class of NSAIDs may result in patients using more opiates (IMS Health, LRX, May 2004 and Aug 2005). Treating pain adequately, particularly chronic pain, is not simply a matter of convenience as data from placebo–controlled trials show that unmanaged pain significantly impairs quality of life [100; 101; 102]. In fact, data also show that the quality of life for people who suffer from chronic musculoskeletal pain, including OA, is lower than that of people who suffer from most other chronic conditions including cancer and heart disease. This reduced quality of life seen with chronic musculoskeletal pain appears to be attributable to bodily pain and reduced physical functioning [103]. Pain and reduced physical functioning from OA results in a large loss of productivity; the overall cost of lost productive work time in the U.S. was estimated at ~7.11 billion dollars in 2005 [104].

In summary, there are a variety of therapies available for the treatment of chronic pain in patients with OA. These therapies vary in the benefit-risk profile reinforcing the need for careful selection of therapy for each individual patient. Despite the multitude of therapies, there is still an unmet medical need for new treatment options with unique profiles for patients and physicians to adequately treat OA given the benefit-risk profiles of available treatment options and considering the individual patient response to available therapies.

1.1.2 Proposed New Treatment - Etoricoxib

Etoricoxib, a COX-2 selective inhibitor, has demonstrated efficacy comparable to high doses of NSAIDs in the treatment of symptomatic OA. Etoricoxib is approved for the treatment of OA (as well as other indications) in greater than 60 countries worldwide.

Etoricoxib 60 mg has been shown to have efficacy in OA comparable to total daily doses of naproxen 1000 mg; etoricoxib 30 mg has been shown to have efficacy in OA comparable to total daily doses of ibuprofen 2400 mg and celecoxib 200 mg. Once-daily treatment with etoricoxib provides significant efficacy in the treatment of OA within the first day of dosing, as well as a sustained treatment effect over the 24-hour dosing interval.

Etoricoxib has been shown to have a superior GI safety and tolerability profile versus traditional NSAIDs, primarily naproxen and diclofenac. The thrombotic CV safety profile of etoricoxib has been well characterized; in comparison to naproxen in the Etoricoxib Development Program, and to diclofenac in the MEDAL Program. In the Etoricoxib Development Program, naproxen was associated with a lower thrombotic CV risk than etoricoxib, consistent with a recent meta-analysis which revealed naproxen as exhibiting a lower risk of thrombotic CV events compared with other NSAIDs [56]. Given the data in comparison to naproxen from the Etoricoxib Development Program, the MEDAL Program was designed to assess thrombotic CV safety of a COX-2 inhibitor compared with a different traditional NSAID: diclofenac, the most widely prescribed NSAID in the world (Data extracted for worldwide NSAID use from: IMS Health, IMS MIDAS(r), 1Q2006). In the MEDAL Program etoricoxib had a comparable thrombotic CV safety profile to that of diclofenac. The renovascular safety profile is consistent with that of NSAIDs, in showing mechanism-based, dose-dependent, reversible side effects including edema, CHF and hypertension. Etoricoxib (30 and 60 mg) has a positive benefit-risk profile consistent with the range of other approved agents. Its specific characteristics include once daily dosing, a non-sulfonamide structure, comparable efficacy to high doses of NSAIDs and an improved GI safety and tolerability profile relative to traditional NSAIDs. Importantly, etoricoxib has shown a benefit compared to diclofenac in patients taking concomitant PPIs. This has never been shown previously and suggests that further GI risk reduction is possible with etoricoxib as compared to a traditional NSAID in the setting of PPI use, of particular importance to patients at high GI risk. These data support that etoricoxib is a valuable additional treatment option for patients with OA and with labeling consistent with other agents, should be an available OA therapy.

1.2 Regulatory Background

The initial IND for etoricoxib was filed with the FDA in 1997. Since then, the clinical safety and efficacy of etoricoxib have been studied for treatment of osteoarthritis (OA), rheumatoid arthritis (RA), acute gouty arthritis, ankylosing spondylitis (AS), acute dental pain, chronic low back pain (CLBP), and dysmenorrhea. In 2002, Merck started the MEDAL Program, consisting of three longer-term clinical studies designed to be pooled for a further assessment of the thrombotic cardiovascular safety profile of etoricoxib. A total of approximately 34700 patients (~24900 OA and ~9780 RA patients) participated in the MEDAL Program studies, with average treatment duration of 18 months (ranging from 0.3 to 42.3 months) on either etoricoxib or diclofenac. In completed clinical studies under the IND, ~24600 patients and subjects have been treated with etoricoxib.

Merck initiated an NDA (NDA 21-389), in 2001 and 2003, that proposed the registration of etoricoxib for symptomatic treatment of osteoarthritis (OA), rheumatoid arthritis (RA), acute gouty arthritis, ankylosing spondylitis (AS) (not included in the 2001 NDA), chronic low back pain (CLBP), acute pain in adults, and primary dysmenorrhea. The proposed doses of etoricoxib varied by indication within the range of 60 to 120 mg per day. In 2004, Merck filed a second NDA (NDA 21-772) to add a 30 mg dose for the OA indication. The FDA issued approvable letters for these NDA applications in 2004 and 2005, respectively, that made several requests for additional efficacy and safety data that would be required before an approval could be granted.

The FDA conducted an Advisory Committee Meeting in February 2005 to discuss overall benefit to risk considerations (including CV and GI safety concerns) for non-selective NSAIDS and COX-2 selective drugs. The relevant data for etoricoxib available at that time was reviewed along with other drugs in the class during this meeting. In an April 2005 memo summarizing its conclusions of the Advisory Committee discussions and additional data review, the FDA stated, "it is not possible to conclude at this point that the COX-2 selective drugs confer an increased [CV] risk over non-selective NSAIDs in chronic use….We believe that it is reasonable to conclude that there is a 'class effect' for increased CV risk for all NSAIDs pending the availability of data from long-term controlled clinical trials that more clearly delineate the true relationships." In June 2005, the FDA published the mandatory template labeling for all prescription NSAIDs (both selective and non-selective) with a boxed warning to highlight the CV and GI risk for this class.

Merck submitted a response to the FDA approvable letters for NDA 21-389 and NDA 21-772 in October 2006, after completion of additional OA clinical studies and the MEDAL Program studies. With this submission, Merck provided additional safety and efficacy data as requested by the FDA and a comprehensive summary of the safety and efficacy profile to support the proposed doses of etoricoxib 30 or 60 mg once daily for symptomatic treatment of OA, with 30 mg as the recommended initial dose. The clinical information included in the submission is summarized in this Briefing Document. Based on the FDA guidance for NSAIDs, Merck has also incorporated the template labeling with the boxed warning and proposed a comprehensive Risk Management Plan. Merck will consider pursuing the other treatment indications proposed in the original NDA filing subsequent to the approval for treatment of OA.

Outside the United States, etoricoxib is currently approved in over 60 countries including most European Union (EU) Member States, with core therapeutic indications of osteoarthritis (60 mg once daily), rheumatoid arthritis (RA) (90 mg once daily), and acute gouty arthritis (120 mg once daily for the acute symptomatic period). In certain countries, indications are also approved for acute pain (120 mg once daily for the acute symptomatic period), primary dysmenorrhea (120 mg once daily for the acute symptomatic period), chronic low back pain (CLBP) (60 mg once daily) and ankylosing spondylitis (AS) (90 mg once daily). Merck has recently filed market applications to add a 30 mg dose for OA. Since 2002, there has been an estimated total of over 2.4 million

patient-year treatment experience for treatment with etoricoxib in these countries. The safety profile of etoricoxib, as assessed by the post-marketing experience in these countries where etoricoxib has market authorization, is consistent with the current knowledge of the safety profile of NSAIDs more generally. Based on an EU referral review in 2005, the Committee for Medicinal Products for Human Use (CHMP) concluded that the balance of benefit to risk remained positive for the approved indications for etoricoxib.

2. Etoricoxib Human Pharmacokinetics, Bioavailability, and Pharmacodynamics

This section summarizes significant pharmacokinetic, biopharmaceutic, and pharmacodynamic results obtained from clinical studies with etoricoxib.

2.1 Chemistry and Dosage Forms of Etoricoxib

The compound 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine, referred to as etoricoxib, is a selective inhibitor of the COX-2 enzyme. The proposed market formulations for etoricoxib are 30- and 60-mg film-coated tablets. The different dose-strength tablets are proportionally formulated and contain 30% active ingredient by weight.

2.2 Pharmacokinetics and Biopharmaceutics in Humans

2.2.1 Metabolism and Excretion of Etoricoxib in Humans

The elimination of etoricoxib occurs primarily through metabolism, with the metabolites largely excreted renally. The main pathway of metabolism for etoricoxib involves the 6'-methyl hydroxylation of etoricoxib. This reaction is catalyzed by CYP3A4 (~60%), CYP2D6, CYP2C9, CYP2C19, and CYP1A2.

2.2.2 Oral Pharmacokinetics

Following single oral doses, the pharmacokinetics of etoricoxib are dose proportional over the 5- to 500-mg range. Etoricoxib administered as the 120-mg tablet is well absorbed, with an estimated absolute bioavailability of 100%. A high-fat meal decreases the rate, without affecting the extent of absorption of etoricoxib. Antacids have only a minimal, clinically insignificant effect on the absorption of etoricoxib.

2.2.3 Pharmacokinetics in Special Populations

The pharmacokinetics of etoricoxib are similar among races (Blacks, Hispanics, and Whites), between men and women, and between the young and elderly.

Neither renal insufficiency nor hemodialysis has a clinically meaningful effect on the pharmacokinetics of etoricoxib.

Mild hepatic insufficiency has no clinically important effect on the pharmacokinetics of etoricoxib following single oral/intravenous doses or multiple oral doses. Because clearance of etoricoxib is decreased with increasing hepatic impairment, a chronic dose of 60 mg once daily should not be exceeded in patients with mild hepatic insufficiency and a chronic dose of 60 mg every other day should not be exceeded in patients with moderate hepatic insufficiency.

2.2.4 Studies of Metabolic Interactions Mediated by Cytochrome P450

Inhibition of CYP3A activity by ketoconazole had no clinically meaningful effect on the pharmacokinetics of etoricoxib. On average, etoricoxib AUC was increased by 43% during ketoconazole treatment.

Induction of metabolism (including CYP3A and other enzyme activities) by rifampin reduced, to a clinically meaningful extent, the systemic exposure of etoricoxib. On average, etoricoxib AUC was decreased by 65% during rifampin treatment.

The effect of etoricoxib on hepatic CYP3A activity was evaluated using the erythromycin breath test (EBT) and at 120 mg/day had no important effect on hepatic CYP3A activity.

2.2.5 Drug Interaction Studies

The potential for interactions with etoricoxib was investigated for those drugs that might be used concomitantly in the intended target populations. Interactions with the following concomitant drugs were noted.

Oral Contraceptives. Etoricoxib 60 mg once daily, coadministered with an oral contraceptive in the morning, increases the $AUC_{(0\text{-}24\ hr)}$ and C_{max} of ethinyl estradiol by 37% and 54%, respectively. Etoricoxib 60 mg once daily has no clinically meaningful effect on serum norethindrone concentrations. The change in exposure to ethinyl estradiol will not compromise the contraceptive efficacy of the oral contraceptive but should be considered when selecting an appropriate oral contraceptive for use with etoricoxib.

Hormone Replacement Therapy (HRT). Administration of etoricoxib 120 mg with HRT consisting of conjugated estrogens (0.625 mg PREMARIN™) for 28 days increases the mean steady-state $AUC_{0\text{-}24\ hr}$ of unconjugated estrone, equilin, and 17β-estradiol by approximately 41%, 76%, and 22%, respectively. The effects of etoricoxib 120 mg on the pharmacokinetics of these estrogenic components of PREMARIN™ are less than half of those observed when PREMARIN™ is administered alone and the dose is increased from 0.625 to 1.25 mg. The clinical significance of these increases is unknown. These increases in estrogenic concentration should be taken into consideration when selecting postmenopausal HRT for use with etoricoxib.

Warfarin. The steady-state prothrombin time ($Average_{24\ hr}$ INR) increases modestly (by approximately 13%) during chronic coadministration of warfarin with once-daily 120 mg etoricoxib. Although this is unlikely to be clinically important in most patients, monitoring of the prothrombin time INR should be considered when therapy with etoricoxib is initiated in patients on a stable warfarin regimen.

2.3 Pharmacodynamic Studies

Etoricoxib was evaluated along with other COX-2 selective and traditional NSAIDs to assess relative effects on COX-1 and COX-2, effects on platelet function, effects on the potential to inhibit antiplatelet effects of aspirin, and effects on sodium excretion.

COX-1 inhibition

In single- and multiple-dose clinical studies at therapeutic doses (up to 500 mg), etoricoxib demonstrated no evidence of clinically relevant COX-1 inhibition in contrast to other traditional NSAIDs, including diclofenac. In addition, at steady-state and at single doses up to 500 mg as well as multiple doses up to 150 mg, etoricoxib did not affect bleeding time as measured by Ivy method indicating that etoricoxib has no effect on COX-1 mediated platelet function at therapeutic doses.

Aspirin Interaction

Some non-selective NSAIDs, like ibuprofen and naproxen [105], interfere with COX-1 inhibition of low-dose aspirin and thus may interfere with the clinical effectiveness of low-dose aspirin for cardioprophylaxis, although this has never been proven in an appropriately designed trial. In a parallel-group study of 120 mg etoricoxib or placebo (N=10 per group) given for 12 days, on Days 6 through 12, 81-mg aspirin was given concomitantly. After 7 days of concurrent therapy, 120 mg etoricoxib once daily had no effect on the antiplatelet actions of low-dose aspirin based on the inhibition of TXB_2 generation and platelet aggregation by the aspirin.

Sodium Excretion Study

A 2-week, parallel group study (22 subjects) compared the effects of etoricoxib 90 mg once daily, celecoxib 200 mg twice daily, naproxen 500 mg twice daily and placebo on sodium excretion, ambulatory blood pressure, body weight, creatinine clearance, serum electrolytes, and urinary excretion of prostanoids (reflecting the systemic synthesis of prostacyclin and thromboxane) in generally healthy elderly subjects (60 to 81 years of age). All active treatments decreased urinary sodium excretion over the first 72 hours; etoricoxib and celecoxib showed similar effects on this parameter. There were no clinically meaningful differences in daily urinary sodium excretion during the 2 weeks of treatment between etoricoxib, celecoxib, and naproxen.

All active comparators showed an increase relative to placebo with respect to systolic blood pressure. Etoricoxib was associated with a moderate increase at Day 14 when compared to celecoxib and naproxen; change from baseline in ambulatory blood pressure averaged over a 24-hour period of 7.7 mmHg for etoricoxib versus 2.4 mmHg for celecoxib and 3.6 mmHg for naproxen. For diastolic blood pressure the differences from baseline were also somewhat greater for etoricoxib than with celecoxib and naproxen but of lesser magnitude; change from baseline of 3.2 mmHg for etoricoxib versus 1.1 mmHg for celecoxib and 1.4 mmHg for naproxen.

Only naproxen was associated with a substantial decrease (~85%) in urinary excretion of the thromboxane A_2 metabolite. All 3 active treatments were associated with substantial reductions in urinary metabolite of prostacyclin (PGI-M), though naproxen decreased urinary excretion of PGI-M (~73%) to a greater extent than the COX-2 selective inhibitors (~60%).

3. Overview of Clinical Studies

3.1 Introduction

The 2 major sets of data that will be presented are the OA Development Program and the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Program.

The OA Development Program is defined by 11 Phase IIb/III clinical studies designed to evaluate the efficacy and safety of etoricoxib in the treatment of osteoarthritis (OA), the indication being sought in the current application.

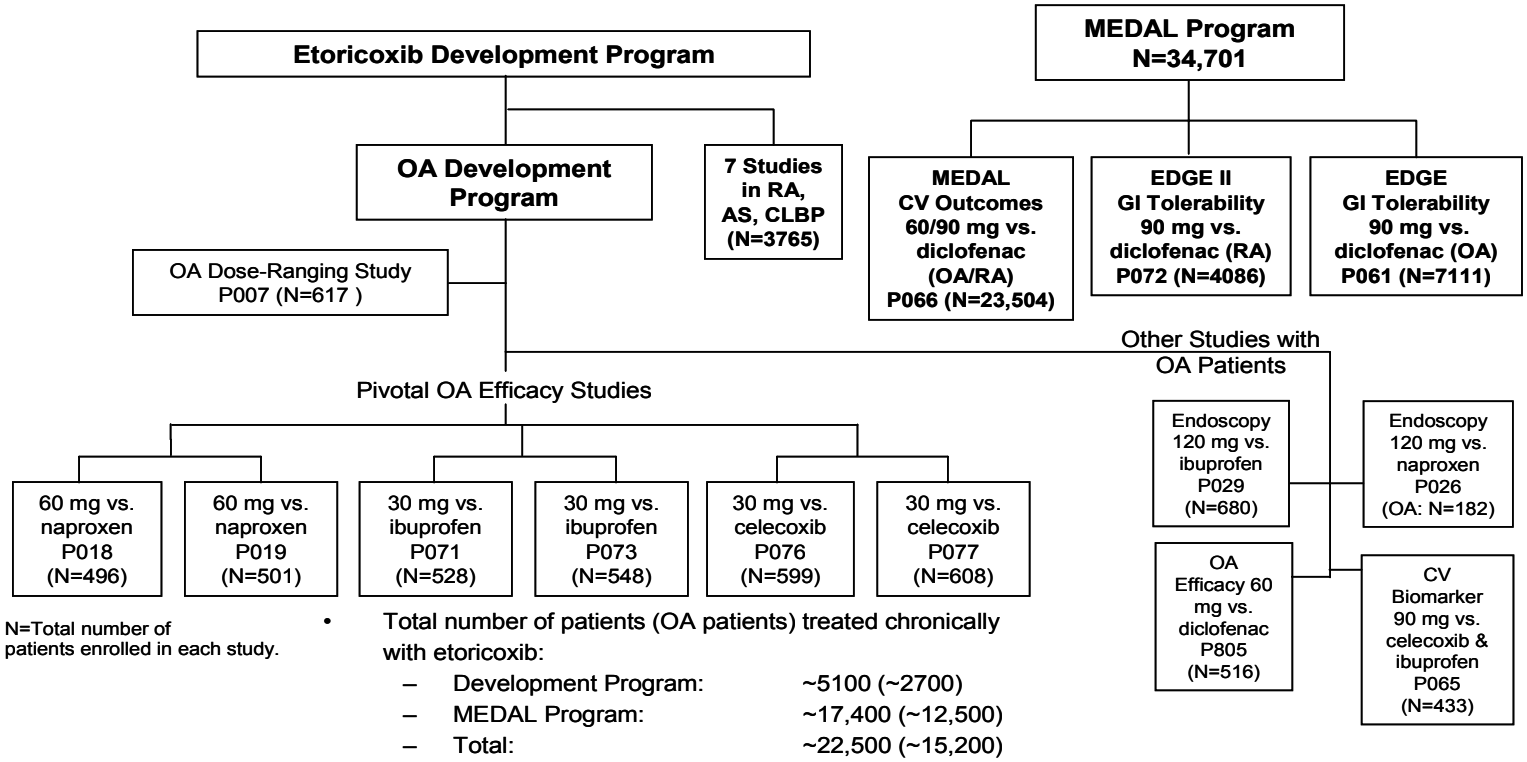
The Etoricoxib Development Program is defined by 18 Phase IIb/III chronic dosing (defined as a treatment period of ≥4 weeks) clinical studies designed to evaluate the efficacy and safety of etoricoxib in the treatment of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS), and chronic low back pain (CLBP).

The MEDAL Program consisted of 3 randomized, double-blind clinical trials in patients with OA and RA comparing etoricoxib (60 mg or 90 mg daily) with diclofenac 150 mg daily. The MEDAL Program was designed specifically to provide long-term thrombotic CV safety data for etoricoxib compared to the traditional NSAID diclofenac. These 3 studies are referred to throughout this background document as the MEDAL Program studies and consist of the MEDAL Study (OA and RA), and the EDGE II (RA) and EDGE (OA) studies.

The studies included within the OA Development Program, the Etoricoxib Development Program, and the MEDAL program are outlined in Figure 1. Additionally, ~2100 patients not included in the presentation of information in this document were treated with etoricoxib in Phase I studies, short-term Phase II/III studies (i.e., single dose and multiple doses up to 7 days) which were performed to evaluate the efficacy of etoricoxib in a range of acute inflammatory pain conditions, and in one study designed to evaluate efficacy in hemophilic arthropathy.

Figure 1

Clinical Studies in the Etoricoxib Development Program, MEDAL Program



3.2 Program Design Considerations

3.2.1 OA Development Program

The Phase IIb portion of the OA Development Program consisted of a dose-ranging study designed to identify doses with efficacy superior to placebo. The results of this study were the basis of the subsequent Phase III program which focused on efficacy and safety relative to both placebo and NSAIDs commonly used in the treatment of OA. The Phase III efficacy studies focused initially on etoricoxib 60 mg relative to placebo and naproxen 1000 mg and subsequently on etoricoxib 30 mg relative to placebo and ibuprofen 2400 mg in replicate studies as well as placebo and celecoxib 200 mg in replicate studies. Upper GI safety and tolerability were also evaluated early in the program through a gastric biopsy study which evaluated the effect of etoricoxib on gastric PGE2, a fecal red blood cell loss study, and 2 GI endoscopy studies.

Upper GI safety and thrombotic CV safety were monitored throughout the OA Development Program (including independent adjudication by expert panels) through pooled analyses of prospectively adjudicated upper GI clinical event and thrombotic CV event data across the Etoricoxib Development Program.

3.2.2 MEDAL Program Design

The MEDAL Program design was finalized in 2002 and patients began enrolling the same year. The Program was designed to test the noninferiority hypothesis of thrombotic CV events for etoricoxib in comparison to diclofenac and is comprised of three component studies; Protocol 061 (EDGE), Protocol 072 (EDGE II), and Protocol 066 (MEDAL) [106]. An external Steering Committee for the MEDAL Program was convened and was involved in making key decisions regarding all aspects of the study, including the design, the protocol and the data analysis plans. The emerging safety data was monitored by an external data safety and monitoring board (DSMB), which was chartered when the MEDAL program was initiated.

In 2005, a combined Arthritis and Drug Safety Advisory Committee recommended that CV outcome studies be conducted for new NSAIDs. They recommended that the studies be conducted in arthritis patients, using a non-inferiority design with a noninferiority bound of 1.5, with naproxen as the primary comparator (and possibly additional comparators).

Many aspects of the MEDAL Program are consistent with this guidance as will become evident after reading the design summary below. However, the comparator chosen for MEDAL was diclofenac, and not naproxen. The rationale for why diclofenac was chosen is discussed in Section 3.2.2.2.

3.2.2.1 Patient Population

A primary aim of the MEDAL Program was to evaluate a patient population that required daily NSAID therapy. Studying such patients ensured that the thrombotic CV safety data from these studies would be directly relevant to the patient population in clinical practice

that requires these therapies. Therefore, an arthritis patient population was chosen, consisting of both OA and RA patients. OA patients represent the most common arthritis population and RA patients were important to include because RA is associated with increased thrombotic CV risk [107] and RA patients can require higher doses of NSAIDS and may be treated for longer periods of time.

The OA and RA patients enrolled across the MEDAL Program studies reflect a range of thrombotic CV risk. Patients with cardiac risk factors as well as patients with known CV disease were included (see Section 4.2.2). Low-dose aspirin for cardiovascular prophylaxis was recommended as per current treatment guidelines; patients with diabetes were also encouraged to use low-dose aspirin. Patients with a range of GI risks were included (see Section 4.2.2) and the use of proton pump inhibitors or misoprostol was recommended per current guidelines in order to reduce the risk of upper GI complications.

3.2.2.2 Comparator Agent Choice and Rationale

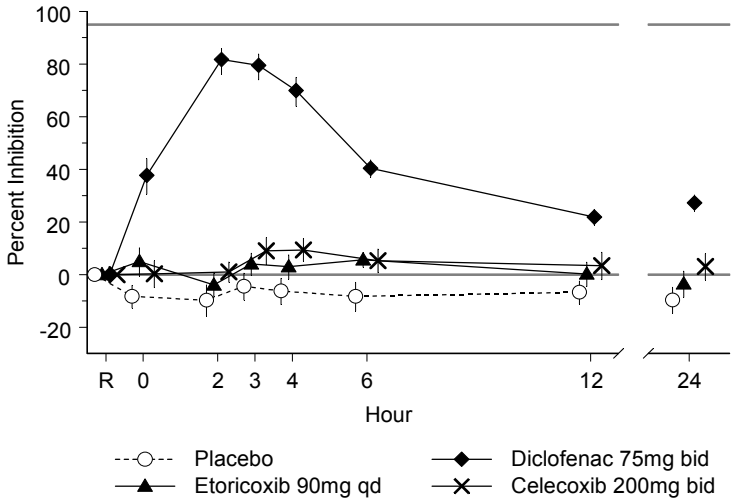
Diclofenac was selected as the sole active comparator for the MEDAL Program. The two other NSAIDs given consideration were naproxen and ibuprofen. The rationale for choosing diclofenac is summarized below.

1. The Etoricoxib Development Program had already collected meaningful amounts of GI and thrombotic CV safety data comparing etoricoxib to naproxen by the time the MEDAL Program was designed. These data were sufficiently robust to begin drawing conclusions about relative upper GI and thrombotic CV safety between etoricoxib and naproxen. These Etoricoxib Development Program studies were continuing and thus would continue to provide additional upper GI and thrombotic CV safety data versus naproxen. However, relatively little data had been collected for etoricoxib in comparison to either ibuprofen or diclofenac. Not unexpectedly, the Etoricoxib Development Program provided compelling evidence that naproxen overall would manifest a lower CV thrombotic risk than etoricoxib whereas etoricoxib would demonstrate reduced risk of GI complications. Thus the profile of etoricoxib relative to naproxen was reasonably well characterized in the Etoricoxib Development Program. MEDAL, therefore, provided an important opportunity to gather safety data for etoricoxib relative to another commonly used NSAID such as ibuprofen or diclofenac that do not have potent and sustained antiplatelet effects.
2. Diclofenac is considered an effective NSAID for the management of symptoms associated with both OA and RA and is the most widely prescribed NSAID in the world (Data extracted for worldwide NSAID use from: IMS Health, IMS MIDAS(r), 1Q2006). Daily doses of 150 mg are effective for the management of symptoms associated with both OA and RA. In contrast, concerns were raised by consulting rheumatologists that ibuprofen 2400 mg would not provide adequate efficacy for the RA patients.
3. Diclofenac can be administered twice daily, rather than three times daily as required with ibuprofen; an important consideration to enhance compliance over an extended period of time in a study designed to evaluate long-term safety of the study therapies.

4. Given the emerging evidence that certain NSAIDs mitigate the anti-platelet effect of aspirin, it was important to choose an NSAID comparator that did not have this property. Diclofenac does not interfere with the antiplatelet effects of low-dose aspirin (used by ~35% of patients in the MEDAL Program) whereas both naproxen and ibuprofen have been shown to interfere with aspirin on the basis of platelet function assays [105]. Although the clinical manifestations of this pharmacodynamic interaction are unknown, the MEDAL investigators involved with the design of the MEDAL Program expressed concern over allowing patients on aspirin to enroll if agents thought to interfere with aspirin would be included as a comparator. Therefore, we chose to avoid any potential ethical issues for patients on low-dose aspirin for CV prophylaxis as well as issues surrounding the scientific interpretation of potentially confounded primary thrombotic CV endpoint results. Of note, the U.S. Food and Drug Administration issued a statement in September of 2006 indicating that concomitant use of ibuprofen and low-dose aspirin should be done cautiously [108].
5. While in vitro assays may suggest modest COX-2 selectivity with diclofenac [109; 110] results from ex vivo assays in patients demonstrate that therapeutic doses of diclofenac substantially inhibit COX-1 whereas celecoxib, rofecoxib, and etoricoxib do not [111; 112; 113]. This COX-1 inhibitory effect by diclofenac is demonstrated by the results from a randomized, double-blind, placebo controlled, crossover study carried out to assess the COX selectivity of etoricoxib 90 mg qd, diclofenac 75 mg bid, and celecoxib 200 mg bid in healthy volunteers (Figure 2). Only treatment with diclofenac was associated with a substantial inhibition of COX-1 activity as measured by TXB_2 generation. The mean difference in peak inhibition (Imax) between diclofenac and placebo was 89% ($p<0.001$). The mean differences in peak inhibition (Imax) between diclofenac and etoricoxib 90 mg were 77% and between diclofenac and celecoxib were 72%, both differences were significant ($p<0.001$). All active treatments substantially inhibited COX-2 to a similar extent. Thus diclofenac is different than etoricoxib which has no inhibitory effect on COX-1 at therapeutic doses.

Figure 2

Percent Inhibition of TXB_2 (Mean ± SE†) – Protocol 091



6. From the perspective of upper GI safety, although diclofenac was not statistically significantly different from celecoxib in clinically important GI outcomes in the CLASS trial [46], endoscopic trials indicate that diclofenac treatment at therapeutic doses significantly increases the incidence of gastroduodenal ulcers compared to the Cox-2 selective agents celecoxib and valdecoxib [114; 115; 116].
7. The inclusion of a placebo control was not deemed to be appropriate or feasible since the patients included in the MEDAL Program were OA and RA patients who required long-term therapy for pain and inflammation. Thus, the MEDAL Program was not designed to evaluate the absolute thrombotic CV risk of etoricoxib.
8. Acetaminophen was also not considered as a comparator because the main objective was to evaluate patients with symptoms severe enough to justify chronic anti-inflammatory therapy with a traditional NSAID or COX-2 selective inhibitor.
9. A sole comparator was chosen so as to provide a definitive answer using a predefined noninferiority bound. Including additional comparators would have reduced the precision for the primary thrombotic CV event rate comparisons, or require a substantial increase in study size which was not warranted given the considerations outlined in paragraphs 1-8 above.

3.2.2.3 Etoricoxib Dose Selection

In countries where etoricoxib is approved, the highest recommended daily dose for chronic use is 90 mg (for RA) and 60 mg (for OA). When the MEDAL Program was originally designed, etoricoxib 90 mg was chosen to evaluate both OA and RA patients because it was the maximal chronic dose approved throughout the world and thus was felt to represent the most rigorous and complete evaluation of the etoricoxib safety profile. Therefore, 90 mg was the etoricoxib dose studied in the EDGE (OA) and EDGE II (RA) studies. It was also the dose initially chosen for both OA and RA patients in the MEDAL Study. However, shortly after initiation, the protocol was amended so that OA patients were randomized to receive etoricoxib 60 mg, the proposed maximum recommended dose for OA. The purpose of the amendment was to have the doses studied in MEDAL mirror the dose approved for clinical practice to maximize the clinical utility of the data. The OA patients who had been started on etoricoxib 90 mg continued on this regimen for the duration of the study. All RA patients remained on 90 mg, the approved dose for RA in countries outside the U.S., throughout the study.

3.2.2.4 Endpoints

The primary endpoint of Confirmed Thrombotic CV events is the same as used in the Etoricoxib Development Program and is described in Section 8. Two secondary endpoints were prespecified: 1) the subset of Confirmed Arterial events; 2) the APTC Combined Endpoint (also used in Etoricoxib Development Program and described in Section 8). The arterial event endpoint was included because it more specifically includes the events that have become of greater clinical interest based on previous clinical trial results.

3.2.2.5 Selection of the Non-Inferiority Bound

The primary hypothesis of the MEDAL Program was that the risk of a confirmed thrombotic CV event on etoricoxib is non-inferior to that on diclofenac. The risk was assessed by determining that the 95% CI for the hazard ratio (HR) was less than the noninferiority bound, which was set at 1.30. The determination of the bound was more of a clinical rather than a statistical decision. The upper bound should represent the highest value that could still be considered clinically noninferior. Note that as designed, a maximum observed HR of approximately 1.12 would yield the upper limit of the 95% CI lower than the non-inferiority bound of 1.30 in the MEDAL program. Because safety differences between etoricoxib and diclofenac are of clinical interest, it was thought that the noninferiority bound should be as small as possible. Even if the 2 treatments have the same underlying risk, there is a 50% chance that the estimated relative risk would be >1.0. Consequently, the noninferiority bound for the CI must be >1.0. It was set at 1.30 in order to yield a study with a precise estimate of the hazard ratio.

3.2.2.6 Study Duration

The MEDAL Program, which was endpoint driven, required at least 635 total thrombotic CV events from all 3 studies to provide about 91% power for the primary analysis, and at least 490 events from the MEDAL Study alone to provide about 83% power.

The mean duration of exposure for the MEDAL Program was approximately 18 months (maximum of 42.3 months). This number was driven by the duration of the MEDAL and EDGE II studies, which were similar in mean duration; mean exposures of 20.3 months (maximum of 42.3 months) and 19.2 months (maximum of 33.1 months), respectively. Importantly, over 21,000 patients received ≥ 12 months of therapy and over 12,000 patients received ≥24 months of therapy.

3.2.2.7 Per-protocol Analyses

The primary analysis for Confirmed Thrombotic CV Events in the MEDAL Program was a per-protocol analysis. Per-protocol analyses are recommended for noninferiority trials by statisticians, regulatory agencies and the CONSORT guidelines [117; 118; 119] because they may provide a more conservative approach to equivalence or noninferiority trials than an intent-to-treat analysis. The use of an intent-to-treat population can predispose the event rates towards similarity because of potential for similar patient care after discontinuation of study drug. Evaluating the treatments only during treatment would allow a direct pharmacologic comparison of risk. In addition to the per-protocol analysis, intention-to-treat analyses were carried out as a secondary analytical approach, and to support interpretation of the results.

3.3 Evaluation of Safety

The presentation of safety data for the OA Development Program is based primarily on safety data from the OA studies. The OA Development Program is the most appropriate set of data to evaluate general safety including renovascular safety for the OA indication.

Data from the entire Etoricoxib Development Program are included in the evaluation of Upper GI safety and thrombotic CV safety. The etoricoxib doses, 30 to 120 mg, were pooled as one treatment group and all the comparators were pooled as one or more treatment groups, depending on the specific analyses, to increase the precision of the evaluation given that these are relatively rare events. This is a conservative approach given the inclusion of patients with other diseases (e.g., RA) who may be at greater GI and CV risk. It is also conservative in that generally higher doses of etoricoxib are included in the analyses due to the inclusion of the RA and AS studies which evaluated higher doses of etoricoxib.

The presentation of the safety data for the MEDAL Program is based on all 3 MEDAL Program studies, either individually or in a pooled manner whereby all 3 studies are combined without regard to the three studies. The presentation of adverse experience data by dose and disease was prespecified and allows one to specifically evaluate etoricoxib at the 60 mg dose for which approval is being sought for OA.

The studies that comprise the evaluation of efficacy and the different safety domains for the OA Development Program and the MEDAL Program are noted in Table 1.

Table 1

Studies Included in the Analysis of Efficacy and Safety

Etoricoxib Development Program							
				Studies Included in Evaluations			
Indi-cation	Protocol No.	Short Study Title, including Phase	Comparator	Efficacy in OA	General Safety†	Upper GI Safety (Pooled)	Thrombotic CV Safety (Pooled)
OA Development Program							
OA	007	IIb OA DRF	PBO, Diclo	√	√	√	√
	018, 019	III OA Pivotal 60 mg	PBO, Nap	√	√	√	√
	026	III Endoscopy #1: OA Portion	PBO, Nap	√	√	√	√
	029	III OA Endoscopy #2	PBO, Ibu	√	√	√	√
	065	IIb CV biomarker	PBO, Cele, Ibu	–§	√	√	√
	071, 073	III OA Pivotal 30 mg	PBO, Ibu	√	√	√	√
	076, 077	III OA Pivotal 30 mg	PBO, Cele	√	√	√¶	√¶
	805	III OA Efficacy	Diclo	√	–‖	√	√
Other Studies in Etoricoxib Development Program							
RA	010	IIb RA DRF Study	PBO, Diclo‡			√	√
	024, 025	III RA Pivotal	PBO, Nap			√	√
	026	III Endoscopy #1: RA Portion	PBO, Nap			√	√
Others	032	III Ankylosing Spondylitis	PBO, Nap			√	√
	041, 042	III Chronic Low Back Pain	PBO			√	√
	806	IV Chronic Low Back Pain	Diclo			√	√
MEDAL Program							
OA	061	III GI Tolerability: EDGE	Diclo	√	√	√	√
OA/RA	066	III CV Outcomes: MEDAL Study	Diclo	√	√	√	√
RA	072	III GI Tolerability: EDGE II	Diclo		√	√	√

† Include renovascular safety (edema, CHF, and hypertension).
‡ In Part II and extensions only.
§ No efficacy data collected.
‖ 6-week active-comparator controlled study (no placebo control); does not meet the definition for inclusion in any OA safety population as shown in Figure 3 and thus not included as part of the evaluation of general safety in the context of these populations.
¶ Includes only data from the placebo-controlled period (Part I) as Part II was a celecoxib-controlled period; the prespecified comparisons do not include a comparison of etoricoxib with another COX-2 selective inhibitor.
DRF=dose-range finding, PBO=placebo, Diclo=diclofenac, Nap=naproxen, Ibu=ibuprofen, Cele= celecoxib.

3.3.1 Statistical Methodology for Safety Analyses

3.3.1.1 Etoricoxib Development Program

All patients who received at least one dose of the study medication were included in the safety analyses. For clinical adverse experiences of prespecified interest, the differences between treatments were tested using Cochran-Mantel-Haenszel test with protocol as a stratification factor. For overall summary of the adverse experiences, the 95% CIs for differences in proportions between treatments were provided using Wilson's score method; no stratification factor was employed.

The analyses of the thrombotic CV events and the upper GI events were performed for the Etoricoxib Development Program studies outlined in Table 1 above. Events included in the analysis for each population were those which occurred following study drug start and up to 14 days after the last dose of study drug in the corresponding analysis period, or the date of death if the patient died, whichever came first. A patient's risk period was censored at the date of the first event if the patient had one or more event.

To display the occurrence of events over time, Kaplan-Meier estimates of the cumulative incidence rates for the thrombotic CV and upper GI events were plotted by treatment. Treatment effects of etoricoxib relative to comparators were represented by the relative risks and the respective 95% confidence intervals (CI) and tested using the Cox proportional hazard model with treatment as an explanatory variable and therapeutic block (OA, RA, or Other) or protocol as the stratification variable, for the thrombotic CV and GI endpoints, respectively. Relative risk estimates and associated 95% confidence intervals (CIs) were obtained from the Cox model. If very few total number of events occurred (<11 total), the ratio of rates with 95% CIs were computed using Clopper-Pearson method, which is based on conditional binomial approach [120]. The proportional hazards (PH) assumption with respect to treatment was tested by including the treatment-by-log (time) term in addition to the treatment term in the Cox model [121]. A p-value >0.05 of this term indicated that the assumption of constant relative treatment effect (in terms of the relative risk) over time was not rejected.

3.3.1.2 MEDAL Program

Thrombotic Cardiovascular Safety

The primary analysis was based on the per-protocol approach; patients with clinically important prespecified deviations were excluded from the analysis. The timeframe for the per-protocol analysis was from Day 1 of therapy up to 14 days after the last dose of study therapy. The modified intention-to-treat (mITT) was a secondary approach; all patients who took at least 1 dose of study drug were analyzed based on the treatment assigned at randomization. The timeframe for the mITT analysis was from Day 1 of therapy up to 14 days after the last dose of study therapy. A sensitivity analysis observed on therapy or up to 28 days after therapy discontinuation, and the true ITT population (i.e., all patients followed up until the end of the trial, regardless of whether or not they discontinued from the study therapy) was also assessed for the key endpoints.

For the thrombotic cardiovascular endpoints, survival analytic methods were used to evaluate the time to first event during the study period. These analyses were based primarily on a Cox proportional hazards model with treatment as an explanatory factor and low-dose aspirin-use (at baseline: yes or no) as a stratification variable. The etoricoxib 60-mg and 90-mg groups were combined for between treatment comparisons. The hazard ratio between the 2 treatment groups (etoricoxib/diclofenac) was estimated and corresponding CI were used as the primary measure for estimating the comparative effects between treatment groups. The proportional hazards assumption was tested by

including the treatment-by-log (time) term in addition to treatment in the Cox model. The event rates were summarized by the number per 100 patient-years (equivalent to percent per year), and 95% CIs for the rates were calculated using the Poisson distribution assumption. Estimates of the cumulative event rates were calculated using the Kaplan-Meier method, and the curves were truncated when the number of patients remaining at risk was <500; however all events were included in the analysis.

The primary thrombotic CV safety objective was to establish non-inferiority (based on pooled MEDAL Program data using per-protocol approach) of etoricoxib as compared to diclofenac in the risk of developing a confirmed thrombotic thrombotic CV serious adverse experience. In order to establish non-inferiority, the upper limit of the interim analysis adjusted CI (slightly higher than 95%) of the hazard ratio needed to be less than 1.30. The consistency of results across studies was quantitatively investigated by testing the treatment-by-study interaction in the Cox model that included the study as main effects. In addition, the treatment effects were also estimated within each study. Additional sensitivity analyses were performed to investigate consistency in treatment response between patients with similar disease and dose.

The subgroup analyses of primary thrombotic CV endpoints were performed by using a Cox regression model with treatment, subgroup, and treatment-by-subgroup as covariates and low-dose aspirin-users as stratification factor. The stratification factor baseline low-dose aspirin use was not included in the analysis of subgroup based on the same factor. It is recognized that the power to detect a treatment-by-subgroup interaction was limited.

GI Safety and Tolerability

The mITT approach was used for the assessment of GI endpoint and GI tolerability data.

For the lower and upper GI endpoints, survival analytic methods similar to the analysis of CV endpoints were utilized to evaluate the time to first event during the study period. The prespecified analysis of upper GI events entailed assessment of incidence rate per 100 patient-years along with the 95% CI within each treatment group. Additionally, a post-hoc evaluation of hazard ratios was performed using a Cox model with a term for treatment effect and stratification factor for baseline low-dose aspirin use. Further, a post-hoc evaluation also examined the consistency of results across studies by testing the treatment-by-study interaction in the Cox model that includes study as the main effects. Further, subgroup analyses were performed related to concomitant use of low-dose aspirin and/or PPI co-therapy and other factors of interest. Caution must be exercised when a between-treatment comparison is made based on results of post-randomization subgroup analysis because it is hard to assess any potential influence of treatment on the subgrouping factors or vice versa.

For GI tolerability (assessed as discontinuation due to any GI related AE), the time to discontinuation was analyzed using survival analytical methods similar to what was described above for the analysis of cardiovascular endpoints.

General Safety

The mITT approach was used for the assessment of general safety data; however, an additional analysis based on the ITT approach was also performed for mortality data.

The 95% CIs for differences in proportions between treatments were provided using Wilson's score test.

For the laboratory safety parameters and vital signs, all randomized patients with a baseline measurement and at least one post baseline measurement were included in the analysis. Only observed data were used in the calculation of the summary statistics and for the graphic display of change from baseline over time.

For mortality data the incidence rate per 100 patient-years and associated 95% CIs were tabulated. All deaths with event onset date on therapy or within 14 days of therapy discontinuations were considered in the analysis based on mITT approach.

The incidences of adverse experiences in the MEDAL Program studies were prespecified to be rounded to the nearest tenth. However, due to the large number of patients within each MEDAL Program study, rounding to the nearest tenth can occasionally result in an incidence of 0% even when there are >1 adverse experience. Given that the general safety tables display the incidence and not the number of events, those adverse experiences with >1 event which would have resulted in 0% due to rounding are footnoted and rounded to the nearest one hundredth.

3.3.2 General Safety

3.3.2.1 OA Development Program

The goal of the OA Development Program was to identify well-tolerated and effective doses of etoricoxib and to assess comprehensively the safety, tolerability and efficacy of etoricoxib at doses identified for clinical use.

To provide a comprehensive assessment of safety in OA patients, data from the OA studies were analyzed and presented using populations and data sets that were defined by the comparator (placebo or active comparator) and duration of exposure: 1) 6-12 weeks; 2) 6 months; 3) 1 year. These populations, which form the basis for the general safety evaluation of the OA Development Program, are outlined in Figure 3.

This figure depicts the studies relatively proportional to the duration of each study portion included in each population.

The 6- to 12-Week Placebo-Controlled Population (hereafter referred to as the Placebo-Controlled Population), consists of the placebo-controlled portions from all of the Phase IIb/III studies of etoricoxib in patients with OA. A comparison to placebo provides the most accurate absolute assessment of clinical safety and therefore was a main focus of the general safety analyses of etoricoxib.

The 6-Month and 1-Year Active-Comparator-Controlled Populations (hereafter referred to in text as the 6-Month Population and the 1-Year Population, respectively) include all Phase IIb/III studies of etoricoxib in patients with OA of up to 6 months and 1 year in

duration, respectively. The 6-Month Population is defined by the duration of treatment of 2 studies (Protocols 076 and 077). This population allows evaluation of the data over 26 weeks directly comparing etoricoxib 30 mg to celecoxib 200 mg. The 1-Year Population is defined by exposure up to 1 year of treatment for all studies up to 1 year in duration (Protocols 007, 018, and 019), which allows assessment of the longer-term safety and tolerability of etoricoxib in OA patients. The Phase IIb dose-ranging study (Protocol 007) and replicate Phase III 1-year OA studies (Protocols 018 and 019) contained extensions beyond 1 year; these data are included in the pooled analyses of upper GI and thrombotic CV safety.

3.3.2.2 MEDAL Program

The MEDAL Program consisted of a cardiovascular (CV) outcomes study (the MEDAL Study) and two GI tolerability studies (EDGE II and EDGE) which were outlined in Figure 1. The MEDAL Program was prospectively designed to combine the data from these 3 studies with the primary purpose of evaluating the thrombotic CV safety of etoricoxib versus diclofenac with a noninferiority approach. The duration of the MEDAL Program was driven by the number of confirmed thrombotic CV events as outlined in Section 3.2.2.6. Figure 3 displays each of the MEDAL Program studies showing the maximum duration of exposure within each study. Additional exposure information is in Section 4.1.

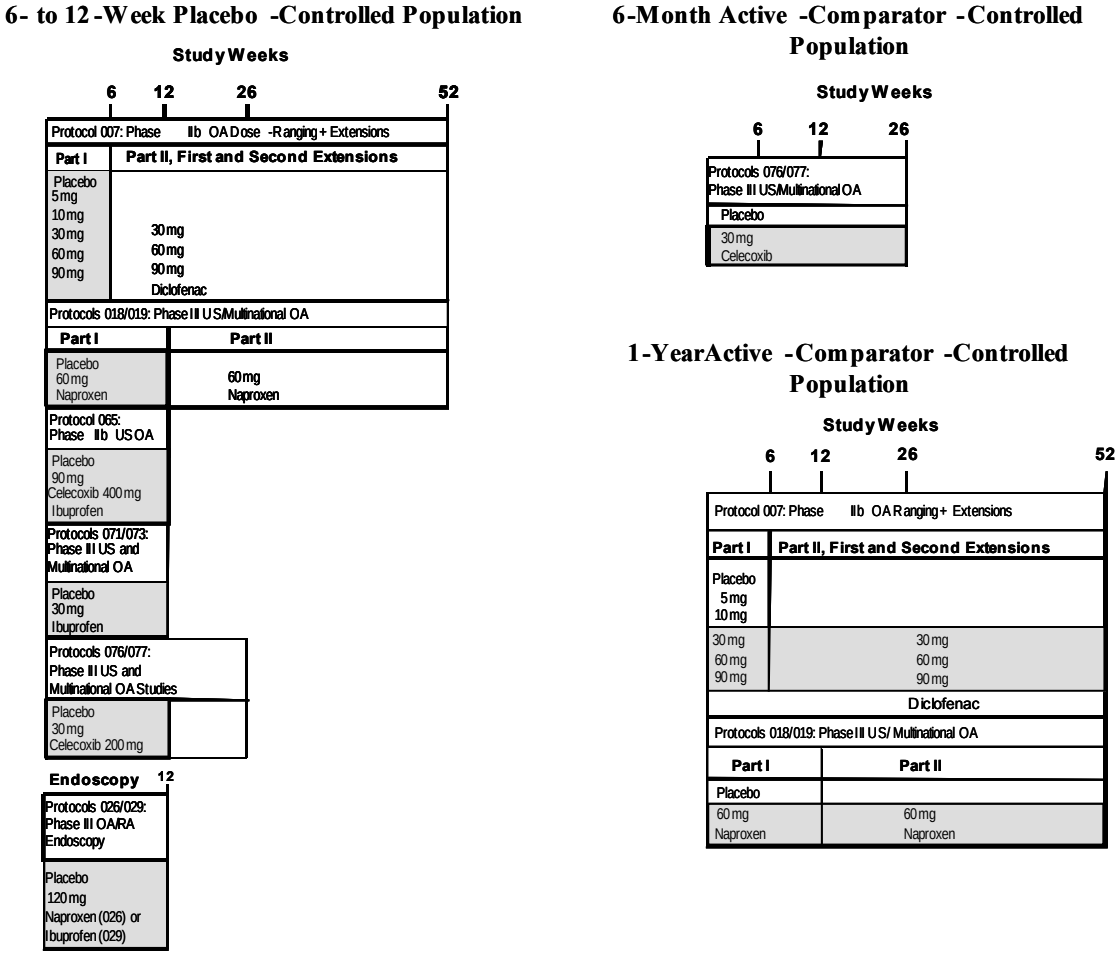
Although the primary objective of the MEDAL Program was an assessment of thrombotic CV safety, general safety information was collected. All adverse experiences were collected in the EDGE II and EDGE studies. Because of the large size of the MEDAL study (23,504 patients randomized), the collection of safety data was limited to adverse experiences that were considered serious or resulted in discontinuation. Limited measures of efficacy were also collected in each MEDAL Program study to ensure that the evaluation of safety was made in the context of equi-efficacious treatment.

Unlike the presentation of the data for the OA Development Program, the general safety data for the MEDAL Program Studies are not distinguished by unique populations of data but were prespecified to be presented separately within each MEDAL Program study.

When viewed in totality, the data from the OA Development Program and the MEDAL Program provide a comprehensive evaluation of the safety and tolerability of etoricoxib at the doses recommended for OA (30 mg and 60 mg) compared with placebo (up to 12-weeks), and the longer-term safety (up to 6-months, 1-year, and >1 year [MEDAL Program]) of etoricoxib compared with approved and commonly used NSAID therapies. Importantly, the MEDAL Program provides an extensive amount of longer-term safety data that allows a precise assessment of the thrombotic CV risk of etoricoxib (60 and 90 mg) compared with diclofenac, a commonly used traditional NSAID. In addition, it provides extensive comparative safety data.

Figure 3

OA Development Program Populations, MEDAL Program Studies



3.3.3 Gastrointestinal and Thrombotic Cardiovascular Safety

The analyses of upper GI clinical events (bleeding, perforation, obstruction, ulcer; PUBs) and thrombotic CV events across the Etoricoxib Development Program and for the MEDAL Program were based on prospectively defined criteria and blindly adjudicated data. The entire program employed the same CV Adjudication Standard Operating Procedure (SOP) and upper GI Adjudication SOP that had been operational at Merck for its COX-2 selective inhibitor program. These SOPs established a process by which potential upper GI events and potential thrombotic CV events could be identified and adjudicated in a blinded manner by external adjudication committees. The lists of investigator reported terms for upper GI clinical events and thrombotic CV events were prespecified. The adjudication committee for GI safety data is referred to as the Case

Review Committee (CRC) while the adjudication committee which evaluated potentially thrombotic CV data is referred to as the Vascular Events Committee (VEC). Each committee was composed of experts in the respective fields of gastroenterology and cardiology and each committee functioned in a similar manner. The primary objective of the adjudication process was to more precisely assess events which occurred during the clinical Etoricoxib Development Program. In addition, the MEDAL Program studies utilized the same CRC to prospectively adjudicate lower GI events, a prespecified endpoint in the MEDAL Program. Additional information on the GI and CV adjudication are in Sections 7 and 8, respectively.

3.3.3.1 Etoricoxib Development Program

The analyses of upper GI and thrombotic CV safety from the Etoricoxib Development Program are based on pooled analyses of all chronic exposure studies in OA, RA, AS and CLBP (excluding the MEDAL Program studies). The analyses of upper GI clinical events are in Section 7.1 and thrombotic CV events are in Section 8.1. The objective of the GI and thrombotic CV analyses was to compare etoricoxib (at doses of 30 to 120 mg) in Phase IIb/III chronic exposure studies with active-comparator NSAIDs and placebo across all indications. These analyses were performed on data sets defined by comparator NSAID and placebo use and not by duration of exposure.

3.3.3.2 MEDAL Program

The assessment of thrombotic CV safety in the MEDAL Program was prespecified to be based on data pooled from the three component studies whereby the studies are combined without regard to the three studies. The largest component, the MEDAL Study, was designed to provide an adequately powered comparison of the thrombotic CV safety profile of etoricoxib to diclofenac without the additional data from the other two component studies. The primary MEDAL Program thrombotic CV analysis is presented in Section 8.2.

As component studies of the MEDAL Program, both EDGE II and EDGE had as their primary objectives a comparison of the GI tolerability of etoricoxib to diclofenac. However, both studies were designed so that as part of the assessment of general safety and tolerability in these studies, thrombotic CV safety data were collected and adjudicated using the standard adjudication process. To examine upper and lower GI clinical events with etoricoxib versus diclofenac, a combined analysis of the 3 studies was performed and is presented in Sections 7.1.2 and 7.3, respectively.

4. Treatment Exposure, Demographics, and Baseline Characteristics

4.1 Exposure and Patient Accounting

In all, ~2500 patients with OA were treated with etoricoxib in the OA Development Program. When considering the 18 studies from the Etoricoxib Development Program (OA, RA, AS, CLBP), ~4700 patients were treated with etoricoxib. The MEDAL Program studies included an additional ~17,400 patients treated with etoricoxib, of whom ~12,500 were OA patients. Cumulatively, ~22,100 patients were treated with etoricoxib, including ~15,100 patients with OA. In addition, ~1900 patients were treated with etoricoxib in the Phase I studies and in the Acute Analgesia studies.

Patient exposure data by dose including total patient numbers and duration of exposure for the OA Development Program for the populations outlined previously in Section 3.2.2.1 are in Table 2. Data from the 6-Month Population and the 1-Year Population are mutually exclusive; however, they include the data from the placebo-controlled periods, and thus overlap with the Placebo-Controlled Population.

Patient exposure data by dose for the MEDAL Program Studies and Pooled MEDAL Program are presented in Table 3. Given the relatively long duration and the non-inferiority design, patient accounting and compliance data are also provided for the MEDAL Program. The total number of patients in the Pooled MEDAL Program (23504) does not exactly match the total number of patients when presented broken out by disease and dose (23498) because 5 RA patients were randomized to etoricoxib 60 mg and 1 patient was missing a disease history. Therefore, in the presentation by disease and dose these 6 patients can not be assigned to a specific treatment group, but are included in the pooled data. None of these 6 patients had any adverse experiences.

Table 2

OA Development Program
Patient Exposure to Etoricoxib by Dose and Duration

Treatment	Total Patients	Months on Drug	
		Mean	Range
6- 12 Week Placebo-Controlled OA Population			
Placebo	1035	2.2	0.0 to 4.1
Etoricoxib			
30 mg	1014	2.4	0.0 to 3.7
60 mg	587	2.2	0.0 to 4.5
90 mg	220	1.8	0.0 to 3.2
120 mg	297	2.4	0.0 to 3.3
Naproxen 1000 mg	494	2.5	0.0 to 3.5
Ibuprofen 2400 mg	752	2.2	0.0 to 3.4
Celecoxib			
200 mg	550	2.2	0.0 to 3.4
400 mg	114	2.2	0.0 to 3.5
6- Month Active-Comparator-Controlled OA Population			
Etoricoxib 30 mg	474	5.1	0.0 to 7.3
Celecoxib 200 mg	488	4.8	0.0 to 7.0
1-Year Active-Comparator-Controlled OA Population			
Etoricoxib			
30 mg	56	6.6	0.0 to 12.8
60 mg	508	9.2	0.1 to 13.3
90 mg	112	7.8	0.3 to 13.7
Naproxen 1000 mg	439	8.5	0.0 to 13.8

Table 3

MEDAL Program
Patient Exposure to Etoricoxib by Dose and Duration

MEDAL Program Studies			
Treatment	Total Patient Number	Months on Drug	
		Mean	Range
MEDAL (P066): OA			
Etoricoxib 60 mg	6769	21	0.3 to 37.2
Etoricoxib 90 mg	2171	20	0.5 to 41.8
Diclofenac 150 mg	8862	20	0.5 to 42.3
MEDAL (P066): RA			
Etoricoxib 90 mg	2841	21	0.5 to 41.0
Diclofenac 150 mg	2855	20	0.5 to 40.6
Total (MEDAL)	23498	20	0.3 to 42.3
EDGE II (P072): RA			
Etoricoxib 90 mg	2032	19	0.3 to 32.9
Diclofenac 150 mg	2054	19	0.5 to 33.1
Total (EDGE II)	4086	19	0.3 to 33.1
EDGE (P061): OA			
Etoricoxib 90 mg	3593	9	0.5 to 16.5
Diclofenac 150 mg	3518	9	0.5 to 16.6
Total (EDGE)	7111	9	0.5 to 16.6
Pooled MEDAL Program			
Etoricoxib	17412	18	0.3 to 41.8
Diclofenac	17289	18	0.5 to 42.3
Total	34701	18	0.3 to 42.3

Patient Accounting and Treatment Compliance in the MEDAL Program

Table 4 accounts for the 34701 patients who were randomized in the MEDAL Program. Other than discontinuations due to laboratory adverse experiences which were higher on diclofenac, no notable differences were noted. The cumulative incidence of discontinuations is provided in Figure 4.

In the MEDAL Program, patients were considered compliant with the dosing regimen if they took at least 75% of the scheduled doses of active study drug. Overall, compliance with study drug was high and was similar between the treatment groups: 97.8% and 96.2% for etoricoxib and diclofenac, respectively.

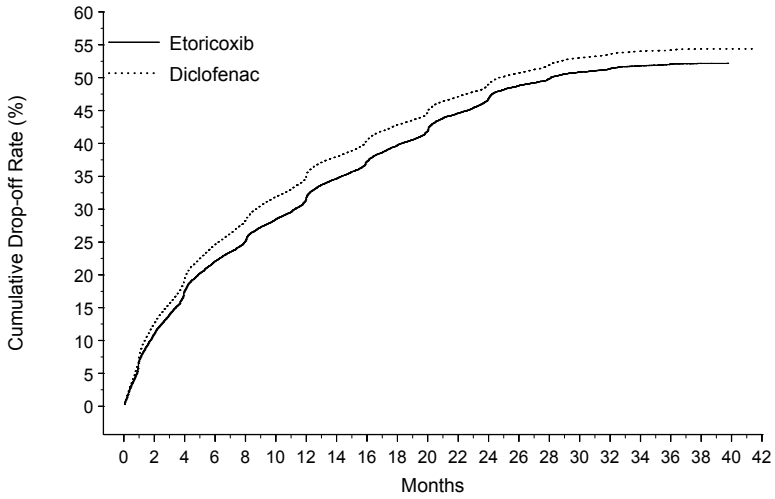
Table 4

MEDAL Program
Patient Accounting

	Etoricoxib (N=17412)	**Diclofenac (N=17289)**	**Total (N=34701)**
	n (%)	n (%)	n (%)
Completed Trial	8328 (47.8)	7887 (45.6)	16215 (46.7)
Discontinued Trial	9084 (52.2)	9402 (54.4)	18486 (53.3)
Clinical AE	3351 (19.2)	3346 (19.4)	6697 (19.3)
Laboratory AE	244 (1.4)	633 (3.7)	877 (2.5)
Lost to Follow-up	117 (0.7)	116 (0.7)	233 (0.7)
Withdrawal of Consent	2706 (15.5)	2591 (15.0)	5297 (15.3)
Protocol Deviation	422 (2.4)	424 (2.5)	846 (2.4)
Lack Efficacy	1566 (9.0)	1687 (9.8)	3253 (9.4)
Patient Moved	161 (0.9)	152 (0.9)	313 (0.9)
Patient Discontinuation for other reason	439 (2.5)	376 (2.2)	815 (2.3)
Site Terminated	78 (0.4)	77 (0.4)	155 (0.4)

Figure 4

Pooled MEDAL Program
Kaplan Meier Estimates of Cumulative Incidence
Discontinuations for Any Reason



Etoricoxib	**17412**	14364	13035	10462	8797	7777	6225	4699	2565	745	32
Diclofenac	**17289**	13919	12408	9942	8393	7452	6014	4516	2457	748	25

4.2 Demographic and Other Patient Baseline Characteristics

This section summarizes the demographics and patient baseline characteristics for the OA Development Program and MEDAL Program.

4.2.1 OA Development Program

Baseline patient characteristics (age, race, and gender) by treatment group for the Placebo-Controlled Population are in Table 5. The majority of patients were female and White with similar percentages across treatment and dose groups. No clinically important differences between treatment groups were observed.

In general, the baseline characteristics for the 6-Month and 1-Year Populations were similar to the Placebo-Controlled Population. No clinically important differences between treatment groups were observed in either Population.

Table 5

6- to 12-Week Placebo-Controlled Population
Baseline Patient Characteristics by Treatment Group

	Pbo N=1035	Etori 30 mg N=1014	Etori 60 mg N=558	Etori 90 mg N=220	Etori 120 mg N=288	Nap 1000 mg N=494	Ibu 2400 mg N=756	Cele 200 mg N=488	Cele 400 mg N=107	Total N=5191
	%	%	%	%	%	%	%	%	%	%
Gender										
Female	71.8	70.3	71.0	65.5	76.4	72.1	69.0	65.8	59.8	70.5
Male	28.2	29.7	29.0	34.5	23.6	27.9	31.0	34.2	40.2	29.5
Age (years)										
≤60	45.7	46.6	42.8	54.5	50.0	41.7	52.0	43.6	52.3	46.4
61 to 70	35.2	30.3	34.9	27.3	33.7	36.8	29.4	36.3	34.6	33.1
≥70	19.1	23.1	22.2	18.2	16.3	21.5	18.7	20.1	13.1	20.5
Mean	61.8	62.2	62.2	60.1	61.7	62.6	61.2	62.4	59.3	61.9
Range	40 - 90	40 - 91	35 - 92	40 - 85	48 - 99	40 - 87	40 - 89	40 - 88	40 - 82	35 - 99
Ethnic Group										
Asian	0.8	0.9	0.4	1.4	0.7	0.6	0.7	0.6	0.0	0.7
Black	7.1	6.0	4.3	6.4	4.5	5.1	4.2	8.2	8.4	6.0
Hispanic	8.6	7.4	8.2	5.9	8.7	7.5	12.0	3.1	5.6	7.8
Multi-Racial	3.9	5.2	4.3	0.0	3.8	4.0	7.8	0.0	0.0	4.0
White	79.0	79.9	82.3	85.0	81.6	82.8	74.7	87.5	85.0	81.0
Other[†]	0.6	0.6	0.5	1.4	0.7	0.0	0.5	0.6	0.9	0.6

[†] The category of "Other" race includes: African, European, American Indian, Native American, and Polynesian.
Pbo=Placebo; Etori=Etoricoxib; Nap=Naproxen; Ibu=Ibuprofen; Cele=Celecoxib.

4.2.2 MEDAL Program

The demographic and baseline patient characteristic data are shown for both the Pooled MEDAL Program (i.e., data pooled across the MEDAL, EDGE II, and EDGE studies) and for the individual MEDAL Program studies to support the various analyses of safety as described later in Sections 6-9.

4.2.2.1 Pooled MEDAL Program and MEDAL Program Studies

The original analysis plan specified providing MEDAL Program data pooled by overall treatment group for the analysis of thrombotic CV, and for upper and lower GI clinical events. The planned approach for general safety, including renovascular safety was to provide the MEDAL Study data by disease (OA, RA) and dose (diclofenac, etoricoxib 60 mg, etoricoxib 90 mg) as presented in Table 6.

Upon examination of the data after unblinding, an imbalance in certain baseline characteristics between the OA treatment groups was noted. As shown in Table 6, ~25% of the patients randomized to the 60 mg group were from the U.S. and ~65% were from Europe or Latin America whereas ~94% of the patients randomized to the 90 mg group

were from the U.S. while only ~2% were from Europe or Latin America. The proportion of OA patients randomized to diclofenac was in between that of the 60 mg and 90 mg etoricoxib groups.

An understanding of the patient enrollment into the MEDAL Study readily accounts for these differences. Patients were initially enrolled into the study under Protocol 066-00 which specified that OA patients receive etoricoxib 90 mg. Enrollment began in the U.S. first. After the initial 4333 patients with OA had been randomized to etoricoxib 90 mg or diclofenac, the protocol was amended. Subsequent OA patients were randomized to receive etoricoxib 60 mg or diclofenac, and by this time, a large number of patients from countries outside of the U.S. were enrolling. Because the baseline characteristics of OA patients in the U.S. differed from patients outside the U.S., the temporal nature of the enrollment as described above, combined with the protocol amendment served to exert this observed cohort effect.

Accordingly, it is only valid to compare characteristics between concurrently randomized patients, that is, between OA patients randomized to etoricoxib 90 mg and the diclofenac patients randomized during the same initial period and between patients randomized to etoricoxib 60 mg and diclofenac patients randomized during the same latter period. Table 7 provides such a presentation, displaying the data by distinct cohort: the OA 60 mg Cohort, the OA 90 mg Cohort, and the RA Cohort (unchanged from initial presentation). When presented in this way, the differences between treatment groups as noted above were no longer evident and the patient characteristics were balanced between treatment groups within each cohort. From this point forward, all MEDAL Study data presented by disease and dose is presented within the separate OA cohorts. All analyses of thrombotic CV safety, with the exception of the subgroup analysis by dose, are based on a comparison of all etoricoxib patients pooled and all diclofenac patients pooled; this cohort effect is not relevant when all patients are pooled.

Baseline patient demographics and characteristics for the Pooled MEDAL Program and the MEDAL Study (by disease and dose) are summarized in Table 7.

Overall, the majority of patients were female, <65 years old, White, and had OA. Within the Pooled MEDAL Program and within each individual study, the treatment groups were balanced for all baseline patient characteristics, including CV and GI baseline risk factors. Baseline use of specific prior medications of interest, including low-dose aspirin was also similar between treatment groups. The baseline demographics for patients included in the per-protocol analysis were similar to those presented in Table 7 which displays the mITT analysis.

Baseline characteristics were generally similar across all of the MEDAL Program Studies with the exception of baseline low-dose aspirin use, baseline antiplatelet use, and baseline PPI use which were higher in the MEDAL Study than in the EDGE II and EDGE studies. With the exception of differences seen between disease types, other baseline characteristics of the individual MEDAL Program Studies reflected the Pooled MEDAL Program.

Table 6

MEDAL Study (OA/RA)
Randomization by Study Region by Disease and Dose

	MEDAL Study				
	Osteoarthritis			Rheumatoid Arthritis	
	Etoricoxib 60 mg (N=6769)	Etoricoxib 90 mg (N=2171)	Diclofenac 150 mg (N=8862)	Etoricoxib 90 mg (N=2841)	Diclofenac 150 mg (N=2855)
Baseline Demographic	n (%)	n (%)	n (%)	n (%)	n (%)
Study Region					
U.S.	1719 (25.4)	2044 (94.2)	3728 (42.1)	1098 (38.6)	1100 (38.5)
Non U.S.	5050 (74.6)	127 (5.8)	5134 (57.9)	1743 (61.4)	1755 (61.5)
Europe	3173 (46.9)	16 (0.7)	3154 (35.6)	727 (25.6)	722 (25.3)
Latin America	1199 (17.7)	27 (1.2)	1223 (13.8)	605 (21.3)	604 (21.2)
Other	678 (10.0)	84 (3.9)	757 (8.5)	411 (14.5)	429 (15.0)

Table 7

Pooled Medal Program and MEDAL Study Cohorts Presented Separately
(OA/RA) Baseline Patient Demographics and Characteristics

	Pooled Medal Program		**MEDAL Study Cohorts Presented Separately**					
			Osteoarthritis				Rheumatoid Arthritis	
			60 mg vs. Diclo Cohort		90 mg vs. Diclo Cohort			
	Etori N=17412	Diclo N=17289	Etori 60 mg N=6769	Diclo 150 mg N=6700	Etori 90 mg N=2171	Diclo 150 mg N=2162	Etori 90 mg N=2841	Diclo 150 mg N=2855
Baseline Demographic	%	%	%	%	%	%	%	%
Gender								
Female	74.2	74.2	73.5	73.9	68.9	70.0	77.5	78.6
Male	25.8	25.8	26.5	26.1	31.1	30.0	22.5	21.4
Age (years)								
<65	58.5	58.6	55.1	54.7	52.1	53.8	66.5	67.3
≥65 to <75	29.9	30.4	31.9	32.8	31.5	32.4	25.4	25.5
≥75 years	11.7	11.0	13.0	12.5	16.4	13.8	8.1	7.2
Mean	63.2	63.2	63.9	64.0	64.5	64.2	61.4	61.4
Range	48 - 93	40 - 94	48 - 93	50 - 93	49 - 92	50 - 94	49 - 92	45 - 91
Ethnic Group								
Asian	3.8	3.8	4.1	3.9	0.6	0.3	6.2	6.5
Black	3.7	3.6	2.7	3.1	6.5	5.8	4.2	3.8
Hispanic American	8.3	8.2	8.1	7.9	4.6	4.2	12.9	12.5
Multi-Racial	5.4	5.3	4.3	4.5	1.2	1.0	7.1	6.6
White	78.3	78.7	80.6	80.3	86.7	88.3	69.0	70.3
Other†	0.4	0.4	0.3	0.3	0.5	0.5	0.6	0.3

Table 7 (Cont.)

Pooled Medal Program and MEDAL Study Cohorts Presented Separately
(OA/RA) Baseline Patient Demographics and Characteristics

	Pooled Medal Program		MEDAL Study Cohorts Presented Separately					
			Osteoarthritis					
Study Region								
U.S.	45.9	46.0	25.4	25.4	94.2	93.6	38.6	38.5
Europe	29.6	29.6	46.9	46.8	0.7	1.0	25.6	25.3
Latin America	15.8	15.8	17.7	18.0	1.2	0.9	21.3	21.2
Other	8.7	8.6	10.0	9.8	3.9	4.5	14.5	15.0
Disease Indication								
OA	72.0	71.6	100.0	100.0	100.0	100.0	--	--
RA	28.0	28.4	--	--	--	--	100.0	100.0
Baseline Cardiovascular Characteristics								
History of Diabetes	10.4	10.7	11.2	11.6	12.4	12.3	9.7	9.4
History of Dyslipidemia	29.3	29.1	29.6	30.3	45.6	44.6	23.5	20.6
History of Hypertension	46.6	47.6	49.8	51.4	53.2	51.7	42.7	43.6
Cigarette User (current)	11.7	11.8	11.3	10.4	9.4	10.0	15.4	15.2
Family History of CV Disease‖	17.8	17.9	16.8	16.8	22.4	24.2	17.6	16.8
History of Symptomatic ASCVD	11.6	11.6	12.9	13.3	15.4	14.4	10.8	11.1
Increased Risk (History of Symptomatic ASCVD or ≥2 CV Factors‡)	37.8	38.4	39.6	40.3	48.3	49.0	34.7	33.1
Baseline Low-dose Aspirin Users§	34.6	34.6	37.6	37.4	52.6	54.3	32.1	33.3
Gastrointestinal Baseline Characteristics								
GI History of Perforations, Ulcers, Obstructions, or Bleeds	6.5	6.6	6.2	6.7	8.4	8.1	9.0	9.1
Use of Systemic Corticosteroids	15.4	15.6	3.2	3.2	2.7	3.5	45.2	44.6
Use of PPIs	38.7	38.5	52.4	52.4	48.3	45.5	59.8	59.8

† The category of "other" race includes: African, Asiatic, European, Indian, Melanesian, Native American and Polynesian.
‡ CV risk factors include history of diabetes, dyslipidemia, hypertension, family history of cardiovascular disease, and current cigarette smokers.
§ Baseline low dose aspirin users were defined as patients using aspirin (≤325) at trial start date or +1 day; OR Patients using aspirin (≤1300 mg) for 50% of time during one month (range from -30 to -1) prior to trial start date.
‖ Data was not reported for between 8.4% and 10.7% of patients in any given treatment group for Family history of CV disease.
ASCVD=Atherosclerotic CV Disease; PUB=Perforation, Ulcers, Obstruction, or Bleeds; PPI=Proton-pump inhibitor.

5. Efficacy of Etoricoxib in OA

Seven of the 11 studies in the OA Development Program (Protocols 007, 018, 019, 071, 073, 076, and 077) were specifically designed to evaluate the efficacy of etoricoxib compared with placebo in the treatment of OA. These studies, along with an eighth study (Protocol 805) were also designed to determine the durability of treatment effects in comparison to regimens of traditional NSAIDs commonly used in the treatment of OA, including total daily doses of naproxen 1000 mg, diclofenac 150 mg, ibuprofen 2400 mg and the COX-2 selective inhibitor celecoxib 200 mg. This ensured that the efficacy data obtained with etoricoxib could be viewed in the context of currently approved therapy. The dose-ranging study evaluated patients with OA of the knee while the subsequent Phase III studies included patients with OA of the knee or hip.

The primary endpoints for the Phase III efficacy studies, which have been well validated for OA, included signs and symptoms such as pain, as well as measures of physical function. Global assessments of OA disease activity and response to therapy were also made from both the patients' and investigators' perspective, as well as on specific signs and symptoms of OA such as difficulties in performing certain tasks such as walking on a flat surface or going up or down stairs. Several of the endpoints used in the efficacy studies derive from the WOMAC questionnaire [122], which is a validated instrument designed to assess the clinical status of patients with OA of the knee or hip with questions divided among 3 subscales: Pain, Physical Function, and Stiffness. The 3 subscales of the WOMAC questionnaire measure the primary clinical symptoms of lower extremity arthritis from the patient's perspective. In addition, OA of the hand was measured in Protocol 018 using validated endpoints.

Limited measures of efficacy were also collected as exploratory endpoints in the Endoscopy studies (Protocols 026 and 029) while no efficacy measures were collected in the CV Biomarker study conducted in OA patients (Protocol 065).

In addition to the efficacy studies described above, the MEDAL Program Studies included limited measures of efficacy. The data for the efficacy studies from the OA Development Program and the limited efficacy data from the MEDAL Program are provided following the description of the statistical methodologies used for the efficacy analyses below.

5.1 Statistical Methods for Efficacy Analyses

5.1.1 Etoricoxib Development Program

All primary efficacy analyses for the Etoricoxib Development Program were based on a modified intention-to-treat (mITT) principle, i.e., inclusion of all patients who had received at least one dose of study medication, and had at least one efficacy response during the analysis period. Time-weighted average endpoints were calculated with observed data only; no imputation of missing data was implemented. Mean treatment responses plotted over time were computed with the last-value-carried-forward method.

Treatment means were estimated from either an analysis of covariance (ANCOVA) or analysis of variance (ANOVA) model with treatment as the main factor and baseline as the covariate, when appropriate.

5.1.2 MEDAL Program

Efficacy data were analyzed in a generally similar fashion as that described above. All observed data for each patient was included in the analysis; no data were carried forward or imputed in the analysis. Change from baseline over the treatment period was computed using the time-weighted average of efficacy measurements during the treatment period. Least-square means of change and 95% CI were based on an ANCOVA model with factors for treatment, stratification factor for baseline low-dose aspirin use (yes, no), and baseline value as covariate. Due to large size, the studies were overpowered to detect between-treatment differences, therefore differences may exist between treatments that are not clinically meaningful. In order to be considered clinically important, the 95% CI for the difference would need to exclude the region from -0.5 to 0.5 on the 0-to 4-point Likert scale.

5.2 Phase IIb Osteoarthritis Dose-Ranging Study (Protocol 007)

The Phase IIb dose-ranging study evaluated etoricoxib at doses of 5, 10, 30, 60, and 90 mg during a 6-week placebo-controlled period (Part I) and included patients with OA of the knee. The results for one of the three primary endpoints, the WOMAC Pain Subscale, are in the left panel of Figure 5 for Part I and the analyses of all 3 primary endpoints are in (Table 8). When averaged over the first 6 weeks of treatment, all etoricoxib doses demonstrated significantly greater efficacy than placebo in the treatment of OA as assessed by the 3 primary endpoints: WOMAC Pain Subscale, Patient Global Assessment of Response to Therapy, and Investigator Global Assessment of Disease Status. Clinically meaningful effects were predefined as differences from placebo of at least -10 mm (100-mm Visual Analogue Scale [VAS]) and at least -0.5 points (5 point Likert scale). Based on these criteria, only etoricoxib 60 and 90 mg provided clinically meaningful effects for all 3 primary endpoints, although 30 mg did pass the benchmark for 2 of the 3 endpoints and was borderline for the third (see Section 5.3.2). The efficacy of etoricoxib 60 mg was significantly greater than etoricoxib 30 mg for the three primary endpoints. In addition, a dose-related trend was observed in the proportion of patients achieving a good-to-excellent response to therapy; 48% and 70% of patients in the 30-mg and 60-mg etoricoxib groups, respectively, had a good to excellent response to therapy ($p<0.01$ for treatment group differences) versus 18% of the patients on placebo. Thus, the minimum dose of etoricoxib to provide maximal efficacy in OA was 60 mg and the difference between the 60 mg and 30 mg, the next lowest dose evaluated, was statistically significant. Nonetheless, it is clear that the 30 mg dose was still effective.

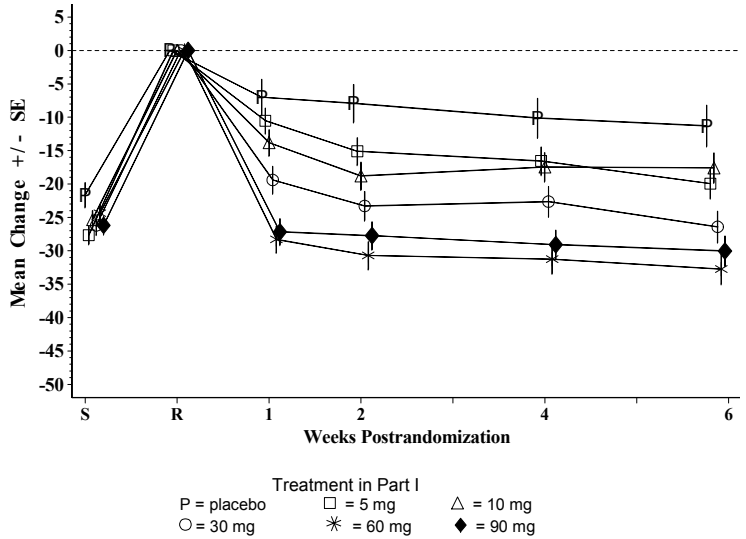
In addition, efficacy superior to placebo was also demonstrated in measures of stiffness and tenderness based on the WOMAC Stiffness Subscale and Study Joint Tenderness questionnaire.

Part II (weeks 7-14) through Extension 2 (weeks 15-52) evaluated etoricoxib doses 30, 60, and 90 mg and diclofenac for up to 52 weeks in the subset of patients who completed Part I, and were assigned to 1 of these 4 treatment groups (predetermined at the time of study randomization). Data provided through the 52 weeks (right panel of Figure 5) demonstrated the sustained efficacy of etoricoxib over the 1-year treatment period. These data also demonstrate that the numerically greater efficacy observed for etoricoxib 60 and 90 mg versus etoricoxib 30 mg in Part I was generally maintained over a treatment period of up to 52 weeks. In addition, diclofenac provided efficacy similar to etoricoxib 60 mg (data not shown).

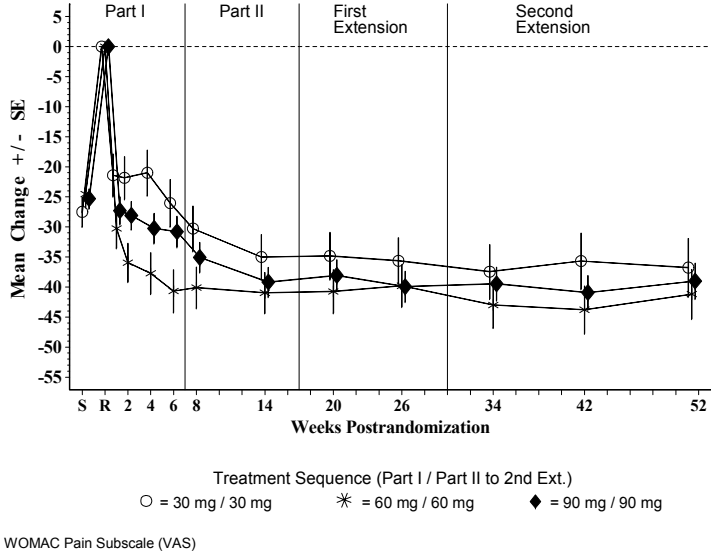
Figure 5

Phase IIb OA Study (Protocol 007)
WOMAC Pain Subscale (VAS): LS Mean Change From Baseline

Part I (6-week Treatment Period)



Part I Through the Second Extension (52-week Treatment Period)



Modified Intention-to-Treat Approach. WOMAC Pain Subscale: 100 mm: Visual Analogue Scale (VAS). Baseline defined as Visit 2 of Part I of the study.
Screening (S) to baseline (R) = NSAID washout period; SE = Standard error. Week number for each treatment group was shifted along the x-axis to maximize legibility.

Table 8

Phase IIb OA Study (P007) Part I
Primary Efficacy Endpoints
Time-Weighted Average Responses

Treatment Group	Pain Subscale (WOMAC)[§] (0- to 100-mm VAS)		Patient Global Assessment of Response to Therapy (0- to 4-point Likert Scale)		Investigator Global Assessment of Disease Status[§] (0- to 4-point Likert Scale)	
	LS Mean Change From Baseline (95% CI)	LS Mean Difference From Placebo (95% CI)	LS Mean Change From Baseline (95% CI)	LS Mean Difference From Placebo (95% CI)	LS Mean Change From Baseline (95% CI)	LS Mean Difference From Placebo (95% CI)
Placebo (N=57 to 58)	-10.22 (-15.58, -4.86)	NA	NA	NA	-0.75 (-0.95, -0.54)	NA
Etoricoxib 5 mg (N=114 to 115)	-17.83 (-21.61, -14.05)	-7.61 (-14.16, -1.05)[‡]	NA	-0.51 (-0.81, -0.21)[†]	-1.07 (-1.22, -0.93)	-0.33 (-0.58, -0.08)[‡]
Etoricoxib 10 mg (N=105)	-19.80 (-23.75, -15.86)	-9.58 (-16.23, -2.94)[‡]	NA	-0.57 (-0.88, -0.27)[†]	-1.07 (-1.22, -0.92)	-0.32 (-0.58, -0.07)[‡]
Etoricoxib 30 mg (N=102)	-24.08 (-28.08, -20.08)	-13.86 (-20.55, -7.17)[†]	NA	-0.66 (-0.97, -0.35)[†]	-1.20 (-1.35, -1.04)	-0.45 (-0.70, -0.20)[†]
Etoricoxib 60 mg (N=109 to 110)	-32.52 (-36.39, -28.64)	-22.29 (-28.91, -15.68)[†]	NA	-1.21 (-1.51, -0.90)[†]	-1.58 (-1.73, -1.43)	-0.83 (-1.09, -0.58)[†]
Etoricoxib 90 mg (N=109)	-29.38 (-33.25, -25.51)	-19.16 (-25.76, -12.55)[†]	NA	-1.04 (-1.34, -0.73)[†]	-1.45 (-1.60, -1.30)	-0.70 (-0.95, -0.45)[†]

[†] $p<0.001$; [‡] $p<0.05$.
[§]Average baseline means were as follows: Pain subscale ~69; Investigator global ~2.9.
LS Mean=Least-squares mean, CI=Confidence interval, VAS=Visual analog scale, NA=Not applicable, WOMAC=Western Ontario McMaster Universities.

5.3 Phase III OA Studies

5.3.1 60 mg Etoricoxib (Protocols 018, 019)

Based on the results of Protocol 007, which demonstrated that 60 mg was the minimal dose with maximal efficacy, replicate Phase III studies (P018, P019) evaluating etoricoxib 60 mg (versus placebo and versus total daily doses of naproxen 1000 mg) were conducted over a 12-week placebo-controlled treatment period (Part I). These studies also included a Part II during which patients receiving etoricoxib 60 mg or naproxen 1000 mg during Part I remained on their allocated treatment for up to 52 weeks. Patients treated with placebo in Part I were reassigned in a blinded manner (determined prior to randomization) to etoricoxib 60 mg or naproxen 500 mg twice daily. The results for the WOMAC Pain Subscale over the 12-week period are shown in Figure 6 for Protocols 18 and 19 and the analyses of all 3 primary endpoints for are in Table 9.

Over the 12-week Part I treatment period, etoricoxib 60 mg showed significantly greater efficacy compared with placebo across all 3 primary endpoints in both studies demonstrating that etoricoxib 60 mg is effective in the treatment of OA. The efficacy of

etoricoxib was comparable to naproxen based on the point estimates for the 3 primary endpoints falling within the prespecified comparability bounds of ±10 mm on the 100 mm VAS.

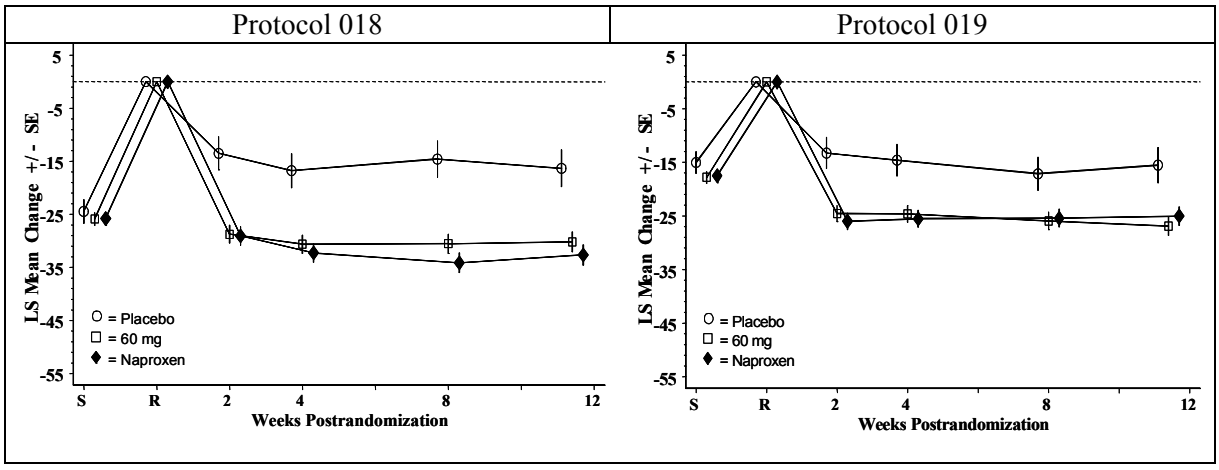
For each primary endpoint, the mean baseline values were between 65 mm and 70 mm on the 0- to 100-mm VAS, indicating that etoricoxib was clinically active in a patient population that was affected by a substantial degree of pain and disability from their OA.

Additional endpoints including assessments of treatment effect from both the patients' and investigators' perspectives, specific and global assessments of the symptoms including the WOMAC Stiffness Subscale, joint tenderness, and physical impairment resulting from OA were all consistent with those of the primary endpoints. Efficacy was consistent in patients with OA of the knee versus those with OA of the hip.

Part II of both Protocols 018 and 019 demonstrated that efficacy of etoricoxib was maintained throughout the 1-year treatment period.

Figure 6

Phase III 60 mg OA Studies (P018, P019)
WOMAC Pain Subscale (LS Mean Change From Baseline)



Modified Intention-to-Treat Approach. WOMAC Pain Subscale: 100 mm: Visual Analogue Scale (VAS) Baseline defined as Visit 2 of Part I of the study. Screening (S) to baseline (R) = NSAID washout period; SE = Standard error. Week number for each treatment group was shifted along the horizontal axis to maximize legibility.

Table 9

Phase III 60 mg OA Studies (P018, 019) Part I
Primary Efficacy Endpoints
Time-Weighted Average Responses

Treatment Group	Pain Subscale (WOMAC) [§] (0- to 100-mm VAS)		Physical Function Scale (WOMAC) [§] (0- to 100-mm VAS)		Patient Global Assessment of Disease Status[§] (0- to 100-mm VAS)	
	LS Mean Change From Baseline (95% CI)	LS Mean Difference From Placebo (95% CI)	LS Mean Change From Baseline (95% CI)	LS Mean Difference From Placebo (95% CI)	LS Mean Change From Baseline (95% CI)	LS Mean Difference From Placebo (95% CI)
Protocol 018						
Placebo (N=55)	-15.74 (-21.54, -9.94)	NA	-8.84 (-14.54, -3.14)	NA	-10.50 (-16.51, -4.50)	NA
Etoricoxib 60 mg (N=220)	-30.41 (-33.51, -27.31)	-14.67 (-20.89, -8.45)[†]	-25.19 (-28.24, -22.15)	-16.35 (-22.47, -10.24)[†]	-27.10 (-30.31, -23.90)	-16.60 (-23.04, -10.16)[†]
Naproxen 1000 mg (N=217)	-32.27 (-35.42, -29.11)	-16.53 (-22.57, -10.30)[†]	-27.28 (-30.39, -24.18)	-18.44 (-24.56, -12.32)[†]	-29.10 (-32.36, -25.83)	-18.59 (-25.04, -12.15)[†]
Protocol 019						
Placebo (N=56)	-15.33 (-20.70, -9.96)	NA	-12.46 (-17.80, -7.12)	NA	-16.59 (-22.26, -10.92)	NA
Etoricoxib 60 mg (N=222 to 223)	-25.76 (-28.58, -22.94)	-10.44 (-16.30, -4.58)[†]	-20.88 (-23.69, -18.08)	-8.42 (-14.25, -2.60)[†]	-25.93 (-28.90, -22.95)	-9.34 (-15.53, -3.14)[‡]
Naproxen 1000 mg (N=218 to 219)	-25.32 (-28.13, -22.50)	-9.99 (-15.86, -4.12)[†]	-20.73 (-23.53, -17.93)	-8.27 (-14.11, -2.43)[†]	-24.18 (-27.15, -21.21)	-7.59 (-13.79, -1.39)[‡]

[†] $p<0.001$; [‡] $p<0.05$
[§]Average baseline means were as follows: Pain subscale ~68; Physical function ~66; Patient global ~69
LS Mean=Least-squares mean, CI=Confidence interval, VAS=Visual analog scale, NA=Not applicable, WOMAC=Western Ontario McMaster Universities.

Additional Endpoints of Interest

Protocol 018 also specifically evaluated OA of the hand using the AUSCAN questionnaire that included the AUSCAN Pain, Stiffness, and Physical Function Subscales. The AUSCAN and the Patient Global Assessment of Response to Therapy for OA of the Hand were both evaluated over the 12-week treatment period. Results showed that both etoricoxib 60 mg and naproxen 1000 mg provided similar efficacy which was significantly ($p<0.001$) greater than placebo in the treatment of OA of the hand.

Onset and duration of efficacy was specifically evaluated in Protocols 018 and 019. In both studies onset of treatment effect was demonstrated within the first 24 hours following randomization to etoricoxib and duration was at least 24 hours.

5.3.2 30 mg Etoricoxib (Protocols 071, 073, 076, 077)

The data from the Phase IIb study indicated that etoricoxib 30 mg exceeded the boundaries for clinically important effects for 2 of the 3 primary efficacy endpoints (WOMAC Pain Subscale and Patient Global Assessment of Response to Therapy) and was borderline for clinically meaningful effects for the third primary efficacy endpoint (Investigator Assessment of Disease Status). Thus, additional Phase III studies were conducted to further evaluate etoricoxib 30 mg.

Replicate 12-week placebo-controlled studies (Protocols 071 and 073) were carried out comparing etoricoxib 30 mg once daily to ibuprofen 800 mg three times daily. Etoricoxib demonstrated significant ($p<0.001$) and clinically meaningful improvements compared with placebo for all 3 primary endpoints (Figure 7). The efficacy of etoricoxib was comparable to (and numerically, slightly greater than) ibuprofen based on the point estimates for the 3 primary endpoints falling within the prespecified comparability bounds of ±10 mm on the 100 mm VAS, with treatment effects maintained over the 12-week treatment period.

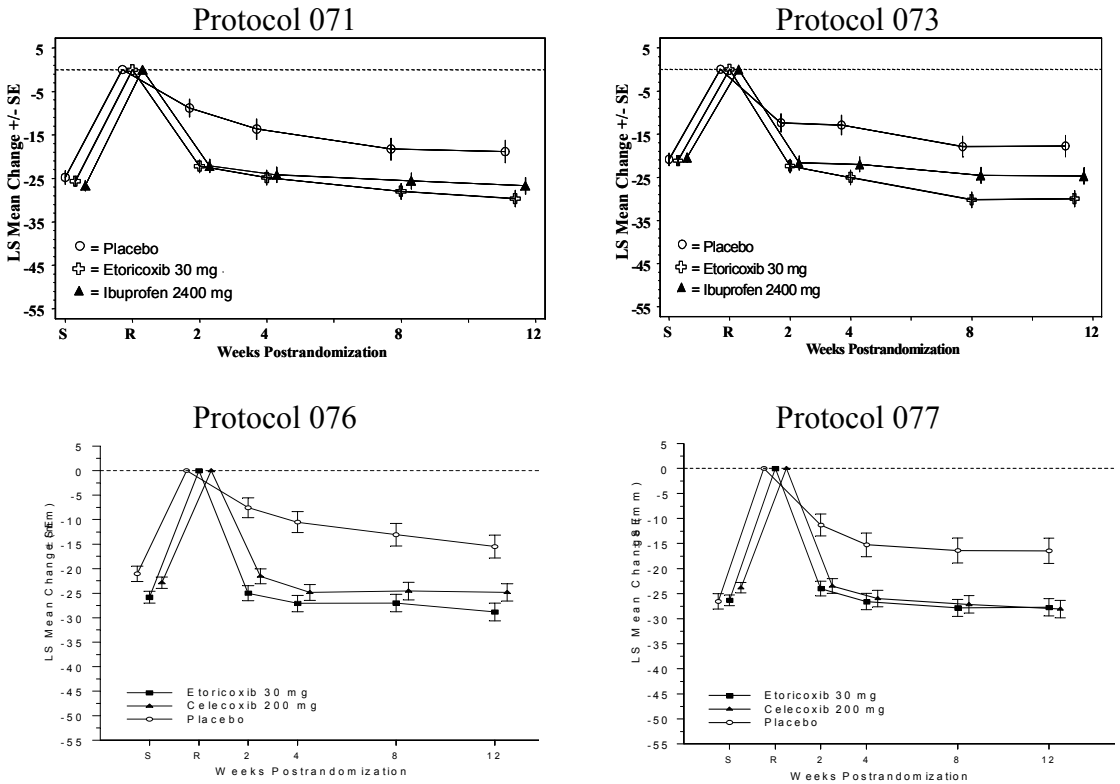
Replicate studies (Protocols 076 and 077) were also carried out over a 12-week placebo-controlled treatment period (Part I), and subsequently over an additional 14-week active-comparator-controlled treatment period (Part II) for etoricoxib 30 mg once daily versus celecoxib 200 mg once daily. The results were very similar to what had been observed in Protocols 071 and 071. Over the 12-week treatment period, etoricoxib 30 mg demonstrated significant ($p<0.001$) and clinically meaningful improvements compared with placebo for all 3 primary endpoints. Again, the efficacy of etoricoxib was comparable to (and numerically, slightly greater than) celecoxib based on the same prespecified comparability bounds described above.

Figure 7 (bottom of figure) illustrates the 12-week treatment period for Protocols 076 and 077; results were similar between Protocols 076 and 077 (Table 10).

For each of the primary endpoints in all 4 of these Phase III 30 mg studies, near maximal efficacy was demonstrated by Week 2 and was maintained throughout the entire 12-week treatment periods. The results for the key secondary endpoints (including measurements of stiffness), as well as other endpoints (including joint tenderness) were consistent in showing significantly greater treatment effects than placebo for etoricoxib 30 mg with similar effects to ibuprofen 2400 mg and to celecoxib 200 mg. Efficacy was consistent in patients with OA of the knee versus those with OA of the hip (evaluated in pooled data from Protocols 076 and 077) . Results for Part II of Protocols 076 and 077 demonstrated efficacy was maintained for etoricoxib 30-mg and celecoxib 200-mg treatment groups throughout the 26-week treatment period.

Figure 7

Phase III 30 mg OA Studies (P071, P073, P076, P077)
WOMAC Pain Subscale LS Mean Change From Baseline
12-Week Treatment Period



Modified Intention-to-Treat Approach, WOMAC Pain Subscale: 100 mm:Visual Analogue Scale (VAS) Baseline defined as Visit 2 of Part I of the study. Screening (S) to baseline (R) = NSAID washout period; SE = Standard error. Week number for each treatment group was shifted along the horizontal axis to maximize legibility.

Table 10

Phase III 30 mg OA Studies (P071, 073, 076, 077)
Primary Efficacy Endpoints
Time-Weighted Average Responses

Treatment Group	Pain Subscale[§] (WOMAC) (0- to 100-mm VAS)		Physical Function Scale[§] (WOMAC) (0- to 100-mm VAS)		Patient Global Assessment of Disease Status[§] (0- to 100-mm VAS)	
	LS Mean Change From Baseline (95% CI)	LS Mean Difference From Placebo (95% CI)	LS Mean Change From Baseline (95% CI)	LS Mean Difference From Placebo (95% CI)	LS Mean Change From Baseline (95% CI)	LS Mean Difference From Placebo (95% CI)
Protocol 071						
Placebo (N=100 to 101)	-16.36 (-20.59, -12.13)	NA	-13.55 (-17.69, -9.40)	NA	-16.53 (-20.99, -12.06)	NA
Etoricoxib 30 mg (N=209 to 212)	-26.90 (-29.97, -23.83)	-10.54 (-15.47, -5.60)[†]	-23.68 (-26.72, -20.65)	-10.14 (-14.98, -5.29)[†]	-27.89 (-31.13, -24.65)	-11.36 (-16.57, -6.16)[†]
Ibuprofen 2400 mg (N=207 to 209)	-25.25 (-28.40, -22.11)	-8.89 (-13.84, -3.94)[†]	-22.97 (-26.06, -19.88)	-9.42 (-14.28, -4.57)[†]	-26.53 (-29.83, -23.22)	-10.00 (-15.22, -4.78)[†]
Protocol 073						
Placebo (N=107 to 109)	-16.47 (-20.55, -12.40)	NA	-13.56 (-17.59, -9.54)	NA	-17.85 (-22.41, -13.29)	NA
Etoricoxib 30 mg (N=219 to 220)	-28.14 (-31.23, -25.04)	-11.66 (-16.31, -7.01)[†]	-23.71 (-26.78, -20.65)	-10.15 (-14.74, -5.57)[†]	-29.50 (-32.91, -26.10)	-11.65 (-16.81, -6.50)[†]
Ibuprofen 2400 mg (N=209 to 211)	-24.10 (-27.20, -20.99)	-7.62 (-12.30, -2.94)[‡]	-20.80 (-23.87, -17.72)	-7.23 (-11.85, -2.61)[‡]	-25.97 (-29.39, -22.54)	-8.11 (-13.30, -2.92)[‡]
Protocol 076						
Placebo (N=125 to 126)	-12.31 (-16.31, -8.32)	NA	-10.38 (-14.29, -6.47)	NA	-13.99 (-18.16, -9.83)	NA
Etoricoxib 30 mg (N=228)	-27.38 (-30.46, -24.30)	-15.07 (-19.72, -10.41)[†]	-23.24 (-26.24, -20.24)	-12.86 (-17.40, -8.31)[†]	-30.44 (-33.66, -27.21)	-16.44 (-21.31, -11.57)[†]
Celecoxib 200 mg (N=236)	-24.26 (-27.29, -21.23)	-11.95 (-16.57, -7.32)[†]	-21.50 (-24.45, -18.54)	-11.11 (-15.63, -6.59)[†]	-26.39 (-29.55, -23.23)	-12.39 (-17.23, -7.56)[†]
Protocol 077						
Placebo (N=111 to 112)	-15.21 (-19.49, -10.94)	NA	-11.44 (-15.60, -7.28)	NA	-12.48 (-16.88, -8.09)	NA
Etoricoxib 30 mg (N=243)	-26.77 (-29.68, -23.86)	-11.56 (-16.45, -6.67)[†]	-22.90 (-25.73, -20.07)	-11.46 (-16.22, -6.71)[†]	-28.34 (-31.33, -25.35)	-15.86 (-20.88, -10.83)[†]
Celecoxib 200 mg (N=246)	-26.91 (-29.86, -23.96)	-11.70 (-16.56, -6.83)[†]	-22.82 (-25.69, -19.95)	-11.38 (-16.11, -6.65)[†]	-28.40 (-31.42, -25.37)	-15.91 (-20.92, -10.91)[†]

[†] $p<0.001$, calculated based on pairwise t-tests and error variance from analysis of covariance.
[‡] $p<0.05$, calculated based on pairwise t-tests and error variance from analysis of covariance.
[§] Average baseline means were as follows: Pain subscale ~67; Physical function ~66; Patient global ~71
LS Mean=Least-squares mean, CI=Confidence interval, VAS=Visual analog scale, NA=Not applicable, WOMAC=Western Ontario McMaster Universities.

5.3.3 Additional OA Efficacy Data

Diclofenac OA Study (Protocol 805)

Protocol 805 was a 6-week, Phase III, active-comparator-controlled, double-blind study that evaluated the safety and efficacy of etoricoxib 60 mg and diclofenac 150 mg in patients with OA of the knee or hip. This study was designed to further test the efficacy of the 60 mg dose in patients with OA against a commonly used traditional NSAID. The effect of etoricoxib 60 mg daily was comparable to the effect of diclofenac150 mg daily over 6 weeks as assessed by the primary endpoint (WOMAC Pain subscale), (-31.3 units for etoricoxib and -30.9 units for diclofenac) and similar to the effect of diclofenac 150 mg daily over 6 weeks as assessed by the secondary endpoints (WOMAC Stiffness Subscale and WOMAC Physical Function Subscale).

Ibuprofen and Naproxen Gastroduodenal Ulcer Studies (Protocols 026, 029)

Efficacy measurements were exploratory in Protocols 026 and 029, which were Phase III, placebo and active-comparator-controlled, double-blind studies that evaluated the incidence of gastric and/or duodenal ulcers after 12 weeks. In Protocol 026, etoricoxib 120 mg was similar to naproxen, and both etoricoxib and naproxen were superior to placebo. In Protocol 029, there was a significantly greater improvement in the etoricoxib 120-mg treatment group compared to ibuprofen or placebo treatment groups. The improvement in the ibuprofen treatment group was also significantly greater than that observed in the placebo group.

MEDAL Program Studies

In all 3 MEDAL Program studies, the Patient Global Assessment of Disease Status (PGADS) was collected. In addition, the Investigator Global Assessment of Disease Status (IGADS) was also collected in the MEDAL Study. Similar improvements from baseline values for each of these endpoints were observed for etoricoxib and diclofenac with no clinically important difference between treatment groups with respect to average change from baseline.

Efficacy Conclusions

- Once daily treatment with etoricoxib 30 mg shows comparable efficacy to ibuprofen 2400 mg (800 mg 3 times daily) and to celecoxib 200 mg once daily in patients with OA. Improvements were seen across multiple domains including pain, physical function, and patient as well as investigator assessments of disease
- Etoricoxib 60 mg demonstrates efficacy that is superior to etoricoxib 30 mg based on Protocol 007.
- Once daily treatment with etoricoxib 60 mg shows comparable efficacy to naproxen 1000 mg (500 mg 2 times daily) and to diclofenac 150 mg (50 mg 3 times daily) in patients with OA. Efficacy of etoricoxib for OA is measurable following a single dose, duration of efficacy is maintained over the 24 hour dosing interval, and efficacy persists over the duration evaluated.

6. Overview of Safety

Table 11 summarizes the planned safety analyses for the OA Development and MEDAL Programs. A description of each safety population, referred to in Table 11 can be found in Section 3.1.

General safety and renovascular safety were assessed using data from the 11 studies in the OA Development Program. The primary comparison of general safety in the OA Development Program was the comparison to placebo over 6 to 12 weeks (Placebo-Controlled Population). The 6-Month and 1-Year Active-Comparator-Controlled Populations of the OA Development Program provide data for longer durations of exposure relative to commonly used NSAIDs. Formal statistical analyses for certain adverse experiences were prespecified for the Placebo-Controlled Population. Thrombotic CV safety and upper GI safety, were analyzed based on pooled data from all 18 Etoricoxib Development Program studies. GI tolerability was analyzed based on pooled data from 16 of the 18 Etoricoxib Development Program studies; the two surveillance endoscopy studies were not included because they had different entry criteria including the restriction of GI medications. In the MEDAL Program, the safety endpoints were divided into the following categories: thrombotic CV endpoints, an overall mortality endpoint, upper and lower GI clinical event endpoints, and general safety endpoints. The primary objective of the MEDAL Program was to compare the thrombotic CV safety of etoricoxib to diclofenac based on pooled data from the entire MEDAL Program, therefore, thrombotic CV safety data were analyzed primarily based on Pooled MEDAL Program data. Analyses of GI safety (upper and lower) and mortality were also performed based on the Pooled MEDAL Program data to maximize precision. Assessments of general safety, however, were carried out based on data from the individual MEDAL Program Studies (MEDAL, EDGE II, and EDGE). Each study was large enough to have sufficient precision to evaluate general safety endpoints and analyzing the studies individually provided an opportunity to evaluate for consistency of the results.

Table 11

OA Development, Etoricoxib Development, and MEDAL Programs
Prespecified Data Analyses

Safety Domain	OA Development Program and Etoricoxib Development Programs	MEDAL Program Dataset			
		Pooled MEDAL Program	MEDAL Study (OA, RA)	EDGE II Study (RA)	EDGE Study (OA)
Thrombotic Cardiovascular	• Pooled across the Etoricoxib Development Program by comparator population (PBO-, Naproxen-, and non-naproxen NSAID controlled datasets) with diseases and doses combined • By Dose as a subgroup analysis	• By Overall Treatment Group (etoricoxib vs. diclofenac, with diseases and doses combined) • By Disease and Dose as a subgroup analysis	• By Overall Treatment Group (etoricoxib vs. diclofenac, with diseases and doses combined)	• By Treatment Group	• By Treatment Group
Overall Mortality	• Pooled across the Etoricoxib Development Program (PBO, non-naproxen, and naproxen NSAIDs with diseases and doses combined)	• By Overall Treatment Group (etoricoxib vs. diclofenac, with diseases and doses combined)	• Incidence only (By Overall Treatment Group; etoricoxib vs. diclofenac, with diseases and doses combined)	• Incidence only	• Incidence only
Lower GI safety	• Not assessed	• By Overall Treatment Group (etoricoxib vs. diclofenac, with diseases and doses combined) • By Disease and Dose as a subgroup analysis	▪ Not assessed within individual MEDAL Program studies		
Upper GI safety	• Pooled across the Etoricoxib Development Program by comparator population (PBO, traditional NSAID controlled datasets) with diseases and doses combined • By Dose as a subgroup analysis	• By Overall Treatment Group (etoricoxib vs. diclofenac, with diseases and doses combined) • By Disease and Dose as a subgroup analysis	• Not assessed within individual MEDAL Program studies		
GI Tolerability	• Pooled across the Etoricoxib Development Program by comparator population (traditional NSAID controlled datasets) with diseases and doses combined	• Not assessed using Pooled MEDAL Program data†	• By Disease and Dose	• By Treatment Group	• By Treatment Group
General Safety including Renovascular Safety	• Prespecified AEs for OA Development Program PBO-controlled population. • Incidence only for all others (PBO-controlled, and 6-Month and 1-Year Populations from OA Development Program).	• Not assessed using Pooled MEDAL Program data†	• By Disease and Dose	• By Treatment Group	• By Treatment Group

AE=Adverse Experience; OA=Osteoarthritis; PBO= Placebo; NSAID=Nonsteroidal Anti-inflammatory Drug; RA=Rheumatoid Arthritis.
†A post-hoc analysis of pooled data was carried out.

The general safety endpoints in both the OA Development Program and MEDAL Program were each divided into 3 categories (Tier 1, Tier 2 and Tier 3) based on the prespecified criteria as described below:

- General Safety Tier 1 endpoints – these were prespecified safety endpoints of special interest (e.g., hypertension and edema adverse experiences) for which hypothesis testing for difference between treatments was carried out.
- General Safety Tier 2 endpoints – these were all other observed general safety adverse experiences which occur more than rarely (defined as ≥8 events in any pair of treatments combined). No hypothesis testing was carried out for Tier 2 endpoints; however, 95% confidence intervals (CIs) for difference in proportions between treatments were provided.
- General Safety Tier 3 endpoints – these were rare but potentially clinically important events, which occurred in fewer than 8 patients in any pair of treatments combined. No statistical analyses were performed for Tier 3 endpoints; rather, they were summarized by counts and percents of patients within treatment groups.

Further inferential statistics for Tier 1 and Tier 2 endpoints were carried out for the OA Development Program using a Cochran-Mantel-Haenszel (CMH) method with protocol as a stratification factor. It is important to note that a difference in event rate (percentage points) by CMH method (comparing only studies with both comparators) for all Tier 1 and Tier 2 adverse experiences are not the same as the difference comparing two treatment groups provided in the overall summaries. The CMH method includes only the protocols in which two treatment groups are directly compared. This situation does not exist within the MEDAL Program studies for which general safety comparisons were based on each study separately due to the large size of the individual studies.

6.1 General Safety

This section summarizes the general safety data from the OA Development Program and MEDAL Program. The following specific safety domain data from these Programs are discussed within each of the following sections and are not repeated here: GI (Section 7), thrombotic CV (Section 8), and renovascular (Section 9). However, all investigator-reported adverse experiences that were collected for each individual study, regardless of type and regardless of whether they were adjudicated, are included in the adverse experience tables which follow. Within this section, the general safety data from the OA Development Program are presented in following order: Placebo-Controlled, 6-Month, and 1-Year Populations. This is followed by data from the MEDAL Program.

Within this section, when tables are presented for Tier-2 analyses, the specific adverse experiences (or organ system if applicable) with potential treatment group differences, based on 95% CIs for differences from placebo that excluded 0 are ***BOLDED and ITALICIZED***. In the case of MEDAL Program studies, corresponding data for the other MEDAL Program studies are provided as well and are presented in plain text.

The adverse experience data from the OA Development Program are summarized in tables for the Placebo-Controlled Population and in text for the 6-Month and 1-Year Populations given that the primary evaluation of general safety was assessed in the Placebo-Controlled Population. Furthermore, the evaluation of adverse experiences with potential treatment group differences (Tier 2) was applied to all adverse experiences that are summarized in tables. Adverse experiences that were serious or resulted in discontinuation are presented in the text for completeness.

6.1.1 Overall and Specific Clinical Adverse Experiences

6.1.1.1 OA Development Program

Table 12 provides the analysis of prespecified clinical adverse experience summaries (Tier 1) for the Placebo-Controlled Population. Naproxen 1000 mg and ibuprofen 2400 mg were associated with a significantly higher incidence of clinical adverse experiences relative to placebo ($p<0.05$).

Table 12

6- to 12-Week Placebo-Controlled Population
Analysis of Prespecified Clinical Adverse Experience Summaries

Adverse Experience (AE) Category	Treatment Group[†]	Frequency Patients With AEs[‡] n/N	(%)	Differences From Placebo in Percentage Points[§]	95% CI on Treatment Differences vs. Placebo	p-Value[§] for Difference vs. Placebo
One or more clinical adverse experiences	Placebo	483/1035	(46.7)			
	Etoricoxib 30 mg	480/1014	(47.3)	2.18%	(-3.04, 7.40)	0.416
	Etoricoxib 60 mg	324/558	(58.1)	6.74%	(-1.86, 15.34)	0.124
	Etoricoxib 90 mg	110/220	(50.0)	7.47%	(-2.52, 17.47)	0.145
	Etoricoxib 120 mg	159/288	(55.2)	3.17%	(-4.93, 11.27)	0.444
	Naproxen 1000 mg	311/494	(63.0)	12.10%	(3.17, 21.04)	0.007
	Ibuprofen 2400 mg	407/756	(53.8)	6.39%	(0.90, 11.88)	0.023
	Celecoxib 200 mg	222/488	(45.5)	2.98%	(-4.53, 10.50)	0.441
Drug-related clinical adverse experiences	Placebo	171/1035	(16.5)			
	Etoricoxib 30 mg	184/1014	(18.1)	3.89%	(0.14, 7.64)	0.051
	Etoricoxib 60 mg	114/558	(20.4)	1.46%	(-5.15, 8.07)	0.677
	Etoricoxib 90 mg	38/220	(17.3)	1.64%	(-5.93, 9.21)	0.667
	Etoricoxib 120 mg	89/288	(30.9)	8.61%	(1.47, 15.74)	0.019
	Naproxen 1000 mg	149/494	(30.2)	14.98%	(7.86, 22.11)	<0.001
	Ibuprofen 2400 mg	225/756	(29.8)	11.52%	(6.96, 16.08)	<0.001
	Celecoxib 200 mg	66/488	(13.5)	2.33%	(-2.61, 7.27)	0.370
Serious clinical adverse experiences	Placebo	21/1035	(2.0)			
	Etoricoxib 30 mg	10/1014	(1.0)	-0.97%	(-2.29, 0.36)	0.114
	Etoricoxib 60 mg	7/558	(1.3)	0.43%	(-1.05, 1.92)	0.609
	Etoricoxib 90 mg	5/220	(2.3)	2.03%	(0.25, 3.81)	0.075
	Etoricoxib 120 mg	7/288	(2.4)	-1.02%	(-3.76, 1.72)	0.467
	Naproxen 1000 mg	9/494	(1.8)	-0.34%	(-2.47, 1.78)	0.790
	Ibuprofen 2400 mg	16/756	(2.1)	0.64%	(-0.82, 2.11)	0.410
	Celecoxib 200 mg	11/488	(2.3)	-1.00%	(-3.61, 1.61)	0.422
Discontinued due to clinical adverse experiences	Placebo	63/1035	(6.1)			
	Etoricoxib 30 mg	44/1014	(4.3)	-1.69%	(-4.08, 0.71)	0.147
	Etoricoxib 60 mg	28/558	(5.0)	-1.77%	(-5.93, 2.38)	0.364
	Etoricoxib 90 mg	19/220	(8.6)	3.49%	(-1.69, 8.68)	0.199
	Etoricoxib 120 mg	24/288	(8.3)	3.15%	(-0.92, 7.21)	0.130
	Naproxen 1000 mg	49/494	(9.9)	2.9%	(-2.88, 7.05)	0.433
	Ibuprofen 2400 mg	66/756	(8.7)	3.22%	(0.46, 5.97)	0.029
	Celecoxib 200 mg	20/488	(4.1)	-3.30%	(-7.03, 0.43)	0.058

Only protocols that involved both treatments were included, hence some differences in percentage points by CMH method are not necessarily similar to the arithmetic differences based on all combined protocols.
[†] The 400-mg Celecoxib group was not analyzed as this comparator was only included in a single study.
[‡] Overall numbers, not stratified by protocol.
[§] By Cochran-Mantel-Haenszel (CMH) method with protocol as a stratification factor. If no events were observed in all protocols, 95% CI and CMH p-value were not computed.

Specific clinical adverse experiences with potential treatment differences versus placebo (based on the CMH method) and 95% CI of the differences not including zero for the Placebo-Controlled Population are summarized in Table 13. In general, these findings are consistent with the adverse experiences typically associated with the use of NSAIDs. No other clinically meaningful differences between-treatment groups were noted. A detailed discussion of edema-related and hypertension-related adverse experiences can be found in Sections 9.1 and 9.2, respectively.

Table 13

6- to 12-Week Placebo-Controlled Population
Patients With Specific Clinical Adverse Experiences
95% CIs for Difference Between Treatments Which Exclude Zero
Based on the CMH Method (Tier 2 Criteria)

	Placebo (N=1035)	Etoricoxib 30 mg (N= 1014)	Etoricoxib 60 mg (N = 558)	Etoricoxib 90 mg (N = 220)	Etoricoxib 120 mg (N = 288)	Naproxen 1000 mg (N = 494)	Ibuprofen 2400 mg (N = 756)	Celecoxib 200 mg (N = 488)
	%	%	%	%	%	%	%	%
Patients With One Or More Adverse Experiences	46.7	47.3	58.1	50.0	55.2	63.0	53.8	45.5
Gastrointestinal Disorders	15.7	15.0	19.0	17.7	31.3	32.4	27.2	11.3
Abdominal Pain Upper	1.4	1.4	2.0	1.4	3.8	4.7	***4.6*** †	0.8
Constipation	0.9	1.1	1.6	1.8	1.4	***3.8*** †	1.7	0.6
Dry Mouth	0.4	0.4	***0.9*** †	0.5	1.0	0.6	0.9	0.2
Dyspepsia	4.8	2.9	4.1	1.8	13.9	***9.9*** †	7.8	1.4
Toothache	0.2	0.2	***1.1*** †	0.0	0.3	0.6	0.3	0.0
Vomiting	1.2	0.6	***1.1*** †	0.5	1.7	***2.0*** †	1.6	0.8
General Disorders And Administration Site Conditions	5.1	6.6	7.7	4.1	6.6	10.1	7.4	5.5
Asthenia	0.6	0.5	1.4	0.0	1.7	***2.2*** †	0.8	0.2
Oedema	0.2	0.7	0.2	0.9	1.4	0.4	***1.5*** †	0.2
Oedema Peripheral	1.5	2.7	2.9	1.4	2.1	2.6	***3.0*** †	2.5
Infections And Infestations	12.9	12.4	18.6	12.7	10.1	17.2	13.9	12.3
Nasopharyngitis	2.3	2.1	***3.2*** †	3.2	1.0	3.8	2.8	1.4
Sinusitis	1.2	1.5	1.1	1.4	1.4	1.2	1.2	***1.4*** †
Urinary Tract Infection	1.3	2.9	2.9	0.9	1.7	***2.6*** †	***2.5*** †	2.5
Musculoskeletal And Connective Tissue Disorders	8.1	6.0	8.8	5.9	7.6	8.9	5.2	9.4
Muscle Spasms	0.7	0.2	***1.6*** †	0.5	***2.1*** †	***1.8*** †	0.9	1.4
Nervous System Disorders	6.6	7.1	11.8	8.6	7.6	8.9	7.7	8.0
Dizziness	1.1	1.6	2.2	2.7	2.4	3.4	1.3	***2.7*** †
Headache	3.2	3.3	***5.6*** †	4.1	3.5	3.8	4.2	3.7
Psychiatric Disorders	1.9	2.4	3.6	2.7	1.4	3.6	1.6	1.4
Depression	0.3	0.9	0.5	0.9	0.0	***0.8*** †	0.5	0.0
Vascular Disorders	3.3	3.9	5.7	3.6	6.3	4.3	6.1	1.8
Hypertension	2.3	***3.0*** †	4.5	2.7	6.3	3.0	***5.4*** †	0.8

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Data are bolded and italicized for specific adverse experiences in those treatment groups for which the 95% CIs excluded 0.

† For the indicated adverse experience and the indicated value, the 95% CI for the difference versus placebo does not include zero based on the CMH method stratified by protocol.

The CMH analysis provided above stratified by protocol includes only the protocols in which 2 treatment groups are directly compared. In order to further evaluate the Placebo-Controlled Population, a pooled review of all Tier 2 clinical adverse experiences (i.e., those that occurred in ≥8 patients between the 2 groups being compared) was performed via a nonstratified approach (using Wilson's score method) as a screening tool. Specific clinical adverse experiences with potential treatment differences versus placebo (based on Wilson's scores) and 95% CI of the differences not including zero are summarized in Table 14. Data are bolded and italicized for specific adverse experiences in those treatment groups for which the 95% CIs for the difference from placebo excluded 0.

As each approach has its limitations using these 2 analyses aid in the clinical review of adverse experiences. In general, the two screening methods identified the same adverse experiences. The nonstratified method identified a limited number of additional adverse experiences, but they were generally within the same overall category (e.g., gastrointestinal disorders).

Table 14

6- to 12-Week Placebo-Controlled Population
Patients With Specific Clinical Adverse Experiences
95% CIs for Difference Between Treatments Which Exclude Zero
Based on Wilson's Score (Tier 2 Criteria)

	Placebo (N=1035)	Etoricoxib 30 mg (N= 1014)	Etoricoxib 60 mg (N = 558)	Etoricoxib 90 mg (N = 220)	Etoricoxib 120 mg (N = 288)	Naproxen 1000 mg (N = 494)	Ibuprofen 2400 mg (N = 756)	Celecoxib 200 mg (N = 488)
	%	%	%	%	%	%	%	%
Patients With One Or More Adverse Experiences	46.7	47.3	58.1	50.0	55.2	63.0	53.8	45.5
Gastrointestinal Disorders	15.7	15.0	19.0	17.7	31.2	32.4	27.2	11.3
Abdominal Distension	0.3	0.5	0.4	0.9	***2.1***†	0.8	***1.3***†	0.2
Abdominal Pain	1.8	***0.8***†	1.2	0.0	3.1	***4.0***†	2.4	1.0
Abdominal Pain Upper	1.3	1.4	2.0	1.4	***3.8***†	***4.7***†	***4.6***†	0.8
Constipation	0.9	1.1	1.6	1.8	1.4	***3.8***†	1.7	0.6
Dyspepsia	4.8	***2.9***†	4.1	***1.8***†	***13.9***†	***9.9***†	***7.8***†	***1.4***†
Flatulence	1.2	0.9	1.6	***3.1***†	0.7	1.4	1.3	0.2
Nausea	3.1	2.2	3.0	3.2	4.2	***6.3***†	2.9	1.8
Toothache	0.2	0.2	***1.1***†	0.0	0.3	0.6	0.3	0.0
General Disorders And Administration Site Conditions	5.1	6.6	7.7	4.1	6.6	10.1	7.4	5.5
Asthenia	0.6	0.5	1.4	0.0	1.7	***2.2***†	0.8	0.2
Fatigue	0.3	0.7	0.2	0.0	0.0	0.0	0.1	***1.2***†
Oedema	0.2	0.7	0.2	0.9	***1.4***†	0.4	***1.5***†	0.2
Oedema Peripheral	1.5	2.7	2.9	1.4	2.1	2.6	***3.0***†	2.5

Table 14 (Cont.)

6- to 12-Week Placebo-Controlled Population
Patients With Specific Clinical Adverse Experiences
95% CIs for Difference Between Treatments Which Exclude Zero
Based on Wilson's Score (Tier 2 Criteria)

	Placebo (N=1035)	Etoricoxib 30 mg (N= 1014)	Etoricoxib 60 mg (N = 558)	Etoricoxib 90 mg (N = 220)	Etoricoxib 120 mg (N = 288)	Naproxen 1000 mg (N = 494)	Ibuprofen 2400 mg (N = 756)	Celecoxib 200 mg (N = 488)
	%	%	%	%	%	%	%	%
Infections And Infestations	12.9	12.4	18.6	12.7	10.1	17.2	13.9	12.3
Upper Respiratory Tract Infection	2.2	1.9	***5.9***†	1.4	0.7	***4.1***†	2.2	2.2
Urinary Tract Infection	1.3	***2.9***†	***2.9***†	0.9	1.7	2.6	2.5	2.5
Injury, Poisoning and Procedural Complications	4.0	4.2	2.7	6.8	8.0	3.0	3.0	6.3
Contusion	0.3	***1.1***†	0.5	***1.4***†	1.0	0.6	0.0	1.0
Investigations	1.1	1.6	1.6	2.7	2.4	1.2	1.8	1.0
Blood pressure increased	0.4	0.6	0.2	***1.8***†	0.3	0.6	0.8	0.2
Musculoskeletal And Connective Tissue Disorders	8.1	6.0	8.8	5.9	7.6	8.9	5.2	9.4
Muscle Spasms	0.7	0.2	1.6	0.4	***2.1***†	***1.8***†	0.9	1.4
Nervous System Disorders	6.6	7.1	11.8	8.6	7.6	8.9	7.7	8.0
Dizziness	1.1	1.6	2.2	2.7	2.4	***3.4***†	1.3	2.7
Headache	3.2	3.2	***5.6***†	4.1	3.5	3.8	4.2	3.7
Respiratory, Thoracic, and Mediastinal Disorders	3.6	4.0	3.4	2.7	2.8	5.9	5.2	4.5
Cough	0.7	0.8	***1.8***†	0.4	0.7	1.6	1.6	0.8
Vascular Disorders	3.3	3.9	5.7	3.6	6.2	4.2	6.1	1.8
Hypertension	2.3	3.0	***4.5***†	2.7	***6.2***†	3.0	***5.4***†	***0.8***†

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
The 400-mg Celecoxib group was not included in this analysis
Data are bolded and italicized for specific adverse experiences in those treatment groups for which the 95% CIs excluded 0.
† For the indicated adverse experience and the indicated value, the 95% CI for the difference versus placebo does not include zero based on the Wilson's score method; no stratification employed.

In the 6-Month Population, the overall incidence of clinical adverse experiences was generally similar between the etoricoxib 30-mg and celecoxib 200-mg groups: 57.8% and 56.6%, respectively. Apart from differences in the incidence of GI- and renovascular-

related adverse experiences which are discussed in Sections 7 and 9, respectively, no notable differences were observed across the treatments in the incidence of specific clinical adverse experiences.

In the 1-Year Population, the overall incidence of clinical adverse experiences was generally similar across the treatment groups: 78.2%, 79.9%, 82.1%, and 83.6% in the etoricoxib 30-, 60-, 90-mg, and naproxen 1000-mg groups, respectively. Aside from differences in the incidence of GI- and renovascular-related adverse experiences which are discussed in Sections 7 and 9, respectively, there were no clinically meaningful differences observed among treatment groups for any specific clinical adverse experience.

Although not included in any of the defined populations, a brief summary for the OA Long-Term (beyond 52 Weeks) Active-Comparator Population is provided for completeness. This population is based on extension data from Protocols 007, 018, and 019 with a maximum study length of 190 weeks. In this Population, the overall incidence of clinical adverse experiences was generally similar between the treatment groups; 79.1%, 85.4%, and 83.4% in the etoricoxib 60-mg, diclofenac 150-mg, and naproxen 1000-mg groups, respectively. Overall, there were few new clinical adverse experiences of importance that occurred in Long-Term Population compared with the Placebo-Controlled and 1-Year Populations. The incidences of most clinical adverse experiences with etoricoxib were generally similar to those seen with naproxen and diclofenac. Any differences noted were small and not clinically meaningful.

6.1.1.2 EDGE II and EDGE Studies

An overall summary of the clinical adverse experiences for the EDGE II and EDGE studies is presented in Table 15. In the EDGE II study the overall incidence of clinical adverse experiences was higher in the etoricoxib 90-mg group compared with the diclofenac group. In the EDGE study no statistically significant differences were observed between etoricoxib 90-mg and diclofenac group in any summary categories.

The collection of adverse experiences in the MEDAL Study was limited to those that were serious or resulted in discontinuation (explained in Section 3.3.1.2) and therefore an overall summary of the MEDAL study using the same categories as presented below for the EDGE and EDGE II studies is not possible. An overall summary of the MEDAL study is presented separately in Section 6.1.2.

Table 15

EDGE II (RA) and EDGE (OA)
Clinical Adverse Experience Summary

	EDGE II			EDGE		
	Etoricoxib 90 mg (N=2032)	Diclofenac 150 mg (N=2054)	Difference in Percentages (95% CI)	Etoricoxib 90 mg (N=3593)	Diclofenac 150 mg (N=3518)	Difference in Percentages (95% CI)
Number (%) of Patients	%	%	Etoricoxib vs. Diclofenac	%	%	Etoricoxib vs. Diclofenac
With one or more adverse experiences	84.2	80.6	3.6 (1.3, 6.0)	76.1	74.4	1.8 (-0.2, 3.8)
With no adverse experience	15.8	19.4	-3.6 (-6.0, -1.3)	23.9	25.6	-1.8 (-3.8, 0.2)
With drug-related adverse experiences†	45.7	44.3	1.5 (-1.6, 4.5)	39.2	37.1	2.0 (-0.2, 4.3)
With serious adverse experiences	17.1	18.3	-1.2 (-3.5, 1.2)	8.3	8.7	-0.3 (-1.6, 1.0)
With serious drug-related adverse experiences†	2.9	3.2	-0.3 (-1.3, 0.8)	1.2	1.4	-0.2 (-0.7, 0.4)
Who died	1.2	0.9	0.3 (-0.3, 1.0)	0.2	0.2	0.1 (-0.2, 0.3)
Discontinued due to adverse experiences‡	20.3	18.9	1.4 (-1.0, 3.9)	17.5	17.3	0.2 (-1.6, 1.9)
Discontinued due to drug-related adverse experiences†	13.6	13.1	0.5 (-1.6, 2.6)	12.8	13.0	-0.2 (-1.7, 1.4)
Discontinued due to serious adverse experiences	6.3	6.2	0.2 (-1.3, 1.7)	3.0	3.0	0.1 (-0.7, 0.9)
Discontinued due to serious drug-related adverse experiences†	2.1	2.6	-0.5 (-1.5, 0.4)	1.0	1.1	-0.1 (-0.6, 0.4)

†Determined by the investigator as possibly, probably, or definitely drug-related.
‡ Includes 1 patient on diclofenac in the EDGE Study who discontinued due to an "other" type of clinical adverse experience.
Includes adverse experiences up to and including 14 days post study therapy.

Table 16 presents all specific clinical adverse experiences with potential treatment differences, based on 95% CIs that excluded 0, observed in either the EDGE II or EDGE studies.

A higher incidence of non-cardiac chest pain was noted in the EDGE II Study but was not observed consistently in the other MEDAL Program Studies or in the Etoricoxib Development Program. There was a higher incidence of palpitation adverse experiences noted in the etoricoxib group of the EDGE Study relative to diclofenac and a similar trend in the EDGE II study but a trend was not observed in the Etoricoxib Development Program.

Table 16

EDGE II (RA) and/or EDGE (OA)
Patients With Specific Clinical Adverse Experiences With
95% CIs for Difference Between Treatments Which Exclude Zero (Tier 2 Criteria)

	EDGE II		EDGE	
	Etoricoxib 90 mg (N=2032)	Diclofenac 150 mg (N=2054)	Etoricoxib 90 mg (N=3593)	Diclofenac 150 mg (N=3518)
Number (%) of Patients	%	%	%	%
With one or more adverse experience	***84.2***	***80.6***	76.1	74.4
Cardiac Disorders	7.3	6.9	***5.3***	***3.9***
Cardiac Failure Congestive	***0.5***	***0.1***	0.3	0.2
Palpitations	1.1	0.6	***1.1***	***0.6***
Tachycardia	***0.3***	***0.8***	0.4	0.2
Ventricular Extrasystoles	***0.6***	***0.1***	0.2	0.2
Ear and Labyrinth Disorders	4.2	3.6	2.9	2.8
Vertigo	***2.6***	***1.4***	1.3	1.2
Eye Disorders	5.2	4.5	2.6	2.3
Conjunctivitis	***1.3***	***0.6***	0.5	0.3
Vision Blurred	***0.4***	***0.0***	0.1	0.2
Gastrointestinal Disorders	39.9	40.1	34.7	36.6
Abdominal Pain	***2.6***	***3.7***	***2.6***	***3.5***
Abdominal Pain Lower	0.1	0.1	***0.8***	***0.4***
Abdominal Pain Upper	9.8	10.1	***4.5***	***6.1***
Colitis	0.05†	0.2	***0.03***†	***0.2***
Constipation	***1.4***	***2.4***	***2.7***	***4.1***
Diarrhoea	9.1	9.7	***6.1***	***8.0***
Gastric Ulcer	***0.4***	***1.0***	0.4	0.3
Gastritis Erosive	0.6	0.4	***0.1***	***0.3***
Haemorrhoidal Haemorrhage	0.3	0.2	***0.1***	***0.4***
Mouth Ulceration	1.2	0.7	***0.4***	***0.1***
Nausea	***6.3***	***4.8***	4.7	5.5
Oesophagitis	0.7	0.3	***0.1***	***0.4***
Reflux Oesophagitis	***0.4***	***0.05***†	0.2	0.1
General Disorders and Administration Site Conditions	***12.0***	***9.8***	***13.5***	***11.7***
Non-Cardiac Chest Pain	***1.5***	***0.6***	0.5	0.3
Oedema	2.1	1.4	***1.4***	***0.8***
Oedema Peripheral	***4.4***	***2.8***	5.4	4.7
Pyrexia	***0.4***	***1.0***	0.3	0.5
Infections and Infestations	39.0	37.6	29.5	28.3
Herpes Zoster	***2.3***	***1.5***	0.5	0.5
Influenza	4.0	4.5	***2.8***	***1.8***
Onychomycosis	1.1	1.1	***0.5***	***0.2***
Injury, Poisoning and Procedural Complications	10.3	9.6	8.5	8.0
Contusion	***1.8***	***0.9***	1.5	1.1
Fall	***0.1***	***0.5***	0.3	0.3
Foot Fracture	***0.4***	***0.05***†	0.3	0.5
Investigations	***6.3***	***4.8***	***6.3***	***5.2***
Blood Pressure Increased	1.7	1.3	***2.8***	***1.4***
Electrogardiogram abnormal	0.05†	0.0	***0.2***	***0.03***†
Metabolism and Nutrition Disorders	5.7	5.6	3.3	3.1
Fluid Retention	0.1	0.3	***0.5***	***0.2***
Nervous System Disorders	***19.1***	***16.7***	***17.1***	***14.4***
Dysgeusia	0.8	0.4	***1.2***	***0.2***
Headache	7.4	6.4	***6.8***	***5.5***
Migraine	0.6	0.6	***0.6***	***0.3***

Table 16 (Cont.)

EDGE II (RA) and/or EDGE (OA)
Patients With Specific Clinical Adverse Experiences With
95% CIs for Difference Between Treatments Which Exclude Zero (Tier 2 Criteria)

	EDGE II		EDGE	
	Etoricoxib 90 mg (N=2032)	Diclofenac 150 mg (N=2054)	Etoricoxib 90 mg (N=3593)	Diclofenac 150 mg (N=3518)
Psychiatric Disorders	9.2	8.6	4.8	3.8
Anxiety	1.9	1.4	***1.2***	***0.5***
Depression	***2.4***	***3.5***	1.4	1.2
Renal and Urinary Disorders	4.1	3.3	2.2	2.4
Nephrolithiasis	***1.2***	***0.4***	0.2	0.3
Respiratory, Thoracic and Mediastinal Disorders	10.5	9.2	9.5	8.5
Rhinorrhoea	***0.1***	***0.4***	0.3	0.3
Skin and Subcutaneous Tissue Disorders	13.1	11.2	8.0	7.6
Alopecia	0.8	0.8	***0.5***	***0.1***
Dermatitis	***1.1***	***0.5***	0.3	0.3
Dermatitis Allergic	0.7	0.4	***0.1***	***0.3***
Vascular Disorders	***21.1***	***16.5***	***11.1***	***6.5***
Hypertension	***17.4***	***13.7***	***8.7***	***4.3***

† incidence displayed to second decimal place to identify values with number of events >1
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
Data are bolded and italicized for specific adverse experiences in those treatment groups for which the 95% CIs excluded 0.

6.1.2 Overall Summary of Clinical Adverse Experiences in the MEDAL Study

An overall summary of clinical adverse experiences for the MEDAL Study is presented in Table 17. In the OA 60-mg Cohort a higher incidence of clinical adverse experiences considered serious or resulting in discontinuation was reported in the diclofenac treatment group. For patients in the OA 90-mg Cohort the incidence of clinical adverse experiences considered serious or resulting in discontinuation was similar between etoricoxib and diclofenac. In RA patients, a higher incidence of serious clinical adverse experiences was reported in the etoricoxib group than in the diclofenac group.

Table 17

MEDAL Study (OA/RA)
Clinical Adverse Experience Summary
Clinical Adverse Experiences Considered Serious or Resulting in Discontinuation‡

	Osteoarthritis						Rheumatoid Arthritis		
	60 mg vs. Diclo Cohort			90 mg vs. Diclo Cohort					
	E 60 mg N=6769	D 150 mg N=6700	Difference in Proportions (95% CI)†	E 90 mg N=2171	D 150 mg N=2162	Difference in Proportions (95% CI)†	E 90 mg N=2841	D 150 mg N=2855	Difference in Proportions (95% CI)†
AE Name	%	%	E 60 mg – D 150 mg	%	%	E 90 mg - D 150 mg	%	%	E 90 mg - D 150 mg
With 1 or more AEs considered serious or resulting in discontinuation	27.5	29.1	-1.60 (-3.12, 0.08)	36.9	35.6	1.33 (-1.54, 4.18)	32.3	30.9	1.35 (-1.07, 3.76)
With drug-related AEs considered serious or resulting in discontinuation§	10.9	12.6	-1.72 (-2.81, -0.64)	17.2	16.1	1.04 (-1.18, 3.26)	13.6	14.6	-0.98 (-2.79, 0.82)
With serious AEs	17.4	17.6	-0.22 (-1.51, 1.06)	21.0	19.5	1.49 (-0.91, 3.88)	21.4	18.9	2.45 (0.37, 4.53)
With serious drug-related§ AEs	2.5	2.4	0.06 (-0.46, 0.59)	4.6	2.9	1.65 (0.52, 2.79)	4.1	3.6	0.51 (-0.49, 1.52)
Who died	0.7	0.9	-0.14 (-0.45, 0.16)	0.6	0.6	-0.00 (-0.49, 0.49)	1.2	1.1	0.04 (-0.52, 0.61)
Discontinued due to AEs	16.7	18.0	-1.29 (-2.57, -0.01)	26.0	24.6	1.42 (-1.17, 4.00)	20.2	19.9	0.31 (-1.77, 2.39)
Discontinued due to drug-related §	10.4	12.0	-1.61 (-2.68, -0.55)	16.3	15.7	0.53 (-1.65, 2.72)	13.1	14.1	-0.99 (-2.77, 0.79)
Discontinued due to serious AEs	6.0	6.0	-0.00 (-0.80, 0.80)	9.3	7.7	1.58 (-0.08, 3.24)	8.6	6.9	1.69 (0.30, 3.08)
Discontinued due to serious drug-related AEs §	2.0	1.8	0.16 (-0.31, 0.62)	3.6	2.4	1.19 (0.17, 2.22)	3.5	3.1	0.44 (-0.50, 1.38)

† 95% confidence interval (CI) is calculated by Wilson's Score Method.
‡ The MEDAL Study collected only adverse experiences considered serious and/or those resulting in discontinuation.
§ Determined by the investigator to be possibly, probably or definitely drug related.
Includes adverse experiences up to and including the 14-day post study therapy, unless otherwise noted.
Although a patient may have had two or more adverse experiences, the patient is counted only once in the overall category. The same patient may appear in different categories.
AE = adverse experience.

6.1.3 Specific Fatal and Non-fatal Serious Clinical Adverse Experiences

6.1.3.1 OA Development Program

In the Placebo-Controlled Population (Table 12), the incidence of nonfatal serious adverse experiences was low (≤1.0%) and similar across the treatment groups. However, based on CMH analysis, a significantly higher incidence ($p<0.05$) of serious adverse experiences was noted in the celecoxib 200 mg group versus the etoricoxib 30 mg group. This increase was not attributable to any specific adverse experience.

In the 6-Month Population, the overall incidence of serious adverse experiences was numerically higher in the celecoxib group (3.9%) compared with the etoricoxib group (1.7%). No one specific nonfatal serious adverse experience accounted for this difference other than a numerically higher incidence of osteoarthritis in the celecoxib group compared with the etoricoxib group

In the 1-Year Population, the overall incidence of serious nonfatal adverse experiences was similar among the etoricoxib 60- (7.1%), 90-mg (7.1%), and naproxen (8.0%) groups and no patient in the etoricoxib 30-mg group experienced a serious nonfatal adverse experience. Apart from the higher incidence of GI-related adverse experiences in the naproxen 1000 mg group as compared with the etoricoxib 60- and 90-mg groups (see Section 7), there were no notable differences for the 1-Year Population in the incidence of serious nonfatal clinical adverse experiences.

6.1.3.1.1 Mortality—Etoricoxib Development Program

Table 18 and Figure 8 summarize mortality rates (per 100 patient-years of exposure in each treatment group), including total, CV, thrombotic CV, and non-CV mortality. The rates, calculated by dividing the absolute number of fatalities by the total treatment exposure, are provided to factor in imbalances in exposure between treatment groups. The mortality rates are low and similar across all treatment groups as noted by the broadly overlapping confidence intervals.

All deaths were adjudicated by the Vascular Events Adjudication Committee to determine specific cause of death. A death was considered a CV death if the term for cause of death belonged on the comprehensive list of CV terms eligible for adjudication of potential thrombotic CV events. Deaths reported with CV terms not considered to be thrombotic (e.g., aortic dissection, cardiomyopathy), and any death confirmed by the VEC as a thrombotic CV death regardless of investigator reported term were also classified as CV Death.

A total of 29 patients died in the Etoricoxib Development Program, either while taking study medication, or within 14 days of discontinuing study medication, or as a result of a serious adverse experience that began within 14 days of discontinuing study drug. All deaths occurred in Phase IIb/III Chronic Exposure Studies (OA, RA, AS, CLBP); none occurred in Phase I/Clinical Pharmacology, Acute Analgesia, or Acute Gouty Arthritis studies.

Table 18

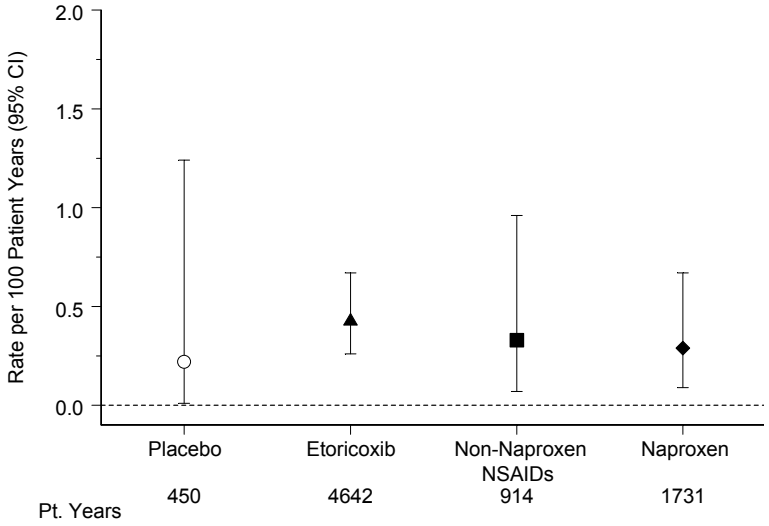
Etoricoxib Development Program
Summary of Mortality

	Placebo PYR = 450	Etoricoxib PYR = 4642	Non-Naproxen NSAIDs PYR = 914	Naproxen PYR = 1731
Rates per 100 PYR (95% CI)[Number of Patients]				
Total No. of Deaths†	**0.22 (0.01, 1.24) [1]**	**0.43 (0.26, 0.67) [20]**	**0.33 (0.07, 0.96) [3]**	**0.29 (0.09, 0.67) [5]**
CV Deaths	0.00 (0.00, 0.82) [0]	0.22 (0.10, 0.40) [10]	0.22 (0.03, 0.79) [2]	0.17 (0.04, 0.51) [3]
Thrombotic CV Deaths‡	0.00 (0.00, 0.82) [0]	0.19 (0.09, 0.37) [9]	0.22 (0.03, 0.79) [2]	0.12 (0.01, 0.42) [2]
Non-CV Deaths	0.22 (0.01, 1.24) [1]	0.22 (0.10, 0.40) [10]	0.11 (0.00, 0.61) [1]	0.12 (0.01, 0.42) [2]

† Total Deaths includes CV deaths + Non-CV deaths.
‡ Thrombotic CV deaths is a subset of CV deaths

Figure 8

Etoricoxib Development Program
Mortality Rates Per 100 Patient-Years (95% CI)



6.1.3.2 MEDAL Program

6.1.3.2.1 MEDAL Program Studies

Fatal and nonfatal serious clinical adverse experiences with treatment differences, based on 95% CIs are summarized in Table 19. In the MEDAL Study, compared to diclofenac, lumbar spinal stenosis was higher in the etoricoxib 90 mg group in OA patients but lower in the etoricoxib 60 mg group in OA patients. In the OA 60-mg Cohort a higher incidence of the serious adverse experience of basal cell carcinoma was noted for etoricoxib compared with diclofenac. However, both of these adverse experiences do not appear to be dose-related and were not consistently observed across the different studies; in fact, the incidence of lumbar spinal stenosis on etoricoxib was 0% in the EDGE study. Aside from differences in the incidence of GI-related adverse experiences and renovascular-related adverse experiences, which are discussed in Sections 7 and 9, respectively, there were no other clinically meaningful differences between groups in the incidence of serious clinical adverse experiences.

Table 19

MEDAL Study (OA/RA), EDGE II (RA), EDGE (OA)
Patients With Specific Fatal and Nonfatal Serious Clinical Adverse Experiences
95% CIs for Difference Between Treatments Which Exclude Zero (Tier 2 Criteria)

	MEDAL Study (OA)				MEDAL Study (RA)		EDGE II		EDGE	
	60 mg vs. Diclo Cohort		90 mg vs. Diclo Cohort							
	E 60 mg N=6769	D 150 mg N=6700	E 90 mg N=2171	D 150 mg N=2162	E 90 mg N=2841	D 150 mg N=2855	E 90 mg N=2032	D 150 mg N=2054	E 90 mg N=3593	D 150 mg N=3518
Number (%) of Patients	%	%	%	%	%	%	%	%	%	%
With one or more adverse experiences	17.4	17.6	21.0	19.5	***21.4***	***18.9***	17.1	18.3	8.3	8.7
Cardiac Disorders	2.9	2.7	4.9	4.7	***3.8***	***2.7***	2.6	2.8	1.5	1.1
Cardiac Failure Congestive	0.1	0.2	***1.0***	***0.4***	0.6	0.3	0.3	0.05†	0.2	0.1
General Disorders And Administration Site Conditions	0.7	0.7	1.0	1.2	***1.1***	***0.6***	0.8	0.4	0.5	0.4
Non-Cardiac Chest Pain	0.4	0.4	0.7	0.9	***0.7***	***0.2***	0.4	0.1	0.1	0.1
Hepatobiliary Disorders	0.5	0.6	0.4	0.6	0.5	0.5	0.3	0.6	***0.2***	***0.6***
Infections and Infestations	1.9	2.3	1.8	1.9	4.5	4.2	3.5	4.1	1.0	0.7
Diverticulitis	0.1	0.1	0.05†	0.1	***0.1***	***0.3***	0.1	0.05†	0.0	0.0
Injury, Poisoning And Procedural Complications	1.7	1.6	1.7	1.2	***2.5***	***1.4***	2.1	2.3	0.6	0.8
Investigations	0.1	0.1	0.1	0.0	0.1	0.1	***0.0***	***0.4***	0.1	0.1
Musculoskeletal And Connective Tissue Disorders	3.9	4.4	4.3	4.0	3.6	4.1	4.3	3.9	1.1	1.5
Lumbar Spinal Stenosis	***0.04***†	***0.2***	***0.5***	***0.1***	0.04†	0.1	0.05†	0.05†	0.0	0.0
Neoplasms Benign, Malignant And Unspecified Including Cysts and Polyps	2.3	1.9	2.5	2.8	2.5	1.9	1.6	1.8	1.3	1.2
Basal Cell Carcinoma	***0.5***	***0.3***	0.5	0.7	0.3	0.3	0.2	0.2	0.4	0.2

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
Data are bolded and italicized for specific adverse experiences in those treatment groups for which the 95% CIs excluded 0.
This table was run using a "percent incidence". This means that a row will appear on this report only if one of the columns is greater than or equal to that percentage, after rounding.
Includes adverse experiences up to and including the 14-day post study therapy.
† incidence displayed to second decimal place to identify values with number of events >1

6.1.3.2.2 Pooled MEDAL Program

A summary of overall mortality by system organ class is presented in Table 20. Overall mortality was balanced between treatment groups. A numerical imbalance between the etoricoxib and diclofenac treatment groups in cardiac disorders was observed, due primarily to more cardiac arrests including cardio-respiratory arrest in the diclofenac group than the etoricoxib group (9 versus 4, respectively) and more myocardial infarctions in the diclofenac group versus the etoricoxib group (17 versus 6, respectively) in the MEDAL Program.

The fatal events presented in Table 20 were categorized into cardiovascular versus non-cardiovascular causes and these results are presented in Table 21. The primary purpose of adjudicating all MEDAL Program deaths was to determine which of the deaths were associated with a thrombotic cardiovascular event. If a thrombotic CV event could not be confirmed, no further categorization of the death as cardiovascular or non-cardiovascular was made by the adjudication committee. Thus, in order to categorize the deaths into CV (including CHF) versus non-CV causes, the investigator-reported term was used. A death was considered a CV death if the term for cause of death belonged on the comprehensive list of CV terms eligible for adjudication of potential thrombotic CV events. Deaths reported with CV terms not considered to be thrombotic (e.g., aortic dissection, cardiomyopathy), and any death confirmed by the VEC as a thrombotic CV death regardless of investigator reported term were also classified as CV Death. Fatal serious adverse experiences reported with eligible CHF terms were classified as CHF death. Deaths which did not meet criteria for inclusion as either CV or CHF death were categorized as non-CV deaths.

An additional mortality analysis ('ITT') was performed to include all serious adverse experiences resulting in death with an onset date on or before the Eligibility Date (defined as Last Patient Out +28 Days) and reported up to the Ascertainment Date (defined as Last Patient Out + 42 Days) in each individual MEDAL Program study. The results (Table 21) are consistent with the primary mortality analysis with similar mortality rates between treatment groups across all the categories.

Table 20

Pooled MEDAL Program (OA/RA)
Summary of Mortality by System Organ Class

	Etoricoxib (N = 17412)		Diclofenac (N = 17289)	
	n	(%)	n	(%)
Patients with one or more adverse experience	127	(0.7)	127	(0.7)
Patients with no adverse experience	17285	(99.3)	17162	(99.3)
Blood And Lymphatic System Disorders	0	(0.0)	1	(0.0)
Cardiac Disorders	28	(0.2)	42	(0.2)
Gastrointestinal Disorders	5	(0.0)	8	(0.0)
General Disorders And Administration Site Conditions	17	(0.1)	11	(0.1)
Hepatobiliary Disorders	0	(0.0)	2	(0.0)
Infections And Infestations	28	(0.2)	19	(0.1)
Injury, Poisoning And Procedural Complications	2	(0.0)	3	(0.0)
Metabolism And Nutrition Disorders	1	(0.0)	1	(0.0)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	32	(0.2)	37	(0.2)
Nervous System Disorders	17	(0.1)	7	(0.0)
Psychiatric Disorders	0	(0.0)	2	(0.0)
Renal And Urinary Disorders	4	(0.0)	3	(0.0)
Respiratory, Thoracic And Mediastinal Disorders	13	(0.1)	12	(0.1)
Skin And Subcutaneous Tissue Disorders	0	(0.0)	1	(0.0)
Vascular Disorders	6	(0.0)	4	(0.0)

Includes all deaths with event onset date up to and including the 14-day post study therapy, unless otherwise noted.
Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
Given the large sample sizes, differences in the number of patients may exist without reflecting a difference in the incidence (%) due to rounding to the 1st decimal place.

Table 21

Pooled MEDAL Program
Summary of Mortality

Deaths	Etoricoxib (N = 17412)			Diclofenac (N = 17289)		
	n†	Rate‡	95% CI	n†	Rate‡	95% CI
14 day mITT Approach§						
Patient-Years	26423			25430		
Total No. of Deaths	127	0.48	(0.40, 0.57)	127	0.50	(0.42, 0.59)
CV Deaths, CHF Deaths	65	0.25	(0.19, 0.31)	66	0.26	(0.20, 0.33)
CHF Deaths	6	0.02	(0.01, 0.05)	7	0.03	(0.01, 0.06)
Non-CV, Non-CHF Deaths	62	0.23	(0.18, 0.30)	61	0.24	(0.18, 0.31)
ITT Approach‖						
Patient-Years	40185			39886		
Total No. of Deaths	195	0.49	(0.42, 0.56)	182	0.46	(0.39, 0.51)
CV Deaths, CHF Deaths	125	0.31	(0.26, 0.37)	116	0.29	(0.24, 0.35)
CHF Deaths	9	0.02	(0.01, 0.04)	10	0.03	(0.01, 0.05)
Non-CV, Non-CHF Deaths	70	0.17	(0.14, 0.22)	66	0.17	(0.13, 0.21)

† Crude incidence rate (%) = (n/N)x 100.

‡ Rate = Events per 100 patient-years.

§ Includes all serious adverse experiences resulting in death with an onset date up to and including the 14-day post study therapy, unless otherwise noted.

‖ Includes all serious adverse experiences resulting in death with an onset date on or before the Eligibility Date (defined as Last Patient Out +28 Days) and reported up to the Ascertainment Date (defined as Last Patient Out + 42 Days) in each individual MEDAL Program Study.

Note: For one patient, there was no serious adverse experience associated with death in the database and the investigator believed the death was due to noncardiac source. The event was adjudicated as a confirmed thrombotic death. This was not included in total deaths, but was considered in the analysis of confirmed thrombotic deaths per committee's decision.

CV: Cardiovascular, CHF: Congestive Heart Failure.

6.1.4 Discontinuations Due to Specific Clinical Adverse Experiences

6.1.4.1 OA Development Program

In the Placebo-Controlled Population, a significantly higher incidence of discontinuations due to clinical adverse experiences was noted for ibuprofen versus both placebo and etoricoxib 30 mg ($p<0.05$) as well as for naproxen versus etoricoxib 60 mg ($p<0.05$) (Table 12). Apart from differences in the incidence of GI-related adverse experiences (see Section 7 for further discussion), no significant differences were noted.

In the 6-Month Population, the overall incidence of discontinuations due to clinical adverse experiences in the 6-Month Population was generally similar for etoricoxib 30 mg and celecoxib 200 mg: 5.9% and 7.0%, respectively.

In the 1-Year Population, the incidence of discontinuations due to clinical adverse experiences was higher for naproxen (18.7%) than for any etoricoxib group (7.3-12.6%) due largely to a higher incidence of discontinuations in the GI Disorders Organ System (see Section 7 for further information on GI adverse experiences). In addition, there was a higher incidence of discontinuations in the Nervous System Disorders Organ System for etoricoxib 30 mg (1.8%) and 60 mg (1.6%) compared with the etoricoxib 90 mg (0%) or naproxen (0.2%) groups, although this was not attributable to any one adverse experience.

6.1.4.2 MEDAL Program Studies

Table 22 presents all specific clinical adverse experiences resulting in discontinuation with potential treatment differences, based on 95% CIs that excluded 0. In both the OA and RA patients of the MEDAL Study, more patients on etoricoxib 90 mg discontinued due to atrial fibrillation. This imbalance was not observed in the 60 mg OA Cohort.

An assessment was carried out for the patients in the MEDAL Study 90-mg OA cohort who had adverse experiences of either atrial fibrillation or atrial flutter that resulted in discontinuation or were serious. The initial assessment included an evaluation of all patients in the 90-mg OA cohort who had a history of one or more medical conditions typically associated with atrial fibrillation. These medical conditions included a history of atrial fibrillation, CHF, hypertension, atherosclerotic CV disease, diabetes, or valvular heart disease. There were a slightly greater incidence of patients in the etoricoxib 90 mg group than in the diclofenac group who had a history of one or medical conditions typically associated with atrial fibrillation; 60.5% versus 58.3%, respectively. Of the patients who had atrial fibrillation adverse experiences, 87% in the etoricoxib group and 67% in the diclofenac group had a history of one or more of these medical conditions associated with atrial fibrillation.

Differences in the incidence of GI- and renovascular-related adverse experiences were also observed in the MEDAL Study; these are discussed in Sections 7 and 9, respectively.

In both the EDGE II and EDGE studies, no clinically meaningful differences were noted between treatment groups aside from differences in the incidence of GI- and renovascular-related adverse experiences which are discussed in Sections 7 and 9, respectively. The imbalance noted in the MEDAL 90 mg OA and RA cohorts for atrial fibrillation was not observed in either EDGE II or EDGE: 0.3% versus 0.2% for etoricoxib 90 mg and diclofenac 150 mg, respectively, in EDGE II, and 0.2% versus 0.1% for etoricoxib 90 mg and diclofenac 150 mg, respectively, in EDGE.

Table 22

MEDAL Study (OA/RA), EDGE II (RA), EDGE (OA)
Patients Discontinued Due to Specific Clinical Adverse Experiences
95% CIs for Difference Between Treatments Which Exclude Zero (Tier 2 Criteria)

	MEDAL Study (OA)				MEDAL Study (RA)		EDGE II		EDGE	
	60 mg vs. Diclo Cohort		90 mg vs. Diclo Cohort							
	E 60 mg N=6769	D 150 mg N=6700	E 90 mg N=2171	D 150 mg N=2162	E 90 mg N=2841	D 150 mg N=2855	E 90 mg N=2032	D 150 mg N=2054	E 90 mg N=3593	D 150 mg N=3518
% of Patients	%	%	%	%	%	%	%	%	%	%
With one or more adverse experiences	***16.7***	***18.0***	26.0	24.6	20.2	19.9	20.3	18.9	17.5	17.3
Cardiac Disorders	2.1	1.9	3.7	3.2	2.6	2.2	1.8	2.3	1.3	0.9
Atrial Fibrillation	0.3	0.2	***0.8***	***0.3***	0.3	0.1	0.3	0.2	0.2	0.1
Myocardial Infarction	0.4	0.4	0.7	0.7	0.4	0.6	***0.3***	***0.8***	0.3	0.2
Gastrointestinal Disorders	***4.7***	***7.0***	***8.8***	***11.3***	***5.1***	***8.2***	5.8	7.3	***7.1***	***9.0***
Abdominal Discomfort	***0.04***†	***0.2***	***0.4***	***1.0***	0.4	0.2	0.2	0.2	0.1	0.1
Abdominal Pain	***0.4***	***0.6***	***0.5***	***1.1***	0.1	0.4	0.2	0.4	***0.7***	***1.2***
Diarrhoea	***0.4***	***1.1***	***0.6***	***1.6***	***0.5***	***1.0***	0.6	1.0	***0.6***	***1.3***
Duodenal Ulcer	0.1	0.1	0.2	0.1	***0.1***	***0.3***	0.3	0.2	0.1	0.1
Dyspepsia	0.8	0.9	1.0	1.0	***0.2***	***0.6***	0.7	0.9	1.4	1.2
Gastric Ulcer	***0.3***	***0.6***	0.4	0.8	0.8	1.3	***0.2***	***0.8***	0.3	0.1
Gastroesophageal Reflux Disease	***0.1***	***0.3***	0.7	0.6	0.2	0.2	0.0	0.05†	0.3	0.4
General Disorders and Administration Site Conditions	1.4	1.1	2.3	1.6	1.4	1.1	1.6	1.1	1.4	1.2
Oedema	0.3	0.2	***0.8***	***0.1***	0.2	0.1	***0.6***	***0.2***	0.1	0.2
Hepatobiliary Disorders	***0.1***	***0.3***	0.1	0.1	0.04†	0.1	0.05†	0.3	0.1	0.1
Infections And Infestations	0.5	0.6	0.2	0.5	***1.1***	***0.6***	1.2	0.7	0.4	0.3
Investigations	0.3	0.3	***1.0***	***0.3***	0.4	0.4	0.6	0.4	***0.9***	***0.4***
Blood Pressure Increased	0.2	0.1	***0.7***	***0.2***	0.2	0.2	0.4	0.2	***0.8***	***0.1***
Musculoskeletal Ands Connective Tissue Disorders	1.0	0.9	***2.1***	***1.2***	0.9	0.8	0.5	0.7	0.8	1.0
Osteoarthritis	0.4	0.4	***0.7***	***0.3***	0.0	0.1	0.05†	0.0	0.1	0.1
Nervous System Disorders	***1.9***	***1.3***	1.9	1.5	1.4	1.8	***2.0***	***1.1***	1.6	1.1
Headache	0.3	0.2	0.3	0.3	0.2	0.4	***0.4***	***0.1***	***0.4***	***0.1***
Respiratory, Thoracic And Mediastinal Disorders	0.5	0.4	***0.5***	***1.1***	1.1	0.7	0.9	0.6	0.4	0.4

Table 22 (Cont.)

MEDAL Study (OA/RA), EDGE II (RA), EDGE (OA)
Patients Discontinued Due to Specific Clinical Adverse Experiences
95% CIs for Difference Between Treatments Which Exclude Zero (Tier 2 Criteria)

	MEDAL Study (OA)				MEDAL Study (RA)		EDGE II		EDGE	
	60 mg vs. Diclo Cohort		90 mg vs. Diclo Cohort							
	E 60 mg N=6769	D 150 mg N=6700	E 90 mg N=2171	D 150 mg N=2162	E 90 mg N=2841	D 150 mg N=2855	E 90 mg N=2032	D 150 mg N=2054	E 90 mg N=3593	D 150 mg N=3518
% of Patients	%	%	%	%	%	%	%	%	%	%
Skin And Subcutaneous Tissue Disorders	0.6	0.8	0.7	0.9	1.1	0.9	1.3	0.8	0.8	1.1
Rash	0.2	0.2	0.2	0.4	0.2	0.3	***0.5***	***0.1***	0.3	0.4
Urticaria	***0.04***†	***0.2***	0.05†	0.1	0.1	0.2	0.05†	0.05†	0.1	0.03†
Vascular Disorders	2.2	1.9	***2.4***	***1.2***	***3.2***	***2.0***	2.6	1.9	***1.7***	***0.7***
Hypertension	1.8	1.4	***1.8***	***0.9***	1.9	1.3	2.0	1.3	***1.5***	***0.5***

† incidence displayed to second decimal place to identify values with number of events >1
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
Data are bolded and italicized for specific adverse experiences in those treatment groups for which the 95% CIs excluded 0.
Includes adverse experiences up to and including the 14-day post study therapy, unless otherwise noted.

6.1.5 Laboratory Adverse Experiences

6.1.5.1 OA Development Program

The number (%) of patients with laboratory adverse experiences by test category including specific, potentially mechanism-based, hematologic and blood chemistry laboratory adverse experiences of primary interest for the Placebo-Controlled Population are in Table 23. In the Placebo-Controlled Population, there were some differences across the various treatment groups with the lowest incidence noted for etoricoxib 90 mg and celecoxib 200 mg, but in general, the incidence of laboratory adverse experiences was similar among the etoricoxib, ibuprofen and naproxen groups.

Table 23

6- to 12-Week Placebo-Controlled Population
Patients With Laboratory Adverse Experiences: Potentially
Mechanism-Based Hematologic and Blood Chemistry Adverse Experiences of Primary Interest

	Placebo (N=924)	Etoricoxib 30 mg (N=1014)	Etoricoxib 60 mg (N=558)	Etoricoxib 90 mg (N=112)	Etoricoxib 120 mg (N=288)	Naproxen 1000 mg (N=494)	Ibuprofen 2400 mg (N=649)	Celecoxib 200 mg (N=488)
	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)
Patients with one or more adverse experiences	40/907 (4.4)	36/1007 (3.6)	31/555 (5.6)	2/111 (1.8)	29/287 (10.1)	34/492 (6.9)	51/645 (7.9)	14/482 (2.9)
Blood Chemistry	24/907 (2.6)	22/1006 (2.2)	18/555 (3.2)	0/111 (0.0)	14/287 (4.9)	21/492 (4.3)	29/645 (4.5)	8/482 (1.7)
Alanine Aminotransferase Increased	6/906 (0.7)	5/1006 (0.5)	3/555 (0.5)	0/111 (0.0)	2/287 (0.7)	3/492 (0.6)	9/645 (1.4)	1/482 (0.2)
Alkaline Phosphatase Increased	3/904 (0.3)	1/999 (0.1)	2/555 (0.4)	0/111 (0.0)	0/287 (0.0)	0/492 (0.0)	1/634 (0.2)	1/482 (0.2)
Aspartate Aminotransferase Increased	6/906 (0.7)	5/1005[†] (0.5)	3/555 (0.5)	0/111 (0.0)	3/287 (1.0)	3/492 (0.6)	3/645 (0.5)	0/482 (0.0)
Blood Bilirubin Increased	2/904 (0.2)	1/999 (0.1)	1/555 (0.2)	0/111 (0.0)	1/287 (0.3)	1/492 (0.2)	0/635 (0.0)	0/482 (0.0)
Blood Creatinine Increased	4/906 (0.4)	4/1006 (0.4)	6/555 (1.1)	0/111 (0.0)	1/287 (0.3)	5/492 (1.0)	8/645 (1.2)	3/482 (0.6)
Blood Urea Nitrogen Increased	3/906 (0.3)	5/1006 (0.5)	7/555 (1.3)	0/111 (0.0)	3/287 (1.0)	5/492 (1.0)	10/645 (1.6)	0/482 (0.0)
Hematology	10/906 (1.1)	6/1006 (0.6)	9/555 (1.6)	2/111 (1.8)	11/287 (3.8)	14/492 (2.8)	22/645 (3.4)	2/481 (0.4)
Haematocrit Decreased	2/906 (0.2)	4/1006 (0.4)	7/555 (1.3)	0/111 (0.0)	6/287 (2.1)	11/492 (2.2)	3/645 (0.5)	0/481 (0.0)
Haemoglobin Decreased	4/906 (0.4)	1/1006 (0.1)	4/555 (0.7)	1/111 (0.9)	7/287 (2.4)	4/492 (0.8)	13/645 (2.0)	0/481 (0.0)
Urinalysis	9/899 (1.0)	9/997 (0.9)	4/555 (0.7)	0/111 (0.0)	7/287 (2.4)	2/492 (0.4)	6/629 (1.0)	4/481 (0.8)

[†] Data for 2 patients with elevated AST was incorrectly captured as on therapy but was actually prior to therapy.
n/m = number of patients with laboratory adverse experiences/number of patients for whom the laboratory test was recorded postbaseline.
Although a patient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

Only 1 patient experienced a serious laboratory adverse experience in the Placebo-Controlled Population; creatine phosphokinase increased (naproxen 1000 mg) which resulted in discontinuation but was not considered drug-related. The incidence of discontinuations due to laboratory adverse experiences in the Placebo-Controlled Population was low and generally similar across treatment groups.

In the 6-Month Population, the percent of patients with one or more laboratory adverse experiences was small and similar between the etoricoxib 30 mg and celecoxib 200 mg groups with no findings of clinical relevance: 4.2% and 3.7%, respectively. No serious laboratory adverse experiences were reported in the 6-Month Population. Few patients discontinued due to laboratory adverse experiences and the incidence was similar among the etoricoxib 30 mg and celecoxib 200 mg groups: 0.6% and 1.0%, respectively.

In the 1-Year Population, the percent of patients with one or more laboratory adverse experiences was small and similar for all treatment groups: 10.9%, 10.3%, 9%, and 11% for etoricoxib 30 mg, etoricoxib 60 mg, etoricoxib 90 mg, and naproxen 1000 mg, respectively. Few patients discontinued due to laboratory adverse experiences in the 1-Year Population (<1.0%) and the incidence was similar in all treatment groups. There were no additional clinically relevant findings beyond those laboratory adverse experiences described for the Placebo-Controlled Population

6.1.5.2 MEDAL Program Studies

In both the EDGE II and EDGE studies, there were substantially more laboratory adverse experiences in the diclofenac group compared with the etoricoxib group: 14.3% versus 18.4% for etoricoxib 90 mg and diclofenac 150 mg, respectively, in EDGE II, and 6.1% versus 15.1% for etoricoxib 90 mg and diclofenac 150 mg, respectively, in EDGE.

Compared with etoricoxib, patients treated with diclofenac in the EDGE II and EDGE studies showed an increased incidence of elevations in liver enzymes, including AST (2.7% versus 5.9% for etoricoxib 90 mg and diclofenac 150 mg, respectively, in EDGE II, and 1.3% versus 8.7% for etoricoxib 90 mg and diclofenac 150 mg, respectively, in EDGE) and ALT (3.6% versus 8.6% for etoricoxib 90 mg and diclofenac 150 mg, respectively, in EDGE II, and 1.5% versus 11.2% for etoricoxib 90 mg and diclofenac 150 mg, respectively, in EDGE).

There were no serious laboratory adverse experiences in MEDAL, EDGE II, and EDGE that met both the Tier 2 criteria and 95% CIs for difference in proportions between treatments which exclude zero.

Table 24 displays all specific laboratory adverse experiences which resulted in discontinuation, with treatment potential differences, based on 95% CIs that excluded 0, that were observed in the MEDAL Study, EDGE II or EDGE. Among the OA and RA patients in the MEDAL Program studies, larger proportions of patients on diclofenac discontinued treatment due to elevations in ALT and AST, compared to both etoricoxib 60 mg and 90 mg. Compared to etoricoxib 60 mg, more OA patients on diclofenac discontinued due to hematocrit decreased and hemoglobin decreased.

Table 24

MEDAL Study (OA/RA), EDGE II (RA), EDGE (OA)
Patients Discontinued Due to Specific Laboratory Adverse Experience
95% CIs for Difference Between Treatments Which Exclude Zero (Tier 2 Criteria)

	MEDAL Study (OA)								MEDAL Study (RA)				EDGE II				EDGE			
	60 mg vs. Diclofenac Cohort				90 mg vs. Diclofenac Cohort															
	Etoricoxib 60 mg (N=6769)		Diclofenac 150 mg (60 mg) (N=6700)		Etoricoxib 90 mg (N=2171)		Diclofenac 150 mg (90 mg) (N=2162)		Etoricoxib 90 mg (N=2841)		Diclofenac 150 mg (N=2855)		Etoricoxib 90 mg (N=2032)		Diclofenac 150 mg (N=2054)		Etoricoxib 90 mg (N=3593)		Diclofenac 150 mg (N=3518)	
Number (%) of Patients	n/m	(%)	n/m	(%)	n/m	%	n/m	%	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
Patients with one or more laboratory adverse experiences	***86/ 6714***	***(1.3)***	***175/ 6633***	***(2.6)***	***61/ 2141***	***(2.8)***	***135/ 2137***	***(6.3)***	***48/ 2821***	***(1.7)***	***81/ 2826***	***(2.9)***	***20/ 2012***	***(1.0)***	***41/ 2029***	***(2.0)***	***23/ 3592***	***(0.6)***	***194/ 3513***	***(5.5)***
Blood Chemistry Test	***74/ 6712***	***(1.1)***	***148/ 6632***	***(2.2)***	***54/ 2141***	***(2.5)***	***120/ 2135***	***(5.6)***	***41/ 2819***	***(1.5)***	***73/ 2824***	***(2.6)***	***15/ 2011***	***(0.7)***	***36/ 2028***	***(1.8)***	***22/ 3592***	***(0.6)***	***190/ 3512***	***(5.4)***
Alanine Aminotransferase Increased	***18/ 6711***	***(0.3)***	***105/ 6628***	***(1.6)***	***5/ 2140***	***(0.2)***	***82/ 2134***	***(3.8)***	***11/ 2819***	***(0.4)***	***46/ 2823***	***(1.6)***	***4/ 2011***	***(0.2)***	***24/ 2027***	***(1.2)***	***8/ 3592***	***(0.2)***	***175/ 3510***	***(5.0)***
Aspartate Aminotransferase Increased	***12/ 6710***	***(0.2)***	***77/ 6628***	***(1.2)***	***2/ 2140***	***(0.1)***	***68/ 2134***	***(3.2)***	***8/ 2819***	***(0.3)***	***31/ 2822***	***(1.1)***	***2/ 2011***	***(0.1)***	***11/ 2027***	***(0.5)***	***6/ 3591***	***(0.2)***	***119/ 3510***	***(3.4)***
Hematology Laboratory Test	***10/ 6616***	***(0.2)***	***28/ 6548***	***(0.4)***	8/ 2140	(0.4)	15/ 2134	(0.7)	7/ 2783	(0.3)	6/ 2793	(0.2)	5/ 2006	(0.2)	4/ 2028	(0.2)	1/ 3592	(0.0)	3/ 3511	(0.1)
Haemoglobin decreased	***8/ 6614***	***(0.1)***	***27/ 6541***	***(0.4)***	7/ 2140	(0.3)	15/ 2134	(0.7)	7/ 2783	(0.3)	5/ 2789	(0.2)	2/ 2006	(0.1)	3/ 2027	(0.1)	1/3592	(0.0)	3/ 3511	(0.1)

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
Data are bolded and italicized for specific adverse experiences in those treatment groups for which the 95% CIs excluded 0.
Includes adverse experiences up to and including the 14-day post study therapy, unless otherwise noted.

6.1.6 Other Adverse Experiences of Interest

6.1.6.1 Hypersensitivity Reactions

As noted in section 1.1.1.2, allergic reactions including cutaneous reactions and systemic anaphylactic reactions can be associated with NSAID use. Because cutaneous reactions such as rash are adverse experiences of concern with many drugs, they were explored in the 6-Month and 1-Year Populations, even though the occurrence of these adverse experiences was not significantly different from placebo. In the 1-Year Population, rash was reported more frequently with etoricoxib at doses of 60 mg and 90 mg than with naproxen but occurred less frequently at 30 mg and 120 mg compared with naproxen; thus, no consistent increase was observed in either the 6-Month or 1-Year Populations. There were no documented cases of serious skin reactions (e.g., Stevens-Johnson syndrome) in the large clinical trial safety database.

Summary

In summary, the general safety profile of etoricoxib was generally similar to the NSAID comparators evaluated. An increased incidence of atrial fibrillation relative to diclofenac was noted in the MEDAL Study in the etoricoxib 90 mg treatment group among the OA patients and to a lesser extent among the RA patients. The majority of atrial fibrillation adverse experiences were noted in patients with 1 or more medical condition associated with atrial fibrillation (history of atrial fibrillation, CHF, hypertension, atherosclerotic CV disease, diabetes, or valvular heart disease).. This increased incidence was not noted in the 60 mg cohort of the MEDAL Study. The number of atrial fibrillation events in the Etoricoxib Development Program was too small to draw conclusions for specific doses. There was also a slightly higher proportion of etoricoxib patients in the 90 mg cohort in the MEDAL Study who had one or more medical condition associated with atrial fibrillation, possibly contributing to this increased incidence. When viewed in this context and the context of a higher incidence of CHF adverse experiences (see Section 9) with etoricoxib 90 mg compared with diclofenac, this observation can be understood.

There was a higher increased incidence of palpitation adverse experiences noted in the EDGE Study relative to diclofenac and a similar trend in the EDGE II study. This imbalance was not noted in the Etoricoxib Development Program and these adverse experiences were rarely considered serious or resulted in discontinuation with similarly small number of events in the Etoricoxib Development and MEDAL Program studies among all active treatment groups.

There was an increased incidence of basal cell carcinoma in the MEDAL Study in the 60 mg OA treatment group relative to the diclofenac group. However, in the OA cohort, the incidence was higher on diclofenac relative to etoricoxib 90 mg. When all cases of basal cell carcinoma were pooled across the MEDAL Program studies, the incidence was similar in the etoricoxib and diclofenac groups. No consistent pattern was noted in the incidence of basal cell carcinoma in the Etoricoxib Development Program.

6.1.7 General Safety Conclusions

The conclusions below are based on the general safety data for the OA Development Program excluding GI, thrombotic CV, and renovascular safety which are specifically discussed in sections 7, 8, and 9, respectively.

- Etoricoxib 30 mg is associated with a safety profile that is generally similar to etoricoxib 60 mg, but in some cases a lower incidence of adverse experiences is observed for etoricoxib 30 mg than for etoricoxib 60 mg, based on an evaluation of the data pooled across all of the studies presented.

7. GI Safety and Tolerability

This section provides a summary of the GI safety and tolerability data for etoricoxib, organized by four clinically distinct areas of interest:

- Upper GI Safety
- GI tolerability
- Lower GI safety
- Hepatic Effects

7.1 Upper GI Safety

Upper GI clinical events (bleeding, perforation, obstruction, or ulcer; PUBs) were evaluated using two data sets: (1) Pooled Etoricoxib Development Program study data (2) Pooled MEDAL Program study data.

Upper GI Clinical Events (PUBs) Adjudication Standard Operating Procedures (SOP)

As noted in Section 3.3.3, an SOP for adjudication of potential upper GI clinical events had been established and used throughout the Etoricoxib Development Program and the MEDAL Program to provide standardized data for analysis of upper GI clinical events. The blinded adjudication of these events by the independent, external CRC allowed for a more specific and precise assessment of these clinical events.

Potential upper GI clinical events (bleeding, perforation, obstruction, ulcer diagnosed on clinical work-up; PUBs) were identified through active surveillance of reported adverse events, and were adjudicated by the CRC using predefined criteria. An upper GI clinical event was considered confirmed if it met the CRC prespecified criteria as described in Table 25. These criteria also allowed the CRC to determine whether the event was clinically complicated (perforation, obstruction, complicated bleeding), and to categorize the specific final event type (e.g., gastric or duodenal ulcer, GI bleeding event, etc.). The CRC could also classify a reported event as not an upper GI event.

Within the Etoricoxib Development Program, approximately 86% of investigator reported upper GI events were confirmed in patients taking either etoricoxib or traditional NSAIDs within the entire follow-up period. Within the MEDAL program,

approximately 79% of investigator reported upper GI events were confirmed in OA and RA patients taking etoricoxib or diclofenac.

Definition of Upper GI Clinical Event Endpoints

For both the Etoricoxib Development Program and the MEDAL Program, the prespecified endpoints of interest were overall upper GI clinical events and the subset of complicated events. Because the total number of confirmed cases was small in the Etoricoxib Development Program, analyses of endpoints in this dataset were prespecified for confirmed cases as well as total reported cases (confirmed and unconfirmed) in order to evaluate the data as comprehensively as possible. As sufficiently large number of endpoints accrued in the MEDAL Program, the analyses of endpoints considered only confirmed cases.

Table 25

CRC Classification of and Criteria for Upper GI Clinical Events

UGI Clinical Event	Criteria
Perforation†	Perforation due to non-malignant gastric or duodenal ulcer confirmed by endoscopy, surgery, radiography (intraperitoneal air or contrast extravasation) or autopsy
Obstruction†	Postprandial nausea and vomiting for ≥24 hours and evidence of narrowing of the distal stomach, pylorus, or duodenum due to a non-malignant ulcer documented by endoscopy, surgery, radiography, or autopsy
Complicated Bleeding†	1. Healthcare provider-witnessed hematemesis, melena, hematochezia, or nasogastric aspirate with blood or coffee grounds material; 2. Active upper GI bleeding documented by endoscopy, angiography, or surgery; 3. Occult blood-positive stool associated with significant bleeding§ and with a documented upper GI lesion judged by the healthcare provider to be the source of the bleeding; or 4. Patient-reported hematemesis or melena or hematochezia associated with significant bleeding§ and a documented upper GI lesion judged by the healthcare provider to be the source of the bleeding
Uncomplicated Bleeding‡	1. Occult blood-positive stool associated with a documented upper GI lesion judged by the healthcare provider to be the source of the bleeding and stigmata of recent bleeding (visible vessel, pigmented spot, or clot in ulcer base) at endoscopy but no significant bleeding§; or 2. Patient-reported hematemesis or melena or hematochezia associated with a documented upper GI lesion judged by the healthcare provider to be the source of the bleeding and stigmata of recent bleeding at endoscopy but no significant bleeding§
Uncomplicated Ulcer‡	Gastric or duodenal ulcer documented on clinical evaluation by endoscopy, surgery, upper GI contrast radiography, or autopsy

† Complicated event.
‡ Uncomplicated event.
§ Hypotension, orthostatic changes in heart rate (>20 beats per minute) or blood pressure (>20 mmHg systolic or 10 mmHg diastolic), hemoglobin drop ≥2 g/dL, or transfusion.
UGI=upper gastrointestinal.

7.1.1 Etoricoxib Development Program Results

In addition to the adjudicated upper GI clinical event data noted above, the Etoricoxib Development Program also evaluated several surrogates of upper GI safety. These included effects on gastric PGE_2 production, fecal red blood cell loss, and endoscopic gastroduodenal ulcers. Results from these studies consistently support the GI safety benefit of etoricoxib as a COX-2 selective inhibitor relative to NSAID comparators including naproxen, ibuprofen, and diclofenac. The data from the endoscopy studies and the pooled upper GI clinical event data are presented below.

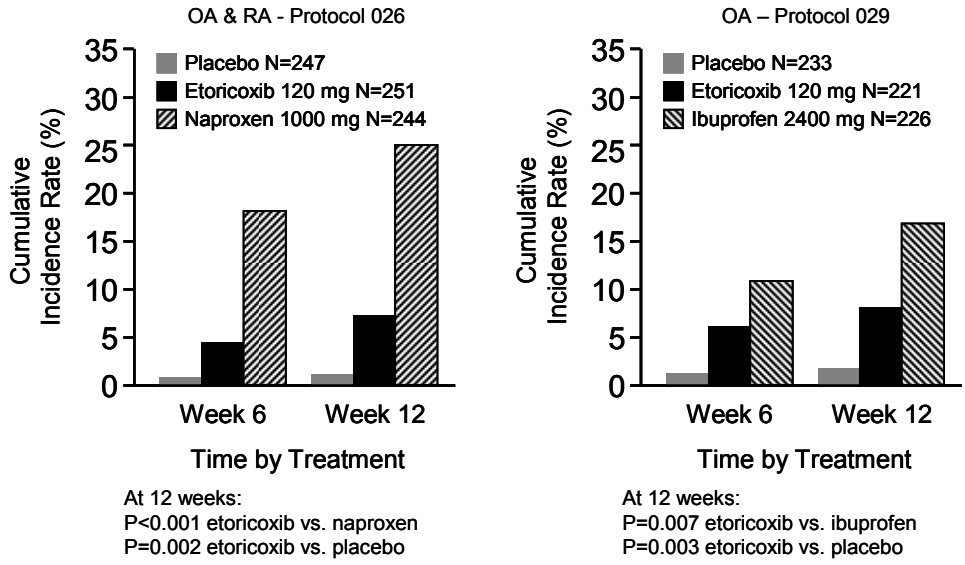
For the purposes of this document the following terminology regarding NSAIDs will be employed. The term traditional NSAIDs will refer to naproxen, ibuprofen and/or diclofenac. The term COX-2 select inhibitor will refer to etoricoxib and celecoxib. Aspirin will be discussed within the section outlining subgroup analyses.

Endoscopy Studies in OA and RA Patients

The two endoscopy studies assessed cumulative rates of endoscopic ulcers (≥3 mm) by 12 weeks in OA patients taking etoricoxib 120 mg, placebo or ibuprofen 2400 mg daily (Protocol 029) or in OA and RA patients taking etoricoxib 120 mg, placebo or naproxen 1000 mg daily (Protocol 026). In both studies, the incidence of ulcers in the etoricoxib group was significantly lower than the corresponding incidence for the individual traditional NSAID (Figure 9). Etoricoxib 120 mg also showed a significantly higher incidence of ulcers than placebo by 12 weeks in both studies. Collectively, the results of these two endoscopy studies provide complementary evidence that the highly selective COX-2 inhibitor etoricoxib presents less risk for clinical manifestations of GI toxicity compared to traditional NSAIDs.

Figure 9

Cumulative Incidence of Gastroduodenal Ulcers (≥3 mm)
Etoricoxib versus Traditional NSAIDs in Endoscopy Studies



Pooled Analysis of Upper GI Clinical Events

A pooled analysis of upper GI clinical events was performed for Etoricoxib Development Program. This analysis included data on etoricoxib (at doses from 30 to 120 mg) and traditional NSAIDs from the placebo-controlled periods of studies, and, for those patients receiving continuous therapy with one agent, the periods beyond the placebo-controlled periods. This was the prespecified comparison of primary interest. Additional analyses were conducted to compare etoricoxib to naproxen, as naproxen contributed the majority of the data in the pooled traditional NSAID treatment group, and to compare etoricoxib, pooled traditional NSAIDs, and placebo during the placebo-controlled period.

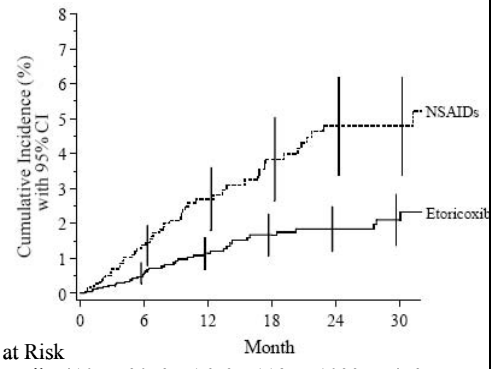
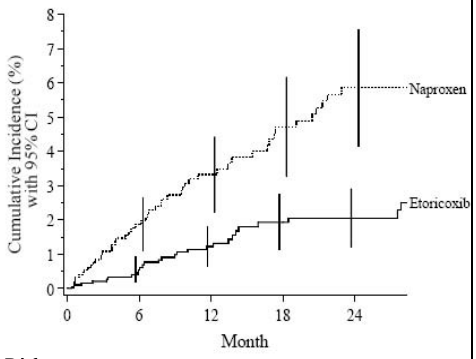
The cumulative incidence curves of overall upper GI clinical events for etoricoxib versus all traditional NSAIDs combined and versus naproxen are shown in Figure 10. For confirmed upper GI clinical events, a significant reduction of ~50% was observed with etoricoxib compared to NSAIDs (Table 26) for data both over the first year of treatment and over the entire treatment period. These data are based on median durations of exposure of 6.4 and 3.3 months for etoricoxib and traditional NSAIDs combined. These data show that the benefit does not diminish over time. The magnitude of the risk reduction for the complicated events (primarily a result of upper GI hemorrhages) was generally consistent with results for overall upper GI clinical events, although the number of events is more limited.

These results are primarily driven by comparisons to naproxen, given that this was the active comparator in the majority of studies in the Etoricoxib Development Program and thus constitutes the majority of data in the combined traditional NSAID group. When considering the comparison of etoricoxib to naproxen alone, the relative risk (95% CIs) for confirmed upper GI clinical events was 0.41 (0.26, 0.65) and for confirmed complicated events was 0.53 (0.27, 1.05). The data for confirmed upper GI clinical events are based on median durations of exposure of 12.5 and 11.2 months for etoricoxib and naproxen, respectively.

There was a numeric trend consistent with an increase in the rate of overall upper GI events with increasing etoricoxib dose; rates (and 95% CIs) for etoricoxib 30, 60, 90 and 120 mg were 0.21 (0.01, 1.15), 0.86 (0.45, 1.51), 0.77 (0.42, 1.30) and 1.68 (0.96, 2.72) events per 100 patient years, respectively. These analyses were based on small numbers of events, particularly for etoricoxib 30 mg.

Figure 10

Etoricoxib Development Program
Kaplan Meier Estimates of Cumulative Incidence
Overall Confirmed Upper GI Clinical Events

Etoricoxib versus Traditional NSAIDs Combined	Etoricoxib versus Naproxen
	

Patients at Risk

Etoricoxib	4107	2073	1679	1185	1033	453
Diclofenac	2967	1112	851	641	563	228

Patients at Risk

Etoricoxib	1960	1412	1124	747	668
Diclofenac	1497	938	718	525	469

Table 26

Etoricoxib Development Program
Relative Risk of Upper GI Clinical Events
Etoricoxib versus Traditional NSAIDs Combined
Events within 1-Year and Over the Entire Treatment Period

Treatment	N	n/PYR	Rate†	Relative Risk (95% CI)
Confirmed Upper GI Events				
Within 1 Year				
Etoricoxib	4107	28/2483.55	1.13	0.47 (0.28, 0.76)
Traditional NSAIDs Combined	2967	39/1476.47	2.64	
Within Entire Treatment Period				
Etoricoxib	4107	40/4294.58	0.93	0.47 (0.31, 0.72)
Traditional NSAIDs Combined	2967	55/2373.41	2.32	
Confirmed Plus Unconfirmed Upper GI Events				
Within 1 Year				
Etoricoxib	4107	35/2483.27	1.41	0.50 (0.32, 0.78)
Traditional NSAIDs Combined	2967	46/1475.62	3.12	
Within Entire Treatment Period				
Etoricoxib	4107	47/4294.30	1.09	0.48 (0.33, 0.70)
Traditional NSAIDs Combined	2967	64/2372.45	2.70	
Confirmed Complicated Upper GI Events				
Within 1 Year				
Etoricoxib	4107	12/2485.07	0.48	0.69 (0.31, 1.53)
Traditional NSAIDs Combined	2967	13/1478.71	0.88	
Within Entire Treatment Period				
Etoricoxib	4107	19/4300.18	0.44	0.57 (0.31, 1.07)
Traditional NSAIDs Combined	2967	23/2377.62	0.97	

† Events per 100 person-years.
‡ If no events occurred within a treatment group, the CI is a one-sided 97.5% CI.
§ Relative risk to traditional NSAIDs combined by Cox model.

7.1.2 Pooled MEDAL Program Results

In the MEDAL Program studies, low-dose aspirin was recommended for secondary cardioprevention in patients with established cardiovascular disease, peripheral arterial or cerebrovascular disease, and also strongly encouraged for patients with diabetes [123]. Use of anti-ulcer medication (proton pump inhibitors or misoprostol) was recommended for the prevention of NSAID-induced gastrointestinal mucosal injury in high GI risk patients (age >65 years, history of GI ulcer or hemorrhage, and/or concurrent use of

corticosteroid, anticoagulant, or antiplatelet therapy). Proton pump inhibitors were also allowed for the symptomatic management of GI tolerability during the studies [124]. Within the MEDAL Program, proton pump inhibitors and misoprostol accounted for approximately 96% of patients taking gastroprotective agents with the vast majority of patients using PPIs.

The number of upper GI events was not prespecified and was determined by the time necessary to accrue the requisite number of thrombotic CV events. No power calculations were performed. The design features mentioned above were felt to preclude the ability to appropriately control potentially confounding factors, thus no formal hypothesis was prespecified. Upper GI clinical events were adjudicated, and calculation of rates of overall and complicated events in each treatment arm was prespecified. Determination of the hazard ratio was performed to better characterize the observed treatment effects.

Table 27 provides the results of patients with confirmed upper GI clinical events. A significant 31% risk reduction was observed for etoricoxib versus diclofenac in the rate of overall upper GI clinical events. No significant difference between treatment groups was observed in complicated events. In order to further understand the dichotomy in results between overall and complicated events, rates of uncomplicated events were evaluated and a significant risk reduction of 43% for etoricoxib was observed. The cumulative incidence of overall and complicated upper GI clinical events in the MEDAL Program is displayed in Figure 11. The cumulative incidence curves for overall upper GI clinical events separate early at about 6 months and the separation increases over time. These data show a continuing trend of lower risk, throughout the course of treatment in the etoricoxib group relative to the diclofenac group. Further, the overall confirmed GI results were estimated within each study. There was no significant treatment-by-study interaction. Sensitivity analyses of the overall GI events were performed by baseline aspirin use and study protocol as a stratification factor and treatment as an explanatory factor in the Cox model; the results were consistent with that obtained from the model that did not include study protocol as a stratification factor.

Table 27

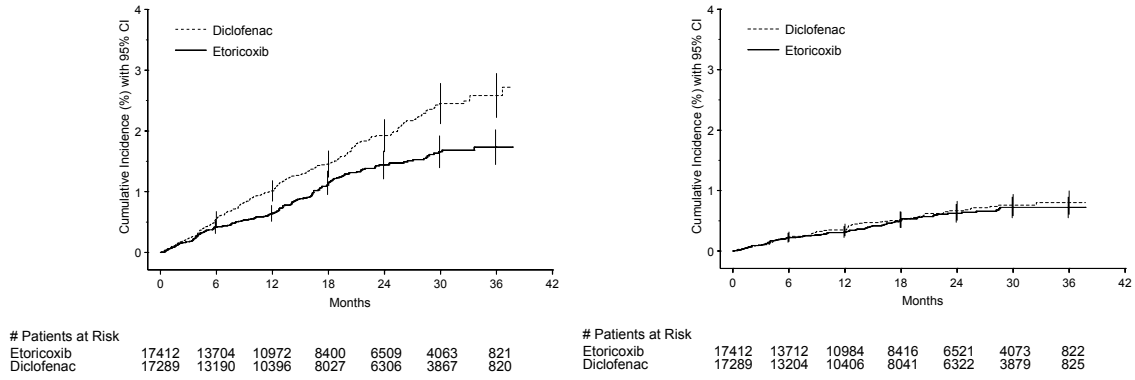
Pooled MEDAL Program[†]
Patients with Confirmed Upper GI Clinical Events

	Etoricoxib (N=17,412)		Diclofenac (N=17,289)		Relative Risk (95% CI)
	n	Rate[‡]	n	Rate[‡]	
Patients with any clinical[‖] event*	**176**	**0.67**	**246**	**0.97**	**0.69 (0.57, 0.83)**
Patients with complicated Events*	**78**	**0.30**	**82**	**0.32**	**0.91 (0.67, 1.24)**
Perforation[§]	5	0.02	11	0.04	
Obstruction	2	0.01	2	0.01	
Bleeding	72	0.27	72	0.28	
Gastric ulcer	40	0.15	26	0.10	
Duodenal ulcer	17	0.06	23	0.09	
Gastric and duodenal ulcer	4	0.02	5	0.02	
Anastomotic ulcer	1	0.00	1	0.00	
Other source	10	0.04	17	0.07	
Patients with uncomplicated events	**98**	**0.37**	**164**	**0.65**	**0.57 (0.45, 0.74)**
Bleeding	6	0.02	4	0.02	
Ulcer[¶]	92	0.35	161	0.63	
Gastric ulcer	57	0.22	110	0.43	
Duodenal ulcer	27	0.10	35	0.14	
Gastric and duodenal ulcer	8	0.03	16	0.06	

[†] mITT analysis: Includes events up to and including the 14-day post study therapy discontinuation
[‡] Events per 100 patient-years.
[§] 4 patients with perforation also had bleeding reported.
[‖] Patients with both a complicated and uncomplicated event (N=4; bleeding ulcer with synchronous uncomplicated ulcer) were counted in the overall clinical event patient group and the complicated event patient subgroup, but not the uncomplicated event patient subgroup.
[¶] 1 patient with uncomplicated bleeding from a Mallory-Weiss tear also had an uncomplicated gastric ulcer identified.
Relative risk from the Cox proportional-hazards model with baseline aspirin use as a stratification factor and treatment as an explanatory factor in the model.

Figure 11

Pooled MEDAL Program
Kaplan Meier Estimates of Cumulative Incidence
Confirmed and Confirmed Complicated Upper GI Clinical Events



† mITT Approach.

Subgroup Analyses

Table 28 displays the rates of overall upper GI clinical events by dose and disease. Numerically lower rates were observed for etoricoxib 60 mg versus diclofenac 150 mg and for etoricoxib 90 mg versus diclofenac 150 mg. The magnitude of the difference was slightly smaller for the etoricoxib 90 mg versus diclofenac 150 mg comparison which is consistent with the limited data in the Phase III program which suggested a dose response. When evaluating upper GI clinical events by disease, a benefit for etoricoxib was maintained in both OA and RA patients with the greater numeric trend among RA patients.

Table 28

Pooled MEDAL Program
Subgroup Analyses of Upper GI Clinical Events by Disease and Dose

	Etoricoxib			Diclofenac			
	N	n/PYR	Rate†	N	n/PYR	Rate†	Relative Risk (95% CI)
OA	**12533**	**113/18210**	**0.62**	**12380**	**139/17367**	**0.80**	**0.77 (0.60, 0.99)**
Etoricoxib 60 mg vs. diclofenac	6769	55/11739	0.47	6700	72/11277	0.64	0.73 (0.51, 1.03)
Etoricoxib 90 mg vs. diclofenac	5764	58/6471	0.90	5680	67/6090	1.10	0.82 (0.58, 1.16)
RA Etoricoxib 90 mg vs. diclofenac	4878	63/8181	0.77	4909	107/8017	1.33	0.58 (0.43, 0.79)

mITT Approach.
† Events per 100 patient-years.
Crude incidence rate (%) = (n/N) x 100.
PYR = Patient-years at risk; CI=Confidence Interval.

Subgroup analyses were also conducted based on concomitant use of low-dose aspirin and/or PPI co-therapy. This analysis also evaluated patients with complicated events and those with uncomplicated events to be able to understand the influence these concomitant therapies had on the different categories of upper GI clinical events. In order to capture all patients who took even modest amounts of concomitant therapy, a definition of concomitant use was pre-specified as follows: the use of low-dose aspirin for at least 10% of time on study therapy or PPIs for at least 20% (or 30 consecutive days) of the study period. The data analysis plan allowed for additional exploratory analyses regarding co-therapies. Therefore, a more restrictive definition was developed after unblinding to better investigate the specific influence of regular aspirin or PPI use on upper GI outcomes. This definition of regular use required concomitant therapy during at least 75% of the study period (and for patients with an event, ≥75% in the period before the event). A value of 75% was chosen because it was the pre-specified definition of compliance for study drug in the MEDAL Program. In addition, data indicates that NSAID users who are prescribed PPIs have a mean compliance rate of ~62% [125], therefore using a 75% compliance rate for this analysis is similar to actual compliance rates. While such concomitant therapy was not a randomization criteria, but rather was the result of the application of treatment guidelines, patient and investigator preference, such use thus reflects the "real world" character of this trial and provides extremely valuable information.

Table 29 presents the analyses by concomitant aspirin and PPI use based on 75% use. No significant treatment-by-subgroup interactions were noted, indicating that differences in

upper GI event rates by treatment group were not affected by use of these concomitant therapies. The results of the treatment-by-subgroup interaction analyses which defined aspirin use as ≥10% and PPI use as ≥20% (or 30 consecutive days) were similar with those for the 75% use when considering PPI users but different for aspirin users. The results of aspirin users (≥10%) showed significant treatment-by-subgroup interactions (p=0.021) for both overall and uncomplicated upper GI clinical events indicating that the magnitude of the decrease in these events with etoricoxib versus diclofenac was smaller in patients taking low-dose aspirin at least 10% of the study period than in those without aspirin use.

Given that patients who use low-dose aspirin for cardioprotection generally do so on a daily basis and that those who use PPIs generally use these therapies routinely while taking NSAIDs, the 75% concomitant therapy definition above would seem to more accurately reflect the actual dosing of these agents in practice.

In summary, the reduction in overall upper GI events (driven by a reduction in uncomplicated events) is maintained in patients treated with PPIs and is also observed in patients taking low-dose aspirin.

Table 29

Pooled MEDAL Program
Upper GI Clinical Events Related to the Concomitant Regular (≥75%) Use of Low-Dose Aspirin and/or Proton Pump Inhibitors

		Etoricoxib		Diclofenac		Relative Risk (95% CI)
		n/N	Rate†	n/N	Rate†	
Patients with any clinical event						
Aspirin use	Yes	100 / 5752	1.14	124 / 5680	1.46	0.78 (0.60, 1.01)
	No	76 / 11660	0.43	122 / 11609	0.72	0.60 (0.45, 0.80)
PPI use	Yes	68 / 6950	0.56	106 / 6906	0.91	0.62 (0.45, 0.83)
	No	108 / 10462	0.76	140 / 10383	1.02	0.74 (0.58, 0.95)
Aspirin use Yes / PPI use No		56 / 2708	1.58	57 / 2645	1.69	0.93 (0.65, 1.35)
Aspirin use Yes / PPI use Yes		44 / 3044	0.84	67 / 3035	1.31	0.64 (0.44, 0.93)
Aspirin use No/ PPI use No		52 / 7754	0·49	83 / 7738	0.80	0.60 (0.43-0.86)
Aspirin use No/ PPI use Yes		24 / 3906	0·35	39 / 3871	0.59	0.59 (0.36-0.98)
Patients with complicated events						
Aspirin use	Yes	50 / 5752	0.57	52 / 5680	0.61	0.93 (0.63, 1.36)
	No	28 / 11660	0.16	30 / 11609	0.18	0.90 (0.53, 1.50)
PPI use	Yes	24 / 6950	0.20	32 / 6906	0.27	0.72 (0.42, 1.22)
	No	54 / 10462	0.38	50 / 10383	0.36	1.03 (0.70, 1.52)
Aspirin use Yes / PPI use No		34 / 2708	0.96	30 / 2645	0.89	1.09 (0.66, 1.77)
Aspirin use Yes / PPI use Yes		16 / 3044	0.30	22 / 3035	0.43	0.70 (0.37, 1.34)
Aspirin use No/ PPI use No		20 / 7754	0.19	20 / 7738	0.19	0.96 (0.52-1.79)
Aspirin use No/ PPI use Yes		8 / 3906	0.12	10 / 3871	0.15	0.77 (0.30-1.95)
Patients with uncomplicated events						
Aspirin use	Yes	50 / 5752	0.57	72 / 5680	0.85	0.67 (0.47, 0.96)
	No	48 / 11660	0.27	92 / 11609	0.54	0.50 (0.35, 0.71)
PPI use	Yes	44 / 6950	0.36	74 / 6906	0.63	0.57 (0.39, 0.83)
	No	54 / 10462	0.38	90 / 10383	0.66	0.58 (0.41, 0.81)
Aspirin use Yes / PPI use No		22 / 2708	0.62	27 / 2645	0.80	0.77 (0.44, 1.34)
Aspirin use Yes/ PPI use Yes		28 / 3044	0.53	45 / 3035	0.88	0.61 (0.38, 0.97)
Aspirin use No/ PPI use No		32 / 7754	0.30	63 / 7738	0.61	0.49 (0.32-0.75)
Aspirin use No/ PPI use Yes		16 / 3906	0.23	29 / 3871	0.44	0.53 (0.29-0.98)

† Rate of events per 100 patient-years.
No treatment-by-subgroup interaction was significant.
PPI = Proton pump inhibitor.
mITT Approach: Includes events up to and including the 14-day post study therapy discontinuation.

Results in the Context of Comparator Agents

In the Etoricoxib Development Program, etoricoxib demonstrated a significant reduction in upper GI clinical events versus comparator NSAIDs. A numeric reduction approaching significance (p=0.079) was also observed in complicated events over the entire treatment period, consistent with that of overall events, primarily due to significant bleeds. These

data were based primarily on comparisons to naproxen, the NSAID comparator in the majority of the studies.

In the MEDAL Program, the rate of upper GI events, specifically ulcers, was decreased with etoricoxib versus diclofenac. There was, however, no difference seen in complicated upper GI events between etoricoxib and diclofenac. Data from randomized clinical trials suggests that diclofenac has a lower risk of serious gastrointestinal complications than many other NSAIDS. This includes data from CLASS, a GI outcomes study comparing the risks of GI ulcers for celecoxib versus diclofenac and ibuprofen, where a benefit was shown for celecoxib relative to ibuprofen, but not relative to diclofenac [46]. When confirmed upper GI clinical events from the pooled Rofecoxib Development Program were evaluated by individual NSAID comparators, a decreased risk relative to each comparator was demonstrated. Of note, however, the risk reduction was almost twice as large for rofecoxib relative to the naproxen and ibuprofen groups compared with the diclofenac group [126] and the 95% CIs for the reduction in risk versus only the diclofenac group included 1.0. These results are also supported by observational data indicating that the GI risk is lower for diclofenac than for many other traditional NSAIDs [127; 128].

A plausible explanation for the reduced GI toxicity of diclofenac, especially with regard to complicated upper GI events could relate to the lack of a potent COX-1 inhibition effect. It has been suggested that gastroduodenal mucosal lesions develop as a consequence of moderate inhibition of COX-1 activity while upper GI bleeding complications occur as a result of high-grade inhibition of platelet COX-1 [129]. Greater than 95% inhibition of COX-1 mediated thromboxane is required to impact platelet function [62; 130]. The mean inhibition observed with diclofenac peaks at 87% [114] and this degree of COX-1 inhibition is sufficient to induce gastrointestinal ulcers in several studies [115; 116; 128] although it is not sufficient to meaningfully decrease platelet function in most patients and thus may not confer as great a risk for GI bleeding as it does for ulcers [131].

The GI benefit for etoricoxib as measured by upper GI clinical events is demonstrated relative to NSAIDs as a class. Taking into account the apparent range of GI risk for NSAIDs and the data from both the Etoricoxib Development Program and the MEDAL Program, a benefit for complicated upper GI events likely exists for etoricoxib, but appears to be dependent on the level of GI toxicity associated with the traditional NSAID being compared to.

Upper GI Safety Conclusions

- A significant ~50% reduction is observed in the rate of upper GI clinical events in patients treated with etoricoxib compared with the combined traditional NSAID group in the pooled analysis of upper GI clinical events for the Etoricoxib Development Program
  - These results were driven by comparisons to naproxen
- A significant ~30% reduction is observed in the rate of upper GI clinical events in the etoricoxib treatment group compared with diclofenac treatment group in the MEDAL Program.
  - The reduction was driven by uncomplicated ulcers; no significant difference in complicated upper GI clinical events was identified.
  - The reduction is maintained in patients taking PPIs.
  - The reduction is observed in patients taking low-dose aspirin, however, the magnitude of the risk reduction may be decreased when aspirin is used concomitantly.

7.2 GI Tolerability

GI tolerability refers to GI symptoms (e.g., abdominal pain, dyspepsia, nausea) commonly associated with the use of NSAIDs and represents one of the most common reasons why patients discontinue NSAID therapy. There is no widely accepted definition in the literature and thus in the analyses presented below, different definitions are used in order to evaluate for consistency in the results.

7.2.1 Etoricoxib Development Program

In the Etoricoxib Development Program, analysis of GI tolerability was performed using the following 5 GI-related endpoints:

- New use of concomitant gastroprotective agents (GPAs; H_2 antagonists, PPIs, misoprostol and sucralfate).
- New use of concomitant GI medications (all GI medications including GPAs).
- Discontinuation due to any adverse experience in the Digestive System category of the medical reporting dictionary that was used.
- Discontinuation due to a composite of 6 prespecified “NSAID-type” GI adverse experiences (acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea, and vomiting) and 'abdominal pain'
- Discontinuation due to abdominal pain, dyspepsia, or epigastric discomfort adverse experience (exploratory).

This tolerability analysis was based on the Etoricoxib Development Program studies. The exception was exclusion of data from the two surveillance endoscopy studies because those studies excluded the use of GPAs. This analysis included doses of etoricoxib from 60-120 mg and pooled data from the active-controlled portions of the Phase IIb/III studies (i.e. Etoricoxib Development Program studies).

Use of etoricoxib was associated with a significant risk reduction (Table 30) relative to the combined NSAID group for all 5 GI tolerability endpoints. Analyses of the data stratified by NSAID comparator suggest that the results are largely accounted for by the differences from naproxen as this was the comparator in the majority of studies and thus the comparator with the most exposure. The amount of exposure for other NSAIDs was substantially less when compared to naproxen. An updated analysis of two of the endpoints, including doses of etoricoxib from 30-120 mg demonstrated a benefit similar to that shown in Table 30. The relative risk (95% CI) of etoricoxib to diclofenac for new use of concomitant GPAs was 0.75 (0.64, 0.87) and for discontinuations due to NSAID-type adverse experiences was 0.62 (0.45, 0.86).

Table 30

Etoricoxib Development Program GI Tolerability Analysis
Relative Risks for the 5 Predefined GI Tolerability Endpoints

Treatment	N	n/PYR	Rate[†]	Relative Risk[‡] (95% CI)
New Use of Concomitant GPAs				
Etoricoxib	2498	331/3634	9.1	0.75[§] (0.64, 0.89)
Traditional NSAIDs Combined	1485	249/1914	13.0	---
New Use of Concomitant GI Medications				
Etoricoxib	2498	379/3567	10.6	0.72[§] (0.61, 0.84)
Traditional NSAIDs Combined	1485	297/1862	15.9	---
Discontinuation Due to NSAID-Type AEs				
Etoricoxib	2498	59/3849	1.5	0.60[‖] (0.41, 0.87)
Traditional NSAIDs Combined	1485	57/2077	2.7	---
Discontinuation Due to Digestive AEs or Abdominal Pain				
Etoricoxib	2498	138/3843	3.6	0.57[§] (0.45, 0.72)
Traditional NSAIDs Combined	1485	144/2070	7.0	---
Discontinuation Due to Abdominal Pain, Dyspepsia or Epigastric Discomfort				
Etoricoxib	2498	38/3851	1.0	0.58[‖] (0.37, 0.91)
Traditional NSAIDs Combined	1485	42/2078	2.0	---

[†] Events per 100 patient-years.
[‡] Relative risk from the Cox proportional-hazards model.
[§] p-values <0.001, [‖] p-values <0.05.
PYR = Patient-years at risk; CI = Confidence Interval.

7.2.2 MEDAL Program Studies

In the MEDAL Program, GI tolerability was defined as a composite endpoint that included patient discontinuations from a MEDAL Program study for prespecified clinical or laboratory GI adverse experiences. The predefined set of GI adverse experiences included all terms in the Medical Dictionary for Regulatory Affairs (MedDRA) within the GI System Organ Class (with the exception of a small number of terms related to specific oral and dental disorders not deemed clinically relevant) and prespecified adverse experience terms related to liver function abnormalities. Only the results for the clinical GI adverse experience component are presented in this document for the sake of brevity, but the results observed for the composite endpoint of clinical and laboratory GI adverse experiences were very consistent with those presented for the clinical endpoint.

Given the sizable number of patients in each of the MEDAL Program studies, GI tolerability was prespecified to be analyzed by individual study as the primary assessment. The primary time period for assessment of GI tolerability endpoints was 1 year from start of therapy for each patient. The rates for discontinuations due to clinical GI adverse experiences by disease and dose in the MEDAL Program Studies over the first year of treatment are presented in Table 31. In all 3 studies, the rate of discontinuation due to clinical GI adverse experiences was significantly lower in the etoricoxib treatment group compared with the diclofenac treatment group. Evaluations over the entire treatment period were also conducted as secondary assessments and, although not shown, were entirely consistent with the data over 1 year. The benefit was maintained for etoricoxib in patients regardless of their concomitant use of PPIs or low-dose aspirin with no significant subgroup-by-treatment interactions. The relative risk (95% CIs) for etoricoxib to diclofenac in PPI users and nonusers was 0.67 (0.59, 0.76) and 0.71 (0.64, 0.79), respectively. The relative risk (95% CIs) for etoricoxib to diclofenac in aspirin users and nonusers was 0.73 (0.64, 0.83) and 0.67 (0.61, 0.75), respectively.

The GI tolerability results observed in the MEDAL Program studies were consistent with the pooled analysis results from the Etoricoxib Development Program, which were driven by comparisons of etoricoxib to naproxen.

Table 31

MEDAL Program Studies by Disease and Dose
Discontinuations Due to Clinical GI Adverse Experiences within
1 Year of Treatment

Treatment	N	n/PYR	Rate†	Relative Risk‡ (95% CI)
MEDAL Study				
60 mg vs. Diclofenac Cohort				
Etoricoxib 60 mg OA	6769	213/5613	3.79	0.56§ (0.47, 066)
Diclofenac 150 mg OA	6700	369/5402	6.83	---
90 mg vs. Diclofenac Cohort				
Etoricoxib 90 mg OA	2171	134/1634	8.20	0.67§ (0.54, 0.83)
Diclofenac 150 mg OA	2162	195/1552	12.56	---
RA Cohort				
Etoricoxib 90 mg RA	2841	96/2315	4.15	0.57§ (0.44, 0.73)
Diclofenac 150 mg RA	2855	169/2278	7.42	---
EDGE II				
Etoricoxib 90 mg RA	2032	84/1668	5.04	0.70§ (0.53, 0.93)
Diclofenac 150 mg RA	2054	120/1668	7.19	---
EDGE				
Etoricoxib 90 mg OA	3593	254/2785	9.12	0.75§ (0.64, 0.89)
Diclofenac 150 mg OA	3518	319/2597	12.28	---

mITT approach: includes events up to and including the 14-day post therapy discontinuation.
† Events per 100 patient-years.
‡ Relative risk from the Cox proportional-hazards model with baseline aspirin use as a stratification factor and treatment as an explanatory factor in the model.
§ p-values <0.001.
n =the number of patients with events; N= total number of patients;
PYR = Patient-years at risk; CI = Confidence Interval; RR = Relative Risk.

GI Tolerability Conclusions

- The results of the prespecified combined analysis of GI tolerability endpoints in the Etoricoxib Development Program demonstrates that the GI tolerability profile of etoricoxib is superior to that of traditional NSAIDs, which was driven primarily by comparisons to naproxen.
- Significant decreases are also noted across all 3 MEDAL Program Studies for the incidence of discontinuation due to GI clinical adverse experiences and are also maintained within the individual clinical and laboratory components of this endpoint.
- Lower rates of discontinuation due to GI clinical adverse experiences are also observed in the etoricoxib group compared with the diclofenac group regardless of concomitant PPI and low-dose aspirin use.

7.3 Lower GI Safety

Lower GI safety refers to lower GI clinical events (small or large bowel perforations, obstructions, or bleeds; POBs). In the MEDAL Program, confirmed lower GI clinical events were a prespecified GI endpoint. A Pooled MEDAL Program analysis of lower GI clinical events was prespecified to help ensure sufficient statistical power to detect between-treatment-group differences as it was anticipated that the number of events occurring in each individual study would be less than 125 events. This number of events represents the required number based to achieve a statistically significantly different from zero based on a maximum observed hazard ratio of 0.70. In addition, confirmed plus unconfirmed cases were considered in order to evaluate the data as comprehensively as possible. The primary hypothesis was that treatment with etoricoxib would be associated with a lower risk of confirmed lower GI events than treatment with diclofenac.

Lower Gastrointestinal Adjudication Standard Operating Procedures (SOP)

Potential lower GI clinical events (perforations, obstructions, bleeds; POBs) were reviewed and adjudicated by an external blinded CRC. The process for adjudication was logistically similar to that used for the adjudication of upper GI clinical events and the same CRC was used.

The pooled analysis of lower GI clinical events included events that occurred while a patient was on treatment and those occurring up to 14 days following completion of treatment. The analyses included the following endpoints: (1) confirmed lower GI clinical events; (2) confirmed plus unconfirmed lower GI clinical events; (3) confirmed complicated lower GI clinical events, and (4) confirmed plus unconfirmed complicated lower GI clinical events.

Etoricoxib Development Program

An analysis of lower GI clinical events was not prespecified as part of the Etoricoxib Development Program and information required for adjudication of these events was not collected.

7.3.1 Pooled MEDAL Program

The summary of lower GI clinical events is in Table 32. Confirmed lower GI clinical events occurred at a numerically lower rate in the etoricoxib treatment group compared with the diclofenac treatment group, although the difference was not significant; relative risk (95% CI) of 0.84 (0.63, 1.13). For confirmed plus unconfirmed events, there was a significant reduction in risk for patients on etoricoxib; relative risk (95% CI) of 0.76 (0.59, 0.98). Results for the subset of complicated events were consistent with the overall results in showing a nonsignificant trend towards a lower rate for etoricoxib. Small or large bowel hemorrhage was the most common lower GI event in both treatment groups.

In addition, 2 sensitivity analyses were conducted on lower GI endpoints: (1) Confirmed Lower GI Events plus confirmed hospitalizations for diverticulitis, except confirmed

hospitalizations for diverticulitis in which response to antibiotic therapy was the only confirmed criteria, and (2) Confirmed Lower GI Events plus confirmed small or large bowel ulcer. For both analyses, rates for patients on etoricoxib were numerically lower than for patients on diclofenac.

Table 32

Pooled MEDAL Program
Summary of Lower GI Events

	Etoricoxib (N = 17412) PYR = 26382		Diclofenac (N = 17289) PYR = 25386		Relative Risk (95% CI)
	n	Rate†	n	Rate†	
Confirmed Lower GI Events					
Patients with at least one event in this category	**84**	**0.32**	**96**	**0.38**	**0.84 (0.63, 1.13)**
Small or Large Bowel Hemorrhage	51	0.19	59	0.23	
Small or Large Bowel Obstruction	16	0.06	19	0.07	
Small or Large Bowel Perforation	21	0.08	24	0.09	
Confirmed and Unconfirmed Lower GI Events					
Patients with at least one event in this category	**109**	**0.41**	**138**	**0.54**	**0.76 (0.59, 0.98)**
Small or Large Bowel Hemorrhage	75	0.28	102	0.40	
Small or Large Bowel Obstruction	18	0.07	22	0.09	
Small or Large Bowel Perforation	22	0.08	26	0.10	
Confirmed Complicated Lower GI Events					
Patients with at least one event in this category	**77**	**0.29**	**87**	**0.34**	**0.85 (0.63, 1.16)**
Small or Large Bowel Hemorrhage	43	0.16	49	0.19	
Small or Large Bowel Obstruction	16	0.06	19	0.07	
Small or Large Bowel Perforation	21	0.08	24	0.09	
Confirmed and Unconfirmed Complicated Lower GI Events					
Patients with at least one event in this category	**78**	**0.30**	**90**	**0.35**	**0.83 (0.62, 1.13)**
Small or Large Bowel Hemorrhage	44	0.17	53	0.21	
Small or Large Bowel Obstruction	16	0.06	19	0.07	
Small or Large Bowel Perforation	21	0.08	25	0.10	

†Events per 100 Patient-Years.

Note: Patients with multiple events may be counted more than once in different terms, but only once in each term

mITT Approach: Includes events up to and including the 14-day poststudy period.

n =the number of patients with events; N= total number of patients;
PYR=Patient-years at risk; CI = Confidence Interval
Relative risk from the Cox proportional-hazards model with baseline aspirin use as a stratification factor and treatment as an explanatory factor in the model.

Lower GI Clinical Events Conclusions

- The Pooled MEDAL Program data reveals rates of lower GI events which are numerically lower on etoricoxib compared with diclofenac and are significantly lower for Confirmed plus Unconfirmed lower GI events.

7.4 Hepatic Effects

Hepatic effects refer primarily to assessments of clinical and laboratory adverse effects relating to alterations in hepatic function, and also includes assessment of transaminases during study treatment. It is another important aspect of overall GI tolerability. Since elevations of liver function laboratory tests have been associated with the use of some non-selective NSAIDs, including diclofenac [81], abnormalities in liver function with treatment were evaluated by examining the following:

- Discontinuations due to hepatic-related adverse experiences (discontinuations were examined given that the MEDAL Study limited collection of adverse experiences to those that were serious or resulted in discontinuation).
- Mean changes from baseline in aspartate aminotransferase (AST) alanine aminotransferase (ALT),
- The percent of patients exceeding pre-defined limits of change in AST and ALT.

7.4.1 Etoricoxib Development Program

Mean change from baseline in AST and ALT and the percent of patients exceeding pre-defined limits of change in ALT and AST (>3 x ULN if normal at baseline or >2 X baseline and >3 x ULN if abnormal at baseline) during the study were examined in the OA Development Program Populations.

In the Placebo-Controlled Population, there were no clinically meaningful differences between the active treatment groups (and placebo in mean change from baseline in serum ALT and AST. In the 6-Month and 1-Year Populations, there were no clinically meaningful differences among the active treatment groups.

In all 3 Populations, few patients exceeded criteria for the predefined limits of change in serum ALT and AST with no significant differences observed between the treatment groups.

7.4.2 MEDAL Program Studies

In the individual MEDAL Program Studies, discontinuations due to adverse experiences related to hepatic dysfunction and the percent of patients exceeding pre-defined limits of change in ALT and AST were examined.

Discontinuations Due to Adverse Experiences Related to Hepatic Dysfunction

In all 3 MEDAL Program Studies, the incidences of hepatic-related adverse experiences resulting in discontinuation were significantly lower for the etoricoxib 60-mg and 90-mg treatment groups then for diclofenac 150-mg treatment group among both OA and RA patients. The number of patients who discontinued due to hepatic-related adverse experiences is summarized in Table 33.

Table 33

MEDAL Program Studies
Discontinuations Due to Hepatic-Related Adverse Experiences

Study	Osteoarthritis						Rheumatoid Arthritis		
	60 mg vs. Diclofenac Cohort			90 mg vs. Diclofenac Cohort					
	Etoricoxib 60 mg	Diclofenac 150 mg	Difference in Proportions (95% CI)†	Etoricoxib 90 mg	Diclofenac 150 mg	Difference in Proportions (95% CI)†	Etoricoxib 90 mg	Diclofenac 150 mg	Difference in Proportions (95% CI)†
	n/N (%)	n/N (%)	Etoricoxib 60 mg - Diclofenac	n/N (%)	n/N (%)	Etoricoxib 90 mg - Diclofenac	n/N (%)	n/N (%)	Etoricoxib 90 mg - Diclofenac
Number (%) of patients who discontinued due to hepatic-related adverse experiences									
MEDAL (OA)	22/6769 (0.3)	119/6700 (1.8)	-1.45 (-1.8, -1.1)	8/2171 (0.4)	88/2162 (4.1)	-3.7 (-4.6, -2.9)			
MEDAL (RA)							12/2841 (0.4)	48/2855 (1.7)	-1.26 (-1.8, -0.7)
EDGE II (RA)							6/2032 (0.3)	30/2054 (1.5)	-1.17 (-1.8, -0.6)
EDGE (OA)				9/3593 (0.3)	182/3518 (5.2)	-4.92 (-5.7,-4.2)			

†The 95% confidence interval is calculated by Wilson's Score Method.
Boxes shaded in grey indicate no applicable data.
Although a patient may have had two or more adverse experiences, the patient is counted only once in the overall category. The same patient may appear in different categories.
n/N=Number of patients discontinuing for adverse experience/number of patients treated; CI=Confidence Interval.
mITT Analysis Approach

Analysis of Predefined Limits of Change in AST and ALT

A summary of the primary analysis for the predefined limits of change for ALT for the 3 individual MEDAL Program Studies is in Table 34. In each individual study, the proportion of patients exceeding the predefined limits of change for ALT was lower in both of the etoricoxib 60-mg and 90-mg treatment groups than in the diclofenac 150-mg treatment groups among both OA and RA patients. These data are consistent with the increased rate of discontinuation for hepatic-related adverse experiences observed with the diclofenac 150-mg treatment groups relative to the etoricoxib 60-mg and 90-mg treatment groups. Further, for each individual MEDAL Program Study, the secondary analysis was consistent with the primary analysis. Results for AST were consistent with those observed for ALT.

Table 34

MEDAL Program Studies
Patients Exceeding the Predefined Limits of Change for ALT

Study	Osteoarthritis: 60 mg vs. Diclofenac Cohort: Etoricoxib 60 mg n/N (%)	Osteoarthritis: 60 mg vs. Diclofenac Cohort: Diclofenac 150 mg n/N (%)	Osteoarthritis: 60 mg vs. Diclofenac Cohort: Difference in Proportions (95% CI)‖ Etoricoxib 60 mg - Diclofenac	Osteoarthritis: 90 mg vs. Diclofenac Cohort: Etoricoxib 90 mg n/N (%)	Osteoarthritis: 90 mg vs. Diclofenac Cohort: Diclofenac 150 mg n/N (%)	Osteoarthritis: 90 mg vs. Diclofenac Cohort: Difference in Proportions (95% CI)‖ Etoricoxib 90 mg - Diclofenac	Rheumatoid Arthritis: Etoricoxib 90 mg n/N (%)	Rheumatoid Arthritis: Diclofenac 150 mg n/N (%)	Rheumatoid Arthritis: Difference in Proportions (95% CI)‖ Etoricoxib 90 mg - Diclofenac
Primary: Consecutive values > 3 x ULN‡ or Consecutive values > 2 x baseline and > 3 x ULN§									
MEDAL (OA)†	11 / 6456 (0.2)	76 / 6361 (1.2)	-1.02 (-1.33, -0.75)	6 / 2082 (0.3)	50 / 2085 (2.4)	-2.11 (-2.88, -1.44)			
MEDAL (RA)†							5 / 2682 (0.2)	20 / 2710 (0.7)	-0.55 (-0.96, -0.19)
EDGE II (RA)†							4 / 1933 (0.2)	20 / 1950 (1.0)	-0.8 (-1.4, -0.3)
EDGE (OA)				6 / 3543 (0.2)	136 / 3452 (3.9)	-3.8 (-4.5, -3.1)			

† Meeting the Criteria on one occasion and discontinuing due to the particular laboratory test (instead of consecutive values and patient continuing in the study) is sufficient to be classified as exceeding the defined limit of change.
‡ If normal at baseline
§ If abnormal at baseline
‖ The 95% confidence interval is calculated by Wilson's Score Method.
Boxes shaded in gray indicate no applicable data.
Although a patient may have had two or more adverse experiences, the patient is counted only once in the overall category. The same patient may appear in different categories.
n/N=Number of patients discontinuing for adverse experience/number of patients treated; CI=Confidence Interval; ULN=Upper limit of normal.
mITT Analysis Approach: Includes events up to and including the 14-day post study therapy discontinuation

A post-hoc analysis for the pooled MEDAL Program was carried out for AST and ALT elevations ≥8 times the upper limit of normal to further evaluate the degree to which these higher elevations affected the study population [132; 22]. In this analysis, diclofenac was associated with increases in aminotransferase (>8 x ULN) relative to etoricoxib; 0.7% on diclofenac versus 0.1% for the 60- and 90-mg doses of etoricoxib combined.

Hepatic Effects Conclusions

- In the Etoricoxib Development Program, etoricoxib demonstrated similar incidences of mean changes from screening in AST and ALT and similar proportions of patients exceeding the predefined limits of change for AST and ALT versus naproxen, ibuprofen, and celecoxib.
- Etoricoxib had a more favorable hepatic safety profile, compared with diclofenac in the MEDAL Program Studies. In all 3 MEDAL Program Studies, regardless of disease and dose, etoricoxib demonstrated a lower incidence of discontinuations due to hepatic-related adverse experiences and lower proportion of patients exceeding the predefined limits of change for AST and ALT versus diclofenac.

8. Thrombotic Cardiovascular Safety

This section provides the results of analyses of thrombotic CV safety data from both Etoricoxib Development Program and from the MEDAL Program.

Cardiovascular Adjudication Standard Operating Procedure (SOP)

A Cardiovascular Adjudication SOP was introduced in the second quarter 1998, prior to initiation of Phase II of the Etoricoxib Development Program to collect data that might help evaluate hypotheses about both potential CV risks and benefits that had been raised with regard to COX-2 inhibitors. These included hypothesized differences in CV event rates between some NSAIDs and COX-2 selective inhibitors due to differences in antiplatelet effects, theoretical implications of a thromboxane-prostacyclin imbalance with selective COX-2 inhibitors, as well as the theoretical potential for COX-2 inhibition to be cardioprotective [133; 134]. This Adjudication SOP has been used for the entire Etoricoxib Development Program and MEDAL Program. The CV Adjudication SOP established a process by which potential thrombotic CV events occurring in clinical trials of etoricoxib could be identified and adjudicated in a blinded manner, by external panels of experts in cardiovascular medicine in order to more precisely assess thrombotic CV events which occurred during the Etoricoxib Development Program, and MEDAL Program studies.

Definition of Cardiovascular Endpoints

As defined in the Adjudication SOP, a comprehensive list of thrombotic CV terms was developed to identify potential CV endpoints thrombotic in etiology. All reported potentially thrombotic CV events with a term belonging to this list from the Etoricoxib Development Program and the MEDAL Program studies were adjudicated by a Vascular

Events Committee (VEC) and reported as an event type as summarized in Table 35 as defined by the CV adjudication SOP.

For the prespecified pooled analysis of the Etoricoxib Development Program data two endpoints were used: (1) Confirmed Thrombotic Events (considered primary) and (2) the Antiplatelet Trialists' Collaboration (APTC) endpoint [135; 136].

For the MEDAL Program, the primary thrombotic CV endpoint was Confirmed Thrombotic Events. The two secondary thrombotic CV endpoints were: (1) Confirmed Thrombotic Arterial Events, and (2) the Confirmed APTC Combined Endpoint. Numerous exploratory endpoints were also prespecified, including myocardial infarctions and ischemic strokes.

In both the Etoricoxib Development Program and the MEDAL Program, power for the secondary endpoints was lower than for the primary endpoint because these are a subset of the primary endpoint and therefore would represent fewer events. Thus, interpretation of the secondary endpoint results must be made with caution and with consideration that they naturally will have wider CIs for the hazard ratio (HR) than the primary endpoint of Confirmed Thrombotic Events.

Table 35

Thrombotic Cardiovascular Primary and Secondary Endpoints
Etoricoxib Development Program, MEDAL Program

Adjudication Committee Categories for Cardiovascular Events	Primary Endpoint	Secondary Endpoints	
	Confirmed Thrombotic Events	Confirmed Thrombotic Arterial Events[†]	Confirmed APTC Combined Endpoint
Thrombotic Events			
Cardiac Events			
Acute MI	√	√	√
Fatal: Acute MI	√	√	√
Unstable Angina Pectoris	√	√	
Sudden and/or Unexplained Death[‡]	√	√	√
Resuscitated Cardiac Arrest	√	√	√
Cardiac Thrombus	√		
Peripheral Vascular Events			
Pulmonary Embolism	√		
Fatal: Pulmonary Embolism	√		√[§]
Peripheral Arterial Thrombosis	√	√	
Fatal: Peripheral Arterial Thrombosis	√	√	√
Peripheral Venous Thrombosis	√		
Cerebrovascular Events			
Ischemic Cerebrovascular Stroke	√	√	√
Fatal: Ischemic Cerebrovascular Stroke	√	√	√
Cerebrovascular Venous Thrombosis	√		
Fatal: Cerebrovascular Venous Thrombosis	√		√
Stroke, Unknown Mechanism	√		√
Fatal: Stroke, Unknown Mechanism	√		√
Transient Ischemic Attack	√	√	
Other Events			
Hemorrhagic Cerebrovascular Stroke			√
Fatal: Hemorrhagic Cerebrovascular Stroke			√
Fatal GI Hemorrhage			√
Fatal Vascular Rupture			√
Other Fatal Hemorrhagic Events[§]			√
Unknown Cause of Death[‖]			√

[†] Thrombotic Arterial Events were not defined separately as an endpoint in the Etoricoxib Development Program; this endpoint was only evaluated for the MEDAL Program

[‡] Defined as witnessed instantaneous or near-instantaneous death that occurred without warning or within 1 hour of non-diagnostic symptoms, or as an unwitnessed unexpected death in which criteria for a fatal coronary or cerebrovascular event were not met.

[§] Based on additional clarification of the APTC Combined Endpoint definition received from the Antiplatelet Trialists' Collaboration coordinating center at Oxford on October 16, 2003, one change was made to the APTC definition for all studies governed by this SOP that had not yet reached frozen file as of that date: hemorrhagic deaths which were documented to have been due to trauma or are post-surgical were not included as APTC endpoints. In addition, as of September 2005, a correction was made to include fatal pulmonary embolism as a cardiovascular death and APTC endpoint.

[‖] Unknown cause of death was defined as a death that was judged to be non-thromboembolic, but where a specific cause of death could not be determined from the available documentation.

APTC = Antiplatelet Trialists' Collaboration, MI = Myocardial infarction, GI = gastrointestinal.

Results

8.1 Etoricoxib Development Program

Patient level data from the Etoricoxib Development Program studies were pooled for an analysis of thrombotic CV safety. Pooled data included studies that were ≥4 weeks in duration and included doses of etoricoxib from 30 to 120 mg. The majority of data where from exposure to etoricoxib doses >60 mg; of the 4500 patient years of exposure in the thrombotic CV analysis, 1800 were from doses ≤60 mg and 2700 were from the 90-120 mg doses. For the tabulation of thrombotic CV events in the Etoricoxib Development Program, the following data sets were defined: (1) Placebo-Controlled data set which compared etoricoxib to placebo and includes the placebo- controlled period of all included studies, (2) Non-naproxen-NSAID-controlled data set which compared etoricoxib to all NSAID comparators pooled other than naproxen (diclofenac, ibuprofen), (3) naproxen-controlled data set which compared etoricoxib to naproxen. The non-naproxen NSAID-controlled and naproxen-controlled data sets included the active treatment periods that contained both etoricoxib and a traditional NSAID comparator (diclofenac, ibuprofen) or naproxen, from the Etoricoxib Development Program Studies.

Naproxen was considered separately in this analysis based on the fact that it is pharmacodynamically different from the other 2 traditional NSAIDs (ibuprofen and diclofenac) in conferring a potent and sustained antiplatelet effect [112] when dosed consistently at 500 mg bid and on the outcome of the FDA 2005 Advisory Committee Meeting in which the Agency indicated that naproxen was possibly different with regard to thrombotic CV safety along with their recommendations to study naproxen in the future. Given that a substantial amount of naproxen comparator data had been accrued in the Etoricoxib Development Program, it was important to provide these data separately. A formal test for heterogeneity for naproxen and non-naproxen data was not significant, however, this analysis is limited in that there were relatively limited data versus NSAID comparators other than naproxen.

Event rates (per 100 patient-years) and 95% CIs for Confirmed Thrombotic Events and the Confirmed APTC Combined Endpoint are provided for the Placebo-Controlled, Non-Naproxen-NSAID-Controlled, and Naproxen-Controlled data sets in Table 36. These data are based on median durations of exposure of 2.8, 3.3, and 11.9 months for the Placebo-Controlled, Non-naproxen NSAID-Controlled, and Naproxen–Controlled data sets. In tabulations of Confirmed Thrombotic Events, no discernible difference was observed for etoricoxib versus placebo; however, due to the limited duration (≤12 weeks), the limited patient years of exposure, and the paucity of events accrued for this data set, no definitive conclusions could be drawn. There was no discernible difference in event rates between patients taking etoricoxib and traditional NSAIDs other than naproxen. The use of naproxen 1000 mg was associated with a rate of Confirmed Thrombotic Events which was numerically lower, but not statistically significantly lower than that observed with etoricoxib; however the rate of the Confirmed APTC Combined Endpoint was significantly lower for naproxen compared to etoricoxib. Of note, although

etoricoxib 30 mg is included in the pooled analysis of the Naproxen-Controlled data set, this dose was not directly compared to naproxen in any of the studies.

Figure 12 displays the Kaplan-Meier plots for cumulative incidence rates for Confirmed Thrombotic Events for all 3 comparator groups.

Results of the Naproxen-Controlled dataset are summarized by class of terms in Table 37. Overall, there were generally more cardiac events than cerebrovascular or peripheral vascular events regardless of treatment. In considering the difference between the naproxen 1000-mg and etoricoxib groups, no single type of event predominated, although a higher incidence of ischemic cerebrovascular stroke was observed with etoricoxib compared to naproxen 1000 mg.

Table 36

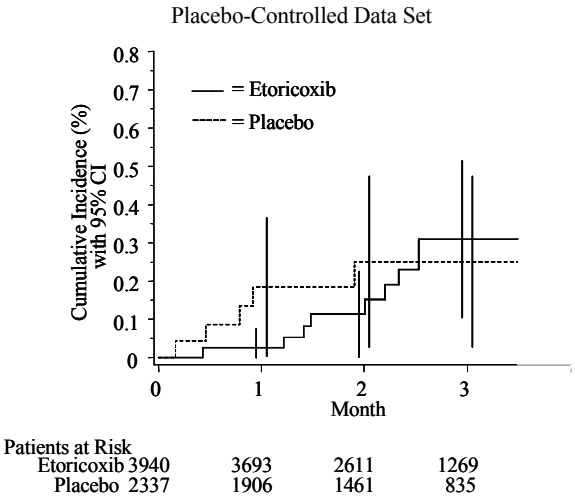
Etoricoxib Development Program
Summary of Confirmed Thrombotic Events and Confirmed APTC Combined Endpoint

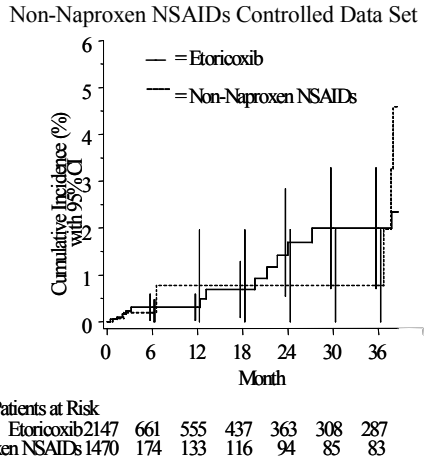
Comparisons	N	n/PYR[†]	Rate[‡] (95% CI)	Relative Risk[§] (95% CI)
Confirmed Thrombotic Events				
Etoricoxib	3940	9/810	1.11 (0.51, 2.11)	1.07 (0.36, 3.22)
Placebo	2337	5/450	1.11 (0.36, 2.59)	--
Etoricoxib	2147	14/1815	0.77 (0.42, 1.29)	0.73 (0.27, 1.98)
Non-Naproxen NSAIDs	1470	6/649	0.92 (0.34, 2.01)	--
Etoricoxib	1960	34/2480	1.37 (0.95, 1.92)	1.70 (0.91, 3.18)
Naproxen 1000 mg	1497	14/1727	0.81 (0.44, 1.36)	--
Confirmed APTC Combined Endpoint				
Etoricoxib	3940	7/810	0.86 (0.35, 1.78)	1.95 (0.37, 19.19)
Placebo	2337	2/450	0.44 (0.05, 1.60)	--
Etoricoxib	2147	11/1817	0.61 (0.30, 1.08)	0.80 (0.25, 2.59)
Non-Naproxen NSAIDs	1470	4/649	0.62 (0.17, 1.58)	--
Etoricoxib	1960	27/2481	1.09 (0.72, 1.58)	2.72 (1.18, 6.27)
Naproxen 1000 mg	1497	7/1728	0.41 (0.16, 0.83)	--

[†] Patient-years at risk.
[‡] Per 100 PYR.
[§] Relative risk using Cox model stratified by therapeutic block where the number of cases is at least 11, otherwise relative risk is ratio of rates.
APTC = Antiplatelet Trialists' Collaboration; CI = Confidence interval; PYR = Patient-years at risk.

Figure 12

Etoricoxib Development Program
Kaplan-Meier Estimates of Cumulative Incidence for
Confirmed Thrombotic Events





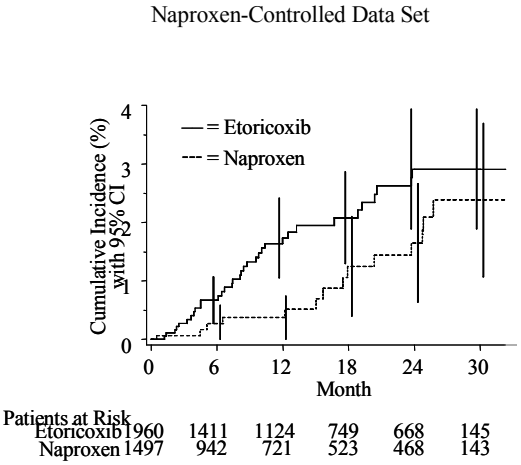


Table 37

Etoricoxib Development Program
Summary of Patients With Confirmed Thrombotic Events
by Class of Terms
Naproxen-Controlled Data Set

Category	Etoricoxib (N=1960) 2480 Patient Years		Naproxen (N=1497) 1727 Patient Years	
	n (%)†	Rate‡	n (%)†	Rate‡
Total number of patients with Confirmed Thrombotic Events	**34 (1.73)**	**1.37**	**14 (0.94)**	**0.81**
Cardiac Events	**21 (1.07)**	**0.85**	**7 (0.47)**	**0.41**
Acute myocardial infarction	10 (0.51)	0.40	5 (0.33)	0.29
Fatal acute myocardial infarction	2 (0.10)	0.08	1 (0.07)	0.06
Sudden/unknown cause of death	3 (0.15)	0.12	0 (0.00)	0.00
Unstable angina pectoris	6 (0.31)	0.24	3 (0.20)	0.17
Cerebrovascular Events	**12 (0.61)**	**0.48**	**2 (0.13)**	**0.12**
Ischemic cerebrovascular stroke	10 (0.51)	0.40	0 (0.00)	0.00
Fatal ischemic cerebrovascular stroke	0 (0.00)	0.00	1 (0.07)	0.06
Transient ischemic attack	2 (0.10)	0.08	1 (0.07)	0.06
Peripheral Vascular Events	**2 (0.10)**	**0.08**	**5 (0.33)**	**0.29**
Pulmonary embolism	2 (0.10)	0.08	2 (0.13)	0.12
Peripheral arterial thrombosis	0 (0.00)	0.00	1 (0.07)	0.06
Peripheral venous thrombosis	0 (0.00)	0.00	2 (0.13)	0.12

† Crude incident (n/Nx100).
‡ Events per 100 patient-years.
Note: Patient with multiple events may be counted more than once in different terms but only once per term.

8.1.1 Subgroup Analyses

Thrombotic CV safety data were also analyzed by various subgroups including aspirin use, thrombotic CV risk (increased risk defined as having either a previous history of symptomatic atherosclerotic CV disease or with ≥2 of the following cardiac risk factors; hypertension, diabetes mellitus, hypercholesterolemia, or tobacco use), and by etoricoxib dose. The Naproxen-controlled data set was used since this is the largest data set, and thus the most suitable for subgroup analysis. The results showed a similar relative risk in aspirin users versus nonusers, as well as patients with an increased thrombotic CV risk versus those without an increased thrombotic CV risk, with no significant treatment-by subgroup interactions.

In addition to the subgroups above, additional treatment-by-factor interactions were assessed by disease type in the Naproxen-Controlled data set. For Confirmed Thrombotic CV Events, the relative risk (95% CI) for etoricoxib versus naproxen in the combined OA/RA, OA only, and RA only studies was similar.

An analysis was performed to investigate the thrombotic CV event rates by dose of etoricoxib (30, 60, 90, and 120 mg). This approach, although comprehensive, must be interpreted cautiously because doses are confounded within protocols, and there are only small sample sizes in the 30 mg and 120 mg subgroups. The results of this analysis in (Table 38), provide no clear evidence of a dose effect across the 30- to 120-mg dose range of etoricoxib.

Table 38

Etoricoxib Development Program
Confirmed Thrombotic Events
by Etoricoxib Dose

	n/Patient Years	Rate[†](95% CI[‡])
Confirmed Thrombotic Events		
Etoricoxib 30 mg	3/484	0.62 (0.13, 1.81)
Etoricoxib 60 mg	17/1390	1.22 (0.71, 1.96)
Etoricoxib 90 mg	23/1813	1.27 (0.80, 1.90)
Etoricoxib 120 mg	7/954	0.73 (0.29, 1.51)

[†] Number of events per 100 patient-years.
[‡] If no events within the treatment group, the CI is a one-sided 97.5% CI.
If a patient received both doses, that patient is counted in both dose groups.
One multiple event(s) was (were) excluded for Etoricoxib 30, 60, and 90 mg.

8.2 Pooled MEDAL Program

The primary approach for the cardiovascular endpoints pooled across the MEDAL Program was based on a per-protocol analysis as recommended in ICH guidelines for studies where the primary hypothesis is non-inferiority. The timeframe for the per-protocol analysis was from Day 1 of therapy to 14 days after the last dose of study therapy. The per-protocol analysis excluded patients with clinically important deviations from protocol specified criteria which were defined as: (1) patients who had not complied with the study drug dosing regimen for any reason (e.g. <75% compliance), or (2) patients who took substantial amount (>10% of time on study therapy) of concomitant NSAIDs (including aspirin >125 mg) or selective COX-2 inhibitors during the study.

The modified intention-to-treat (mITT) was a secondary approach and included all patients who took at least 1 dose of study therapy (analysis based on the treatment assignment at randomization) and included patients from day 1 of therapy up to 14 days after the last dose of study therapy. Additional sensitivity analyses performed included an mITT analysis of all confirmed events for up to 28 days after the last dose of study medication as well as an intention-to-treat (ITT) analysis of all confirmed thrombotic CV events through the end of the trial which included events regardless of whether a patient had discontinued. The Eligibility date for a thrombotic CV event to be included in the

ITT analysis was 28 days after the last patient's last dose of study therapy for each respective MEDAL Program trial. The Ascertainment date for potential thrombotic cardiovascular events to be submitted to the VEC in order to be included in the ITT analysis was 42 days after the last patient's last dose of study drug.

Approximately 4% of patients in the ITT analysis were excluded from the per-protocol analysis (1399 patients); 593 (3.4%) and 806 (4.7%) in the etoricoxib and diclofenac groups, respectively.

Accounting of Events

Table 39 provides an overall accounting summary for the primary endpoint, Confirmed Thrombotic Events, in the MEDAL Program for each data set analyzed.

Table 39

Pooled MEDAL Program
Overall Accounting of Confirmed Thrombotic Events
by Analytical Approach

	Confirmed Thrombotic Events† Patients (Events)		
	Etoricoxib	Diclofenac	Total
Primary Analysis			
Per-protocol Approach	320 (335)	323 (338)	643 (673)
Secondary Analysis			
Within 14 Days (mITT)‡	345 (360)	345 (362)	690 (722)
Sensitivity Analyses			
Within 28 Days (mITT)‡	366 (382)	357 (382)	723 (764)
All Events (ITT)	495 (539)	468 (517)	963 (1056)

† Primary Endpoint.
‡ Events between trial start date and within *specified* days after study therapy discontinuation.
ITT=Intention-to-Treat; mITT=modified Intention-to-Treat.

8.2.1 Primary Endpoint and Secondary Endpoints

This section summarizes the primary and secondary endpoints for the Pooled MEDAL Program data.

As noted in Section 3.2.2.7, the primary analysis for the MEDAL Program was based on a per-protocol approach for the primary and secondary thrombotic CV endpoints pooled across the MEDAL Program.

Table 40 provides the event rates (per 100 patient-years) and 95% CIs for the primary and secondary endpoints for the primary per-protocol approach and also for the mITT, and ITT approaches. For the primary endpoint, the event rates for the primary analysis (per-protocol approach) for etoricoxib and diclofenac were comparable, yielding a relative risk of 0.95 (95% CI: 0.81, 1.11). The interim analyses adjusted confidence interval around the relative risk was (95.87% CI: 0.807, 1.113) and the upper bound of the adjusted confidence interval was less than the prespecified non-inferiority bound of 1.30, thus satisfying the primary hypothesis of the MEDAL Program. Etoricoxib was comparable to diclofenac for all primary and secondary endpoints for the Pooled MEDAL Program, regardless of the analytical approach (per-protocol, mITT, and ITT), with relative risks that approximate 1.0.

Kaplan-Meier plots of the cumulative incidence rate for the primary and secondary endpoints based on the per-protocol analysis are provided in Figure 13. For each of the endpoints, the proportional hazard assumption was satisfied indicating constant hazard ratios over time.

Table 41 provides a summary of the rates (and associated 95% CIs) for all Confirmed Thrombotic Events by class of terms for etoricoxib and diclofenac based on the per-protocol analysis. There were events reported in all 3 vascular beds, with more cardiac than cerebrovascular or peripheral vascular events, irrespective of treatment group. Overall, there were no discernible differences between treatment groups in any of the events reported in all 3 vascular beds.

Table 40

Pooled MEDAL Program
Summary of Primary and Secondary Endpoints
by Analytical Approach

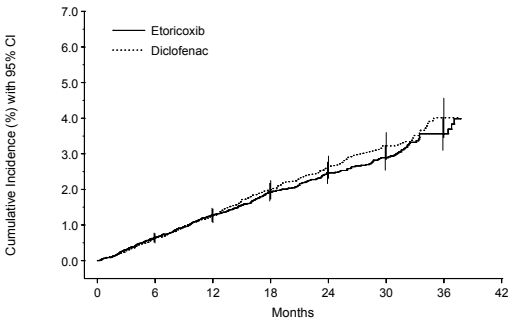
Analysis Approach	Treatment	N	n/ PYR[†]	Rate[†] (95% CI)	Relative Risk (95% CI)
Confirmed Thrombotic Events (primary endpoint)					
Per-Protocol Approach[§]	**Etoricoxib**	**16819**	**320 / 25836**	**1.24 (1.11 , 1.38)**	**0.95 (0.81 , 1.11)**
	Diclofenac	**16483**	**323 / 24766**	**1.30 (1.17 , 1.45)**	
Within 14 Days (mITT)[‡‖]	Etoricoxib	17412	345 / 26384	1.31 (1.17 , 1.45)	0.96 (0.83 , 1.11)
	Diclofenac	17289	345 / 25394	1.36 (1.22 , 1.51)	
Within 28 Days (mITT)[‡¶]	Etoricoxib	17412	366 / 27036	1.35 (1.22 , 1.50)	0.98 (0.85 , 1.14)
	Diclofenac	17289	357 / 26042	1.37 (1.23 , 1.52)	
All Events (ITT)[¶]	Etoricoxib	17412	495 / 39654	1.25 (1.14 , 1.36)	1.05 (0.93 , 1.19)
	Diclofenac	17289	468 / 39413	1.19 (1.08 , 1.30)	
Confirmed Arterial Events (secondary endpoint)					
Per-Protocol Approach[§]	Etoricoxib	16819	272 / 25839	1.05 (0.93 , 1.19)	0.96 (0.81 , 1.13)
	Diclofenac	16483	272 / 24771	1.10 (0.97 , 1.24)	
Within 14 Days (mITT)[‡‖]	Etoricoxib	17412	297 / 26386	1.13 (1.00 , 1.26)	0.97 (0.83 , 1.14)
	Diclofenac	17289	293 / 25399	1.15 (1.03 , 1.29)	
Within 28 Days (mITT)[‡¶]	Etoricoxib	17412	305 / 27040	1.13 (1.00 , 1.26)	0.98 (0.83 , 1.15)
	Diclofenac	17289	300 / 26049	1.15 (1.03 , 1.29)	
All Events (ITT)[¶]	Etoricoxib	17412	407 / 39767	1.02 (0.93 , 1.13)	1.03 (0.89 , 1.18)
	Diclofenac	17289	394 / 39513	1.00 (0.90 , 1.10)	
Confirmed APTC Combined Endpoint (secondary endpoint)					
Per-Protocol Approach[§]	Etoricoxib	16819	216 / 25851	0.84 (0.73 , 0.95)	0.96 (0.79 , 1.16)
	Diclofenac	16483	216 / 24787	0.87 (0.76 , 1.00)	
Within 14 Days (mITT)[‡‖]	Etoricoxib	17412	231 / 26402	0.87 (0.77 , 1.00)	0.96 (0.80 , 1.15)
	Diclofenac	17289	232 / 25416	0.91 (0.80 , 1.04)	
Within 28 Days (mITT)[‡¶]	Etoricoxib	17412	237 / 27059	0.88 (0.77 , 0.99)	0.95 (0.80 , 1.14)
	Diclofenac	17289	239 / 26068	0.92 (0.80 , 1.04)	
All Events (ITT)[¶]	Etoricoxib	17412	332 / 39894	0.83 (0.75 , 0.93)	1.02 (0.87 , 1.18)
	Diclofenac	17289	325 / 39623	0.82 (0.73 , 0.91)	

[†] Number of events per 100 patient-years.
[‡] Events between trial start date and within *specified* days of study therapy discontinuation.
[§] The per-protocol approach was the primary analysis.
[‖] The mITT approach within 14 days was the secondary analysis.
[¶] The mITT within 28 days and the ITT approaches were sensitivity analyses.
PYR= Patient-years at risk; N=total number of patients; n=the number of patients with events.
Relative risk from the Cox proportional-hazards model with baseline aspirin use as a stratification factor and treatment as a factor in the model.

Figure 13

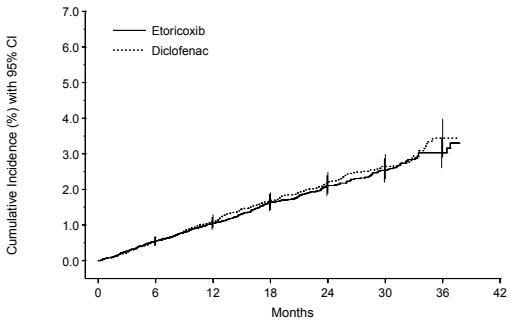
Pooled MEDAL Program†
Kaplan Meier Estimates of Cumulative Incidence for
Primary and Secondary Endpoints

Confirmed Thrombotic Events



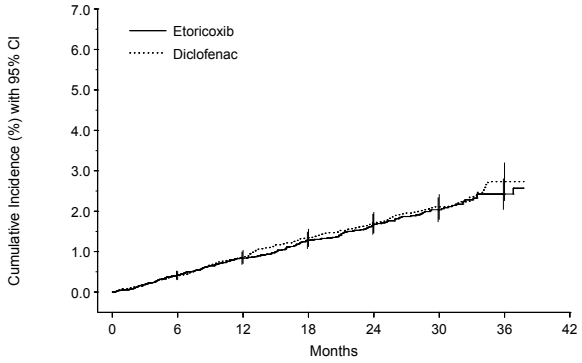
# Patients at Risk							
Etoricoxib	16819	13359	10733	8277	6427	4024	805
Diclofenac	16483	12800	10142	7901	6213	3832	815

Confirmed Arterial Events



# Patients at Risk							
Etoricoxib	16819	13362	10735	8277	6427	4024	805
Diclofenac	16483	12801	10144	7903	6214	3832	815

Confirmed APTC Combined Endpoints



# Patients at Risk							
Etoricoxib	16819	13366	10745	8282	6429	4026	805
Diclofenac	16483	12814	10155	7906	6218	3832	816

† Per Protocol Approach

Table 41

Pooled MEDAL Program
Confirmed Thrombotic Events[†] by Class of Terms

Confirmed Thrombotic Event	Etoricoxib (N=16819) 25836 Patient-Years		Diclofenac (N=16483) 24766 Patient-Years	
	n(%)[‡]	Rate[§] (95% CI)	n(%)[‡]	Rate[§] 95% CI
Total number of patients with Endpoint	320 (1.90)	1.24 (1.11 , 1.38)	323 (1.96)	1.30 (1.17 , 1.45)
Cardiac Events	183 (1.09)	0.71 (0.61 , 0.82)	194 (1.18)	0.78 (0.68 , 0.90)
Non-fatal acute myocardial infarction	105 (0.62)	0.41 (0.33 , 0.49)	105 (0.64)	0.42 (0.35 , 0.51)
Fatal acute myocardial infarction	6 (0.04)	0.02 (0.01 , 0.05)	17 (0.10)	0.07 (0.04 , 0.11)
Sudden cardiac death	29 (0.17)	0.11 (0.08 , 0.16)	23 (0.14)	0.09 (0.06 , 0.14)
Unstable angina pectoris	42 (0.25)	0.16 (0.12 , 0.22)	51 (0.31)	0.21 (0.15 , 0.27)
Resuscitated cardiac arrest	2 (0.01)	0.01 (0.00 , 0.03)	1 (0.01)	0.00 (0.00 , 0.02)
Cardiac thrombus	4 (0.02)	0.02 (0.00 , 0.04)	3 (0.02)	0.01 (0.00 , 0.04)
Cerebrovascular Events	89 (0.53)	0.34 (0.28 , 0.42)	79 (0.48)	0.32 (0.25 , 0.40)
Non-fatal Ischemic cerebrovascular stroke	53 (0.32)	0.21 (0.15 , 0.27)	55 (0.33)	0.22 (0.17 , 0.29)
Fatal ischemic cerebrovascular stroke	6 (0.04)	0.02 (0.01 , 0.05)	2 (0.01)	0.01 (0.00 , 0.03)
Cerebrovascular venous thrombosis	1 (0.01)	0.00 (0.00 , 0.02)	1 (0.01)	0.00 (0.00 , 0.02)
Transient Ischemic Attack	31 (0.18)	0.12 (0.08 , 0.17)	22 (0.13)	0.09 (0.06 , 0.13)
Peripheral Vascular Events	53 (0.32)	0.21 (0.15 , 0.27)	55 (0.33)	0.22 (0.17 , 0.29)
Non-fatal pulmonary embolism	17 (0.10)	0.07 (0.04 , 0.11)	25 (0.15)	0.10 (0.07 , 0.15)
Fatal pulmonary embolism	1 (0.01)	0.00 (0.00 , 0.02)	0 (0.00)	0.00 ---
Non-fatal peripheral arterial thrombosis	5 (0.03)	0.02 (0.01 , 0.05)	4 (0.02)	0.02 (0.00 , 0.04)
Fatal peripheral arterial thrombosis	1 (0.01)	0.00 (0.00 , 0.02)	1 (0.01)	0.00 (0.00 , 0.02)
Peripheral venous thrombosis	29 (0.17)	0.11 (0.08 , 0.16)	27 (0.16)	0.11 (0.07 , 0.16)

[†] Per-Protocol Approach.
[‡] Crude Incidence (n/N×100).
[§] Events per 100 Patient-Years.
Patients with multiple events may be counted more than once in different terms, but only once in each term.

8.2.2 Exploratory Endpoints

This section summarizes the prespecified exploratory endpoints for the Pooled MEDAL Program.

The exploratory endpoint analyses based on the per-protocol and ITT approaches are in Table 42.

Among all the exploratory endpoints analyzed, there were no discernible differences between etoricoxib and diclofenac based on the rates per 100 patient-years for both the per-protocol and ITT approaches. The point estimates for the Confirmed Cerebrovascular Events were slightly numerically higher for both the per-protocol and

ITT approaches. The data from all of these exploratory endpoints support the conclusion that there were no discernible differences in event rates for etoricoxib and diclofenac for either the per-protocol or ITT approaches. Results for the 14 and 28 day mITT analyses were consistent with the results shown in Table 43.

Table 42

Pooled MEDAL Program
Summary of Exploratory Thrombotic Cardiovascular Events
by Analysis Approach

Analytical Approach	Treatment	N	n / PYR[†]	Rate[‡] (95% CI)	Relative Risk (95% CI)
Confirmed Thrombotic Deaths					
Per-Protocol Approach	Etoricoxib	16819	43 / 25873	0.17 (0.12 , 0.22)	0.96 (0.63 , 1.46)
	Diclofenac	16483	43 / 24806	0.17 (0.13 , 0.23)	
All Events (ITT)[§]	Etoricoxib	17412	87 / 40200	0.22 (0.17 , 0.27)	1.05 (0.78 , 1.43)
	Diclofenac	17289	82 / 39918	0.21 (0.16 , 0.25)	
Confirmed Cardiac Events					
Per-Protocol Approach	Etoricoxib	16819	183 / 25853	0.71 (0.61 , 0.82)	0.90 (0.74 , 1.10)
	Diclofenac	16483	194 / 24785	0.78 (0.68 , 0.90)	
All Events (ITT)[§]	Etoricoxib	17412	277 / 39920	0.69 (0.61 , 0.78)	0.99 (0.84 , 1.17)
	Diclofenac	17289	277 / 39664	0.70 (0.62 , 0.79)	
Confirmed MIs					
Per-Protocol Approach	Etoricoxib	16819	111 / 25859	0.43 (0.35 , 0.52)	0.87 (0.67 , 1.13)
	Diclofenac	16483	122 / 24797	0.49 (0.41 , 0.59)	
All Events (ITT)[§]	Etoricoxib	17412	164 / 40008	0.41 (0.35 , 0.48)	1.00 (0.81 , 1.24)
	Diclofenac	17289	163 / 39751	0.41 (0.35 , 0.48)	
Confirmed Cerebrovascular Events					
Per-Protocol Approach	Etoricoxib	16819	89 / 25860	0.34 (0.28 , 0.42)	1.08 (0.80 , 1.46)
	Diclofenac	16483	79 / 24793	0.32 (0.25 , 0.40)	
All Events (ITT)[§]	Etoricoxib	17412	132 / 40041	0.33 (0.28 , 0.39)	1.12 (0.87 , 1.44)
	Diclofenac	17289	117 / 39769	0.29 (0.24 , 0.35)	
Confirmed Ischemic Stroke					
Per-Protocol Approach	Etoricoxib	16819	59 / 25866	0.23 (0.17 , 0.29)	0.99 (0.69 , 1.43)
	Diclofenac	16483	57 / 24797	0.23 (0.17 , 0.30)	
All Events (ITT)[§]	Etoricoxib	17412	90 / 40092	0.22 (0.18 , 0.28)	1.00 (0.75 , 1.35)
	Diclofenac	17289	89 / 39803	0.22 (0.18 , 0.28)	
Confirmed Peripheral Vascular Events					
Per-Protocol Approach	Etoricoxib	16819	53 / 25870	0.20 (0.15 , 0.27)	0.92 (0.63 , 1.35)
	Diclofenac	16483	55 / 24800	0.22 (0.17 , 0.29)	
All Events (ITT)[§]	Etoricoxib	17412	98 / 40080	0.24 (0.20 , 0.30)	1.08 (0.81 , 1.44)
	Diclofenac	17289	90 / 39803	0.23 (0.18 , 0.28)	

Table 42 (Cont.)

Pooled MEDAL Program
Summary of Exploratory Thrombotic Cardiovascular Events
by Analysis Approach

Analytical Approach	Treatment	N	n / PYR[†]	Rate[‡] (95% CI)	Relative Risk (95% CI)
Investigator Reported Cardiovascular Events					
Per-Protocol Approach	Etoricoxib	16819	532 / 25766	2.06 (1.89 , 2.25)	0.95 (0.84 , 1.07)
	Diclofenac	16483	537 / 24682	2.18 (2.00 , 2.37)	
All Events (ITT)[§]	Etoricoxib	17412	767 / 39323	1.95 (1.81 , 2.09)	1.02 (0.92 , 1.13)
	Diclofenac	17291	746 / 39053	1.91 (1.78 , 2.05)	

[†] Patient-years at risk.

[‡] Number of events per 100 patient-years

[§] All events regardless of time of study therapy discontinuation.

N=total number of patients; n=the number of patients with events; MI=myocardial infarction; CI=confidence interval; ITT=intention-to-treat.

Relative risk from the Cox proportional-hazards model with baseline aspirin use as a stratification factor and treatment as a factor in the model.

8.2.3 Subgroup Analyses

To explore whether the treatment effect was consistent across various subgroups, treatment-by-subgroup interaction analyses were assessed for selected subgroups for the primary endpoint of Confirmed Thrombotic Events.

Table 43 displays the results of the subgroup analyses for the primary endpoint. Overall, for each of the subgroups of key interest, no significant treatment-by-subgroup interactions were identified.

Table 43

Pooled MEDAL Program
Confirmed Thrombotic Events[†]
Subgroup Analyses of Key Interest

Subgroup	Etoricoxib N	Etoricoxib n/PYR	Etoricoxib Rate[‡]	Diclofenac N	Diclofenac n/PYR	Diclofenac Rate[‡]	Between Treatment Comparison Relative Risk (95% CI)
Age (0.622) [§]							
< 65	9855	134 / 15761	0.85	9693	135 / 15261	0.88	0.96 (0.75, 1.21)
≥ 65 to <75	5034	123 / 7567	1.63	4997	120 / 7309	1.64	0.99 (0.77, 1.27)
≥ 75 years	1930	63 / 2508	2.51	1793	68 / 2196	3.10	0.81 (0.57, 1.14)
Gender (0.155) [§]							
Female	12468	191/19190	1.00	12209	176/18433	0.95	1.04 (0.85, 1.28)
Male	4351	129/6646	1.94	4274	147/6333	2.32	0.83 (0.66, 1.05)
Baseline Low Dose Aspirin User (0.459)[§]							
No	11005	173 / 17047	1.01	10810	166 / 16391	1.01	1.00 (0.81, 1.24)
Yes	5814	147 / 8789	1.67	5673	157 / 8375	1.87	0.89 (0.71, 1.12)
History of Hypertension (0.351)[§]							
No	9010	120/14139	0.85	8669	128/13177	0.97	0.87 (0.68, 1.12)
Yes	7809	200/11697	1.71	7814	195/11589	1.68	1.01 (0.83, 1.23)
History of Diabetes Mellitus (0.194) [§]							
No	15077	266 / 23285	1.14	14736	279 / 22252	1.25	0.91 (0.77, 1.07)
Yes	1742	54 / 2552	2.12	1747	44 / 2514	1.75	1.21 (0.81, 1.80)
History of Symptomatic ASCVD (0.896) [§]							
No	14899	235 / 23113	1.02	14573	234 / 22092	1.06	0.96 (0.80, 1.15)
Yes	1920	85 / 2723	3.12	1910	89 / 2674	3.33	0.94 (0.70, 1.26)
Increased Cardiovascular risk (History of Symptomatic ASCVD or ≥2 Cardiovascular Risk Factors [‖])(0.208) [§]							
No	10486	134 / 16552	0.81	10188	149 / 15727	0.95	0.85 (0.67, 1.08)
Yes	6333	186 / 9285	2.00	6295	174 / 9039	1.93	1.04 (0.85, 1.28)

[†] Per-Protocol Approach
[‡] Number of events per 100 patient-years.
[§] p-value for subgroup-by-treatment interaction.
[‖] CV risk factors include: history of diabetes, history of hypertension, history of dyslipidemia, family history of CV disease, and cigarette use.
N: Number of patients; n: Number of patients with events; ASCVD: Atherosclerotic cardiovascular disease; PYR: Patient-years at risk; CI=confidence interval

In addition to the subgroups of interest discussed above, additional treatment-by-factor interaction analyses were prespecified to be assessed for dose and disease to determine whether the treatment effect was consistent across these 2 additional subgroups.

Table 44 displays the results of the subgroup analyses by disease and dose for the primary endpoint. For the analysis of dose in OA patients for the Pooled MEDAL Program, no meaningful difference between the etoricoxib 60-mg and 90-mg doses was identified and the point estimate for the relative risk for etoricoxib 60 mg versus diclofenac was similar to the point estimate for etoricoxib 90 mg versus diclofenac (<1.0). The analysis by disease showed similar relative risks between the OA and RA patient subgroups. Further, the confirmed thrombotic results were estimated within each study. There was no significant treatment-by-study interaction. Sensitivity analyses were performed by baseline aspirin use and study protocol as a stratification factor and treatment as an explanatory factor in the Cox model; the results were consistent with that obtained from the model that did not include study protocol as a stratification factor.

Table 44

Pooled MEDAL Program
Confirmed Thrombotic Events[†]
Subgroup Analyses by Dose and Disease

	Etoricoxib			**Diclofenac**			Relative Risk (95% CI)
	N	n/PYR	Rate[‡]	N	n/PYR	Rate[‡]	
OA	12078	207/17793	1.16	11773	206/16902	1.22	0.95 (0.79, 1.16)
Etoricoxib 60 mg vs. Diclofenac	6585	115/11550	1.00	6392	118/11003	1.07	0.92 (0.71, 1.19)
Etoricoxib 90 mg vs. Diclofenac	5493	92/6243	1.47	5381	88/5899	1.49	0.99 (0.74, 1.33)
RA Etoricoxib 90 mg vs. Diclofenac	4740	113/8044	1.40	4710	117/7864	1.49	0.94 (0.73, 1.22)

[†] Per-protocol Approach.
[‡] Events per 100 patient-years.
Treatment by subgroup interactions: by Dose in OA Patients: p-value=0.703
Treatment by subgroup interactions by Disease (OA vs. RA): p-value=0.959
PYR = Patient-years at risk; CI=Confidence Interval.

MEDAL Study Alone

A secondary objective of the MEDAL Program was to compare the thrombotic CV safety profile of etoricoxib and diclofenac based on the MEDAL Study alone. The MEDAL study per-protocol analysis for Confirmed Thrombotic Events yielded a relative risk of 0.96 (0.81, 1.14). All other analyses for the MEDAL Study were consistent with those for the MEDAL Program.

8.2.4 Interpretation of MEDAL Program Results with Diclofenac as the Comparator

The rationale for the choosing diclofenac as the active comparator in the MEDAL Program is provided in Section 3.2.2.2.

The MEDAL Program thrombotic CV safety data (Section 8.2) clearly demonstrate that the thrombotic CV safety profile of etoricoxib is comparable to that of diclofenac. In order to fully interpret this result, the thrombotic CV safety profile of diclofenac requires review.

No long-term placebo-controlled trials are available to assess the thrombotic CV safety of diclofenac. A meta-analysis of tabular data from published and unpublished randomized clinical trials comparing either COX-2 selective inhibitors to placebo or COX-2 selective inhibitors to traditional NSAIDs was used to indirectly compare traditional NSAIDS (diclofenac and ibuprofen) to placebo [56]. Results of this analysis suggest that high doses of both diclofenac and ibuprofen are associated with a moderate increase in thrombotic CV risk. The summary ratio for vascular events compared to placebo was 1.63 (1.12, 2.37) for diclofenac and 1.51 (0.96, 2.37) for ibuprofen. This was in contrast to naproxen whose summary ratio was 0.92 (0.67, 1.26).

A number of observational studies of thrombotic CV (cardiac, cerebrovascular, and/or sudden cardiac death outcomes) events with the use of non-selective NSAIDs have been published. This literature is summarized in two recent systematic reviews [57; 58] and in Appendix 1. The observational evidence suggests that diclofenac is associated with a small to moderately increased risk of cardiovascular events (mostly myocardial infarction / sudden cardiac death) when compared with non-use of NSAIDs. However, these reviews did not include the data from a very large cohort study with 44,500 patient years of diclofenac exposure in which diclofenac was associated with an adjusted odds ratio for MI of 1.02 at doses ≤150 mg (approximately 91% of usage) and 1.37 at doses >150 mg [137]. In addition, the estimates of thrombotic CV risk from individual observational studies of diclofenac vary greatly, from 0.5 to 1.6 [58].

Among NSAID users, there are only two studies directly comparing cardiovascular risk with diclofenac to that with other non-selective NSAIDs (ibuprofen and non-naproxen NSAIDs [1; 2]; the results for MI risk (the common endpoint between them) from these two studies are conflicting. Thus firm conclusions cannot be drawn about thrombotic CV risk with diclofenac relative to other NSAIDs from these data.

Given the potential for bias and residual confounding in the observational studies (especially with non-users of NSAIDs as the referent group), the relatively low magnitude estimates of effect for diclofenac and other NSAIDs versus non-use, the limited and conflicting data from direct comparisons of diclofenac with other NSAIDs, and the variability of the estimates of thrombotic CV risk with diclofenac, it is not possible to determine whether diclofenac is different from many other non-selective NSAIDs using the observational data.

The FDA concluded in 2005 that the available data are best interpreted as being consistent with a class effect of an increased risk of thrombotic CV events for both COX-2 selective as well as traditional NSAIDs with the possible exception of naproxen. To our knowledge, there are no new data or analyses of existing data currently published, including data on diclofenac, that are inconsistent with this position. The MEDAL Program data corroborates the above FDA conclusion of a class effect for thrombotic CV risk. The MEDAL Program data does not, however, provide any additional data on the thrombotic CV risk for etoricoxib in comparison to naproxen, which was already evaluated substantially in the Etoricoxib Development Program.

8.3 Thrombotic Cardiovascular Safety Conclusions

- The rate of thrombotic CV events are comparable for etoricoxib (60 and 90 mg) and Diclofenac 150 mg
  - Results with subgroups are consistent in showing no difference between etoricoxib and diclofenac
  - There are no differences in thrombotic CV events when assessed across the various vascular beds, with additional endpoints, or analytical approaches.
- The rate of thrombotic CV events is similar for etoricoxib (30 to 120 mg pooled) compared with non-naproxen NSAIDs (ibuprofen 2400 mg and diclofenac 150 mg).
- The rate of thrombotic CV Events for naproxen 1000 mg is lower than etoricoxib; numerically less for Thrombotic CV Event endpoint and statistically less for the APTC combined endpoint.
- The thrombotic CV event data for etoricoxib relative to placebo are too limited to draw conclusions. The presumption is that the increased thrombotic CV risk seen in long-term, placebo-controlled chemoprevention studies with other COX-2 selective inhibitors could apply to etoricoxib as well – but this has not been studied.
- There is no evidence of a dose effect in the rate of thrombotic CV events for etoricoxib
  - No dose-related effect noted from 30 to 120 mg from the Etoricoxib Development Program, although the data are limited
  - No difference in the relative risk of etoricoxib 60 mg and 90 mg to diclofenac in the MEDAL Program

9. Renovascular Safety

Overview

In susceptible individuals, NSAIDs can be associated with dose-dependent salt and fluid retention, increases in blood pressure, and less frequently, worsening renal function. The renovascular safety profile of etoricoxib has been evaluated in both the OA Development Program and the MEDAL Program Studies. In general, our approach was to be as

comprehensive as possible within the limitations of the respective data sets. For both sets of studies (the OA Development Program and the MEDAL Program), the clinical impact of potential renovascular effects with etoricoxib was evaluated using prespecified composites of investigator-reported edema-, congestive heart failure-, and hypertension-related adverse experiences. The MEDAL Program studies also pre-specified renal-related adverse experiences, however, in the MEDAL study, the collection of adverse experiences was limited to those events that resulted in discontinuation and/or were considered serious.

In addition, based on a recommendation by the MEDAL Program DSMB and endorsed by the MEDAL Program Steering Committee in December 2005, the 3 studies in the MEDAL Program provided for adjudication of all serious adverse experiences of congestive heart failure (CHF) which resulted in hospitalization (or an emergency room visit) and which occurred on study drug or within 28 days of last dose of study drug. A CHF Adjudication SOP was developed and all eligible cases from the MEDAL Program Studies were adjudicated by an external blinded adjudication review committee as set forth in the Congestive Heart Failure Adjudication Guidelines document.

9.1 Edema and Congestive Heart Failure

9.1.1 OA Development Program

Edema-related adverse experiences

Table 45 summarizes edema-related adverse experience information for the three OA populations providing incidence and differences between the comparisons of interest with 95% CIs. Within the Placebo-Controlled Population, the overall incidence of edema-related adverse experiences was higher than placebo for etoricoxib 30 mg and ibuprofen 2400 mg, with the highest incidence on ibuprofen. In this Population, there was no evidence of a dose-related trend for edema with etoricoxib. Within the 6-Month Population, etoricoxib 30 mg was similar to celecoxib 200 mg in the overall incidence of edema-related adverse experiences. In the 1-Year population the incidence of edema-related adverse experiences for etoricoxib was dose-related. In all three populations, the incidence of discontinuations due to edema-related adverse experiences, a potential indicator of more severe adverse experiences, was low and generally similar across treatment groups.

CHF-related adverse experiences

As shown in Table 46, the incidence of congestive heart failure adverse experiences was low in all treatment groups with no meaningful differences.

Table 45

OA Development Program
Edema-Related Adverse Experiences

	Pbo	Etori 30 mg	Etori 60 mg	Etori 90 mg	Etori 120 mg	Nap 1000 mg	Ibu 2400 mg	Cele 200 mg	Cele 400 mg
Patients With One or More Edema-Related AE									
Placebo Controlled Population									
N	1035	1014	558	220	288	494	756	488	107
Incidence (%)	1.8	3.6	2.9	1.8	3.1	2.8	4.6	3.3	2.8
Difference from Pbo% (95% CI)		1.81 (0.40, 3.31)	1.03 (-0.46 2.89)	-0.02 (-1.5, 2.82)	1.29 (-0.50, 4.07)	1.00 (-0.53, 2.98)	2.79 (1.16, 4.65)	1.44 (-0.17, 3.53)	0.97 (-1.1,6.13)
With a serious edema-related AE	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
With a SBP of ≥180 mmHg) or ≥110 mmHg DBP	0.0	0.1	0.0	0.0	0.7	0.2	0.1	0.0	0.0
With a ≥2 kg wt. gain at the visit AE was reported	0.1	0.4	0.2	0.0	0.3	0.4	1.1	0.0	0.9
6-Month Population									
N		474						488	
Incidence (%)		5.3						4.9	
Difference from Cele% (95% CI)		0.36 (-2.5, 3.23)							
1-Year Population									
N		55	508	112		439			
Incidence (%)		3.6	5.3	7.1		6.4			
Difference from Nap% (95% CI)		-2.7 (-6.5, 6.16)	-1.1 (-4.2, 1.94)	0.76 (-3.6, 7.37)					

Table 45 (Cont.)

OA Development Program
Edema-Related Adverse Experiences

	Pbo	Etori 30 mg	Etori 60 mg	Etori 90 mg	Etori 120 mg	Nap 1000 mg	Ibu 2400 mg	Cele 200 mg	Cele 400 mg
Patients Discontinued Due to an Edema-Related AE									
Placebo Controlled Population									
N	1035	1014	558	220	288	494	756	488	107
Incidence (%)	0.1	0.3	0.0	0.5	0.3	0.2	0.8	0.2	0.0
Difference from Pbo% (95% CI)		0.20 (-0.29, 0.78)	-0.10 (-0.55, 0.59)	0.36 (-0.23, 2.43)	0.25 (-0.28, 1.85)	0.11 (-0.37, 1.04)	0.70 (0.08, 1.63)	0.11 (-0.37, 1.06)	-0.10 (-0.55, 3.37)
6-Month Population									
N		474						488	
Incidence (%)		0.6						0.2	
Difference from Cele% (95% CI)		0.36 (-0.25, 3.23)							
1-Year Population									
N		55	508	112		439			
Incidence (%)		1.8	0.4	0.9		0.5			
Difference from Nap% (95% CI)		-2.7 (-6.5, 6.16)	-1.1 (-4.2, 1.94)	0.76 (-3.6, 7.37)					

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. N=Total number of patients. Pbo=Placebo, Etori=Etoricoxib, Nap=Naproxen, Ibu=Ibuprofen, Cele=Celecoxib, AE=Adverse Experience, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, Wt.= Weight
The 95% confidence interval (CI) is calculated by Wilson's Score Method.
Boxes shaded in gray indicate no applicable data.

Table 46

OA Development Program Populations
Congestive Heart Failure Adverse Experiences

Patients With One or More CHF AE	Pbo	Etori 30 mg	Etori 60 mg	Etori 90 mg	Etori 120 mg	Nap 1000 mg	Ibu 2400 mg	Cele 200 mg	Cele 400 mg
Placebo -Controlled Population									
N	1035	1014	558	220	288	494	756	488	107
Incidence (%)	0.1	0.1	0.2	0.0	0.0	0.2	0.1	0.2	0.0
Difference from Pbo% (95% CI)		0.00 (-0.45, 0.47)	0.08 (-0.39, 0.92)	-0.10 (-0.55, 1.62)	-0.10 (-0.55, 1.22)	0.11 (-0.37, 1.04)	0.04 (-0.43, 0.65)	0.11 (-0.37, 1.06)	-0.10 (-0.55, 3.37)
6-Month Population									
N		474						488	
Incidence (%)		0.0						0.2	
Difference from Cele% (95% CI)		-0.20 (-1.2, 0.62)							
1-Year Population									
N		55	508	112		439			
Incidence (%)		0.0	0.4	0.0		0.5			
Difference from Nap% (95% CI)		-0.46 (-1.6, 6.08)	-0.06 (-1.3, 1.02)	-0.46 (-1.6, 2.88)					

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
N=Total number of patients, Pbo= Placebo, Etori=Etoricoxib, Nap=Naproxen, Ibu=Ibuprofen, Cele=Celecoxib, CHF= Congestive Heart Failure, AE=Adverse Experience
The 95% confidence interval (CI) is calculated by Wilson's Score Method.
Boxes shaded in gray indicate no applicable data.

9.1.2 MEDAL Program Studies

Edema-Related Adverse Experiences

The edema-related adverse experiences for the individual EDGE II and EDGE studies are summarized in Table 47. The incidences of edema-related adverse experiences in the etoricoxib 90-mg groups were significantly higher than those in the respective diclofenac 150-mg comparator groups. Serious edema-related adverse experiences were rare and similar in both the etoricoxib 90-mg and diclofenac 150-mg groups in the EDGE II and EDGE studies. Additional categories in Table 47 were generally consistent with the overall finding for edema-related adverse experiences.

Table 47

EDGE II, EDGE
Edema-Related Adverse Experiences[†]

	EDGE II (RA)		EDGE (OA)	
	Etoricoxib 90 mg	Diclofenac 150 mg	Etoricoxib 90 mg	Diclofenac 150 mg
	(N=2032)	(N=2054)	(N=3593)	(N=3518)
	%	%	%	%
Percent of patients:				
With an edema-related adverse experience	6.5[‡]	4.6	7.5[‡]	5.9
With a serious edema-related adverse experience	0.0	0.05[§]	0.0	0.03[§]
With an edema-related adverse experience associated with a systolic BP ≥180 mmHg or a diastolic BP ≥110 mmHg	0.3	0.05[§]	0.2	0.1
With a >2 kg weight gain at the visit adverse experience was reported	1.2	0.9	1.9	1.4

Includes adverse experiences up to and including the 14 day post therapy discontinuation.
[†] Data are provided only for the EDGE II and EDGE studies as the MEDAL Study collected only adverse experiences considered serious and/or those resulting in discontinuation.
[‡] p-value < 0.05, p-value is from Fisher's exact test. BP= Blood Pressure
[§] incidence displayed to second decimal place to identify values with number of events >1

Discontinuations due to Edema-Related Adverse Experiences

Discontinuations due to edema-related adverse experiences for the individual MEDAL Program studies are presented by disease and dose in Table 48. The incidence of discontinuation due to edema-related adverse experiences was generally low (<1% in the shorter duration EDGE study and <2% in the longer duration MEDAL and EDGE II studies). Among OA patients in the MEDAL Study, the incidence resulting in discontinuation was similar for etoricoxib 60 mg and diclofenac 150 mg, while the

incidence was higher for etoricoxib 90 mg versus diclofenac 150 mg. This observation did not extend to the EDGE study, where the incidence was similar for etoricoxib 90 mg and diclofenac 150 mg. Among RA patients the incidence was significantly higher for etoricoxib 90 mg than for diclofenac in the EDGE II study.

Table 48

MEDAL Program Studies
Discontinuations Due to Edema-Related Adverse Experiences

	MEDAL Study (OA/RA)						EDGE II (RA)		EDGE (OA)	
	Osteoarthritis				Rheumatoid Arthritis					
	60 mg vs. Diclo Cohort		90 mg vs. Diclo Cohort							
	Etori 60 mg N=6769	Diclo 150 mg N=6700	Etori 90 mg N=2171	Diclo 150 mg N=2162	Etori 90 mg N=2841	Diclo 150 mg N=2855	Etori 90 mg N=2032	Diclo 150 mg N=2054	Etori 90 mg N=3593	Diclo 150 mg N=3518
Number (%) of patients: With an Edema-related AE resulting in discontinuation										
Incidence %	0.8	0.7	1.9†	0.8	1.0	0.6	1.1†	0.4	0.9	0.7
Difference in Proportions (95% CI) Etoricoxib-Diclofenac	0.10§ (-0.21, 0.40)		1.10 (0.42, 1.83)		0.43 (-0.04, 0.91)		0.74 (0.21, 1.34)		0.18 (-0.25, 0.62)	
Number (%) of patients who discontinued due to an edema-related AE's:										
Which were serious	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Which were associated with a SBP ≥180 mmHg or a DBP ≥110 mmHg	0.01‡	0.0	0.05‡	0.0	0.04‡	0.1	0.05‡	0.05‡	0.1	0.03‡
Who had a >2 kg wt. gain at the same visit the AE was reported	0.2	0.1	0.9	0.2	0.1	0.1	0.2	0.0	0.4	0.2

Includes adverse experiences up to and including the 14 day post therapy discontinuation.
† p<0.01. p-value is from Fisher's exact test.
‡ incidence displayed to second decimal place to identify values with number of events >1.
§ Relative risk (95% CI) for etoricoxib 60 mg versus diclofenac: 1.11 (0.75, 1.62)
The 95% confidence interval (CI) is calculated by Wilson's Score Method.
Etori = Etoricoxib, Diclo= Diclofenac, AE= Adverse experience, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, Wt.= Weight

Confirmed Congestive Heart Failure Resulting in Hospitalization or ER visits

Investigator reported CHF-related events from the MEDAL Program Studies that resulted in hospitalization (or emergency department visits) were adjudicated and classified as confirmed or unconfirmed. Of 124 cases of CHF that were adjudicated (78 on etoricoxib and 46 on diclofenac), 102 were confirmed. The analysis of confirmed CHF for the MEDAL Program Studies is shown in Table 49. The rate of confirmed CHF was similar between etoricoxib 60 mg and diclofenac and there was a trend towards a greater rate for etoricoxib 90 mg compared with diclofenac.

Table 49

MEDAL Program Studies
Confirmed Congestive Heart Failure Resulting in
Hospitalization or an ER Visit

Study	N	n/PYR	Rate†	Relative Risk‡ (95% CI)
MEDAL (OA/RA)				
60 mg vs. Diclofenac Cohort (OA)				
Etoricoxib 60 mg	6769	19/11743	0.16	1.29 (0.64, 2.56)
Diclofenac 150 mg	6700	14/11284	0.12	
90 mg vs. Diclofenac Cohort (OA)				
Etoricoxib 90 mg	2171	15/3683	0.41	2.15 (0.88, 5.28)
Diclofenac 150 mg	2162	7/3490	0.20	
RA Cohort				
Etoricoxib 90 mg	2841	18/4913	0.37	1.98 (0.89, 4.41)
Diclofenac 150 mg	2855	9/4782	0.19	
EDGE II (RA)				
Etoricoxib 90 mg	2032	7/3274	0.21	1.75 (0.51, 5.96)
Diclofenac 150 mg	2054	4/3260	0.12	
EDGE (OA)				
Etoricoxib 90 mg	3593	5/2793	0.18	1.17 (0.32, 4.38)
Diclofenac 150 mg	3518	4/2608	0.15	

mITT = Modified-Intention-to-Treat.
† Number of events per 100 patient-years.
‡ Relative risk from the Cox proportional-hazards (PH) model.
§ incidence displayed to second decimal place to identify values with number of events >1
N=total number of patients; n=the number of patients with events;
CI = Confidence Interval; PYR = Patient–Years-at risk.
Relative risk from the Cox proportional-hazards model with baseline aspirin use as a stratification factor and treatment as an explanatory factor in the model.

Summary: Edema and CHF

In general etoricoxib 60 was similar to comparator NSAIDs in both the OA Development Program (versus naproxen) and in MEDAL Program studies (versus diclofenac) for both edema and CHF. There was however, a dose related trend with a trend toward a greater incidence for etoricoxib 90 mg than the NSAID comparators in edema and CHF and either similar or numerically lower incidence for etoricoxib 30 mg than the NSAID/COX-2 comparator.

9.2 Hypertension

9.2.1 OA Development Program

Hypertension-Related Adverse Experiences

In the OA Developmental Program there was a dose-related trend in the incidence of hypertension-related adverse experiences for etoricoxib (Table 50). The incidences were highest on etoricoxib 120 and ibuprofen and lowest on celecoxib. The incidence for etoricoxib 30 mg and 60 mg was generally similar to that observed for naproxen and ibuprofen. Hypertension-related adverse experiences were analyzed further based on whether they were serious, occurred in patients with a history of hypertension, or were associated with significant elevations in blood pressure (≥180 [systolic] or ≥110 [diastolic]). The results of these additional analyses were generally consistent with those of the overall incidence of hypertension-related adverse experiences and showed similar proportions of patients with these measures in all treatment groups.

Among patients with significant elevations in blood pressure, ~90% had a history of hypertension at baseline in the etoricoxib 30- and 60-mg groups. In the other treatment groups, 40% to 100% of patients had a history of hypertension (data not shown).

In the 6-Month Population, the incidence of hypertension-related adverse experiences was higher on etoricoxib 30 mg than on celecoxib 200 mg. In the 1-Year Population there were no significant between-group differences, although numerically there were slightly higher incidences in the etoricoxib 60-mg and 90-mg groups than in the naproxen 1000-mg group; the 30 mg group was slightly lower (based on few events).

As the duration of the exposure increased (i.e., over 6 months and 1 year), the cumulative incidence of hypertension increased in all groups. The number of patients who discontinued due to a hypertension-related adverse experience was low across all treatment groups.

Table 50

OA Development Program
Hypertension-Related Adverse Experiences

	Pbo	Etori 30 mg	Etori 60 mg	Etori 90 mg	Etori 120 mg	Nap 1000 mg	Ibu 2400 mg	Cele 200 mg	Cele 400 mg
Patients with One or More Hypertension-Related AE term									
Placebo Controlled Population									
N	1035	1014	558	220	288	494	756	488	107
Incidence (%)	2.9	3.7	4.8	5.0	6.6	4.0	6.3	1.2	1.9
Difference from Placebo: % (95% CI)		0.85 (-0.72, 2.45)	1.94 (0.02, 4.22)	2.10 (-0.40, 5.93)	3.70 (1.07, 7.28)	1.15 (-0.71, 3.44)	3.45 (1.50, 5.60)	-1.7 (-3.0, 0.0)	-1.0 (-2.8, 3.74)
With a serious hypertension-related AE: %	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
With a hypertension-related AE who had a history of hypertension: %	1.5	2.4	2.7	3.2	4.2	2.4	3.6	0.8	0.9
With a hypertension-related AE associated with a SBP ≥180 mmHg or DBP ≥110 mmHg: %	0.8	0.8	1.3	0.5	4.2	1.2	1.6	0.4	0.0
6-Month Population									
N		474						488	
Incidence (%)		5.7						2.3	
Difference from Cele: % (95% CI)		3.44 (0.97, 6.10)							
1-Year Population									
N		55	508	112		439			
Incidence (%)		7.3	11.8	9.8		8.4			
Difference from Nap: % (95% CI)		-1.2 (-6.5, 9.08)	3.38 (-0.52, 7.21)	1.39 (-3.8, 8.66)					

Table 50 (Cont.)

OA Development Program
Hypertension-Related Adverse Experiences

	Pbo	Etori 30 mg	Etori 60 mg	Etori 90 mg	Etori 120 mg	Nap 1000 mg	Ibu 2400 mg	Cele 200 mg	Cele 400 mg
Patients Discontinued Due to a Hypertension-Related AE									
Placebo Controlled Population									
N	1035	1014	558	220	288	494	756	488	107
Incidence (%)	0.1	0.6	0.2	0.9	0.7	0.2	0.7	0.0	0.0
Difference from Pbo: % (95% CI)		0.50 (-0.06, 1.19)	0.08 (-0.39, 0.92)	0.81 (0.01, 3.16)	0.60 (-0.08, 2.40)	0.11 (-0.37, 1.04)	0.56 (-0.02, 1.45)	-0.10 (-0.55, 0.69)	-0.10 (-0.55, 3.37)
6-Month Population									
N		474						488	
Incidence (%)		0.4						0.0	
Difference from Cele: % (95% CI)		0.42 (-0.42, 1.53)							
1-Year Population									
N		55	508	112		439			
Incidence (%)		0.0	0.6	0.9		0.2			
Difference from Nap: % (95% CI)		-0.23 (-1.3, 6.30)	0.36 (-0.76, 1.51)	0.67 (-0.62, 4.66)					

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. N=Total number of patients, Pbo=Placebo, Etori=Etoricoxib, Nap=Naproxen, Ibu=Ibuprofen, Cele=Celecoxib, AE=Adverse Experience, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure
The 95% confidence interval (CI) is calculated by Wilson's Score Method.
Boxes shaded in gray indicate no applicable data.

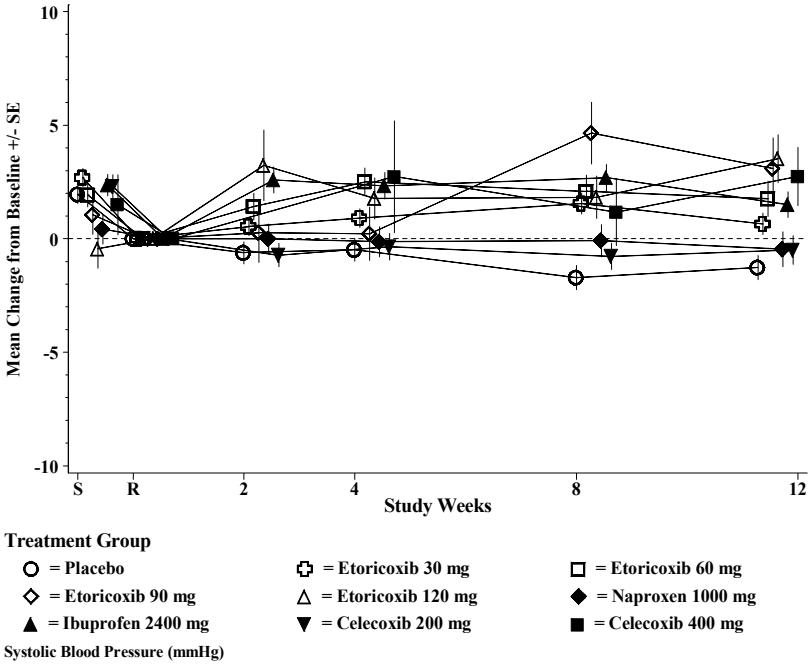
Mean Change from Baseline in Systolic and Diastolic Blood Pressure

Figure 14 and Figure 15 display the mean changes from randomization in systolic and diastolic blood pressure by treatment group for the Placebo-Controlled Population respectively. In general, across treatment groups patients showed a decrease from screening to randomization (baseline) over the prestudy NSAID washout period. The magnitude of effects for systolic blood pressure seen in the etoricoxib 30-mg and 60-mg groups over the treatment period ranged from approximately 0.5 to 1.6 mmHg and 1.4 to 2.5 mmHg, respectively. The magnitude of effects seen in naproxen 1000 mg, ibuprofen 2400 mg, and celecoxib 400 mg ranged from -0.5 to 0.0 mmHg, 1.5 to 2.7 mmHg, and 1.2 to 2.7 mmHg, respectively. In general, over the 12-week period, etoricoxib 120 mg had the greatest mean changes in systolic blood pressure. Naproxen 1000 mg and celecoxib 200 mg were generally similar to each other with values slightly higher than placebo.

The magnitude of effects for diastolic blood pressure in the etoricoxib 30-mg and 60-mg groups over the treatment period ranged from -0.1 to 0.2 mmHg and 0.2 to 1.2 mmHg, respectively. The magnitude of effects in ibuprofen 2400 mg group ranged from 0.3 to 0.9 mmHg. Mean changes from baseline in diastolic blood pressure for the naproxen 1000-mg and celecoxib 200-mg groups were generally similar to placebo over the treatment period.

Figure 14

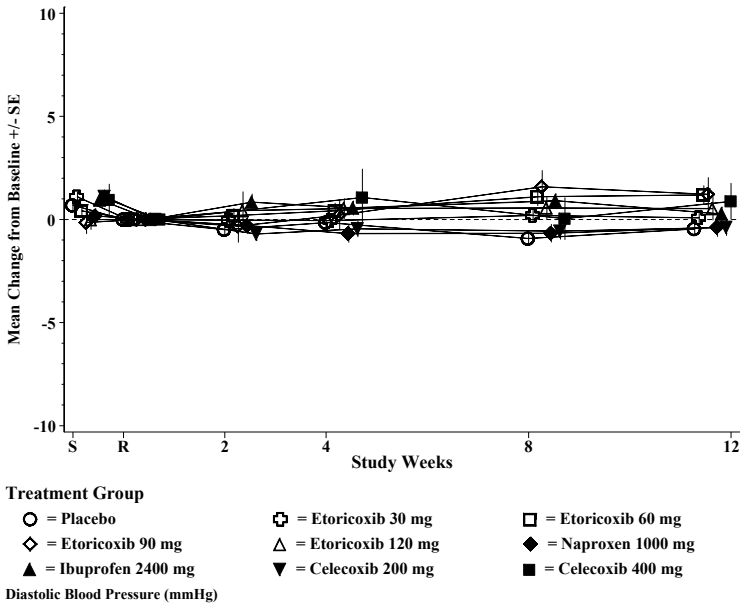
6- to 12-Week Placebo-Controlled Population
Mean Changes (±SE) From Baseline in Systolic Blood Pressure (mmHg) Over Time



S=Screening, R=Randomization, SE=Standard Error.
Week number for each treatment group was shifted on the horizontal axis to maximize legibility.

Figure 15

6- to 12-Week Placebo-Controlled Population
Mean Changes (±SE) From Baseline in Diastolic Blood Pressure (mmHg) Over Time



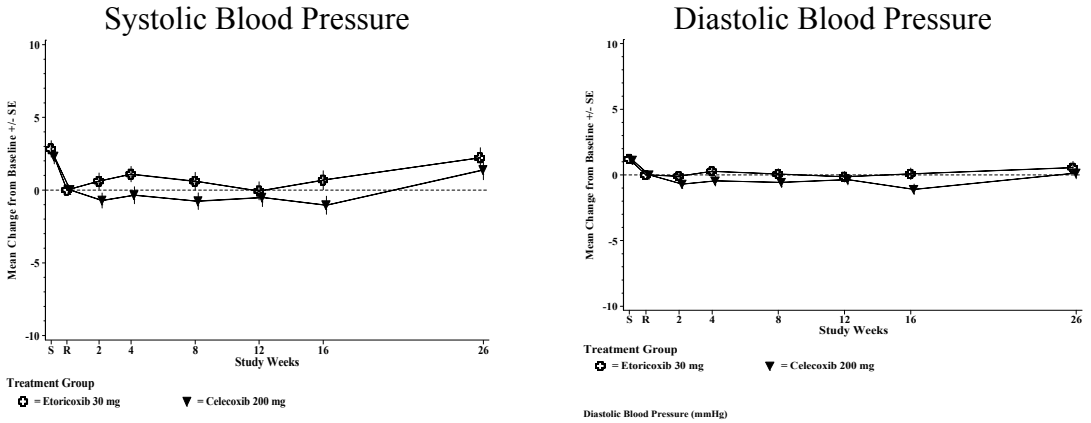
S=Screening, R=Randomization, SE=Standard Error.
Week number for each treatment group was shifted on the horizontal axis to maximize legibility.

Figure 16 displays the mean change from baseline for systolic and diastolic blood pressure for the 6-Month Population. A slight increase from baseline (<0.7 mmHg) in systolic blood pressure was noted for the etoricoxib 30-mg group through Week 16 whereas celecoxib 200 mg was generally below baseline. At Week 26, a similar increase (~2 mmHg) in systolic blood pressure was noted for both treatment groups.

The mean changes from baseline in diastolic blood pressure were similar for the etoricoxib 30 mg and celecoxib 200-mg groups and were generally maintained at about baseline over the 26-week treatment period.

Figure 16

6-Month Active-Comparator-Controlled Population
Mean Change (±SE) From Baseline in Systolic and Diastolic Blood Pressure (mmHg) Over Time



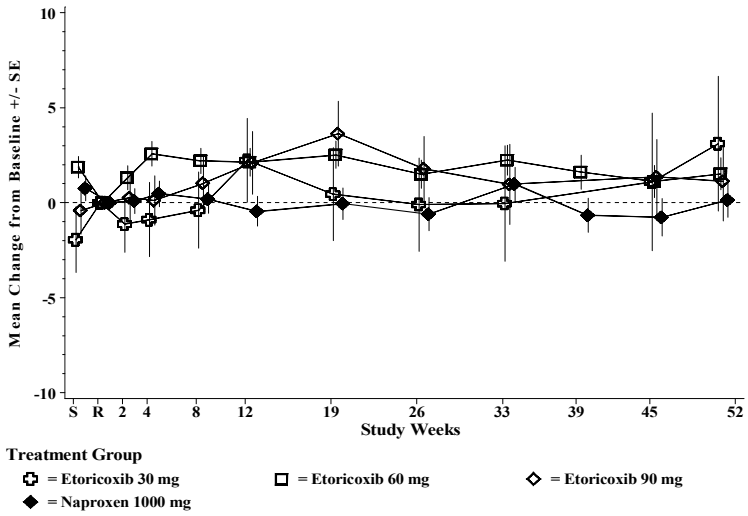
S=Screening, R=Randomization, SE=Standard Error.
Week number for each treatment group was shifted on the horizontal axis to maximize legibility.

Figure 17 displays the mean changes from baseline for systolic blood pressure over the 1-year period. Mean changes in systolic blood pressure in the etoricoxib 30-mg group were generally smaller than the etoricoxib 60- and 90-mg groups except for the last timepoints where there were fewer patients and large error bars. The magnitude of effects for systolic blood pressure seen in the etoricoxib 30-mg group over the treatment period ranged from approximately 1.1 to 3.1 mmHg. The magnitude of effects for systolic blood pressure in the etoricoxib 60 mg and 90 mg groups over the treatment period were generally similar, ranging from approximately 1.1 to 2.6 mmHg and 0.1 to 3.6 mmHg, respectively. Mean changes in the naproxen 1000 mg group were lower than the etoricoxib 60 an 90 mg groups and were <1 mmHg across the treatment period.

Mean changes from baseline in diastolic blood pressure were generally similar and small for the etoricoxib 30-, 60-, and 90-mg groups and slightly higher than naproxen 1000 mg. There were no increased effects over time observed for any of the treatment groups. No increase in diastolic blood pressure was observed for naproxen 1000 mg (data not shown).

Figure 17

1-Year Active-Comparator-Controlled Population
Mean Changes (±SE) From Baseline in Systolic Blood Pressure (mmHg) Over Time



S=Screening, R=Randomization, SE=Standard Error.
Week number for each treatment group was shifted on the horizontal axis to maximize legibility

Analysis of Predefined Limits of Change in Blood Pressure

Although not prespecified for the Etoricoxib Development Program, the predefined limits of change in blood pressure were evaluated based on those prespecified for the MEDAL Program studies.

Systolic Blood Pressure:

- Consecutive values exceeding 140 mmHg with an increase of more than 20 mmHg above baseline.

Diastolic Blood Pressure:

- Consecutive values exceeding 90 mmHg and increased more than 15 mmHg above baseline.

The analysis of patients who exceeded the predefined limits of change in systolic blood pressure and diastolic blood pressure are in Table 51 and Table 52, respectively.

Table 51

OA Development Program
Patients Exceeding the Predefined Limits of Change for Systolic Blood Pressure

	Placebo	Etori 30 mg	Etori 60 mg	Etori 90 mg	Etori 120 mg	Nap 1000 mg	Ibu 2400 mg	Cele 200 mg	Cele 400 mg
Placebo Controlled Population									
N	1008	1006	555	214	284	491	743	482	102
Incidence %)	1.1	1.2	3.1	2.3	5.6	2.0	4.0	0.6	0.0
6-Month Population									
N		472						482	
Incidence %)		3.2						1.7	
1-Year Population									
N		55	505	111		436			
Incidence %)		3.6	6.9	6.3		5.0			

Table 52

OA Development Program
Patients Exceeding the Predefined Limits of Change for Diastolic Blood Pressure

	Placebo	Etori 30 mg	Etori 60 mg	Etori 90 mg	Etori 120 mg	Nap 1000 mg	Ibu 2400 mg	Cele 200 mg	Cele 400 mg
Placebo Controlled Population									
N	1008	1006	554	214	284	491	743	482	102
Incidence %)	0.1	0.2	1.3	0.5	0.4	0.0	0.4	0.0	0.0
6-Month Population									
N		472						482	
Incidence %)		0.2						0.0	
1-Year Population									
N		55	505	111		436			
Incidence %)		0.0	2.6	3.6		0.5			

9.2.2 MEDAL Program Studies

Hypertension-Related Adverse Experiences

A summary of hypertension-related adverse experiences for the individual EDGE II and EDGE studies is in Table 53. The incidence was higher in the etoricoxib 90-mg groups than in the diclofenac 150-mg groups in both studies. The incidence of serious hypertension-related adverse experiences was low and similar among the two treatment groups in both studies. Of the patients who had a hypertension-related adverse experience approximately one half had a history of hypertension in all treatment groups. Among patients who had a hypertension-related adverse experience, the proportion of those associated with significant elevations in blood pressure (≥180 mmHg [systolic] or ≥110 mmHg [diastolic]) was similar in the etoricoxib 90-mg groups and in the diclofenac 150-mg groups within each study.

Among patients with significant elevations of blood pressure, ~60% and ~70% had a history of hypertension at baseline in the EDGE II and EDGE studies respectively (data not shown).

Table 53

EDGE II, EDGE
Hypertension-Related Adverse Experiences[†]

	EDGE II (RA)		EDGE (OA)	
	Etoricoxib 90 mg	Diclofenac 150 mg	Etoricoxib 90 mg	Diclofenac 150 mg
	N=2032	N=2054	N=3593	N=3518
	%	%	%	%
Percent of patients:				
With a hypertension-related AE	19.5[‡]	15.2	11.7[‡]	5.9
With a serious hypertension-related AE	0.4	0.6	0.1	0.1
With a hypertension-related AE who had a history of hypertension	8.6	7.7	6.6	3.7
With a hypertension-related AE associated with a systolic BP ≥180 mmHg or a diastolic BP ≥110 mmHg	3.3	2.6	1.9	0.9

Includes adverse experiences up to and including the 14 day post therapy discontinuation.
[†] Data are provided only for the EDGE II and EDGE studies as the MEDAL Study collected only adverse experiences considered serious and/or those resulting in discontinuation.
[‡] p-value<0.001. p-value is from Fisher's exact test.
BP= Blood Pressure; AE= adverse experience

Discontinuations due to Hypertension-Related Adverse Experiences

Discontinuations due to hypertension-related adverse experiences for the individual MEDAL Program studies are presented by disease and dose in Table 54. The incidence of discontinuations due to hypertension-related adverse experiences was significantly greater ($p<0.05$) in the 60- and 90-mg etoricoxib groups compared with the diclofenac 150-mg groups among OA and RA patients across the 3 studies.

Among patients with significant elevations in blood pressure, 70-80% of OA patients had a history of hypertension at baseline and ~60% of RA patients had a history of hypertension at baseline (data not shown).

Table 54

MEDAL Program Studies
Discontinuations Due to Hypertension-Related Adverse Experiences

	MEDAL Study (OA/RA)						EDGE II (RA)		EDGE (OA)	
	Osteoarthritis				Rheumatoid Arthritis					
	60 mg vs. Diclo Cohort		90 mg vs. Diclo Cohort							
	Etori 60 mg N=6769	Diclo 150 mg N=6700	Etori 90 mg N=2171	Diclo 150 mg N=2162	Etori 90 mg N=2841	Diclo 150 mg N=2855	Etori 90 mg N=2032	Diclo 150 mg N=2054	Etori 90 mg N=3593	Diclo 150 mg N=3518
Number (%) of patients: With a hypertension-related AE resulting in discontinuation										
Incidence %	2.2†	1.6	2.5‡	1.1	2.4†	1.6	2.5†	1.5	2.3‡	0.7
Difference in Proportions (95% CI) Etoricoxib-Diclofenac	0.53‖ (0.07, 1.00)		1.42 (0.63, 2.26)		0.82 (0.08, 1.57)		1.00 (0.14, 1.89)		1.60 (1.06, 2.18)	
Number (%) of patients who discontinued due to a hypertension-related adverse experience:										
Which were serious	0.1	0.2	0.0	0.0	0.4	0.1	0.1	0.3	0.03§	0.0
Who had a history of hypertension	1.4	1.1	1.8	0.5	1.6	0.8	1.3	0.6	1.4	0.4
Who had a hypertension-related AE associated with a SBP ≥180 mmHg or DBP ≥110 mmHg	0.7	0.4	0.5	0.2	0.6	0.6	0.8	0.5	0.5	0.1

Includes adverse experiences up to and including the 14 day post therapy discontinuation.
†$p<0.05$, ‡$p<0.001$. p-value is from Fisher's exact test.
§ incidence displayed to second decimal place to identify values with number of events >1
‖ Relative risk (95% CI) for etoricoxib 60 mg versus diclofenac: 1.29 (1.00, 1.65)
AE= Adverse Experience, Etori= Etoricoxib, Diclo= Diclofenac, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure
The 95% confidence interval (CI) is calculated by Wilson's Score Method.

Measurements of Blood Pressure

The mean changes from baseline for blood pressure measurements are outlined below for each MEDAL Program study. The data for systolic blood pressure are followed by a summary of the data for diastolic blood pressure. In general, the analysis of blood pressure was consistent with the analyses of hypertension-related adverse experiences indicating a greater treatment-related effect with etoricoxib 60 mg and 90 mg compared with diclofenac. Predefined limits of change in systolic and diastolic blood pressure were also carried out for the MEDAL Program studies and were consistent with the hypertension-related adverse experience profile and mean changes in blood pressure.

Mean Change from Baseline in Systolic Blood Pressure

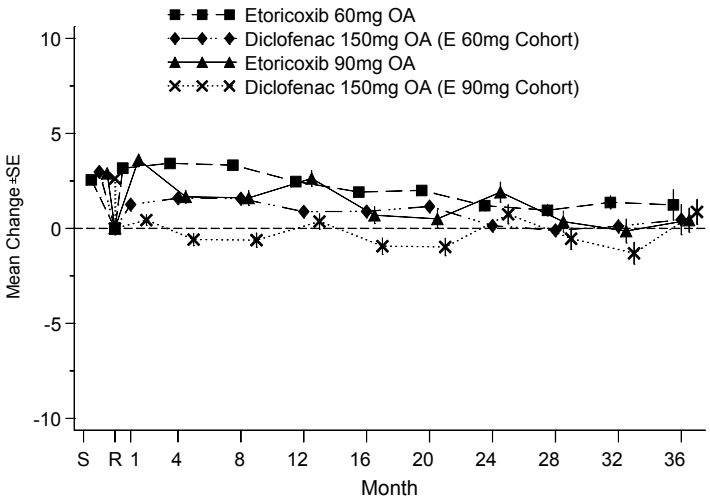
Plots of mean changes from baseline in systolic blood pressure by treatment group for the MEDAL Study are in Figure 18. Relative to baseline values (after NSAID washout), both etoricoxib and diclofenac were associated with small mean increases in systolic blood pressure but the changes from baseline for etoricoxib were greater. In the 60 mg OA cohort of the MEDAL Study, the magnitude of effects for systolic blood pressure seen in the etoricoxib 60 mg and diclofenac groups over the treatment period ranged from 1.0 to 3.4 mmHg and -0.1 to 1.6 mmHg. In the 90 mg OA cohort of the MEDAL Study, the magnitude of effects for systolic blood pressure seen in the etoricoxib 90 mg and diclofenac groups over the treatment period ranged from -0.3 to 3.6 mmHg and -1.3 to 0.9 mmHg, respectively.

Etoricoxib treatment was associated with small mean increases in systolic blood pressure relative to screening (before NSAID washout). In the 60 mg OA cohort of the MEDAL Study, the magnitude of effects for systolic blood pressure based on change from screening in the etoricoxib 60 mg and diclofenac groups over the treatment period ranged from -2.5 to 0.9 mmHg and -3.2 to -1.4 mmHg. In the 90 mg OA cohort of the MEDAL Study, the magnitude of effects for systolic blood pressure based on change from screening in the etoricoxib 90 mg and diclofenac groups over the treatment period ranged from -2.8 to 0.7 mmHg and -4.4 to -1.9 mmHg, respectively. In the MEDAL Study, systolic blood pressure values for patients on etoricoxib were similar to screening values and on diclofenac were generally slightly lower than screening values.

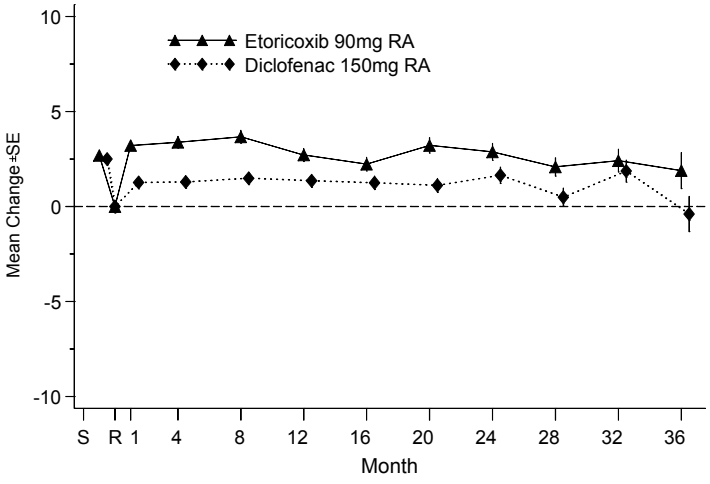
Figure 18

MEDAL Study (OA/RA) †
Mean Changes from Baseline in Systolic Blood Pressure Over Time

In Patients With Osteoarthritis



In Patients With Rheumatoid Arthritis



†*mITT approach*

Mean Change from Baseline in Diastolic Blood Pressure

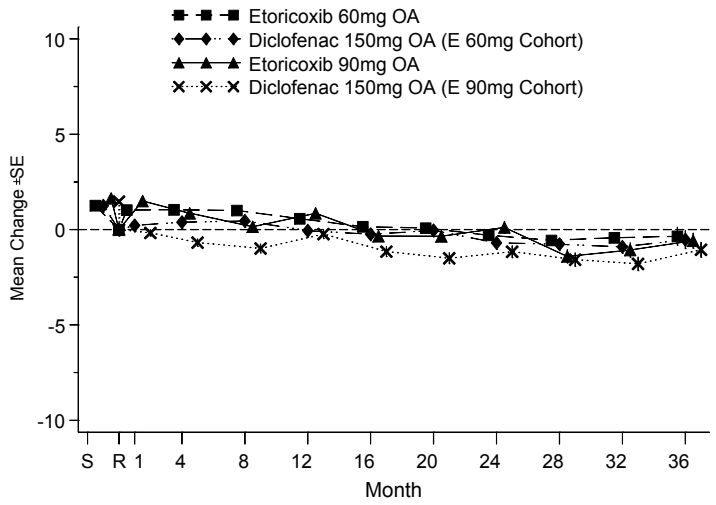
Plots of mean changes from baseline in diastolic blood pressure by treatment group are in Figure 19 for the MEDAL Study. Relative to baseline values (after NSAID washout), both etoricoxib and diclofenac were associated with small mean increases in diastolic blood pressure but the differences for etoricoxib were slightly greater. In the 60 mg OA cohort of the MEDAL Study, the magnitude of effects for diastolic blood pressure seen in the etoricoxib 60 mg and diclofenac groups over the treatment period ranged from -0.6 to 1.0 mmHg and -0.9 to 0.5 mmHg. In the 90 mg OA cohort of the MEDAL Study, the magnitude of effects for diastolic blood pressure seen in the etoricoxib 90 mg and diclofenac groups over the treatment period ranged from -1.4 to 1.5 mmHg and -1.8 to -0.2 mmHg, respectively.

Etoricoxib treatment was generally associated with small mean increases in diastolic blood pressure relative to screening (before NSAID washout). In the 60 mg OA cohort of the MEDAL Study, the magnitude of effects for diastolic blood pressure based on change from screening in the etoricoxib 60 mg and diclofenac groups over the treatment period ranged from -2.2 to -0.2 mmHg and -2.3 to -0.8 mmHg. In the 90 mg OA cohort of the MEDAL Study, the magnitude of effects for diastolic blood pressure based on change from screening in the etoricoxib 90 mg and diclofenac groups over the treatment period ranged from -2.8 to -0.2 mmHg and -3.3 to -1.4 mmHg, respectively.

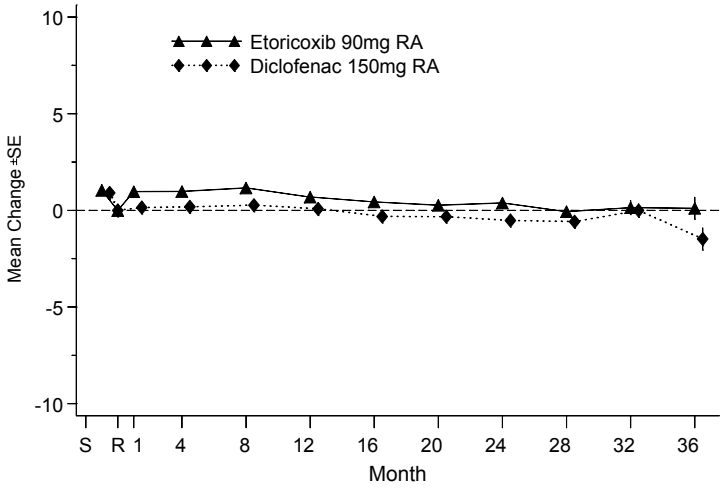
Figure 19

MEDAL Study (OA/RA) †
Mean Changes from Baseline in Diastolic Blood Pressure Over Time

In Patients with Osteoarthritis



In Patients with Rheumatoid Arthritis



† *mITT approach*

Analysis of Predefined Limits of Change in Blood Pressure

Predefined limits of change for systolic and diastolic blood pressure were limited to the MEDAL Program Studies and consisted of a primary analysis for both systolic and diastolic blood pressure as outlined below:

Systolic Blood Pressure:

- Consecutive values exceeding 140 mmHg with an increase of more than 20 mmHg above baseline.

Diastolic Blood Pressure:

- Consecutive values exceeding 90 mmHg and increased more than 15 mmHg above baseline.

Predefined Limits of Change in Systolic Blood Pressure

The analyses of patients who exceeded the predefined limits of change in systolic and diastolic blood pressure are in Table 55.

The incidence of patients exceeding the predefined limits of change for systolic blood pressure was significantly higher in both the etoricoxib 60-mg and 90-mg groups compared with the diclofenac 150-mg groups for OA and RA patients within the 3 MEDAL Program studies. Among patients who exceeded the predefined limits of change in systolic blood pressure greater than 50% of the patients in all treatment groups within the 3 MEDAL Program studies had a baseline history of hypertension.

In the MEDAL Study the proportions of OA and RA patients who exceeded the predefined limits of change for diastolic blood were slightly higher in the etoricoxib 60-mg and 90-mg groups than in the diclofenac 150-mg groups. In the EDGE II Study the proportion of RA patients who exceeded the predefined limits of change for diastolic blood pressure was similar for etoricoxib 90 mg and diclofenac 150 mg, while in the EDGE Study the proportion of OA patients exceeding the predefined limits of change for diastolic blood pressure was slightly greater for etoricoxib 90 mg than for diclofenac 150 mg.

Table 55

MEDAL Program Studies
Patients Exceeding the Predefined Limits of Change for Systolic Blood Pressure

	MEDAL Study (OA/RA)						EDGE II (RA)		EDGE (OA)	
	Osteoarthritis				Rheumatoid Arthritis					
	60 mg vs. Diclo Cohort		90 mg vs. Diclo Cohort							
	Etori 60 mg N=6721	Diclo 150 mg N=6640	Etori 90 mg N=2140	Diclo 150 mg N=2130	Etori 90 mg N=2804	Diclo 150 mg N=2809	Etori 90 mg N=2015	Diclo 150 mg N=2036	Etori 90 mg N=3558	Diclo 150 mg N=3471
Patients with Consecutive Values of SBP > 140 mmHg and Increases > 20 mmHg†										
Incidence %	8.2	6.0	7.7	4.7	8.5	5.4	7.9	5.6	4.9	2.7
Difference in Proportions (95% CI) Etoricoxib-Diclofenac	2.22 (1.35, 3.09)		2.97 (1.52, 4.43)		3.11 (1.78, 4.45)		2.25 (0.7, 3.8)		2.20 (1.3, 3.1)	
Patients with Consecutive Values of DBP > 140 mmHg and Increases > 20 mmHg†										
Incidence %	1.4	1.1	1.0	0.7	1.7	1.1	1.0	1.1	0.7	0.5
Difference in Proportions (95% CI) Etoricoxib-Diclofenac	0.28 (-0.10, 0.67)		0.37 (-0.19, 0.96)		0.54 (-0.08, 1.18)		-0.12 (-0.7, 0.6)		0.20 (-0.1, 0.6)	

†Meeting the criteria on one occasion and discontinuing due to the elevated blood pressure value (instead of consecutive values and patient continuing in the study) is sufficient to be classified as exceeding the defined limit of change. Note: A patient may have exceeded the predefined limits of change for more than one parameter and may appear in more than one category. The 95% confidence interval is calculated by Wilson's Score Method.
N= total number of patients with valid values of the laboratory test; CI = Confidence Interval; SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, Etori=Etoricoxib, Diclo=Diclofenac

9.3 Renal Function

In the OA Development Program and MEDAL Program Studies, renal function was assessed by predefined limits of change for serum creatinine which consisted of two primary analyses and 2 secondary analyses as outlined below:

- Primary: Consecutive values >2 x baseline and >ULN
  - Secondary: One or more values >2 x baseline and >ULN
- Primary: Consecutive values with absolute increase ≥0.5 and >ULN
  - Secondary: One or more values with absolute increase ≥0.5 and >ULN

In addition, the Primary criteria could be satisfied if met on one occasion and the patient discontinued due to the serum creatinine elevation. Also the MEDAL Program Studies included a prespecified analysis of discontinuations due to renal-related adverse experiences.

9.3.1 OA Development Program

The incidence (%) of patients who exceeded the predefined limits of change for serum creatinine and the incidence (%) who exceeded the criteria and discontinued due to a related clinical or laboratory adverse experience for the Placebo-Controlled population is in Table 56. No significant differences were seen between any of the etoricoxib groups and placebo in the Placebo-Controlled Population; however, ibuprofen 2400 mg was associated with an increase relative to etoricoxib 30 mg and placebo in the incidence of patients who exceeded the predefined limits for serum creatinine ($p<0.05$). In the 6-Month and 1-Year Populations the incidence of patients exceeding the predefined limits of change was similar across the treatment groups. The analyses of predefined limits of change for serum creatinine demonstrated that the adverse experiences of increased serum creatinine consisted mostly of small changes.

Table 56

Patients Exceeding the Predefined Limits of Change for Serum Creatinine
6- to 12-Week Placebo-Controlled Population

Laboratory Test	Predefined Limit of Change From Baseline	Treatment	Total[†] n/m (%)	Discon-tinuation[‡] n/m (%)
6- to 12-Week Placebo-Controlled Population				
Serum creatinine (mg/dL)	**Primary: Consecutive values with absolute increase ≥0.5 and >ULN[§]**	Placebo	0/863 (0.0)	0/863 (0.0)
		Etoricoxib 30 mg	0/996 (0.0)	0/996 (0.0)
		Etoricoxib 60 mg	2/553 (0.4)	0/553 (0.0)
		Etoricoxib 90 mg	0/111 (0.0)	0/111 (0.0)
		Etoricoxib 120 mg	0/279 (0.0)	0/279 (0.0)
		Naproxen 1000 mg	0/488 (0.0)	0/488 (0.0)
		Ibuprofen 2400 mg	5/638 (0.8)	3/638 (0.5)
		Celecoxib 200 mg	2/468 (0.4)	2/468 (0.4)

[†] n/m = total number of patients meeting criteria, regardless of related discontinuation/number of patients for whom the laboratory test was recorded.
[‡] Discontinuation indicates that the patient discontinued due to a corresponding laboratory adverse experience or a related clinical experience.
[§] Meeting the criteria on one occasion and discontinuing due to the particular laboratory test (instead of consecutive values and patient continuing in the study) was sufficient to be classified as exceeding the defined limit of change.
ULN = Upper limit of normal range; bln = baseline.

9.3.2 MEDAL Program

Discontinuations Due to Renal-Related Adverse Experiences

Renal-related adverse experiences are defined as clinical or laboratory adverse experiences related to renal dysfunction. The analysis of discontinuations due to renal-related adverse experiences is in Table 57. Overall, the incidence of discontinuations due to renal-related adverse experiences was low and similar for the etoricoxib 60-mg and 90-mg groups compared with the diclofenac 150-mg groups across all 3 studies among OA and RA patients.

Table 57

Discontinuations Due to Renal-Related Adverse Experiences
MEDAL Program Studies

	MEDAL Study (OA/RA)						EDGE II (RA)		EDGE (OA)	
	Osteoarthritis				Rheumatoid Arthritis					
	60 mg vs. Diclo Cohort		90 mg vs. Diclo Cohort							
	Etori 60 mg N=6769	Diclo 150 mg N=6700	Etori 90 mg N=2171	Diclo 150 mg N=2162	Etori 90 mg N=2841	Diclo 150 mg N=2855	Etori 90 mg N=2032	Diclo 150 mg N=2054	Etori 90 mg N=3593	Diclo 150 mg N=3518
Incidence %	0.81	0.75	2.3	1.8	1.02	0.98	0.7	0.7	0.4	0.4
Difference in Proportions (95% CI) Etoricoxib-Diclofenac	0.07 (-0.24, 0.37)		0.5 (0.36, 1.37)		0.04 (-0.49, 0.57)		0.01 (-0.55, 0.56)		0.02 (-0.30, 0.33)	
The 95% confidence interval is calculated by Wilson's Score Method. N= number of patients treated; CI=Confidence Interval, Etori=Etoricoxib, Diclo=Diclofenac										

Analysis of Predefined Limits of Change for Measurements of Serum Creatinine

The incidence and differences among treatment groups for the primary analyses of patients who exceeded the predefined limits of change for serum creatinine are in Table 58. Few patients (≤0.4%) exceeded the predefined limit of having consecutive values of serum creatinine of >2 x baseline and >ULN, and the incidences were similar among etoricoxib and diclofenac treatment groups in all 3 MEDAL Program studies. The incidence of patients exceeding this predefined limit of change of serum creatinine of having consecutive values of serum creatinine with an absolute increase of ≥0.5 and >ULN was similar for etoricoxib 60 mg and diclofenac 150 mg among OA patients in the MEDAL Study and between etoricoxib 90 mg and diclofenac 150 mg among RA patients in the MEDAL and EDGE II studies. However, among OA patients on etoricoxib 90 mg in the MEDAL Study a higher incidence was noted versus diclofenac 150 mg with the 95% CI for the difference that did not cross zero. In the EDGE Study the incidence of patients exceeding this predefined limit of change was similar for etoricoxib 90 mg and diclofenac 150 mg among OA patients.

The results of the secondary analyses were generally consistent with the primary analyses although a difference was also noted for etoricoxib 90 mg among RA patients in the EDGE II Study for one or more values with absolute increase ≥0.5 and >ULN with a 95% CI for the difference between etoricoxib and diclofenac that did not cross zero.

Table 58

Patients Exceeding the Predefined Limits of Change for Serum Creatinine
MEDAL Program Studies

	MEDAL Study (OA/RA)						EDGE II (RA)		EDGE (OA)	
	Osteoarthritis				Rheumatoid Arthritis					
	60 mg vs. Diclo Cohort		90 mg vs. Diclo Cohort							
	Etori 60 mg N=6451	Diclo 150 mg N=6352	Etori 90 mg N=2079	Diclo 150 mg N=2085	Etori 90 mg N=2677	Diclo 150 mg N=2706	Etori 90 mg N=1933	Diclo 150 mg N=1950	Etori 90 mg N=3548	Diclo 150 mg N=3462
Primary: Consecutive values >2x bln and >ULN†										
Incidence %	0.1	0.2	0.4	0.4	0.3	0.1	0.1	0.1	0.1	0.03‡
Difference in Proportions (95% CI) Etoricoxib-Diclofenac	-0.03 (-0.18, 0.11)		0.5 (0.36, 1.37)		0.15 (-0.10, 0.44)		0.1 (-0.2, 0.3)		0.1 (-0.1, 0.3)	
Primary: Consecutive values with absolute increase ≥0.5 and >ULN†										
Incidence %	1.8	1.5	4.0	2.8	2.2	2.1	1.2	1.2	0.6	0.7
Difference in Proportions (95% CI) Etoricoxib-Diclofenac	0.26 (-0.19, 0.70		1.26 (0.15, 2.38)		0.17 (-0.61, 0.96)		-0.0 (-0.8, 0.7)		-0.0 (-0.4, 0.3)	

† Meeting the criteria on one occasion and discontinuing due to a single value (instead of consecutive values and patient continuing in the study) is sufficient to be classified as exceeding the defined limit of change.
‡ incidence displayed to second decimal place to identify values with number of events >1
Note: A patient may have exceeded the predefined limits of change for more than one parameter and may appear in more than one category. Boxes shaded in gray indicate no applicable data. The 95% confidence interval is calculated by Wilson's Score Method.
N= total number of patients with valid values of the laboratory test; CI = Confidence Interval; ULN = Upper normal limit; BLN = Baseline value, Etori=Etoricoxib, Diclo=Diclofenac

Renovascular Safety Conclusions

- The incidence of edema-related adverse experiences for etoricoxib 30 and 60 mg is similar to comparator NSAIDs with evidence of a dose-related trend based on the 1-Year Population.
- The incidence of congestive heart failure for etoricoxib 30 and 60 mg is low and similar to comparator NSAIDs.
- The incidence of hypertension-related adverse experiences for etoricoxib 30 mg is similar to naproxen, numerically lower than ibuprofen 2400 mg and significantly higher than celecoxib 200 mg.
- The incidence of hypertension-related adverse experiences for etoricoxib 60 mg is numerically greater than naproxen and numerically lower than ibuprofen. Discontinuations due to hypertension-related adverse experiences are significantly greater on etoricoxib 60 mg than diclofenac.

10. Published Observational Data for Etoricoxib

To date, there are very limited data from published epidemiological studies of the association of etoricoxib with thrombotic cardiovascular risk. Three such studies have been published. Andersohn et al. conducted two nested case-control studies using the GPRD (2000-2004) database to investigate the risk of acute MI [138] and ischemic stroke [139] associated with the use of traditional NSAIDs or COX-2 selective inhibitors [138; 139]. The methods were very similar for the two studies. The study populations included approximately 485,000 and 470,000 patients for the MI and stroke studies respectively, and consisted of patients aged ≥40 years with at least one prescription for an NSAID or COX-2 selective inhibitors between June 1, 2000, and October 31, 2004 and who had been registered for at least one year with a practice with ensured data quality standards. A total of 3643 cases with acute myocardial infarction (AMI) and 3094 cases with ischemic stroke were identified. Controls (n=13918 for MI cases and n=11859 for ischemic stroke cases) were matched on age, sex, year of cohort entry, and general practice. Current exposure to NSAIDs or COX-2 selective inhibitors was defined as having a prescription that lasted into the 14 day period before the 'event date'; non-use of NSAIDs was defined as having no NSAID prescription in the year before the 'event date'.

There were a total of 16 MI cases exposed to etoricoxib in the analyses. Relative risks (RRs) for current use of NSAIDs or COX-2 selective inhibitors compared with non-use of NSAIDs were calculated. Current use of etoricoxib was reported to be associated with a RR of 2.09 (95% CI 1.10 to 3.97) risk of AMI compared with no use of NSAIDs. Other RRs (95% CI) for current use of NSAIDs or COX-2 selective inhibitors were: rofecoxib 1.29 (1.02 to 1.63), celecoxib 1.56 (1.22 to 2.00), valdecoxib 4.60 (0.61 to 34.51), diclofenac 1.37 (1.17 to 1.59), ibuprofen 1.04 (0.86–1.25), and naproxen 1.15 (0.84–1.58) In general, the RRs for the study drugs were higher with higher doses. These analyses were limited by the small numbers of events available for study [138].

In the analyses of ischemic stroke, there were a total of 10 cases exposed to etoricoxib. Odds ratios (ORs) of ischemic stroke associated with the use of NSAIDs or COX-2 selective inhibitors were calculated by conditional logistic regression. Current use of etoricoxib was reported to be associated with an OR of 2.38 (95% CI 1.10 to 5.13). Other ORs (95% CI) for current use of NSAIDs or COX-2 selective inhibitors were: rofecoxib 1.71 (1.33 to 2.18), celecoxib 1.07 (0.79 to 1.44), diclofenac 1.32 (1.10–1.57), ibuprofen 1.12 (0.91–1.37), and naproxen 1.16 (0.80–1.70). In general, the ORs for the study drugs were higher with higher doses and longer duration of use. These analyses were limited by the small numbers of events available for study [139].

The third epidemiological study was a nested case-control study to evaluate the risk of first MI associated with the use of various NSAIDs or COX-2 selective inhibitors during 2000 to 2003 in outpatient residents of Finland [140]. The National Hospital Discharge, Population, Prescription, and Special Reimbursement Registers were used to

identify all patients with first MI requiring hospitalization, matched controls, and all prescriptions for NSAIDs. There were 33309 persons with first time MI identified. A total of 138949 controls individually matched for age, gender, hospital catchment area, and index day were selected. Current exposure to NSAIDs or COX-2 selective inhibitors was defined as having a prescription that lasted until or after the 'event' date; non-use of NSAIDs was defined as having no NSAID prescription in the two years before the 'event date'.

There were a total of 10 MI cases exposed to etoricoxib. Adjusted (for diabetes mellitus, rheumatoid arthritis, CAD, hypertension, and the use of a beta-blocker, a statin, hormone replacement therapy, and clopidogrel 4 months prior to the index day) ORs for ischemic stroke associated with the use of NSAIDs or COX-2 selective inhibitors were calculated by conditional logistic regression. Current use of etoricoxib was reported to be associated with a OR of 2.21 (95 CI 1.18–4.14). Other ORs (95% CI) for current use of NSAIDs or COX-2 selective inhibitors were: rofecoxib 1.44 (1.20–1.72), celecoxib 1.06 (0.83–1.34), diclofenac 1.35 (1.18–1.54), ibuprofen 1.41 (1.28–1.55), naproxen 1.19 (1.02–1.38), indomethacin 1.56 (1.21–2.03), and ketoprofen 1.11 (0.94–1.31). The adjusted ORs were similar for combined conventional (1.34, 95% CI 1.26–1.43), semi-selective (etodolac, nabumetone, nimesulide, and meloxicam combined) (1.50, 95% CI 1.32–1.71), and COX-2 selective inhibitors (rofecoxib, celecoxib, valdecoxib, and etoricoxib combined) (1.31, 95% CI 1.13–1.50). Risk did not vary importantly by patient age nor by duration of use for conventional NSAIDs. The estimated risk was not consistently elevated with longer duration of use of COX-2 selective inhibitors [140].

As noted above, there are very limited observational data available for etoricoxib. These need to be interpreted in light of the small numbers of events in the analyses and the limitations of epidemiological studies as discussed in Appendix 1. Given the availability of randomized controlled studies that directly assess these endpoints, the observational data need to be considered subordinate.

11. Post-Marketing Experience

The safety profile of etoricoxib, as assessed by the post-marketing experience in countries where ARCOXIA has market authorization, is consistent with the current knowledge of the safety profile of NSAIDs more generally. Ten periodic safety update reports (PSURs), at 6 month intervals, have been submitted to regulatory authorities where etoricoxib has been available to patients. These PSURs have supported continued market authorization for etoricoxib. In addition, based on a EU referral review in 2005, the Committee for Medicinal Products for Human Use (CHMP) concluded that the balance of benefit to risk remained positive for the approved indications.

11.1 Post-Marketing History

Etoricoxib tablets are available for a range of indications worldwide, including acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis,

treatment of ankylosing spondylitis, treatment of acute gouty arthritis, relief of acute and chronic pain and treatment of primary dysmenorrhea. Etoricoxib was first approved in Mexico on 01-Oct-2001 and at the time of this report had been registered and approved in 66 countries. It should be noted that the 30 mg tablet is not available currently as a marketed dose.

11.2 Patient Exposure

Reliable patient estimates and reliable information with regard to the usage of etoricoxib by patients on a worldwide basis is not available. Therefore, patient exposure was calculated from the number of tablets distributed worldwide. Using the assumption of one tablet per patient per day for 365 days per year, 865 million tablets distributed (cumulative) equal approximately 2.4 million patient years of treatment for all strengths and 761,860 patient years of treatment for the 60 mg dose.

It is important to note that the estimated patient-years of treatment are not equivalent to the absolute number of patients treated. It should also be noted that the overall patient-years of treatment (PYT) estimates are likely to underestimate the true number of patients exposed to etoricoxib, due to the fact that PYT estimates are calculated number of patients who could have been treated for one year based on the tablets distributed. However, since most patients do not stay on therapy for a whole year, even for chronic conditions, the real number of patients is likely to be higher. This is especially true for etoricoxib 120 mg, which is only indicated for a treatment duration of up to 8 days.

A summary of the worldwide distribution of etoricoxib tablets between market introduction (01-Oct-2001) and 31-Dec-2006 is presented in Table 59. Estimates of patient-years of treatment are also provided (based on the assumption of one tablet daily).

Table 59

Etoricoxib Estimated Patient Years of Treatment
01-Oct-2001 through 31-Dec-2006

Strength	Distribution (total number of tablets)	Patient-Years of Treatment
	Cumulative through 31-Dec-2006	Cumulative through 31-Dec-2006
60 mg	278,079,020	761,860
90 mg	418,673,145	1,147,050
120 mg	168,379,542	461,314
Total	865,131,717	2,370,224

11.3 Postmarketing Experience

The Worldwide Adverse Experience System (WAES) database was searched for spontaneous reports for etoricoxib received from market introduction (01-Oct-2001) through 31-Dec-2006. A total of 4273 spontaneous reports from both healthcare professionals, including regulatory agencies, and consumers were identified. These 4273 spontaneous reports included 3492 reports received from healthcare professionals and 781 reports received from consumers. One thousand one hundred seventy-five (1175) of the 3492 healthcare professional reports identified met the regulatory criteria for a serious report and 82 of the 781 consumer reports met the regulatory criteria for a serious report.

The majority of the reports in which an association between therapy with etoricoxib and patients' adverse experiences cannot be ruled out are consistent with the expected adverse event profile for etoricoxib and describe well recognized adverse experiences of gastrointestinal events, renovascular events (including hypertensive events, oedema, and congestive heart failure) as well as hypersensitivity events including very rarely Steven's Johnson syndrome. As a result of the ongoing review of post-marketing data since the product launch, post marketing adverse experiences have been included in the Side Effects section of the proposed label.

12. Risk Management Plan

The safety profile of etoricoxib has been extensively assessed and characterized in the comprehensive clinical programs with ~24,600 patients exposed to etoricoxib and post marketing exposure of approximately 2.4 million patient years of treatment. Merck has proposed a risk management plan to continually assess use of etoricoxib in clinical practice. Merck will to work with the FDA to finalize the risk management plan.

The evidence from extensive clinical trials, post-marketing surveillance and limited observational study data support the conclusion that the safety profile for etoricoxib is within the broad spectrum of the safety profile of NSAIDs as a class. Renovascular and gastrointestinal effects have been observed in patients treated with etoricoxib, which are associated with all agents in the NSAID class. Regarding thrombotic CV risk, the thrombotic CV safety data that have accrued with etoricoxib, particularly the MEDAL Program data which demonstrated comparable thrombotic CV safety for etoricoxib in comparison to diclofenac, are consistent with the conclusion previously made by the FDA that the available data are consistent with a class effect of traditional NSAIDs and COX-2 selective inhibitors.

The proposed U.S. product circular for etoricoxib are consistent with the FDA NSAID template and have been updated with language that takes into consideration findings from all clinical trials and post-marketing surveillance and restrict the use of the drug to the appropriate patient population. Similarly all product circulars in countries where the product is approved have been updated with language consistent with local templates/guidelines.

An analysis of the UK General Practice Research Database was conducted as a post-licensure commitment to the European Medicines Agency (EMEA). The study examined the characteristics of new and continuing users of etoricoxib before and after the 17 February 2005 Urgent Safety Restriction on the use of COX-2 selective inhibitors issued by the EMEA. While etoricoxib use in the UK GPRD practices is somewhat limited, the results of the study indicate that the characteristics of patients prescribed etoricoxib during the study period were as expected based on the indications for use. A considerable proportion of patients prescribed etoricoxib have risk factors for gastrointestinal ulcers and bleeding and cardiovascular events. Prescribing of etoricoxib by GPs in the UK is generally consistent with product labeling. The incidences of clinical events of interest (renovascular, gastrointestinal, cardiovascular) were generally as expected given the characteristics of the patient population prescribed etoricoxib. These estimates were hampered somewhat by sparse data for some events. As expected, most clinical events were more commonly observed in older patients and some events, such as edema and hypertension, appear to occur more commonly with higher doses of etoricoxib.

Merck also will continue its long standing policy and practice to ensure that all of our communications with health care providers are aligned with the approved labeling for all our products. Merck will test all educational materials with both physicians and patients to ensure communication is appropriately understood by the target audience. Additionally, Merck will continue to monitor post marketing reports, via our routine pharmacovigilance program. Furthermore, upon approval a pregnancy registry will be operational in the United States

In addition to the pharmacovigilance activities and interventions described above which are designed to identify, characterize and prevent or minimize risk related to therapy with etoricoxib, Merck is proposing to initiate activities which may be helpful to further characterize and assess usage patterns and patient profiles in the post marketing environment. Details of these additional risk management activities would be finalized upon final approved labeling of the product and discussions with the agency.

One appropriate tool may include drug utilization studies. A drug utilization study could be helpful to examine to whom etoricoxib is prescribed and how it is used in actual clinical practice. Special attention will be directed towards drug usage patterns in terms of starting dosage and maintenance dosage. An additional tool to be considered is physician surveys to assess physician awareness of safety communications as outlined in the product label. Results of the above studies could be communicated via updates to the risk management plan, PSURs, and publications as appropriate.

Merck would like to emphasize our commitment to continue a close dialogue with the FDA regarding the potential need for revisions to the risk management plan and the proposed product label.

13. Benefit and Risk Assessment

13.1 Introduction

Pain, loss of function and impairment of quality of life characterize OA for many patients. Treating these signs and symptoms is a clinically important goal of therapy, and not simply a matter of convenience. Despite the availability of a range of nonpharmacologic and pharmacologic options, NSAIDs (both COX-2 selective inhibitors and traditional NSAIDs) are the mainstays of therapy for many arthritis patients suffering from daily moderate to severe pain. The choice of treatment options needs to carefully balance desired benefits with possible risks.

13.2 Benefits

Efficacy

In the treatment of OA of the knee and hip, etoricoxib 30 and 60 mg resulted in clinically meaningful improvements in pain, physical function, and in patient and physician global assessments. Etoricoxib 60 mg was shown to have efficacy comparable to naproxen 1000 mg, while etoricoxib 30 mg was shown to have efficacy comparable to ibuprofen 2400 mg and celecoxib 200 mg. Etoricoxib 60 mg also demonstrated comparable efficacy to naproxen 1000 in OA of the hand. These data establish that both etoricoxib 30 mg and 60 mg are efficacious in the treatment of OA. The onset of action with etoricoxib 30 and 60 mg was rapid with a duration lasting over the entire dosing interval. Treatment with etoricoxib 30 mg and 60 mg provided sustained efficacy for treatment periods for up to 1 year. The available data comparing the relative efficacy of 30 mg versus 60 mg demonstrates that etoricoxib 60 mg provided significantly greater treatment effects than etoricoxib 30 mg suggesting that the 60 mg dose may provide greater efficacy in some OA patients than the 30 mg dose. Given these data, approval is being sought for etoricoxib 30 and 60 mg once daily to treat the signs and symptoms of OA with 30 mg as the recommended initial dose.

Improved GI Safety and GI Tolerability

COX-2 selective inhibitors were developed to provide efficacy comparable to traditional NSAIDs with an improved GI safety profile. This remains an important advance in medical treatment given that gastrointestinal toxicity is the most common morbidity of NSAID use [31].

The Etoricoxib Development Program evaluated several surrogates of GI safety. These included effects on gastric PGE_2 production, fecal red blood cell loss, and gastroduodenal ulcers monitored through scheduled endoscopy – all at the 120 mg dose, a dose that exceeds that proposed for use in patients with OA by 2-4 times. In each case, etoricoxib demonstrated a significant GI benefit versus traditional NSAID comparators.

The occurrence of upper GI clinical events (perforations, obstructions, ulceration and bleeds; PUBs) was evaluated from pooled data across all chronic exposure studies from the Etoricoxib Development Program (at dosages ranging from 30 mg to 120 mg) and

separately for the pooled MEDAL Program studies. In the Etoricoxib Development Program, a significant (47%) reduction in the rate of upper GI events was observed with etoricoxib treatment (doses up to 120 mg) relative to combined data for traditional NSAIDs and mostly drive by studies in which naproxen was the comparator. In the pooled analysis, a trend was also observed with a 31% reduction for clinically complicated upper GI events (e.g., significant bleeds). The difference was mainly driven by clinically significant bleeding events on naproxen as the comparator.

Unlike many other trials of COX-2 inhibitors, the MEDAL Program studies did not restrict the use of low-dose aspirin and gastroprotective agents such as proton pump inhibitors. Despite these potential confounding factors, a significant reduction (31%) in the rate of upper GI clinical events was still observed for etoricoxib compared to diclofenac. This result was driven principally by the difference in uncomplicated ulcers (mainly gastric ulcers); no significant difference was identified in the subset of complicated events. Importantly, the magnitude of the reduction observed in uncomplicated events for etoricoxib was the same whether or not patients took PPIs. Although a reduction in the GI event rate was also observed whether or not patients took concomitant low-dose aspirin, the magnitude of the GI benefit may be partially diminished with low-dose aspirin use, consistent with what has been observed in other large studies with GI outcomes [47; 41]. This is the first study with GI outcomes to allow PPI use and the fact that a benefit was maintained in patients on PPIs (almost half of the patients) is an important finding given the outstanding question of whether concomitant administration of a PPI with a traditional NSAID attenuates the benefit of COX-2 selective inhibition. The lowest GI risk strategy is not NSAID plus PPI but etoricoxib plus PPI.

Neither the lower rates of upper GI events observed in the MEDAL Program relative to prior GI outcomes trials nor the concomitant use of PPIs and low-dose aspirin appear to explain the lack of a significant difference in complicated upper GI events. Even among the nearly 15,500 patients not using PPIs or low-dose aspirin regularly, no evidence of a decrease in complicated events was identified while a 51% relative risk reduction in uncomplicated events was seen. It is possible that PPIs have a differential effect on the prevention of complicated and uncomplicated ulcers. A plausible explanation for the dichotomy between complicated and uncomplicated events could relate to diclofenac's lack of anti-platelet effect. It has been suggested that gastroduodenal mucosal lesions develop as a consequence of moderate inhibition of COX-1 activity while upper GI bleeding complications occur as a result of high-grade inhibition of platelet COX-1 [129]. Greater than 95% inhibition of COX-1 mediated thromboxane is required to impact platelet function [62; 130]. Diclofenac's inhibition peaks at 87% [114] and although this degree of COX-1 inhibition is sufficient to induce gastrointestinal ulcers in several studies [115; 116; 128], it is not sufficient to maximally decrease platelet function in most patients [131].

When subgroups of patients from the MEDAL Program were further evaluated, etoricoxib provided a consistent GI safety benefit compared with diclofenac across a wide range of patient subgroups that were tested including both OA and RA disease-types. The relative benefit was maintained but diminished at the 90 mg dose of etoricoxib but a greater absolute benefit is obtained in RA patients given the greater risk for upper GI events in this patient population. In particular, the improved upper GI safety of etoricoxib was seen in all age subgroups, including patients older than 75 years, who are also at greater risk for GI events compared to younger patients.

GI tolerability is a very important factor in determining patient compliance, and therefore whether a patient derives clinical benefit and pain relief from an NSAID. Upper GI symptoms (e.g., dyspepsia, abdominal pain, and nausea) are the most common side effects of NSAID use and are one of the primary reasons for discontinuation of an NSAID [96]. In both the Etoricoxib Development Program and the MEDAL Program studies patients treated with etoricoxib were significantly less likely to discontinue treatment due to GI adverse experiences than those patients treated with traditional NSAIDs. In the Etoricoxib Development Program etoricoxib use was also associated with significantly less new use of gastroprotective agents, a prespecified measure for the program. In the MEDAL Program at both the 60 mg and 90 mg doses of etoricoxib, a significant decrease in discontinuations was observed for GI adverse experiences relative to diclofenac. This significant decrease was demonstrated individually for the clinical component and the laboratory component both for the pooled MEDAL Program as well as each individual MEDAL program study. The MEDAL Program also included an evaluation of Confirmed Lower GI Clinical Events (perforations, obstructions, and bleeds; POBs) from data pooled from the 3 MEDAL Program studies. The rates of Confirmed Lower GI Clinical Events were numerically lower with etoricoxib than with diclofenac with a nominally significant difference noted for Confirmed plus Unconfirmed POBs. The evaluation of lower GI events by dose in OA patients did show a dose effect with a diminution of the numeric benefit at the 90 mg dose. Finally, a significant decrease in the incidence of discontinuations due to hepatic-related adverse experiences was also demonstrated for etoricoxib relative to diclofenac in the individual MEDAL Program studies.

Overall, GI Safety data from the Etoricoxib Development Program and the MEDAL Program demonstrate that etoricoxib represents a significant improvement, with regard to upper GI clinical events relative to traditional NSAIDs as a class. Taking into account the apparent range of GI risk for NSAIDs, a benefit for complicated upper GI events likely exists for etoricoxib, but is probably dependent on the level of GI toxicity associated with the traditional NSAID being compared. A significant GI tolerability benefit across the Etoricoxib Development Program and the MEDAL Program was also demonstrated for etoricoxib based on discontinuations due to GI clinical adverse experiences.

Sulfonamide-Allergic Patients

Therapy with etoricoxib may have several advantages over non-selective as well as some COX-2 selective NSAIDs when it comes to hypersensitivity reactions. First, etoricoxib is not a sulfonamide and therefore can be used safely in patients with sulfonamide allergies, an important consideration for some patients. Drugs with a sulfonamide component, such as certain antibiotics, and celecoxib, are contraindicated in patients with sulfonamide allergies. Second, many hypersensitivity reactions, previously thought to be of immunologic origin, are now thought to be of non-immunologic origin and may be related to COX-1 inhibition. These data suggest a potential advantage to using COX-2 selective inhibitors such as etoricoxib as a safe treatment alternative in this population of patients who cannot tolerate traditional non-selective NSAIDs and thus are restricted in the medications they use for pain and inflammation.

Platelet Effects

Etoricoxib has no effect on COX-1 at therapeutic doses and thus produces its analgesic and anti-inflammatory benefit without increasing the risk of bleedings due to inhibition of platelet COX-1. Thus etoricoxib, unlike traditional NSAIDs, can be used in the preoperative period (i.e., patients do not need to stop therapy before surgery) and may have advantages in patients receiving anti-thrombotic therapy. It should be noted that all NSAIDs are contraindicated for use immediately post-operatively for coronary artery bypass (CABG) surgery.

Metabolism

With a half-life of ~21 hours, etoricoxib can effectively be administered on a once-daily basis. The onset of efficacy was observed within the first 24 hours in patients with OA. Etoricoxib is metabolized by multiple cytochrome P450 enzymes and does not inhibit CYP3A4. The metabolism of etoricoxib is not affected by the genetic polymorphism associated with CYP2C9 unlike the other available COX-2 inhibitor celecoxib, which is primarily metabolized by CYP2C9.

13.3 Potential Risks

Thrombotic CV Safety

Certain long-term, randomized trials have shown an increased risk of thrombotic CV events with COX-2 selective inhibitors compared to placebo (4797, 5111, 5321, 3878, 5112}, largely in chemopreventive patient populations. Comparable long-term placebo-controlled assessments in arthritis patients with traditional NSAIDs are not available. Observational study results suggest that at least some NSAIDs also increase thrombotic CV risk as compared with non-use of NSAIDs. In 2005 the FDA concluded, based on information known at that time which included complete data from the Etoricoxib Development Program, that the available data are best interpreted as being consistent with a class effect of an increase in serious adverse thrombotic CV effects for COX-2

selective and some traditional NSAIDs. However, additional studies were called for to address remaining questions, including the question of a differential thrombotic CV risk between COX-2 selective inhibitors and traditional NSAIDs, given the great clinical relevance in assessing overall benefits and risks of treatment in patients who require NSAID therapy.

We designed the MEDAL Program to assess the relative long-term CV safety of two anti-inflammatory treatments in patients with OA and RA and it is the first clinical research program designed with the primary aim of prospectively assessing thrombotic CV safety with a COX-2 selective inhibitor, etoricoxib (60 and 90 mg), compared to a traditional NSAID, diclofenac (150 mg) [62]. The MEDAL Program was not designed to compare the thrombotic CV risk of etoricoxib to placebo as it is impractical to maintain arthritis patients in need of significant analgesic and anti-inflammatory therapy on a placebo long-term. In addition, the relevant question for patients and physicians applies to patients who are in need of therapy, rather than those who do not seek treatment. Therefore, a comparison to a broadly used traditional NSAID was critical.

The MEDAL Program provides estimates of thrombotic CV safety of substantially greater precision than prior trials. The assessment of thrombotic CV risk in the MEDAL Program is highly relevant to patients and physicians because it was performed in a "real-world" population of arthritis patients with a broad range of thrombotic CV risk and a worldwide distribution including the participation of patients from 38 countries. Importantly, ~21,400 and ~12,800 patients were on therapy for ≥12 and ≥24 months, respectively, thereby providing substantial experience with long-term treatment.

In the MEDAL Program, thrombotic CV safety was assessed using several endpoints (Confirmed Thrombotic Events, Confirmed Arterial Events, and the Antiplatelet Trialists' Collaboration [APTC] combined endpoint) as well as several analytical approaches (per-protocol, mITT, and ITT). Regardless of the endpoint or the approach to analysis, the results from both the Pooled MEDAL Program and the MEDAL Study alone consistently demonstrated comparable rates of thrombotic CV events between etoricoxib and diclofenac. The annual incidence of thrombotic CV events in the combined MEDAL Program population was approximately 1.25%, and the absolute difference in event rates between treatments was less than one patient per thousand treated for a year. Based on the 95% confidence level for this difference in the primary analysis, etoricoxib could be associated with at most, an increase of 1.3 events (or a decrease of 2.6 events) per thousand patients treated for a year as compared to diclofenac.

The comparable thrombotic CV safety for etoricoxib and diclofenac was consistent across different statistical approaches, endpoints, studies, vascular beds (including cardiovascular, cerebrovascular, and peripheral vascular), and patient populations, (including males and females, younger and older, with or without prior histories of symptomatic cardiovascular disease or risk factors, with or without low dose aspirin use, osteoarthritis patients and rheumatoid arthritis patients), and was consistent across a

prolonged period of study drug therapy. These results are also consistent with the results of previous etoricoxib studies. Most importantly, the MEDAL Program analysis is based on far more data and is therefore more robust.

A recent published review of observational studies suggesting an increased thrombotic CV risk with some non-selective, "traditional" NSAIDs versus no NSAIDs [58] is consistent with previous findings [56]. The observational studies include data which suggest diclofenac may be associated with increased thrombotic CV risk compared to non-use. However, taking into account all of the available data, the range of the risk associated with diclofenac precludes rank ordering the NSAIDs (including diclofenac) based on thrombotic CV risk, with the exception of naproxen [56]. Although naproxen was considered as a comparator for the MEDAL Program a large amount of data had already been accrued comparing etoricoxib to naproxen. It is important to understand the Thrombotic CV safety for traditional NSAIDs other than naproxen because not all patients achieve adequate efficacy or are able to tolerate naproxen therapy. The gastrointestinal side effects of naproxen, including upper GI clinical events, are well recognized. The data from the Etoricoxib Development Program showed that use of naproxen was associated with the highest rate of discontinuations due to GI adverse events and a higher rate of GI events (PUBs) compared to etoricoxib. The sustained high level of COX-1 inhibition and potent antiplatelet effects of naproxen [112], which are hypothesized to be responsible for its more favorable thrombotic CV profile [141] are also likely to be responsible for the higher incidence of more serious upper GI effects associated with naproxen use than with use of other traditional NSAIDs [129].

The relevance of the MEDAL Program remains high given the need to assess therapies in arthritis patient populations requiring chronic treatment. The choice of diclofenac remains well founded, based on its world-wide acceptance as an efficacious therapy and its lack of interference with the antiplatelet effects of aspirin. Both ibuprofen and naproxen do interfere, and in fact ibuprofen's interference with aspirin's antiplatelet effects was the subject of a recent MedWatch announcement by the U.S. Food and Drug Administration [108]. The fact that diclofenac does not possess a potent and sustained antiplatelet effect makes the thrombotic CV results of the MEDAL Program more relevant given that the majority of traditional NSAIDs, with the exception of naproxen, do not have potent and sustained antiplatelet effects.

Renovascular Effects

Accumulating data with COX-2 selective inhibitors suggest that their renovascular safety profile is generally similar to that of traditional NSAIDs, namely a dose-dependent risk for the development of adverse effects related to elevations in blood pressure and/or the development of edema and congestive heart failure [68; 142; 143; 144; 145]. Therefore, in both the Etoricoxib Development Program and the MEDAL Program studies, particular attention was paid to the evaluation of the known mechanism-based

adverse effects (edema, congestive heart failure, and hypertension). Renal function was also specifically measured in the MEDAL Program studies.

In the OA Development Program and in the MEDAL Program studies, hypertension was a common baseline comorbidity; 36 to 52% and approximately 50% of patients, respectively, had a history of hypertension at baseline. In each case, the incidence of discontinuations was low; <1% for the OA Development Program and <3% for the MEDAL Program studies in any treatment group.

Data from the OA Development Program indicates that etoricoxib use is associated with a shallow, dose-related trend in hypertension-related adverse experiences with an incidence greater than placebo, but within the range of that observed for comparator NSAIDs depending on the etoricoxib dose and the comparator studied, including naproxen and ibuprofen. A significant difference was observed between etoricoxib 30 mg and celecoxib 200 mg but not between etoricoxib and naproxen or ibuprofen.

In the MEDAL Program studies, treatment with etoricoxib 60 mg and 90 mg was associated with a significantly higher incidence of discontinuations due to hypertension-related adverse experiences compared with diclofenac 150 mg. There appeared to be a dose effect – the 90-mg dose of etoricoxib was associated with a higher incidence, however, discontinuation due to these side effects even at the 90-mg dose were still relatively uncommon (<3%). Significant elevations in blood pressure (systolic BP ≥180 or diastolic BP ≥110) were seen in a third of the patients who discontinued (less than 1% of patients). Hypertension-related serious adverse experiences were rare, as were reports of malignant hypertension and hypertensive crisis (based on investigator reported terms). The effects of etoricoxib on systolic blood pressure were generally small across the study population (maximum increase in mean systolic blood pressure of 1 to 2 mmHg versus screening values). The incidence of discontinuations due to edema-related adverse experiences and CHF were similar for etoricoxib 60 mg and diclofenac while higher for etoricoxib 90 mg versus diclofenac. Analyses of discontinuations due to renal-related adverse experiences (a composite of clinical and laboratory events), within the individual MEDAL Program studies showed similar rates for etoricoxib 60 and 90 mg versus diclofenac in both OA and RA patients. There are a gradient of renovascular effects across the available NSAIDs and there are data to indicate that diclofenac use is associated with a lower incidence of hypertension than some other NSAIDs [146]. Overall, the data show that the renovascular effects associated with etoricoxib use are within the range observed for NSAIDs, depending on the dose of etoricoxib and the comparator.

For patients taking NSAIDs, including etoricoxib, a renovascular risk is present but can be monitored and managed. The possibility of fluid retention, edema or hypertension should be taken into consideration when etoricoxib is used in patients with pre-existing edema, hypertension, or heart failure. Attention should be paid to blood pressure monitoring during treatment with etoricoxib. If blood pressure rises significantly, alternative treatment should be considered.

13.4 Summary

Etoricoxib, at doses of 30 mg and 60 mg, provides a treatment option for OA with efficacy comparable to traditional and COX-2 selective NSAIDs, superior GI safety and tolerability compared with traditional NSAIDs and otherwise a safety and tolerability profile that is consistent with the class of traditional and COX-2 selective NSAIDs providing an overall favorable benefit/risk relationship. The thrombotic CV safety profile is comparable to diclofenac, a widely used traditional NSAID. The renovascular effects of edema, CHF, and hypertension for etoricoxib are dose-related and at the doses recommended for OA (30 mg and 60 mg), these effects are within the range of other NSAIDs. Individual patient's responses to NSAIDs, including COX-2 inhibitors are variable. The reasons for these differential responses are not understood. This phenomenon underscores the need for patients to have a variety of NSAIDs available to them, including COX-2 selective inhibitors for patients who specifically require an agent with better GI safety. Etoricoxib provides a unique profile including superior GI safety relative to traditional NSAIDs that is maintained with PPI use. It is able to be dosed once daily and is a nonsulfonamide therapy with efficacy maintained throughout the dosing period. In clinical practice, the selection of an anti-inflammatory agent for a specific patient needs to take into consideration the individual's prior treatment history, their risk for thrombotic CV and GI events, as well as potential renovascular effects (e.g., blood pressure, fluid retention), GI tolerability profile, and needs for symptomatic relief.

The MEDAL Program provides a robust amount of information to address the safety aspects for etoricoxib relative to diclofenac, and combined with the large amount of efficacy and safety data from the Etoricoxib Development Program, provides patients and practitioners information to help make informed decisions about their choice of treatment. Given the consistent benefit of an improved GI safety profile demonstrated across multiple parameters relative to traditional NSAIDs (even in the context of PPI use) etoricoxib, with appropriate labeling, should be an option for the treatment of OA.

Appendix 1: Review of Observational Data Evaluating Thrombotic CV Safety of Diclofenac Compared with Other NSAIDs.

Summary

The observational literature on the thrombotic cardiovascular (CV) risk with non-selective NSAIDs is summarized in two recent systematic reviews [57; 58]. The observational evidence suggests that diclofenac is associated with a small to moderately increased risk of thrombotic cardiovascular events (mostly myocardial infarction / sudden cardiac death) when compared with non-use of NSAIDs. However, these reviews did not include the data from a very large cohort study with 44,500 patient years of diclofenac exposure in which diclofenac was associated with an adjusted odds ratio for MI of 1.02 at doses ≤150 mg (approximately 91% of usage) and 1.37 at doses >150 mg [137]. In addition, the estimates of thrombotic CV risk from individual observational studies of diclofenac vary greatly, from 0.5 to 1.6 [58].

Among NSAID users, there are only two studies directly comparing cardiovascular risk with diclofenac to that with other non-selective NSAIDs (ibuprofen and non-naproxen NSAIDs [1; 2]; the results for MI risk (the common endpoint between them) from these two studies are conflicting. Thus firm conclusions cannot be drawn about thrombotic CV risk with diclofenac relative to other NSAIDs from these data.

Given the potential for bias and residual confounding in the observational studies (especially with non-users of NSAIDs as the referent group), the relatively low magnitude estimates of effect for diclofenac and other NSAIDs versus non-use, the limited and conflicting data from direct comparisons of diclofenac with other NSAIDs, and the variability of the estimates of thrombotic CV risk with diclofenac, it is not possible to determine whether diclofenac is different from many other non-selective NSAIDs using the observational data.

BACKGROUND

Systematic Reviews of Observational Studies

A number of observational studies of thrombotic CV (cardiac, cerebrovascular, and/or sudden cardiac death outcomes) events with the use of non-selective NSAIDs have been published. This literature is summarized in two recent systematic reviews, 12 individual studies in common between them [57; 58]. The two reviews are summarized in this section, and recent relevant data that was not included in them is mentioned.

The first analysis, by Hernandez-Diaz et al, was a systematic review of 16 original cohort and case-control studies of NSAIDs and COX-2 selective inhibitors and the risk of myocardial infarction (MI) published between 2000 and 2005 [57]. The authors calculated pooled relative risk (RR) estimates of MI for specific NSAIDs compared with non-use of NSAIDs using both fixed- and random-effects models. The second analysis by McGettigan et al. was a systematic review of 23 cohort and case-control studies comparing the risk of serious cardiovascular events (mostly MI and cardiac death) with

individual NSAIDs and COX-2 selective inhibitors compared with non-use of NSAIDs published between 2000 and 2005 [58]. Data were combined using a random-effects model. Both reviews reported statistically significant heterogeneity in the results of their analyses. Hernandez-Diaz et al reported the pooled estimates for cohort and nested case-control studies were relatively similar, but that there was statistically significant heterogeneity within case-control studies [57]. McGettigan et al. reported statistically significant heterogeneity in the data contributing to the overall summary RRs for both naproxen and diclofenac [58].

RESULTS

Results of Systematic Reviews of Observational Studies

Comparisons of non-selective NSAIDs to non-use of NSAIDs

The results for individual drugs, compared with non-use of NSAIDs, from the two systematic reviews, are shown in the Table 1.

Table 1
Overall Relative Risk of Thrombotic CV events with Individual NSAIDs Versus Non-Use of NSAIDs
Two Systematic Reviews with All Doses Combined

	Relative Risk (95% CI)	
Drug	Hernandez-Diaz (16 studies)	McGettigan† (23 studies)
All non-selective NSAIDs†	1.09 (1.06–1.13)	1.10 (1.00-1.21)
Naproxen	0.98 (0.92–1.05)	0.97 (0.87-1.07)
Ibuprofen	1.07 (1.02–1.12)	1.07 (0.97-1.18)
Diclofenac	1.44 (1.32–1.56)	1.40 (1.16-1.70).
Piroxicam	--	1.06 (0.70-1.59)
Indomethacin	--	1.30 (1.07-1.60)
Meloxicam	--	1.25 (1.00-1.55)

† In the McGettigan study the pooled estimate includes NSAIDs other than those reported individually from some studies and all non-selective NSAIDs from other studies
CI = confidence interval

Neither review included the diclofenac data from a very large study with 44,500 patient years of diclofenac exposure published in abstract form only [137]. That study was conducted using the California Medicaid program and compared the risk of MI with individual non-selective NSAIDs and selective COX-2 inhibitors to remote use (not defined) to any of these agents. The odds ratios (OR) (95% CI) for MI with the various drugs studied ranged from 0.83 (0.60-1.14) with nabumetone to 1.71 (1.35-2.17) for

indomethacin compared with remote use. An overall estimate of risk for MI was not reported for use of diclofenac; however dose-specific results were reported as 1.02 at doses ≤150 mg (approximately 91% of the diclofenac usage) and 1.37 at doses >150 mg compared with remote use [137].

A recently published nested case-control study that examined the risk of acute MI / acute coronary syndrome (ACS) in a large cohort of US veterans with a diagnosis of osteoarthritis was also not included in either above systematic review [147]. Compared with non-use of NSAIDs, the ORs (95% CI) for MI / ACS / angina with use of individual NSAIDs among men with and without prior coronary artery disease were as follows:

	Pre-existing coronary disease	
	No	Yes
Naproxen	1.21 (1.04-1.40)	1.01 (0.84-1.20)
Ibuprofen	1.10 (0.96-1.27)	1.45 (1.26-1.67)
Diclofenac	1.42 (1.03-1.94)	1.01 (0.67-1.52).

Direct Comparisons of Diclofenac with other non-selective NSAIDs

Neither systematic review presented pooled RR estimates of the thrombotic CV risk with diclofenac directly compared with other NSAIDs.

Results of Other Observational Literature

Individual Observational Studies that Directly Compare Diclofenac with NSAIDs and Acetaminophen.

There are two published studies that directly compare thrombotic CV risk with current use of diclofenac (any dose) with use of other NSAIDs [1; 2]. One study directly compared diclofenac to ibuprofen [1]. That study reported a RR (95% CI) for sudden cardiac death of 2.16 (0.88-5.32) but not MI (RR 0.59, 95% CI 0.32-1.08), stroke or TIA (RR 0.91, 95% CI 0.60-1.38), or the combined endpoint of all these events (RR 0.90, 95% CI 0.65-1.23). Another study compared diclofenac to other non-selective NSAIDs (excluding naproxen), and reported a RR (95% CI) for MI /ACS of 1.33 (1.03-1.73) with diclofenac [2].

A recent study, not included in either systematic review summarized above, compared the risk of acute MI with use of non-selective NSAIDs and COX-2 selective inhibitors with use of acetaminophen [148]. Among non-users of aspirin the hazard ratios (95% CI) for MI with non-selective NSAIDs relative to use of acetaminophen were: naproxen 1.59 (1.31, 1.93), diclofenac 1.17 (0.99, 1.38) and ibuprofen 1.05 (0.74, 1.51).

Individual Observational Studies of thrombotic CV Risk with Diclofenac According to Dose and Duration of Use

Four studies reported analyses of thrombotic CV risk with current use of diclofenac compared with non-use or remote use of non-selective NSAIDs according to dose

[138; 149; 150; 1]. Two studies categorized diclofenac <100 mg versus ≥100 mg daily [149; 150]. One study categorized diclofenac ≤100 mg versus >100 mg daily. [138]. The fourth study specified three mean daily dosage levels of 100 mg, 101-149 mg, or ≥150 mg [1]. Three of the four studies reported no important difference in thrombotic CV risk by dose of diclofenac [138; 149; 1]. One reported the risk for re-admission for MI to be 1.27 (95% CI 0.92-1.76) and that of death to be 0.89 (95% CI 0.66-1.20) with use of diclofenac <100 mg daily, while the risks for were 1.89 (95% CI 1.40-2.55) and 4.44 (95% CI 3.79-5.19) respectively, for use of diclofenac ≥100 mg daily [150].

The results of three individual studies that examined thrombotic CV risk with diclofenac according to duration of diclofenac use are limited; these data suggest risk may be higher with longer-term use of diclofenac compared with non-use of NSAIDs [59; 149; 138]. There are o studies that compare the effect of duration of use with diclofenac directly to use of other NSAIDs.

DISCUSSION

The published observational literature on thrombotic CV risk with use of non-selective NSAIDs, most of which has been included in recent systematic reviews, suggests that use of diclofenac (all doses combined) is associated with a relative risk of about 1.4 for cardiovascular events (mostly MI or sudden cardiac death), compared with non-use of non-selective NSAIDs or COX-2 selective drugs. One large study, published in abstract form only and summarized above, was not included in systematic reviews of the literature, and its inclusion may have altered the summary relative risks from these reviews [137]. Other studies have been published since the systematic reviews also suggest that the overall summary estimates of 1.4 may not be completely accurate.

Dose-specific analyses of thrombotic CV risk with diclofenac compared with non-use of NSAIDs are limited and the results conflicting. Results of analyses that examined thrombotic CV risk with diclofenac compared with non-use according to duration of use are limited; these suggest risk may be higher with longer-term use compared with non-use of NSAIDs.

Data directly comparing thrombotic CV risk with diclofenac versus other NSAIDs or acetaminophen are very limited, and the results are not conclusive with respect to whether diclofenac is different from other chronic analgesics with respect to thrombotic CV risk. There are no data on dose-specific or duration-specific thrombotic CV risk with diclofenac versus other NSAIDs or COX-2 selective inhibitors.

Given the potential for bias and residual confounding in the observational studies (especially with non-users of NSAIDs as the referent group), the relatively low magnitude estimates of effect for diclofenac and other NSAIDs versus non-use, the limited and conflicting data from direct comparisons of diclofenac with other NSAIDs, and the variability of the estimates of thrombotic CV risk with diclofenac, it is not

possible to determine whether diclofenac is different from many other non-selective NSAIDs using the observational data.

Limitations of Observational Studies of NSAIDs and Cardiovascular Risk

Observational studies are more prone to bias than randomized clinical trials and for that reason are considered to provide weaker evidence for cause and effect than randomized experiments. Hence, it is generally accepted that relative risks <2.0 in observational studies should be viewed cautiously because they may easily arise due to confounding or bias [151]. The observational literature on the thrombotic cardiovascular effects of non-selective NSAIDs and COX-2 inhibitors suffer from a number of common and unique limitations. Some study designs (e.g., case-control) are more prone to possible biases than others. It was noted in one of the meta-analyses that the estimate of effect was modified by type of study (case-control versus cohort design) [152]. The data sources for these studies vary; they used administrative and pharmaceutical databases, chart review, clinical or practice-based databases, telephone interviews, or combinations of these data sources to determine outcomes, exposures, and comorbidities. It is not known whether the quality of the data from these many different sources are equivalent. Many potential confounders of the association of medications and cardiovascular disease are not routinely present in the commonly used databases. These include, for example, diet, alcohol use, family history, income or education level, obesity, smoking status, physical activity level, use of over the counter aspirin or NSAIDs, etc. Failure to measure or completely control for these factors may result in biased estimates of effect (and the potential confounding effect of unmeasured over the counter use of NSAIDs may differentially affect the results of studies using U.S. data, where such use is commonplace, as opposed to studies using UK data, where it occurs less commonly due to universal prescription coverage). The extent to which these various possible confounders are operative in a given database is for the most part unknown. On the other hand, analyses may also overly control for potential confounders if they adjust for cardiovascular risk factors identified after the exposure(s) of interest when in fact those risk factors are actually intermediate effects of the drugs themselves (such as hypertension brought on by use of NSAIDs). Assessment of exposure in these studies relies almost exclusively on records of prescriptions written or dispensed. Therefore patient compliance, patterns of usage, and persistence with medications is unknown. This makes analyses according to dose or duration of use problematic. In addition, the definition of current exposure varies among the studies reviewed. For some studies, prior exposures were given the same importance as current or more recent exposures, and this may confound results because it is unknown whether there are latent effects of COX-2 inhibitors or NSAIDs. Although it is commonly accepted that cardiovascular diagnoses in administrative and hospital databases are reasonably accurate, there will always remain some misclassification of outcomes resulting from the lack of endpoint verification through clinical chart review in the majority of these studies. The implicit assumption is that this misclassification is non-differential; however rarely is that assumption assessed or verified.

A unique difficulty for these studies as a group is confounding by indication. Comparisons of the use of COX-2 selective or non-selective NSAIDs to non-use are most likely biased. It is known that COX-2 inhibitors are preferentially prescribed over non-selective NSAIDs to older patients and to those with higher baseline risk of MI than those prescribed other therapies for their pain (i.e., high risk patients are "channeled" to COX-2 selective inhibitors) [153; 46; 154]. While the studies published to date have attempted to control for differential prescribing of COX-2 inhibitors and NSAIDs, limited information is available from claims databases to allow for complete control of such differences.

CONCLUSIONS

The observational evidence suggests that diclofenac is associated with a small to moderately increased risk of cardiovascular events (mostly myocardial infarction / sudden cardiac death) when compared with non-use of NSAIDs. However, these reviews did not include the data from a very large cohort study with 44,500 patient years of diclofenac exposure in which diclofenac was associated with an adjusted odds ratio for MI of 1.02 at doses ≤150 mg (approximately 91% of usage) and 1.37 at doses >150 mg [137]. In addition, the estimates of thrombotic CV risk from individual observational studies of diclofenac vary greatly, from 0.5 to 1.6 [58].

Among NSAID users, there are only two studies directly comparing cardiovascular risk with diclofenac to that with other non-selective NSAIDs (ibuprofen and non-naproxen NSAIDs [1; 2]; the results for MI risk (the common endpoint between them) from these two studies are conflicting. Thus firm conclusions cannot be drawn about thrombotic CV risk with diclofenac relative to other NSAIDs from these data.

Given the potential for bias and residual confounding in the observational studies (especially with non-users of NSAIDs as the referent group), the relatively low magnitude estimates of effect for diclofenac and other NSAIDs versus non-use, the limited and conflicting data from direct comparisons of diclofenac with other NSAIDs, and the variability of the estimates of thrombotic CV risk with diclofenac, it is not possible to determine whether diclofenac is different from many other non-selective NSAIDs using the observational data.

Appendix 2: Key Publications

Rheumatology 2002;41:1052–1061

Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis

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Abstract

Objectives. To evaluate the clinical efficacy and tolerability of etoricoxib in the treatment of osteoarthritis (OA) of the knee and define the clinically active dose range for further clinical trials.

Methods. This two-part, randomized, double-blind, placebo- and active comparator-controlled trial was conducted in 617 adults with knee OA. In Part 1 (6 weeks), patients received placebo, etoricoxib 5, 10, 30, 60 or 90 mg q.d. In Part 2 (8 weeks), patients received etoricoxib 30, 60 or 90 mg q.d. or diclofenac 50 mg t.i.d., predetermined at Part 1 allocation. Efficacy and safety were evaluated. Primary efficacy end-points were the Western Ontario and McMaster's University Osteoarthritis Index (WOMAC) Pain subscale, Patient Global Assessment of Response to Therapy, and Investigator Global Assessment of Disease Status.

Results. At 6 weeks, etoricoxib 5, 10, 30, 60 and 90 mg each demonstrated clinical efficacy superior to placebo. Maximal efficacy was seen with 60 mg. In Part 2, etoricoxib 30, 60 and 90 mg were generally similar to diclofenac. Patients receiving etoricoxib 30, 60 or 90 mg in Parts I and II had sustained effects over 14 weeks. All treatments were well tolerated.

Conclusions. Etoricoxib 60 mg once daily showed maximal efficacy in treating OA in this study. Etoricoxib 5–90 mg once daily was generally well tolerated in OA patients for up to 14 weeks.

KEY WORDS: Etoricoxib, Osteoarthritis, Efficacy, Safety, Tolerability.

Agents that selectively inhibit the enzyme cyclo-oxygenase (COX) 2 isoform (COX-2), including rofecoxib and celecoxib, were developed to provide clinical efficacy comparable to non-selective NSAIDs with a reduced risk of gastrointestinal (GI) toxicity. Previous studies have shown that these agents inhibit COX-2 to a greater degree than COX-1, with varying degrees of selectivity, and that they impart important therapeutic benefits [1–8]. Large-scale clinical GI outcome trials of celecoxib and rofecoxib have shown a significant risk reduction in the development of gastromucosal injuries compared with non-selective NSAIDs [5, 8]. Etoricoxib [5-chloro-2-(6-methylpyridin-3-yl)-3-(4-methylsulfonylphenyl) pyridine] (Merck; also known as MK-0663) is a novel dipyridinyl agent that selectively inhibits COX-2. Etoricoxib is more than 100-fold selective for COX-2 *vs* COX-1 in whole-blood assays [9], and has similar efficacy to traditional NSAIDs in various rodent models of inflammation, pain and fever, and also in a primate model of pyresis [9]. Furthermore, etoricoxib selectively inhibits COX-2 in humans and is more selective *in vitro* than any COX-2-selective NSAID currently available [9, 10]. Etoricoxib has a half-life of approximately 25 h [11], which supports once-daily dosing. This study was undertaken to evaluate the efficacy and safety of etoricoxib in patients with osteoarthritis (OA) of the knee and to refine the dose selection for further clinical investigation.

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Methods

This study was conducted in accordance with guidelines for the ethical treatment of study patients, as outlined in the Declaration of Helsinki. All subjects gave written informed consent before any study procedures were performed. The study protocol and procedures were approved by the appropriate institutional review board (IRB) for each investigative site. IRBs that approved the study include the Western IRB, Saint Luke's Medical Center, Providence IRB, Preventive and Nutrition Medicine Clinic Human Investigation Committee, University of Utah Health Sciences Center IRB, Hospital for Special Surgery Review Board, and the Northwestern University Office for the Protection of Research Subjects.

Study design

This was a two-part dose-finding study conducted over 14 weeks (Fig. 1). The study objectives were to demonstrate the clinical efficacy of etoricoxib in the treatment of OA of the knee, to define the clinically active dose range of etoricoxib in the treatment of OA in order to permit dose selection for further clinical trials, and to evaluate the overall safety and tolerability of etoricoxib with once-daily administration.

Part 1 was a 6-week, placebo-controlled period. At the beginning of Part 1, eligible patients were randomized according to a computer-generated allocation schedule (1:2:2:2:2:2) to placebo, etoricoxib 5, 10, 30, 60 or 90 mg once daily. The allocation schedule was generated by a project statistician. Patients were given blister packs of medication by study site personnel; each blister pack was labelled with an allocation number and assigned in the order in which patients were enrolled. Investigators and patients remained blinded to individual patient allocation throughout the study.

Part 2 was an 8-week active comparator-controlled period. Treatments in Part 2 were etoricoxib 30, 60 and 90 mg once daily and diclofenac 50 mg three times daily, and were preassigned by the same allocation schedule as that used in Part 1. Patients receiving etoricoxib 5 or 10 mg or placebo in Part 1 received etoricoxib 30 mg or diclofenac in Part 2. Half of those patients receiving etoricoxib 30 or 60 mg in Part 1 received etoricoxib 60 or 90 mg respectively in Part 2, and the remaining patients received the same study medication during Part 1 and Part 2.

Study blinding was maintained by using a matching placebo for each study medication; all treatments were double-dummy. In Part 1, patients took two tablets each morning. In Part 2, patients took three tablets each morning (etoricoxib 30 mg or placebo, etoricoxib 60 mg or placebo, and diclofenac or placebo), one tablet (diclofenac or placebo) at midday and one (diclofenac or placebo) in the evening. After completing 2 weeks of treatment, patients were provided open-label acetaminophen, maximum daily dose of 2.6 g, that could be taken for osteoarthritic pain that was not adequately controlled by the study medication. Patients returned to the study centre following 1, 2, 4, 6, 8 and 14 weeks of therapy for efficacy and safety assessments. Patients who did not enter a voluntary extension at the end of Part 2 returned 7–10 days after their last dose of study medication for post-therapy safety assessments.

Entry criteria

Patients were a minimum of 40 yr old and had both clinical and radiographic evidence of OA. Patients with OA of the knee (tibiofemoral joint only) were eligible. Radiographic criteria were joint-space narrowing with the presence of osteophytes. The study joint had to be the primary source of pain or disability. Patients were in American Rheumatism Association (ARA) functional class I, II or III. All patients required NSAIDs for their OA pain for at least 25 of the 30 days prior to screening. Patients who satisfied entry criteria discontinued their prior NSAID therapy. Following a washout period of 3–15 days (depending on the dose and half-life of the prior therapy), these patients' Walking Pain (Question 1 of the WOMAC Pain Subscale) was assessed on a patient-reported 100 mm visual analogue scale (VAS) ranging from 0 (no pain) to 100 (severe pain). Patients were randomized into the study if they had moderate Walking Pain (at least 40 mm on VAS), a minimum increase (worsening) in Walking Pain (15 mm VAS) and an increase (worsening) in the Investigator's Assessment of Disease Status of 1 point [on a 5-point Likert scale ranging from 0 (very well) to 4 (very poor)], compared with values obtained at screening while patients were receiving their prior NSAID therapy.

Patients were excluded if they had significant renal impairment, clinically significant abnormalities on screening physical or laboratory examinations (calculated creatinine clearance $\leqslant 30$ ml/min), Class III/IV angina or uncontrolled congestive heart failure, uncontrolled hypertension, stroke or a transient ischaemic attack within 2 yr, active hepatic disease, a history of recent neoplastic disease, acute meniscal injury to the study joint within 2 yr of study entry, arthroscopy in the study joint within 6 months of study entry, weight in excess of 280 pounds (127 kg) or allergy to acetaminophen or NSAIDs. Patients were excluded if they required corticosteroids, warfarin, low-dose aspirin or ticlopidine, or if they had required systemic corticosteroids or intra-articular steroids for joints other than the study joint within the month prior to study entry or to the study joint in the 2 months prior to study entry. Patients with a prior history of gastroduodenal ulcer or GI bleeding were allowed to participate. Patients were also excluded for any other condition which, in the opinion of the investigator, might confound study results, interfere with participation in the study or pose an undue risk to the patient.

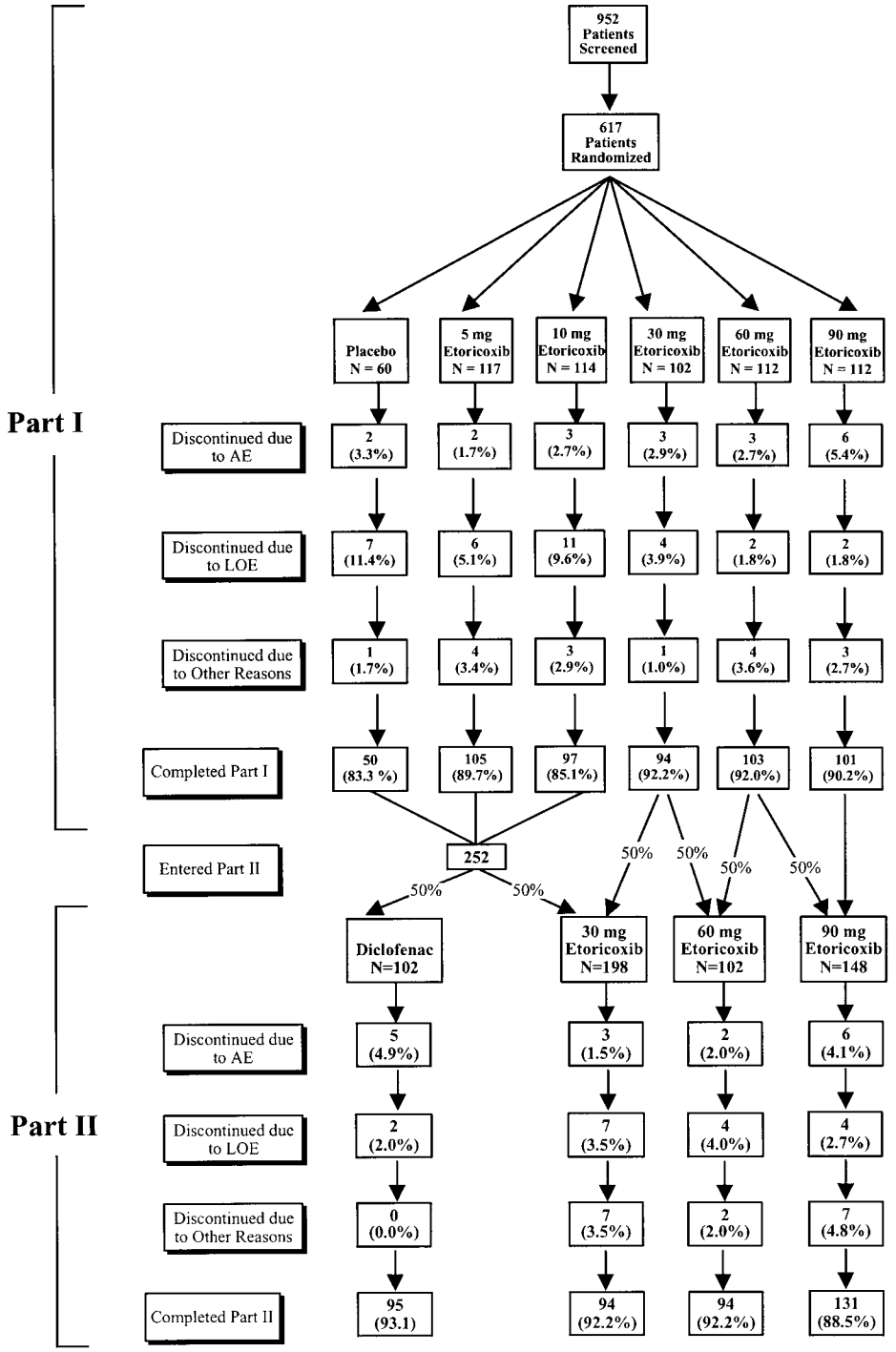

FIG. 1. Dose escalation is illustrated. Etoricoxib 5 and 10 mg and placebo were randomized to 30 mg etoricoxib and 50 mg diclofenac (t.i.d) in a 1:1 fashion. Fifty per cent of patients receiving etoricoxib 30 mg were escalated to 60 mg and half of those receiving 60 mg were escalated to 90 mg.

Efficacy and safety assessments

Efficacy measurements were obtained at a screening visit, at randomization (after flare and prior to initiation of study therapy) and following 1, 2, 4, 6, 8 and 14 weeks of treatment. At each of these visits, the patients completed the WOMAC and patients and investigators completed global assessments of response to therapy and disease status.

There were three primary end-points for this study: the WOMAC Pain Subscale (100 mm VAS); Patient Assessment of Response to Therapy (5-point scale from

0 = excellent to 4 = none); and Investigator Assessment of Disease Status (5-point scale).

Other end-points included Patient Assessment of Disease Status (100 mm VAS ranging from 0 = very well to 100 = very poor), Investigator Assessment of Response to Therapy (5-point scale from 0 = excellent to 4 = none), WOMAC subscales of Stiffness and Physical Function (100 mm VAS ranging from 0 = no stiffness/difficulty to 100 = extreme stiffness/difficulty), Study Joint Tenderness (0–3 scale ranging from 0 = no pain to 3 = patient states there is pain, winces and withdraws), patient discontinuations due to lack of efficacy, the presence or absence of study joint swelling, and the amount (number of 325 mg tablets) of rescue acetaminophen consumed.

Spontaneously reported adverse experiences were recorded throughout the study. Vital signs were monitored and laboratory investigations, including haematology, chemistry and urinalysis, were performed at all visits. For each clinical adverse experience, the investigator recorded the intensity, relationship to test drug (related or not related), outcome and action taken. The investigator also assessed any laboratory adverse event as drug-related or not drug-related. All adverse experiences were identified and evaluated while the patient and investigator remained blinded to study treatment. Any experience meeting a regulatory definition of 'serious' was also identified by the investigator while still blinded to study treatment. All potential episodes of upper GI perforation, ulceration or bleeding or thrombotic cardiovascular events were submitted to blinded, external review committees for adjudication using prespecified case definitions [8].

Statistical analysis

The placebo-controlled period (Part 1) tested the hypothesis that etoricoxib 5, 10, 30, 60 and 90 mg once daily would have dose-related clinical efficacy compared with placebo. The primary efficacy evaluation for Part 1 of the study was based on the average treatment response over weeks 2–6 of the treatment period with a modified intention-to-treat approach. Patients with a baseline value and at least one value while on treatment were included in the analysis. In order to show efficacy, treatments had to show a significant difference from placebo for each of the primary end-points. Secondary and other end-points were used for confirmatory purposes only; thus, no adjustment for multiplicity was needed.

Changes from baseline in the primary and secondary end-points were analysed using an analysis of covariance (ANCOVA) model with treatment as the main factor and baseline as a covariate. Disease status at the flare/randomization visit was used as the baseline covariate for Global Assessment of Response to Therapy. Acetaminophen use for rescue purpose was analysed using an analysis of variance (ANOVA) model with treatment as the main factor.

For means and mean changes, comparisons of the MK-0663 doses with placebo were made using the Tukey–Ciminera–Heyse trend test [12]. Between-dose comparisons were made using a pairwise *t*-test. Ninety-five per cent confidence intervals were calculated based on a pairwise *t*-test using the error variance from the ANCOVA or ANOVA model. The confidence limits were used to assess the clinical importance of the observed difference in treatment response [13].

To examine the treatment response over time, the least squares (LS) mean change from baseline at each study week was plotted against the standard error for each treatment group across the treatment period. The last-value-carried-forward method was used to impute missing values.

There was $\geqslant 96\%$ power to detect treatment differences between the active dose ($n = 100$) and placebo ($n = 50$) groups for the three end-points simultaneously. In active-dose, pairwise comparisons, there was 86% power to detect a difference of 0.5 for Likert scales and 10 mm for VAS with a sample size of 100 patients in each dose group. For reference, clinical doses of rofecoxib resulted in a change of ~ 15 mm on a VAS scale and 0.5 on a Likert scale [14–16].

The efficacy evaluation in Part 2 focused on the dose escalation, the consistency of treatment effect over the 14 weeks and comparison of the treatment effect between diclofenac and etoricoxib. The effect of dose-escalation from Part 1 to Part 2 was assessed by analysing the difference in treatment response between weeks 6 and 8, based primarily on the graphical representation of the LS mean changes for the three primary end-points. Consistency of the treatment effect over 14 weeks was evaluated by examining plots of LS mean changes from baseline for those patients who maintained the same dose during Part 1 and Part 2 of the study. The comparative efficacies of diclofenac and etoricoxib were evaluated by comparing the LS mean changes from baseline among the Part 2 treatments (diclofenac 150 mg and MK-0663 30, 60 and 90 mg) at weeks 8 and 14. For all analyses in Part 2, the LS mean changes were estimated from an ANCOVA model with treatment as the main factor and baseline as the covariate.

For all adverse experiences reported during Part 1, the difference between the placebo group and the etoricoxib doses was evaluated using the Cochran–Armitage trend test (a step-down procedure starting with the comparison of the 90 mg dose with placebo) for the overall rate of adverse experiences considered by the investigator to be related to the study drug and for the rates of specific adverse experiences potentially associated with NSAID use or COX-2 inhibition (oedema, hypertension, congestive heart failure, pulmonary oedema, cardiac failure) and the rates of discontinuation due to hypertension and oedema. No inferential testing of safety data was performed in Part 2 due to the absence of a placebo group.

All statistical tests were two-tailed with $\alpha = 0.050$. All *P*-values were rounded to three decimal places

TABLE 1. Baseline patient characteristics

	Placebo ($n=60$)	Etoricoxib 5 mg ($n=117$)	Etoricoxib 10 mg ($n=114$)	Etoricoxib 30 mg ($n=102$)	Etoricoxib 60 mg ($n=112$)	Etoricoxib 90 mg ($n=112$)
Gender: *n* (%)						
Female	47 (78.3)	90 (76.9)	88 (77.2)	67 (65.7)	74 (66.1)	76 (67.9)
Male	13 (21.7)	27 (23.1)	26 (22.8)	35 (34.3)	38 (33.9)	36 (32.1)
Race						
Hispanic American	0 (0.0)	3 (2.6)	3 (2.6)	7 (6.9)	5 (4.5)	4 (3.6)
Native American	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	2 (1.8)	0 (0.0)
Black	5 (8.3)	12 (10.3)	7 (6.1)	8 (7.8)	6 (5.4)	5 (4.5)
White	55 (91.7)	102 (87.2)	103 (90.4)	87 (85.3)	99 (88.4)	103 (92.0)
Mean age (yr)	62.52	61.74	62.47	61.25	60.03	60.10
Age range (yr)	41–79	40–83	42–87	40–84	40–79	41–84
ARA functional class: *n* (%)						
I	12 (20.0)	17 (14.5)	18 (15.8)	12 (11.8)	15 (13.4)	18 (16.1)
II	40 (66.7)	78 (66.7)	72 (63.2)	72 (70.6)	77 (68.8)	74 (66.1)
III	8 (13.3)	22 (18.8)	24 (21.1)	18 (17.6)	20 (17.9)	20 (17.9)
Mean height (cm)	166.48	165.96	166.19	167.32	167.34	166.62
Mean body weight (kg)	88.38	88.15	89.17	87.90	88.29	89.82
Mean OA duration (yr)	7.18	7.39	8.60	8.86	7.60	7.16
WOMAC Pain Subscale (VAS): mean (S.D.)	70.62 (16.27)	68.73 (17.33)	70.09 (16.64)	67.56 (18.63)	66.86 (16.51)	68.54 (16.74)
Patient Global Assessment of Response to Therapy (no baseline values)						
Investigator Global Assessment of Disease Status (Likert): mean (S.D.)	2.85 (0.68)	2.95 (0.69)	2.91 (0.59)	2.79 (0.67)	2.87 (0.66)	2.93 (0.60)
WOMAC Physical Function Subscale (VAS): mean (S.D.)	69.99 (16.76)	67.59 (18.74)	67.89 (18.11)	65.55 (21.28)	64.12 (19.66)	66.81 (17.67)
WOMAC Stiffness Subscale (VAS): mean (S.D.)	72.04 (21.91)	73.27 (19.05)	72.16 (17.57)	70.39 (20.03)	69.71 (18.84)	70.59 (18.38)
Patient Global Assessment of Disease Status (VAS): mean (S.D.)	69.47 (19.41)	68.38 (20.28)	70.82 (18.39)	66.27 (21.36)	65.34 (20.92)	70.78 (18.83)
Investigator Global Assessment of Response to Therapy (no baseline values)						
Study joint tenderness (0–3): mean (S.D.)	1.68 (0.75)	1.68 (0.81)	1.83 (0.73)	1.78 (0.70)	1.65 (0.75)	1.84 (0.70)
Patients with swelling in study joint: *n* (%)						
Study joint swelling absent	24 (40.0)	46 (39.3)	52 (45.6)	43 (42.6)	49 (44.1)	44 (39.3)
Study joint swelling present	36 (60.0)	71 (60.7)	62 (54.4)	58 (57.4)	62 (55.9)	68 (60.7)

and a rounded $P \leqslant 0.050$ was considered statistically significant.

Results

Between June 1998 and February 1999, 952 patients were screened and 617 (65%) were enrolled at 56 clinical centres in the USA. Three hundred thirty-five patients were excluded from study entry for at least one reason, including but not limited to the following: not ARA functional class I, II or III/failure to meet OA diagnostic criteria; medical history exclusions; and requiring concomitant therapies not permitted in the trial. All treatment groups had similar baseline characteristics and primary efficacy measures at randomization (Table 1).

In total, 550 of 617 (89.1%) patients completed the 6-week placebo-controlled period (Part 1). Significantly more patients discontinued study therapy due to lack of efficacy in the placebo and 10 mg etoricoxib groups compared with 30, 60 and 90 mg etoricoxib: seven (11.7%), six (5.1%), 11 (9.6%), four (3.9%), two (1.8%) and two (1.8%) respectively. Two (3.3%), two (1.7%), three (2.7%), three (2.9%), three (2.7%) and six (5.4%) patients in the placebo and 5, 10, 30, 60 and 90 mg etoricoxib groups respectively discontinued due to an adverse experience.

There were no clinically important differences in the rate of discontinuation due to clinical adverse experience among treatment groups. Of the 550 patients who completed the 6-week placebo-controlled period and entered into Part 2 (198, 102, 148 and 102 in the 30, 60 and 90 mg etoricoxib and diclofenac groups respectively), 510 (91.1%) completed the eight-week active comparator-controlled period.

Three (1.5%), two (2.0%), six (4.1%) and five (4.9%) patients in the 30, 60 and 90 mg etoricoxib and diclofenac groups respectively discontinued due to an adverse experience. There were no significant differences in the rates of discontinuation due to lack of efficacy or adverse experiences between groups in Part 2.

Only six patients were discontinued due to a protocol deviation. Twenty-one patients (3.4%) were excluded from one or more efficacy analyses due to missing baseline data or absence of on-treatment data; absence of data was determined as prespecified in the protocol and prior to unblinding. All available data from each of these 27 patients were included in all safety analyses.

Efficacy

Placebo-controlled period (Part 1). The response over time for the three primary end-points is presented in Fig. 2.

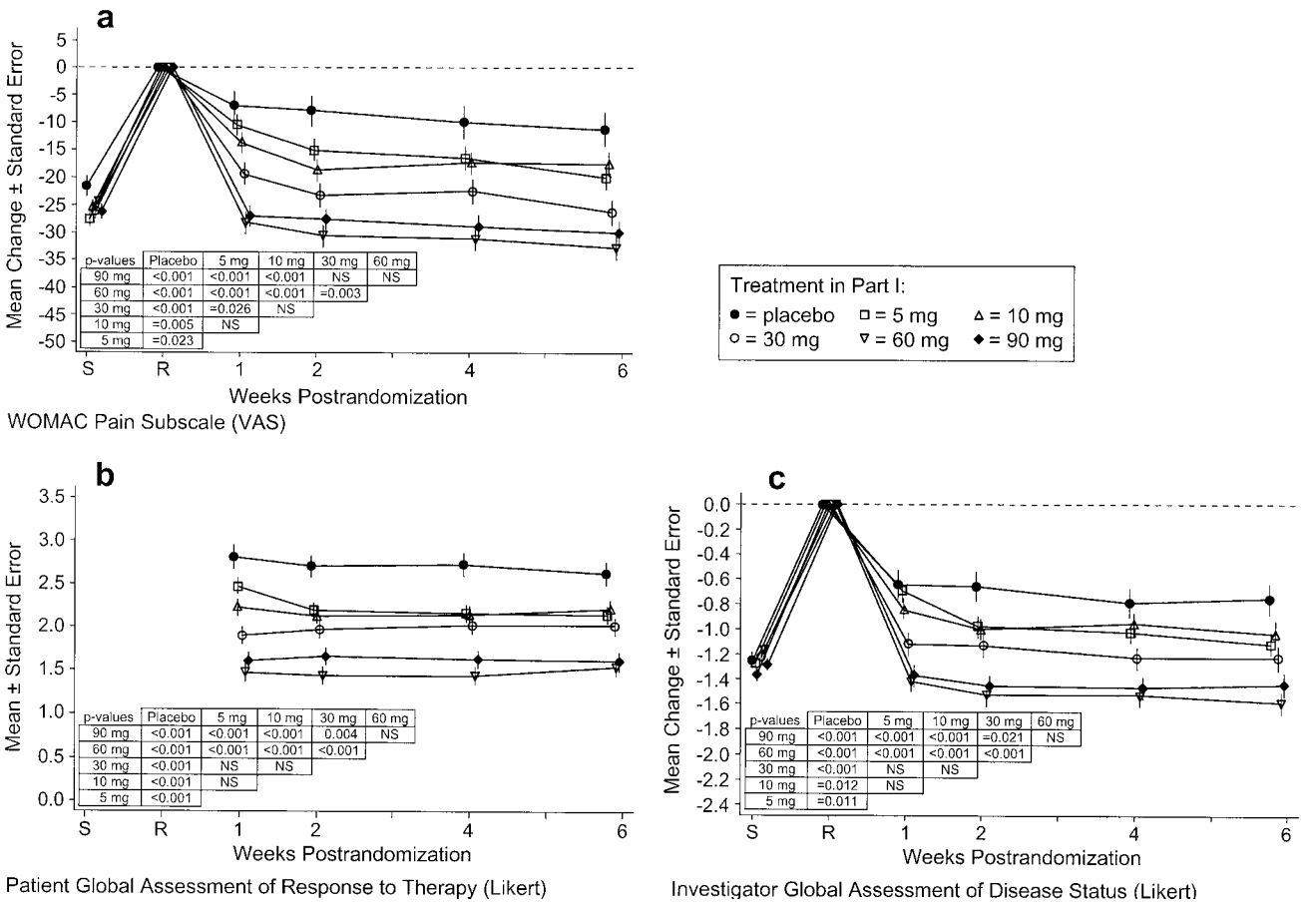

FIG. 2. Primary end-points for the placebo-controlled period (Part 1).

When averaged over weeks 2–6 of the treatment period, all doses of etoricoxib (5–90 mg) demonstrated greater efficacy compared with placebo, as assessed by all three primary end-points: WOMAC Pain Subscale (VAS), Patient Global Assessment of Response to Therapy (Likert) and Investigator Global Assessment of Disease Status (Likert). The etoricoxib doses and placebo exhibited a strong dose-related trend for improvement in all primary end-points. The maximal degree of improvement with etoricoxib was similar for 60 and 90 mg *vs* placebo for all primary end-points. However, the treatment responses for 60 mg were numerically greater. In general, the effect size for the 30 mg dose was approximately half to two-thirds of that with MK-663 60 or 90 mg (Fig. 2, Table 2).

Improvement from baseline, assessed by the primary end-points, with etoricoxib 60 and 90 mg was significantly greater than with 5 and 10 mg ($P \leqslant 0.023$). Etoricoxib 60 mg was significantly different from 30 mg for all primary end-points ($P \leqslant 0.003$); 90 mg was different from 30 mg for two of the three end-points (Fig. 2).

These results were consistent with those for all secondary end-points (Table 2).

Active comparator-controlled period (Part 2). In general, improvements seen at week 2 (Part 1) were sustained without significant changes across the 14-week treatment period for patients receiving etoricoxib 30, 60 or 90 mg during Parts 1 and 2 (Fig. 3).

Patients who received placebo or 5 or 10 mg etoricoxib in Part 1 and then switched to diclofenac or etoricoxib 30 mg in Part 2 showed improvements in OA signs and symptoms, as assessed by the three primary end-points, after 2 weeks of Part 2 therapy. On average, the additional benefit was between −8.7 and −21.0 mm in the WOMAC Pain Subscale (VAS), −0.44 and −1.10 Likert units in Patient Global Assessment of Response to Therapy (Likert scale), and between −0.22 and −0.89 for Investigator Global Assessment of Disease Status (Likert scale) respectively. Patients who switched from 30 to 60 mg or from 60 to 90 mg exhibited minor differences in efficacy, as assessed by the primary end-points: the differences in effects from dose escalation were approximately 0.8 mm on a 100 mm VAS or 0.0–0.1 on a 5-point Likert scale for the three primary end-points (data not shown). A confirmatory analysis including all patients was also consistent with the primary analysis (data not shown).

At the first measurement in Part 2, the efficacies of etoricoxib 30, 60 and 90 mg were generally similar for all end-points. Comparisons with diclofenac showed modest decreases in the diclofenac group (0.0–0.2 Likert units) *vs* individual etoricoxib groups on the Patient Global Assessment of Response

TABLE 2. Efficacy results

	Difference from placebo in LS mean (with 95% confidence intervals)				
	5 mg	10 mg	30 mg	60 mg	90 mg
Primary end-points					
WOMAC Pain Subscale (VAS)	−7.61 (−14.16, −1.05)	−9.58 (−16.23, −2.94)	−13.86 (−20.55, −7.17)	−22.29 (−28.91, −15.68)	−19.16 (−25.76, −12.55)
Patient Global Assessment of Response to Therapy (Likert)	−0.51 (−0.81, −0.21)	−0.57 (−0.88, −0.27)	−0.66 (−0.97, −0.35)	−1.21 (−1.51, −0.90)	−1.04 (−1.34, −0.73)
Investigator Global Assessment of Disease Status (Likert)	−0.33 (−0.58, −0.08)	−0.32 (−0.58, −0.07)	−0.45 (−0.70, −0.20)	−0.83 (−1.09, −0.58)	−0.70 (−0.95, −0.45)
Secondary end-points					
WOMAC Physical Function Subscale (VAS)	−6.17 (−12.45, 0.10)‡	−7.87 (−14.24, −1.49)	−11.72 (−18.13, −5.30)	−19.01 (−25.36, −12.66)	−18.22 (−24.55, −11.88)
WOMAC Stiffness Subscale (VAS)	−8.67 (−15.43, −1.91)	−9.93 (−16.80, −3.06)	−14.28 (−21.17, −7.39)	−22.87 (−29.69, −16.05)	−21.1 (−27.91, −14.29)
Patient Global Assessment of Disease Status (VAS)	−11.15 (−18.01, −4.30)	−11.42 (−18.35, −4.48)	−16.27 (−23.26, −9.28)	−25.33 (−32.26, −18.40)	−24.91 (−31.80, −18.01)
Investigator Global Assessment of Response to Therapy (Likert)	−0.36 (−0.65, −0.08)	−0.42 (−0.71, −0.13)	−0.50 (−0.80, −0.21)	−0.94 (−1.23, −0.65)	−0.85 (−1.14, −0.56)
Discontinuation due to lack of efficacy	−7% (−16%, 3%)	−2% (−12%, 8%)	−8% (−17%, 1%)	−10% (−18%, −1%)	−10% (−18%, −1%)
Study joint tenderness (0–3)	−0.22 (−0.40, −0.03)	−0.21 (−0.40, −0.02)	−0.26 (−0.44, −0.07)	−0.38 (−0.57, −0.20)	−0.39 (−0.58, −0.20)
Study joint swelling present	−7% (−22%, 9%)	−4% (−20%,11%)	−13% (−29%, 2%)	−13% (−28%, 2%)	−15% (−30%, 1%)
Acetaminophen use (tablets/day)	−0.36 (−0.61, −0.11)	−0.37 (−0.62, −0.12)	−0.46 (−0.71, −0.21)	−0.65 (−0.90, −0.41)	−0.59 (−0.84, −0.34)

‡Confidence intervals that include zero generally indicate that the etoricoxib dose was not significantly different from placebo.

FIG. 3. Patients maintained on a single dose of etoricoxib during 14 weeks of treatment.

to Therapy (Likert scale) and Investigator Global Assessment of Disease Status (Likert scale), but general similarity on the WOMAC Pain Subscale (VAS). At 14 weeks, all treatments appeared similar, as measured by the WOMAC Pain Subscale, Patient Global Assessment of Response to Therapy and Investigator Global Assessment of Disease Status (data not shown).

Safety

Most adverse experiences were transient and self-limited; few resulted in discontinuation of study therapy. No deaths occurred during Part 1 or Part 2 of the study.

Placebo-controlled period (Part 1). The percentages of patients with adverse experiences considered drug-related by investigators were generally similar across all treatment groups; those occurring in more than 3% of patients are presented in Table 3.

Eighteen (2.9%) of 617 patients discontinued due to a clinical adverse experience which began during Part 1 (Table 3). Four patients discontinued for digestive adverse experiences, four for nervous system adverse experiences (including dizziness), five for musculoskeletal adverse experiences and one each for various unrelated experiences, including urinary tract infection, anxiety disorder, rash, atrial fibrillation, oedema and oliguria, and astrocytoma. These events were not clustered in any one particular treatment group. Statistical analyses revealed no significant differences between groups.

Individual NSAID-type GI adverse experiences of abdominal pain, acid reflux, dyspepsia, epigastric discomfort, nausea or vomiting considered to be related to the study drug occurred in 0–5 patients in each treatment group. Those reported in 3% or more of patients are included in Table 3. Of note, there was a small numerical increase in the percentage of patients experiencing diarrhoea in the etoricoxib 10, 30, 60 and

TABLE 3. Clinical adverse experience summary: no. (%) of patients

Part 1: placebo-controlled period

	Placebo ($n=60$)	Etoricoxib 5 mg ($n=117$)	Etoricoxib 10 mg ($n=114$)	Etoricoxib 30 mg ($n=102$)	Etoricoxib 60 mg ($n=112$)	Etoricoxib 90 mg ($n=112$)
With adverse experiences considered to be drug-related by investigators	13 (21.7)	17 (14.5)	16 (14.0)	12 (11.8)	17 (15.2)	18 (16.1)
With any serious AE[†]	0 (0.0)	2 (1.7)	2 (1.8)	1 (1.0)	1 (0.9)	4 (3.6)
Died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to any AE	2 (3.3)	2 (1.7)	2 (1.8)	3 (2.9)	3 (2.7)	6 (5.4)
Most common drug-related adverse experiences						
Diarrhoea	1 (1.7)	1 (0.9)	4 (3.5)	4 (3.9)	5 (4.5)	3 (2.7)
Heartburn	2 (3.3)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)
Nausea	1 (1.7)	1 (0.9)	1 (0.9)	4 (3.9)	1 (0.9)	4 (3.6)
Headache	2 (3.3)	3 (2.6)	3 (2.6)	2 (2.0)	0 (0.0)	2 (1.8)

Part 2: active comparator-controlled period

	Etoricoxib 30 mg	Etoricoxib 60 mg	Etoricoxib 90 mg	Diclofenac 150 mg
With adverse experiences considered to be drug-related by investigators	17 (8.6)	10 (9.8)	15 (10.1)	14 (13.7)
With any serious AE[†]	3 (1.5)	0 (0.0)	3 (2.0)	3 (2.9)
Died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to any AE	2 (1.0)	2 (2.0)	4 (2.7)	3 (2.9)

[†]Serious adverse experiences: (Part I) basal cell carcinoma, renal colic, joint prosthesis complication, deep venous thrombosis, atrial fibrillation with chest pain and angina pectoris, dyspnoea, atrial fibrillation, astrocytoma, lower GI haemorrhage, ventricular tachycardia; (Part 2) ovarian malignant neoplasm, arthralgia, malignant melanoma, cellulitis, cholecystitis, abdominal hernia, anorectal haemorrhage, obstructive bronchitis.

90 mg groups compared with etoricoxib 5 mg and placebo. No significant differences among groups were noted, nor were there significant dose-related trends in the incidence of these adverse experiences.

Renovascular adverse experiences were examined specifically. Drug-related hypertension and oedema occurred in fewer than 3% of patients in each group. Among those experiences considered to be related to study drug by investigators, hypertension was reported by one patient each in the placebo (1.7%) and 30 mg etoricoxib (1.0%) groups, and increased blood pressure in one patient each in the placebo (1.7%) and 10 mg etoricoxib groups (0.9%). Reports of drug-related oedema or lower extremity oedema occurred in one patient each in the placebo (1.7%) and 5 mg etoricoxib (0.9%) groups, two patients in the 10 mg group (1.8%), three (2.7%) patients in the 60 mg and three (2.7%) patients in the 90 mg group. No statistically significant or clinically relevant dose-related trends were noted for oedema or hypertension adverse experiences.

Ten patients had one or more serious adverse experiences; none were considered by investigators to be related to study drug. Four patients, in the 30, 60 or 90 mg etoricoxib groups, had serious cardiovascular adverse experiences (deep venous thrombosis, chest pain associated with angina pectoris and atrial fibrillation, atrial fibrillation and ventricular tachycardia); none were confirmed as cardiovascular thrombotic events by a blinded external review committee. The remaining serious adverse experiences were isolated events (dyspnoea, astrocytoma, renal colic, joint prosthesis complication) reported in one or two patients (basal cell carcinoma; 5 and 10 mg groups). No episodes of upper GI perforation, ulceration or bleeding were reported in Part 1, although one patient receiving 90 mg etoricoxib had a serious lower GI bleed. No episodes of congestive heart failure or acute renal failure were reported.

Eight patients (1.3%) had drug-related laboratory adverse experiences, including alanine aminotransferase (ALT) increase, aspartate aminotransferase (AST) increase, increased serum creatinine, increased alkaline phosphatase, decreased haemoglobin, decreased leucocytes or hyperkalaemia. One (0.2%) patient receiving 10 mg etoricoxib discontinued due to a laboratory adverse experiences of increased ALT/AST. No dose-related trends or clinically important patterns were observed in specific laboratory adverse experiences.

Active comparator-controlled period (Part 2). The overall percentage of patients with drug-related adverse experiences was generally similar across treatment groups for Parts 1 and 2 (Table 3). Only laboratory adverse experiences occurred at a rate of 3% or more in any individual treatment group during Part 2. No new dose-related trends or clinically important patterns were observed in specific clinical adverse experiences during Part 2.

In Part 2, 14 patients discontinued due to a clinical adverse experience. Of these, six were in the digestive system, two were episodes of dizziness (one associated with irregular heartbeat), two were skin adverse experiences and four were other adverse experiences (Menière's disease, taste loss, pneumonia and leg pain). All clinical adverse experiences resulting in discontinuation from the diclofenac group were GI-related; no other trends were seen in adverse experiences resulting in discontinuation.

Individual specific NSAID-type GI experiences (abdominal pain, dyspepsia, heartburn, nausea, diarrhoea or vomiting) considered to be related to the study drug were reported in fewer than 3% of patients in each treatment group. No one group had a specific increase compared with other groups and no new trends were noted for these events.

An examination of renovascular adverse experiences showed that 1% or fewer of patients in each group had an adverse experience of lower extremity oedema. One patient in each of the etoricoxib groups and three patients in the diclofenac group had an adverse experience of hypertension.

Serious adverse experiences were reported in three patients in each group except the 60 mg etoricoxib group; none were considered related to study drug. With the exception of malignancies ($n=2$; 30 mg) and cellulitis ($n=2$; 90 mg and diclofenac), all were isolated occurrences (arthralgia, abdominal hernia, cholecystitis, obstructive bronchitis). One patient in the diclofenac group had a serious lower GI bleed. No cardiovascular thrombotic event or episode of upper GI perforation, ulceration or bleeding was reported in Part 2.

Overall, nine patients (1.6%) had drug-related laboratory adverse experiences during Part 2: two patients on 90 mg etoricoxib and seven on diclofenac. The most common laboratory adverse experiences among the diclofenac-treated patients were increased ALT/AST (Table 4). Two (0.4%) patients receiving diclofenac discontinued due to laboratory adverse experiences, one for increased ALT/AST and one for increased serum creatinine and decreased haemoglobin.

Discussion

In this two-part, 14-week, dose-ranging study, etoricoxib once daily caused clinically significant improvements in the signs and symptoms of OA of the knee. Compared with placebo, there were statistically significant improvements in the three primary end-points for all etoricoxib doses, the effect sizes exhibiting a strong dose-related trend for the 5–60 mg doses. The 90 mg dose did not exhibit additional therapeutic benefits compared with 60 mg. Improvements seen in the first 6 week treatment period (Part 1) for etoricoxib 30, 60 and 90 mg were sustained for an additional 8 weeks (Part 2). The degree of improvement with etoricoxib 60 and 90 mg (*vs* placebo) exceeded this trial's predefined criteria for clinically important effects for all primary end-points. As the effectiveness of etoricoxib appeared to be maximal at 60 mg, this dose was carried forward as the recommended dose in Phase III trials. Further study will be required to define the efficacy profile of etoricoxib 60 mg in patients with OA.

Etoricoxib was generally well tolerated in this study. Most adverse experiences were transient and self-limited; few resulted in discontinuation of study therapy. No statistically significant, dose-related trends were identified in the rates of hypertension or oedema adverse experiences, and none of these experiences occurred at a rate of more than 3% in any treatment group. However, the sample size in this trial is too small to make definitive conclusions about the safety and tolerability profile of etoricoxib. This study was primarily designed as a dose-ranging study and therefore added study will be required to further define etoricoxib's safety profile. This holds true for generalizations to older patient populations with comorbid conditions, such as congestive heart failure and uncontrolled hypertension, who were excluded from this study.

Current American College of Rheumatology guidelines for the treatment of OA specifically mention the role of COX-2 inhibitors in combination with exercise, education and social support [17]. However, the variable response to NSAIDs in individual patients is well documented, and no specific factors have been shown to predict treatment failure with individual NSAIDs among patients with OA [18]. Physicians often manage treatment failure with NSAIDs by switching patients from one NSAID to another until they identify a compound which provides relief [19]. Currently, only two COX-2 selective NSAIDs are available, which limits choices for patients and physicians interested in using COX-2 inhibitors.

It should be noted that previous studies with NSAIDs have demonstrated a plateau of clinical analgesic efficacy, although additional anti-inflammatory effects might be seen with higher doses, which provides a rationale for the use of higher doses in chronic conditions with inflammatory components, such as rheumatoid arthritis [20]. This study defined a maximally effective clinical dose of etoricoxib in patients with OA, 60 mg. Identification of a clinically maximal dose is important information for clinicians, and may help prevent the use of higher doses than necessary to provide relief of painful symptoms without exposing patients to higher risks of adverse experiences.

In this study, etoricoxib doses of 5, 10, 30, 60 and 90 mg were generally well tolerated and the 30, 60 and 90 mg doses were generally effective in OA patients. All doses studied were generally safe and well tolerated for the 14 week treatment period. However, with regard to discontinuations due to clinical adverse experiences, there was a numerical increase in the 90 mg group compared with the other doses studied, in Parts 1 and 2. While no significant differences were noted between groups and the number of discontinuations on 90 mg etoricoxib and diclofenac was similar in Part 2, taking

into account both safety and efficacy, the 60 mg dose provided the optimal benefit/risk relationship. With a greater degree of *in vitro* selectivity, a favourable pharmacokinetic profile and proven efficacy in the OA in this study, etoricoxib may prove to be an important addition to the therapeutic armamentarium. Further clinical studies with etoricoxib will explore more fully the therapeutic potential and tolerability of this selective COX-2 inhibitor in a broad spectrum of inflammatory conditions, cancer and neurological diseases.

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E. Ehrich contributed to study design, M. Huntington conducted additional study monitoring, J. Ng contributed to the data analysis plan for this study, L. Griffin and T. Garay provided data tables and A. Compton contributed to a preliminary in-house report of study data. A. Mehta provided additional document and data support.

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ORIGINAL ARTICLE

Evaluation of the Comparative Efficacy of Etoricoxib and Ibuprofen for Treatment of Patients With Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial

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OBJECTIVE: **To directly compare the efficacy and safety of etoricoxib, 30 mg once daily, ibuprofen, 800 mg 3 times daily, and placebo for treatment of osteoarthritis (OA) of the hip and knee.**

PATIENTS AND METHODS: **A randomized, double-blind, placebo-controlled trial of patients with OA of the knee or hip was performed between February 2003 and November 2003 in 61 medical centers in the United States. Qualified patients aged 40 to 89 years were randomized to receive placebo, etoricoxib, 30 mg once daily, or ibuprofen, 800 mg 3 times daily, for 12 weeks. Primary efficacy end points included the Western Ontario and McMaster Universities Osteoarthritis Index pain and physical function subscales and Patient Global Assessment of Disease Status. Response to treatment was assessed by the time-weighted average change from baseline over 12 weeks.**

RESULTS: **In 528 patients, baseline values for the 3 primary end points ranged from 67.78 to 72.60 mm (0-100 mm visual analog scale). Near-maximal efficacy was achieved by week 2 with both active treatments and sustained over the course of the trial. During the 12-week period, least squares mean changes in the primary end points (Western Ontario and McMaster Universities Osteoarthritis Index and Patient Global Assessment of Disease Status subscales) ranged from –16.53 to –13.55 mm, –27.89 to –23.68 mm, and –26.53 to –22.97 mm in the placebo, etoricoxib, and ibuprofen groups, respectively. Both etoricoxib and ibuprofen were more effective ($P<.001$) than placebo for all primary end points. Etoricoxib and ibuprofen treatment responses for the primary end points were determined to be comparable with use of prespecified comparability criteria. Results for all other efficacy end points were consistent with responses observed for the primary end points. Etoricoxib and ibuprofen generally were well tolerated.**

CONCLUSION: **For patients with OA, treatment with etoricoxib, 30 mg/d, is well tolerated and provides sustained clinical effectiveness that is superior to placebo and comparable to ibuprofen, 2400 mg/d.**

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AE = adverse experience; CI = confidence interval; COX = cyclooxygenase; IGADS = Investigator Global Assessment of Disease Status; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PGADS = Patient Global Assessment of Disease Status; VA = visual analog; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Osteoarthritis (OA) is a highly prevalent disease that affects more than 25 million patients in the United States.[1] Joints of the knees, hip, spine, hands, and feet are most often affected in OA. Osteoarthritis is a chronic focal degenerative disease characterized by progressive loss of articular cartilage, thickening of subchondral bone, and development of bone spurs, leading to chronic pain, joint stiffness and tenderness, and in the most advanced stages of OA, loss of joint function and/or disability. The functional disability that results from the pain of OA is one of the most common disabilities in the elderly population, and OA accounts for approximately half of all chronic conditions in persons older than 65 years.[2] Osteoarthritis is the most common form of arthritis in middle-aged adults and can lead to a significant reduction in the overall quality of life in patients of any age.[3]

Risk factors for OA include obesity and previous sports-related or work-related joint injuries such as anterior cruciate ligament damage.[4,5] Obesity has reached epidemic proportions in the United States and is a significant risk factor for the development of OA of the hip and knee, major weight-bearing joints.[6,7] With the growing epidemic of obesity and the aging of the population, the prevalence of symptomatic OA along with its substantial social and economic burden will no doubt continue to increase. In fact, OA is projected to be the fourth leading cause of disability worldwide by 2020.[8]

Acetaminophen and nonpharmacological approaches such as exercise and measures to improve joint biomechanics can be effective first-line treatment options for patients with OA.[9-11] The cyclooxygenase (COX) 2 selective class of nonsteroidal anti-inflammatory drugs (NSAIDs) can provide more potent pain relief in patients who do not

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experience adequate therapeutic benefits from the first-line therapies.[9,11] The NSAIDs act via inhibition of COX-2, a key enzyme involved in the pain and inflammation associated with OA.[12,13] Although nonselective NSAIDs can be effective for managing the pain and other symptoms of OA, the elevated risk of gastrointestinal toxicity associated with these agents, due to their additional inhibition of the COX isoenzyme COX-1, often limits their use.[14]

Etoricoxib is a potent member of the COX-2 selective class of NSAIDs and exhibits a reduced risk of gastrointestinal toxicity compared with nonselective NSAIDs.[15,16] Its clinically important anti-inflammatory and analgesic efficacy in the treatment of acute and chronic pain and its favorable safety and tolerability profile as a once-daily dosing regimen have been shown in numerous disease and treatment settings and have been reviewed elsewhere.[17] An initial 14-week dose-ranging study determined that etoricoxib, 30 mg once daily, provided clinically important effects in patients with OA.[9]

The aim of this first of 2 replicate, randomized controlled clinical trials was to examine the safety and efficacy profiles of etoricoxib, 30 mg once daily, compared with a commonly prescribed nonselective NSAID, ibuprofen, 800 mg 3 times daily, and placebo in patients with OA of the knee and hip.

PATIENTS AND METHODS

The protocol for this study was approved by the institutional review boards of each study center. All patients provided written informed consent before participating in the study, which was performed between February 2003 and November 2003 in 61 medical centers throughout the United States.

We enrolled otherwise healthy male and female patients aged 40 years or older who had a clinical and radiographic diagnosis of OA of the knee (tibiofemoral joint) or hip for at least the previous 6 months as well as patients with newly diagnosed clinical symptoms of OA in the study joint that met American Rheumatism Association functional class I, II, or III criteria for at least the preceding 6 months. The primary source of pain for each patient was in the lower extremity. In patients in whom both knees and/or hips were affected, the most painful joint was selected for study evaluation. Women of childbearing potential were determined to be in a nongravid state with use of serum β-human chorionic gonadotropin measurements and instructed to use contraceptive measures during the study. Patients who were regular NSAID users (at least 25 of the last 30 days preceding enrollment) were required to have experienced a positive therapeutic benefit for their OA of the hip or knee after NSAID therapy. Prior NSAID users were required to have a prestudy score of less than 80 mm (0- to 100-mm visual analog scale [VAS]) for patient assessment of walking on a flat surface. After cessation of NSAID therapy during an NSAID-specific "washout" period, these patients were required to experience a flare of OA pain. A flare was classified as sufficient if the minimum patient-reported pain score was 40 mm while the patient walked on a flat surface, was at least 15 mm greater than at the prestudy visit, and had worsened at least 1 unit (0- to 5-point Likert scale) in Investigator Global Assessment of Disease Status (IGADS).

Patients who were daily users of acetaminophen (1.2-4 g) for at least 25 of the last 30 days preceding enrollment and had used no NSAIDs for treatment of OA were required to have minimum scores of 40 mm for patient-reported pain while walking on a flat surface and Patient Global Assessment of Disease Status (PGADS) and IGADS of fair, poor, or very poor. Because acetaminophen acts only as an analgesic without the associated anti-inflammatory activity of etoricoxib and ibuprofen, the decision was made to limit the number of acetaminophen users enrolled at each study site to 20%.

Exclusion Criteria

Patients were excluded from the study if they had any past or current medical conditions such as joint injuries or rheumatologic, autoimmune, or musculoskeletal diseases that could confound or interfere with efficacy evaluations.

Study Design

The 12-week, 61-center, placebo-controlled, and active-comparator–controlled study was performed under double-blind (with in-house blinding) conditions to evaluate the efficacy, safety, and tolerability of etoricoxib, 30 mg/d, for the treatment of OA of the knee and hip compared with ibuprofen, 2400 mg/d, and placebo treatment. Before randomization, prior NSAID users were required to experience a flare of OA symptoms after the washout period that met the criteria described previously. The NSAID users and acetaminophen users were required to stop taking acetaminophen rescue medication at least 12 hours (or 24 hours with extended-release formulations) before all visits except for visit 1 for the NSAID users. Qualified patients (aged 40-89 years) were randomized to receive placebo, etoricoxib, 30 mg once daily, or ibuprofen, 800 mg 3 times daily, for 12 weeks. Study medication was supplied in 2 coded study bottles labeled bottle A (containing etoricoxib, 30-mg tablets, or matching placebo) and bottle B (containing ibuprofen, 800-mg tablets, or matching placebo). Patients were instructed to take 1 tablet in the morning from bottles A and B and 1 tablet in the afternoon and evening

from bottle B. Only acetaminophen was permitted for rescue pain medication if needed. Efficacy was evaluated at 2, 4, 8, and 12 weeks after initiation of therapy, and adverse experiences (AEs) were documented throughout the study.

Included and Excluded Medications

Patients taking medications for chronic conditions were required to continue taking stable doses 2 weeks before and throughout the 12-week study. Use of intra-articular corticosteroids or hyaluronic acid injections to the study knee within the past 3 months, immunosuppressants within the past 3 months, corticosteroids by any systemic route, and hyaluronic injections or intra-articular corticosteroids for any joint in the past month were not permitted. Patients taking stable doses of glucosamine or chondroitin sulfate for at least 6 months before the study were allowed to enroll.

Low-dose aspirin (≤100 mg/d) for cardioprophylaxis was allowed during the study. However, patients were excluded if they were required to take any other antiplatelet therapy. Gastroprotective agents such as proton pump inhibitors, H_2 blockers, sucralfate, and misoprostol were allowed as necessary.

Efficacy Assessments

Primary efficacy end points included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) visual analog (VA) 3.0 pain subscale, WOMAC VA 3.0 physical function subscale, and the PGADS (0- to 100-mm VAS).[18-20] Secondary end points included Patient Global Assessment of Response to Therapy, IGADS, Investigator Global Assessment of Response to Therapy (0- to 4-point Likert scale), WOMAC stiffness subscale, WOMAC overall score and subscale averages, WOMAC pain while walking on a flat surface question (0- to 100-mm VAS), study joint tenderness (0- to 3-point Likert scale), proportion of patients discontinuing the study because of lack of efficacy, and rescue acetaminophen use. Exploratory end points included WOMAC nighttime pain and WOMAC VA 3.0 stiffness on awakening (0- to 100-mm VAS).

Safety and Tolerability Assessments

Clinical safety and tolerability were assessed on the basis of physical examination results, clinical laboratory test results, and the collection of AEs throughout the study. A serious AE was predefined as any AE that resulted in death, was deemed by the investigator to be life-threatening, or resulted in a persistent or significant disability or incapacity. Drug-related AEs were those determined by the investigator to be possibly, probably, or definitely drug-related. Specific prespecified safety-related end points were collected to more closely examine gastrointestinal tract safety and possible clinical sequelae of modulating renal prostaglandin biosynthesis. These prespecified end points included the proportion of patients with edema-related AEs; hypertension-related AEs; AEs of congestive heart failure, pulmonary edema, or cardiac failure; discontinuation due to digestive system or abdominal pain AEs; discontinuation due to edema-related AEs; and discontinuation due to hypertension-related AEs. A blinded, external, adjudication committee was organized before the initiation of the study to evaluate any potential cardiovascular thrombotic events that occurred during the trial.

Statistical Analyses

The primary objectives of this study were to show greater clinical efficacy of etoricoxib, 30 mg daily, compared with placebo, to compare the clinical efficacy of etoricoxib, 30 mg daily, with ibuprofen, 800 mg 3 times daily, and to evaluate the safety and tolerability of etoricoxib administration for a 12-week period. Results from 3 previous etoricoxib and 2 previous rofecoxib randomized, placebo-controlled studies in patients with OA[21-25] indicated that the expected differences between response to etoricoxib relative to placebo were approximately 11 mm for the WOMAC pain subscale, 10 mm for the WOMAC physical function subscale, and 13 mm for the PGADS. Using variability estimates from 2 etoricoxib phase 3 studies,[22,23] it was predicted that planned sample sizes of 100 placebo patients and 200 patients taking etoricoxib, 30 mg daily, provided greater than 97% power to detect (α=.050, 2-sided) these expected mean differences for the 3 primary end points. For the secondary objective, the study was sized to provide greater than 95% power to yield all three 95% confidence intervals (CIs) with ±10 mm if the true differences in efficacy between etoricoxib, 30 mg/d, and ibuprofen, 2400 mg/d, are zero. The primary efficacy analyses conformed to the modified intention-to-treat principle and included all randomized patients who received study medication and had at least 1 measurement after initiation of treatment.

The time-weighted average change from baseline for each efficacy end point was analyzed by using an analysis of covariance model with treatment and the primary OA study joint as the main effects and the baseline value as the covariate. For end points with no relevant baseline measurement, the on-treatment response was analyzed with use of analysis of variance. No adjustments for multiplicity were made on the basis of the following. The between-treatment comparisons of interest were divided into 3 families of tests by using the Dunnett-Tamhane approach[26]: (1) testing of the efficacy of etoricoxib relative to placebo, (2)

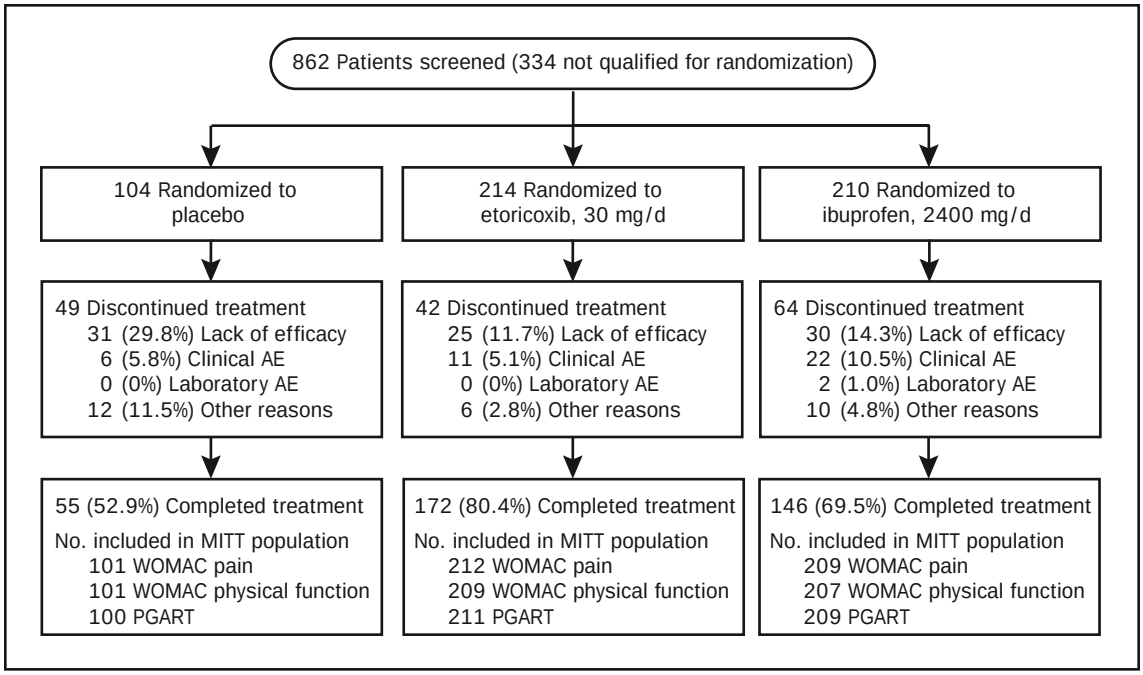

FIGURE 1. Patient accounting. AE = adverse experience; MITT = modified intention-to-treat; PGART = Patient Global Assessment of Response to Therapy; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

comparing the relative efficacy of etoricoxib, 30 mg/d, to ibuprofen, 2400 mg/d, and (3) evaluating the study sensitivity, ie, comparing ibuprofen to placebo. The differences in treatments in each family area addressed related yet different questions. Therefore, no adjustments for multiple between-treatment comparisons were made among these 3 families of tests. Also, there is only 1 test within each family, making it unnecessary to adjust for multiple between-treatment comparisons. Because the primary hypothesis must be satisfied for each of the 3 primary end points, the overall α level was less than .050, and no α adjustment was necessary. For comparisons to placebo, all 3 primary end points were required to reach statistical significance at α=.050, 2-tailed. Statistical tests and estimators of the secondary end points and other secondary statistical analyses were supportive and helped in interpreting the primary analyses, establishing efficacy profiles, and checking the consistency of findings for the primary end points. Therefore, no multiple testing adjustments were made. All tests for difference in means were made at the customary 2-sided α=.050 level.

To show clinical comparability between etoricoxib, 30 mg once daily, and ibuprofen, 800 mg 3 times daily, the 95% CIs for the mean differences between the 2 groups in the time-weighted average response had to fall entirely within ±10 mm on a 100-mm VAS for all 3 primary end points. This 10-mm range for comparability is similar to the difference expected between etoricoxib and placebo on the basis of results of previous clinical studies.[18,22-25] For prespecified clinical AEs and laboratory parameters, each of the 2 active treatments was compared with the placebo using the Fisher exact test. Differences between treatment groups in the proportions of patients with AEs or those exceeding predefined limits of change in laboratory safety parameters were evaluated using 95% CIs calculated by the Wilson score method.

RESULTS

PATIENTS

A total of 862 patients were screened, of whom 528 met the eligibility criteria and were randomized (Figure 1). A higher proportion of patients in the etoricoxib treatment group completed the trial compared with those in the placebo and ibuprofen groups. The most common reason for discontinuing the study was lack of efficacy, with the highest proportion of patients discontinuing for this reason in the placebo group (29.8%; P<.001 vs both active treatments) compared with 11.7% and 14.3% in the etoricoxib and ibuprofen groups, respectively. Baseline patient characteristics were similar among the treatment groups (Table 1). Most enrolled patients were female with a mean age of about 62 years. The mean duration of OA was 7.8 years, and most patients' symptoms met American Rheumatism

TABLE 1. **Baseline Patient Characteristics***

Characteristic	Placebo (n=104)	Etoricoxib, 30 mg/d (n=214)	Ibuprofen, 2400 mg/d (n=210)
Sex, No. (%)			
Female	75 (72.1)	150 (70.1)	147 (70.0)
Male	29 (27.9)	64 (29.9)	63 (30.0)
Race, No. (%)			
Asian	1 (1.0)	1 (0.5)	1 (0.5)
Black	3 (2.9)	11 (5.1)	15 (7.1)
White	93 (89.4)	190 (88.8)	185 (88.1)
Other	7 (6.7)	12 (5.6)	9 (4.3)
Age (y)			
Mean (SD)	59.5 (8.4)	63.1 (10.6)	61.3 (9.6)
Median	59.0	63.0	60.0
Range	42-82	40-84	42-89
Primary OA joint, No. (%)			
Knee	80 (76.9)	168 (78.5)	170 (81.0)
Hip	24 (23.1)	46 (21.5)	40 (19.0)
Mean duration of OA (SD) (y)	6.9 (6.8)	7.9 (8.6)	8.2 (7.7)
ARA functional class, No. (%)			
I	22 (21.2)	39 (18.2)	39 (18.6)
II	58 (55.8)	124 (57.9)	134 (63.8)
III	24 (23.1)	51 (23.8)	37 (17.6)
Mean height (cm)	167.0	165.9	167.7
Mean weight (kg)	86.0	88.9	92.2
Low-dose aspirin use ≤100 mg/d, No. (%)	20 (19.2)	53 (24.8)	44 (21.0)

*ARA = American Rheumatism Association; OA = osteoarthritis.

Association functional class II criteria. Most patients had OA of the knee, and approximately 91% were prior NSAID users. Typical of patients in this age group, one of the most common secondary diagnoses at baseline was hypertension. Hypertension at baseline was diagnosed in 216 enrolled patients (40.9%).

Efficacy

Mean values for all efficacy end points were qualitatively similar among the placebo, etoricoxib, and ibuprofen treatment groups (Table 2; Figure 2) at baseline. Baseline values for the 3 primary end points ranged from 67.78 to 72.60 (VAS). Near-maximal efficacy was achieved by week 2 with both active treatments (Figure 2, upper left, upper right, and lower left) followed by slight continued improvement (4-7 mm) for all primary end points in all treatment groups through week 12. Over the 12-week period, the least squares mean changes in the primary end point WOMAC subscales and PGADS ranged from –16.53 mm (95% CI, –20.99 to –12.06 mm) to –13.55 mm (95% CI, –17.69 to –9.40 mm), –27.89 mm (95% CI, –31.33 to –24.65 mm) to –23.68 mm (95% CI, –26.72 to –20.65 mm), and –26.53 mm (95% CI, –29.83 to –23.22 mm) to –22.97 mm (95% CI, –26.06 to –19.88 mm) in the placebo, etoricoxib, and ibuprofen groups, respectively. Both active treatments were significantly more effective ($P<.001$) than placebo for all primary end points. Etoricoxib was shown to have comparable efficacy to ibuprofen with use of prespecified comparability criteria. Etoricoxib, 30 mg/d, and ibuprofen, 2400 mg/d, displayed comparable efficacy with least squares mean differences for WOMAC pain and physical function subscales and PGADS ranging from –1.65 mm (95% CI, –5.63 to 2.33 mm) to –0.71 mm (95% CI, –4.63 to 3.20 mm) (Figure 2, lower right). Treatment responses to etoricoxib, 30 mg/d, and ibuprofen, 2400 mg/d, were consistent among patients of different age groups (<65 years, ≥65 years), racial backgrounds, and sexes.

Analyses of secondary end points, which included Patient Global Assessment of Response to Therapy, IGADS, WOMAC stiffness subscale, and WOMAC overall score and subscale averages, provided additional perspective of etoricoxib's overall efficacy profile for treatment of OA compared with ibuprofen and placebo. Etoricoxib and ibuprofen displayed comparable treatment effects and superior ($P<.001$) efficacy vs placebo (Tables 2 and 3) for these secondary end points. These results were generally consistent with clinical responses observed for the primary end points. Patients receiving etoricoxib experienced a 1.61-point (95% CI, 1.46-1.75 point) improvement in Investigator Global Assessment of Response to Therapy and –30.92-mm (95% CI, –34.23 to –27.61 mm) improvement of pain status when walking on a flat surface (WOMAC score), similar results to those of ibuprofen. When compared with placebo, treatment with etoricoxib provided significant reduction of study joint tenderness ($P=.006$) but when compared with placebo, ibuprofen therapy was not significant ($P=.06$).

Examination of exploratory end points also showed consistent therapeutic benefit for etoricoxib and ibuprofen over placebo (Tables 2 and 3). Both etoricoxib and ibuprofen significantly reduced WOMAC nighttime pain and stiffness on awakening vs placebo ($P\leq.006$) by a similar magnitude ($P\geq.28$).

Patients receiving etoricoxib used 22% less ($P=.04$) acetaminophen than those receiving placebo for treatment of breakthrough pain. Although patients in the ibuprofen group used 15% less acetaminophen than patients in the placebo group, this difference was not significant ($P=.16$).

Safety and Tolerability

Etoricoxib, 30 mg/d, and ibuprofen, 2400 mg/d, were generally safe and well tolerated (Table 4). The overall rates of AEs and serious AEs were similar in the active and placebo treatment groups. The incidence of drug-related AEs in patients receiving ibuprofen was significantly greater compared with that in patients receiving placebo treatment ($P<.001$). Also, the number of patients who discontinued the study because of drug-related AEs was significantly

TABLE 2. **Secondary and Other Exploratory End Points***

End point	Treatment group	No. of patients†	Baseline mean (SD)‡	LS mean change (95% CI)§
Secondary				
Patient Global Assessment of Response to Therapy//	Placebo	100	NA	2.45 (2.25 to 2.65)
	Etoricoxib, 30 mg/d	212	NA	1.74 (1.60 to 1.89)
	Ibuprofen, 2400 mg/d	208	NA	1.78 (1.63 to 1.92)
Investigator Global Assessment of Disease Status//	Placebo	103	3.03 (0.59)	–0.99 (–1.16 to –0.82)
	Etoricoxib, 30 mg/d	213	3.06 (0.60)	–1.46 (–1.59 to –1.34)
	Ibuprofen, 2400 mg/d	210	3.03 (0.64)	–1.47 (–1.60 to –1.34)
WOMAC stiffness subscale¶	Placebo	104	71.19 (20.79)	–13.68 (–18.23 to –9.13)
	Etoricoxib, 30 mg/d	210	72.01 (17.36)	–25.71 (–29.05 to –22.38)
	Ibuprofen, 2400 mg/d	208	72.62 (16.62)	–24.97 (–28.36 to –21.59)
WOMAC questionnaire overall score average¶	Placebo	104	69.71 (16.52)	–14.20 (–18.32 to –10.07)
	Etoricoxib, 30 mg/d	210	68.68 (16.64)	–24.52 (–27.54 to –21.49)
	Ibuprofen, 2400 mg/d	208	68.13 (17.02)	–23.65 (–26.72 to –20.57)
WOMAC questionnaire overall subscale average¶	Placebo	104	70.04 (16.30)	–14.55 (–18.73 to –10.37)
	Etoricoxib, 30 mg/d	210	69.69 (15.79)	–25.44 (–28.51 to –22.38)
	Ibuprofen, 2400 mg/d	208	69.32 (15.70)	–24.48 (–27.59 to –21.36)
Other				
Investigator Global Assessment of Response to Therapy¶	Placebo	100	NA	2.25 (2.05 to 2.45)
	Etoricoxib, 30 mg/d	210	NA	1.61 (1.46 to 1.75)
	Ibuprofen, 2400 mg/d	209	NA	1.66 (1.52 to 1.81)
Study joint tenderness#	Placebo	104	1.83 (0.73)	–0.72 (–0.79 to –0.51)
	Etoricoxib, 30 mg/d	213	1.80 (0.78)	–0.93 (–0.99 to –0.78)
	Ibuprofen, 2400 mg/d	209	1.73 (0.73)	–0.82 (–0.92 to –0.70)
WOMAC pain walking on a flat surface¶	Placebo	104	72.83 (14.43)	–20.30 (–24.86 to –15.73)
	Etoricoxib, 30 mg/d	214	73.86 (15.45)	–30.92 (–34.23 to –27.61)
	Ibuprofen, 2400 mg/d	210	73.16 (16.32)	–30.48 (–33.87 to –27.09)
WOMAC nighttime pain¶	Placebo	104	67.71 (21.73)	–16.05 (–20.71 to –11.40)
	Etoricoxib, 30 mg/d	214	63.51 (24.34)	–26.12 (–29.48 to –22.76)
	Ibuprofen, 2400 mg/d	210	63.72 (24.10)	–23.73 (–27.17 to –20.28)
WOMAC stiffness on awakening¶	Placebo	104	72.82 (22.99)	–14.98 (–19.79 to –10.17)
	Etoricoxib, 30 mg/d	210	74.15 (19.65)	–25.71 (–29.23 to –22.18)
	Ibuprofen, 2400 mg/d	208	74.44 (18.00)	–25.59 (–29.18 to –22.01)

*Time-weighted average response during the 12-week treatment period. CI = confidence interval; LS = least squares; NA = not applicable; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
†Enrolled at baseline.
‡Mean (SD) for all patients enrolled at baseline.
§For VAS and Likert measures, a lower value indicates a greater treatment effect. Where there is no baseline value, the mean on-treatment response is given.
//0- to 4-point Likert scale.
¶0- to 100-mm VAS.
#0- to 3-point scale.

higher in the ibuprofen treatment group compared with the placebo group ($P<.001$). Only 1 serious AE, which was in the ibuprofen group, was considered drug-related. The proportion of patients who discontinued the study because of AEs in the ibuprofen group was about twice that in either the placebo or etoricoxib groups. The 95% CI of the difference between etoricoxib and ibuprofen for drug-related AEs and discontinuation due to AEs did not cross zero, consistent with higher incidence in the ibuprofen group. Discontinuation due to AEs related to the digestive system or abdominal pain was similar in the placebo and etoricoxib groups but numerically higher in the ibuprofen group. The incidence of edema-related and hypertension-related AEs was generally low across the groups but numerically highest in the ibuprofen group. A significantly higher percentage (9.0%; $P<.001$) of patients in the ibuprofen group experienced edema-related AEs compared with those in the placebo group. The percentage of patients who experienced edema-related AEs in the etoricoxib group was lower (3.3%) and not significantly different from placebo (0%). The 95% CI for the difference between etoricoxib and ibuprofen groups did not cross zero, consistent with higher incidence of edema-related AEs in the ibuprofen group compared with etoricoxib. No patients in the study experienced congestive heart failure, pulmonary edema, or cardiac failure. There were 2 nonfatal cardio-

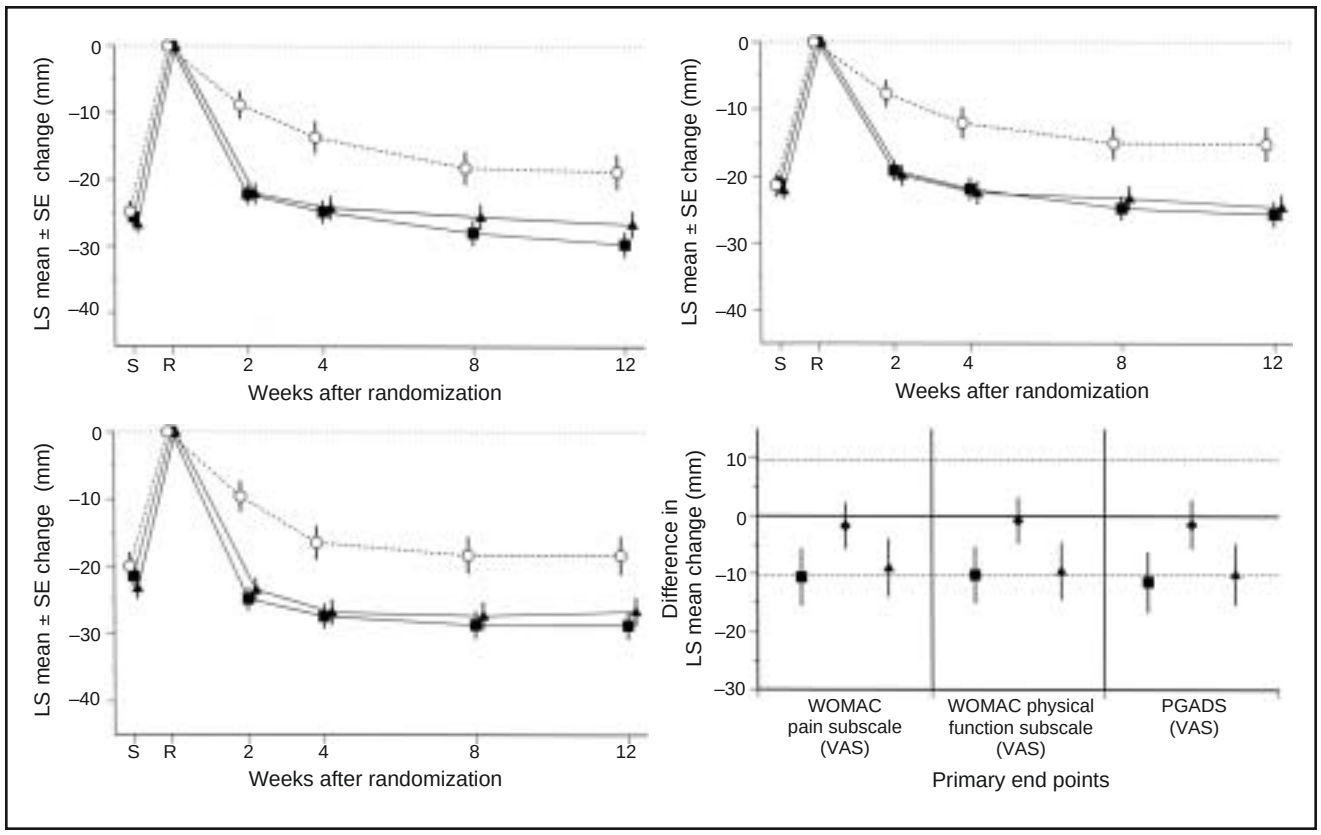

FIGURE 2. Upper left, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale. Upper right, WOMAC physical function subscale. Lower left, Patient Global Assessment of Disease Status (PGADS). Least squares (LS) mean change is from baseline (flare/randomization visit) during the 12-week treatment period. R = randomization visit with patients experiencing flare and start of treatment; S = screening visit and start of nonsteroidal anti-inflammatory drug washout period. O = Placeo; ■ = etoricoxib, 30 mg/d; ▲ = ibuprofen, 2400 mg/d. Lower right, WOMAC pain and physical function subscales and PGADS. Pairwise treatment differences in LS mean change from baseline during the 12-week treatment period. Error bars represent the 95% confidence intervals. VAS = visual analog scale. ■ = Etoricoxib, 30 mg/d – placebo; ◆ = etoricoxib, 30 mg/d – ibuprofen, 2400 mg/d; ▲ = ibuprofen – placebo.

vascular events confirmed by blinded adjudication. One patient in the etoricoxib group experienced a pulmonary embolism deemed by the investigator as not drug-related. One patient in the ibuprofen group experienced deep venous thrombosis that was classified by the investigator as possibly drug-related. The incidence of drug-related laboratory AEs was low in all groups: placebo, 2.0%; etoricoxib, 3.8%; and ibuprofen, 3.8%. The most common drug-related laboratory AEs were increased levels of serum urea nitrogen or serum creatinine and decreased hemoglobin levels. Two patients, both in the ibuprofen group, discontinued the study because of drug-related laboratory AEs.

DISCUSSION

We used validated clinical end points[18-20] to show the efficacy of etoricoxib, 30 mg once daily, for treatment of the signs and symptoms of OA in patients induced to experience a flare of their OA symptoms. Consistent with a previous dose-ranging study,[21] the results of this trial confirm the superior clinical efficacy of etoricoxib, 30 mg/d, compared with placebo for treatment of patients with OA of the hip and knee. Near-maximal efficacy was achieved within 2 weeks after initiation of treatment with etoricoxib and ibuprofen (the first time point measured), and improvement was sustained throughout the course of the study. The magnitude of the treatment responses for WOMAC subscales of pain and physical function in the etoricoxib group was in the range of changes known to be clinically important to patients with OA of the hip or knee.[27] Etoricoxib, 30 mg/d, displayed comparable efficacy to ibuprofen, 2400 mg/d, in this study. The significant efficacy of etoricoxib vs placebo across multiple efficacy end points shows its overall clinical effectiveness for treatment of OA. Consistent with its pharmacokinetic profile, etoricoxib relieves morning stiffness, indicative of its sustained efficacy during the 24-hour dosing interval.[28]

TABLE 3. **Secondary, Other, and Exploratory End Points***

End point	Etoricoxib, 30 mg/d, vs placebo†	Etoricoxib, 30 mg/d, vs ibuprofen†	Ibuprofen vs placebo†
Secondary			
Patient Global Assessment of Response to Therapy‡	–0.71 (–0.94 to –0.48)	–0.04 (–0.22 to 0.15)	–0.67 (–0.90 to –0.44)
Investigator Global Assessment of Disease Status‡	–0.47 (–0.67 to –0.27)	0.01 (–0.15 to 0.17)	–0.48 (–0.68 to –0.28)
WOMAC stiffness subscale§	–12.03 (–17.34 to –6.72)	–0.74 (–5.04 to 3.56)	–11.29 (–16.61 to –5.98)
WOMAC questionnaire overall score average§	–10.32 (–15.14 to –5.50)	–0.87 (–4.77 to 3.03)	–9.45 (–14.28 to –4.62)
WOMAC questionnaire overall subscale average§	–10.90 (–15.78 to –6.01)	–0.97 (–4.92 to 2.99)	–9.93 (–14.82 to –5.03)
Other			
Investigator Global Assessment of Response to Therapy‡	–0.65 (–0.88 to –0.41)	–0.06 (–0.24 to 0.13)	–0.59 (–0.82 to –0.35)
Study joint tenderness//	–0.24 (–0.82 to –0.01)	–0.07 (–0.21 to 0.06)	–0.16 (–0.33 to 0.01)
WOMAC pain walking on a flat surface§	–10.62 (–15.94 to –5.30)	–0.43 (–4.73 to 3.86)	–10.19 (–15.52 to –4.85)
Exploratory			
WOMAC nighttime pain†	–10.07 (–15.49 to –4.65)	–2.40 (–6.76 to 1.96)	–7.67 (–13.10 to –2.24)
WOMAC stiffness on awakening†	–10.72 (–16.34 to –5.10)	–0.11 (–4.66 to 4.44)	–10.61 (–16.24 to –4.98)

*Pairwise treatment differences of the time-weighted average response during the 12-week treatment period. CI = confidence interval; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
†Difference (95% CI). For VAS and Likert measures, a lower value indicates a greater treatment effect.
‡0- to 4-point Likert scale.
§0- to 100-mm VAS.
//0- to 3-point scale.

Etoricoxib and ibuprofen generally were well tolerated in this study. However, the incidences of drug-related AEs and discontinuation due to drug-related AEs were significantly greater in patients treated with ibuprofen compared with those treated with etoricoxib. Etoricoxib's favorable gastrointestinal safety and tolerability profile in this study are consistent with other clinical studies.[15,16] Because of the role of prostaglandins in the regulation of renal homeostasis,[29] we closely monitored the occurrence of renovascular AEs in this trial. Hypertension is also a common comorbid condition in patients with OA. Data from the Third National Health and Nutrition Examination Survey[30] indicate that approximately 40% of adults with OA also have hypertension, similar to the baseline status of our study population. Incidences of hypertension-related and edema-related AEs were found to be low in the group treated with etoricoxib, 30 mg/d, and were numerically higher in the group treated with ibuprofen, 2400 mg/d. Recent events have increased attention on the long-term cardiovascular safety of NSAIDs and COX-2 selective inhibitors.[31-33] The long-term cardiovascular safety of etoricoxib is being assessed further in 2 large ongoing studies totaling approximately 27,500 patients (currently with up to 2 years' duration of treatment) monitored by an external safety data monitoring board.

CONCLUSION

For patients with OA, treatment with etoricoxib, 30 mg/d, is well tolerated and provides sustained therapeutic efficacy that is superior to placebo and clinically comparable to ibuprofen, 2400 mg/d.

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TABLE 4. **Safety Data***

	Placebo (n=104)	Etoricoxib, 30 mg/d (n=214)	Ibuprofen, 2400 mg/d (n=210)
Patients			
With any AE	43 (41.3)	105 (49.1)	108 (51.4)
With any drug-related AE	9 (8.7)	34 (15.9)	56 (26.7)†
With any serious AE	1 (1.0)‡	4 (1.9)§	3 (1.4)∥
Who discontinued study due to AE	6 (5.8)	11 (5.1)	22 (10.5)
Who discontinued study due to drug-related AE	2 (1.9)	7 (3.3)	19 (9.0)†
Most common drug-related AEs			
Edema	0 (0.0)	1 (0.5)	5 (2.4)
Lower extremity edema	0 (0.0)	4 (1.9)	10 (4.8)
Heartburn	0 (0.0)	2 (0.9)	5 (2.4)
Nausea	4 (3.8)	3 (1.4)	3 (1.4)
Headache	1 (1.0)	1 (0.5)	9 (4.3)
Patients with prespecified clinical AEs			
Edema-related AEs¶	0 (0.0)	7 (3.3)	19 (9.0)†
Hypertension-related AEs#	1 (1.0)	4 (1.9)	8 (3.8)
AEs of congestive heart failure, pulmonary edema, or cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued study due to digestive system or abdominal pain AE	2 (1.9)	3 (1.4)	11 (5.2)
Discontinued study due to edema-related AEs	0 (0.0)	0 (0.0)	3 (1.4)
Discontinued study due to hypertension-related AEs	1 (1.0)	2 (0.9)	3 (1.4)

*Values represent number (percentage) of patients. AE = adverse experience.
†$P<.001$ vs placebo.
‡Angina pectoris.
§Pulmonary embolism, chest pain, cholecystitis, spinal stenosis.
∥Pyelonephritis, deep venous thrombosis (considered drug-related), prostatic malignant neoplasm.
¶Edema-related AEs included edema, lower extremity edema, and peripheral edema.
#Hypertension-related AEs included development of hypertension or worsening of preexisting hypertension.

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Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies

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***Objective*. To compare the efficacy of etoricoxib 30 mg with the generally maximum recommended dose of celecoxib, 200 mg, in the treatment of osteoarthritis (OA) in two identically designed studies.**
***Methods*. Two multi-centre, 26-week, double-blind, placebo-controlled, non-inferiority studies were conducted, enrolling patients who were prior non-steroidal anti-inflammatory drug (NSAID) or acetaminophen users. There were 599 patients in study 1 and 608 patients in study 2 randomized 4:4:1:1 to etoricoxib 30 mg qd, celecoxib 200 mg qd or one of two placebo groups for 12 weeks. After 12 weeks, placebo patients were evenly distributed to etoricoxib or celecoxib based on their initial enrollment randomization schedule. The primary hypothesis was that etoricoxib 30 mg would be at least as effective as celecoxib 200 mg for the time-weighted average change from baseline over 12 weeks for Western Ontario and McMaster (WOMAC) Pain Subscale, WOMAC Physical Function Subscale and Patient Global Assessment of Disease Status. Active treatments were also assessed over the full 26 weeks. Adverse experiences were collected for safety assessment.**
***Results*. In both studies, etoricoxib was non-inferior to celecoxib for all three efficacy outcomes over 12 and 26 weeks; both were superior to placebo ($P < 0.001$) for all three outcomes in each study over 12 weeks. The safety and tolerability of etoricoxib 30 mg qd and celecoxib 200 mg qd were similar over 12 and 26 weeks.**
***Conclusions*. Etoricoxib 30 mg qd was at least as effective as celecoxib 200 mg qd and had similar safety in the treatment of knee and hip OA; both were superior to placebo.**
ClinicalTrials.gov Identifiers: NCT00092768; NCT00092791

KEY WORDS: Celecoxib, COX-2 inhibitor, Efficacy, Etoricoxib, Osteoarthritis, WOMAC.

Introduction

Osteoarthritis (OA) is the most common joint disorder, affecting approximately 21 million people in the US alone [1, 2]. Prevalence of the condition increases with age, with radiographic evidence in ~70% of people in the US over age 55 yrs and 80% of people over 75 yrs [2–4]. Non-steroidal anti-inflammatory drugs (NSAIDs), the mainstay for the symptomatic treatment of OA, are effective analgesic and anti-inflammatory agents [5–7], but have a side effect profile with known risk. Toxicity, particularly in the gastrointestinal (GI) tract, is a potential occurrence with NSAIDs resulting from cyclo-oxygenase (COX)-1 inhibition [8], with over 100 000 hospitalizations annually in the US due to NSAID gastropathy [9]. The typical OA patient is at higher risk for NSAID gastropathy because of potential inter-related factors including older age, the presence of multiple medical conditions requiring additional medical treatments, and the use of higher doses of NSAIDs for longer periods [10, 11]. In clinical studies, COX-2 inhibitors have similar efficacy as NSAIDs in the treatment of OA pain [12–15], but with improved GI safety profiles [16–22]. These agents thus provide important treatment options not only for patients with OA pain and typical risks in general, but also for those patients with prior GI haemorrhage, those taking anticoagulants, or with a known bleeding diathesis, who would be at additional risk of NSAID-related GI bleeding.

Etoricoxib is a selective COX-2 inhibitor available in 55 countries in Europe, Latin America and the Asia-Pacific region, and is under development in the US. At its recommended dose of 60 mg once daily [23], etoricoxib demonstrated similar efficacy to diclofenac 50 mg three times daily (tid) and naproxen 500 mg twice daily (bid) in studies of patients with OA [24–26]. When compared with non-selective NSAIDs, there were significantly ($P < 0.001$) fewer perforations, ulcers and bleeds (PUBs) with etoricoxib 60 mg [20], and a lower rate of endoscopically identified ulceration and erosion with etoricoxib 120 mg (twice the recommended OA dose [21]). Studies have also shown etoricoxib at a dosage of 30 mg/day to be efficacious in OA compared with either ibuprofen 800 mg tid [27] or diclofenac 50 mg tid [25]. To our knowledge, etoricoxib has never been compared, in a clinical trial, with another selective COX-2 inhibitor in OA.

The primary purpose of the current two studies was to compare the efficacy of etoricoxib 30 mg qd and the generally recommended dose of celecoxib (200 mg qd) in the treatment of OA of the knee and hip over a 12-week period using the Western Ontario and McMaster (WOMAC) Universities' OA Index Pain and

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Physical Function Subscales, and the Patient Global Assessment of Disease Status (PGADS), as co-primary end points. These end points are widely used and accepted measures of response to treatment for OA and provide a comprehensive assessment of response to treatment. The two studies are presented together in order to directly compare the results of these identically designed trials.

Methods

Study patients

Patients were otherwise healthy males or non-pregnant females, ≥40 yrs of age, with a diagnosis of OA of the knee or hip >6 months, and were American Rheumatology Association (ARA) functional Class I, II or III. Prior to study enrollment, patients were required to be taking an NSAID at prescription strength for at least 30 days or acetaminophen 1200–4000 mg a day on a regular basis (at least 25 of the last 30 days) with a history of therapeutic benefit. Eligibility required patients to meet specific flare criteria upon medication washout, described subsequently. Exclusion criteria included concurrent medical or arthritic disease which could confound evaluation of efficacy (e.g. inflammatory arthritis, history of septic arthritis of the study joint, osteochondritis desiccans or osteonecrosis of the study joint, Wilson's disease, haemochromatosis, ochronosis or primary osteochondromatosis), candidates for imminent joint replacement, serum creatinine >2.0 mg/dl, congestive heart failure (CHF) or unstable angina, uncontrolled hypertension, stroke or transient ischaemic attack within 6 months, certain neoplastic diseases, and allergy to aspirin, ibuprofen, rofecoxib, celecoxib, valdecoxib, other NSAID, acetaminophen or sulpha drugs. Contraindicated prior medications within pre-specified times of initiating the study included: intravenous, intramuscular or oral corticosteroids; glucosamine and/or chondroitin sulphate; intra-articular steroids, intra-articular hyaluronans; topical, oral or systemic analgesics; warfarin, heparin and high-dose aspirin (defined as >325 mg, once daily), weight loss agents, appetite suppressants and chronic medications used for <1 month at a stable dose. Low-dose aspirin (325 mg or less, once daily) was allowed for cardio-protective benefit. Patients could continue with existing physical therapy, but were not permitted to initiate physical therapy during the study period.

All participants signed informed consent to participate in these studies. The protocols were approved by the institutional review board or ethical review board for each site.

Study design

Two 26-week, multi-centre, randomized, double-blind, double-dummy, placebo-controlled, two-part studies were conducted [Protocols 076 (study 1) and 077 (study 2)] at 74 centres each. Eligible patients were randomized in a 4:4:1:1 allocation ratio to etoricoxib 30 mg qd, celecoxib 200 mg qd or one of two placebo groups for 12 weeks (part I) (Fig. 1). Patients who successfully completed part I were enrolled directly into part II, an active comparator 14-week follow-up. Patients on active treatment in part I remained on the same treatment in part II; patients receiving placebo in part I received either etoricoxib 30 mg or celecoxib 200 mg in part II, based on their initial randomization schedule at enrollment.

At screening, NSAID users had to demonstrate an assessment of pain walking on a flat surface (WOMAC OA Index Version VA 3.0, Question 1) of <80 mm on a 100 mm visual analogue scale (VAS). Acetaminophen users had to demonstrate a minimum of 40 mm; a score of fair, poor or very poor on Investigator Global Assessment of Disease Status (IGADS); and a minimum of 40 mm on PGADS.

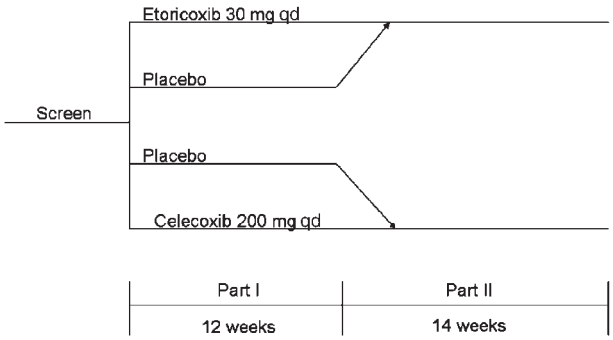

FIG. 1. Study design.

Following screening, prior NSAID users discontinued treatment to allow for washout and symptom flare; acetaminophen users remained on treatment. To qualify for enrollment, at the flare/baseline visit, NSAID users had to demonstrate a minimum score of 40 mm with an increase of 15 mm on patient-assessed pain walking on a flat surface, and IGADS worsening of at least one point on a 5-point Likert scale. Acetaminophen users had to demonstrate a minimum of 40 mm of patient-assessed pain walking on a flat surface, fair, poor or very poor on IGADS, and a minimum of 40 mm on PGADS.

Eligible patients were evaluated at the study centres following 2, 4, 8 and 12 weeks of treatment (part I), and following 16 and 26 weeks of treatment (part II). Clinical efficacy and safety data were collected at each visit, including vital signs and a physical examination. Acetaminophen 325 mg tablets were available as rescue analgesia at a maximum daily dose of 2600 mg. Patients were requested to use as little acetaminophen as possible, and discontinued acetaminophen use at least 12 h before visits 2–8. A tablet count of study medication was performed at each visit. Patients who missed >20% of scheduled doses were considered non-compliant.

Patients unable to complete the 26-week study were scheduled within 48 h for a discontinuation visit at which the reason for discontinuation was noted.

Efficacy and safety end points

The co-primary efficacy end points were: WOMAC Pain Subscale, WOMAC Physical Function Subscale and PGADS. The Pain Subscale was the average of the first five questions of the WOMAC and measured by VAS from 0 ('no pain') to 100 mm ('extreme pain') for each question. The Physical Function Subscale was the average of questions 8 through 24 of the WOMAC and measured by VAS from 0 ('no difficulty') to 100 mm ('extreme difficulty') for each question. PGADS was measured by VAS from 0 ('very well') to 100 mm ('very poor'). Analyses of these end points were based upon the time-weighted average (TWA) change from baseline over 12 weeks.

Safety was monitored by clinical and laboratory assessments at study visits and patient reported adverse experiences (AEs). Pre-defined AEs of interest included discontinuation due to any AE, discontinuation due to oedema, hypertension or GI event or CHF.

All potentially serious thrombotic cardiovascular (CV) AEs, deaths and serious upper GI AEs (PUBs) were adjudicated by separate, blinded expert Case Review Committees. Serious thrombotic CV AEs were confirmed and classified by vascular bed, specific event type and by the Anti-Platelet Trialists' Collaboration (APTC) criteria [28].

Statistical methods

The primary efficacy analysis was a modified intention-to-treat (mITT) approach on TWA response. The equation for TWA is $\sum_{i=1}^{n} x_i w_i$, where x is the measurement value and w is the weight. The equation for weight is $w_i = (t_i - t_{i-1})/t_n$, where t_i is the current time point, $t_{(i-1)}$ is the previous time point, and t_n is the final time point. All patients with a baseline value and at least one post-baseline observation were included in the primary efficacy analysis. Only observed data were included in each patient's TWA response; no data were carried forward or imputed for this computation. A secondary per-protocol analysis removing pre-specified protocol violators was also carried out.

Primary efficacy variables were assessed by an analysis of covariance (ANCOVA) model with factors for study site, treatment group, primary OA joint and baseline score (flare/randomization visit) of the dependent variable. Consistency of treatment effect across different subgroups was assessed using an ANCOVA model including factors for subgroup and treatment by subgroup interaction. The interactions were tested for significance at the $\alpha = 0.05$ level as an index to determine if further exploratory analyses were needed to examine the nature of the interaction.

With 200 patients each in the etoricoxib and celecoxib groups and 100 patients in the placebo group, each study provided an overall power of at least 87% to satisfy the primary hypothesis of non-inferiority between actives, and of actives demonstrating superiority over placebo. This assumes no difference between actives for the three co-primary end points, and active-placebo differences of −11.1, −10.2 and −11.5 mm for WOMAC pain, WOMAC physical function and PGADS TWA change from baseline, respectively, with standard deviations of 20.5, 20.1 and 22.0, respectively. To satisfy the primary hypothesis, the following were required: (i) the upper bound of the 95% confidence intervals (CIs) for difference between active treatments (etoricoxib 30 mg–celecoxib 200 mg) was not >10 mm with respect to the TWA change from baseline over 12 weeks for the three primary end points; and (ii) etoricoxib 30 mg qd was superior ($P \leq 0.05$) to placebo for the TWA change from baseline over 12 weeks for these end points.

Safety analyses included all randomized patients who took at least one dose of study medication. AEs occurring during treatment or within 14 days of discontinuing treatment were tabulated. A subset of clinical AEs was pre-specified for further analysis, with pairwise treatment differences analysed using Fisher's exact test. Summary statistics for observed values and changes from baseline were tabulated at each study week by treatment group for systolic and diastolic blood pressures (SBP and DBP), and the percentage of patients who exceeded pre-defined limits of change was provided for SBP (consecutive values >140 mmHg and increases from baseline >20 mmHg) and DBP (consecutive values >90 mmHg and increases from baseline >15 mmHg).

Results

Patient disposition

Between March 2004 and February 2005, 599 patients were randomized in study 1 and 608 in study 2 (Fig. 2a and b), of which 468 (78.1%) patients in study 1 and 474 (78.0%) patients in study 2 completed the studies through 12 weeks (part I). The most common cause of discontinuation was lack of efficacy. Significantly more patients in the placebo group ($P < 0.001$) discontinued due to lack of efficacy than either active treatment group in both studies. The difference in withdrawals between etoricoxib and celecoxib was not significant in either study. A total of 417 (69.6%) patients in study 1 and 419 (68.9%) patients in study 2 completed the full 26-week treatment period (parts I and II).

Baseline characteristics

The treatment groups in both studies were similar with respect to gender, age, race, prior medication use, pain severity and primary OA joint (Table 1). The distribution of pain scores based on medians and percentiles was also similar for all groups in both studies indicating that there were comparable proportions of subjects across pain strata (e.g. minimal, moderate, severe).

Primary efficacy end points

Etoricoxib 30 mg and celecoxib 200 mg were similar to each other for all three end points in both studies. For each primary end point, the upper limit of the 95% CI on the mean difference (etoricoxib minus celecoxib; negative value favours etoricoxib) did not exceed 10 mm; therefore etoricoxib was at least as effective as celecoxib over 12 weeks (Figs 3–5, Table 2a and b). Both etoricoxib and celecoxib were superior to placebo ($P < 0.001$) over 12 weeks.

For the 26-week end points, the upper limit of the 95% CI on the difference did not exceed 10 mm, therefore etoricoxib was at least as effective as celecoxib over 26 weeks as well (Figs 2–4).

The results of a pooled subgroup analysis including both studies yielded similar treatment responses by study joint (i.e. knee *vs* hip) for the three co-primary end points and were consistent with the overall results; there was no significant interaction (P-range 0.765–0.870) between the primary joint affected and treatment for any of the co-primary efficacy outcomes at 12 and 26 weeks (data not shown).

Secondary efficacy end points

In study 1, the mean change from baseline (95% CI) in IGADS was −1.41 (−1.53, −1.28), −1.22 (−1.34, −1.10) and −0.71 (−0.87, −0.55) for etoricoxib, celecoxib and placebo, respectively; values in study 2 were −1.29 (−1.40, −1.17), −1.35 (−1.46, −1.24) and −0.63 (−0.79, −0.46), respectively. In both studies, active treatments were significantly better than placebo. Etoricoxib was significantly greater than celecoxib in study 1 [pairwise difference (95% CI) −0.19 (−0.34, −0.03), but not in study 2 [0.06 (−0.08, 0.21)].

Safety

Part I: 12 weeks

Overall AEs. AE rates were generally similar between the active treatment groups (Table 3). The most commonly reported AEs in both studies were upper respiratory tract infection, urinary tract infection, headache, peripheral oedema and diarrhoea. Discontinuations due to drug-related AEs were similar for all treatment groups in both studies.

Pre-specified AEs. In study 1, there were no significant differences between etoricoxib, celecoxib and placebo for any of the pre-specified AEs (Table 3). In study 2, both etoricoxib ($P = 0.017$) and celecoxib ($P = 0.012$) had significantly fewer AEs leading to discontinuation than placebo. Additionally, celecoxib had significantly fewer discontinuations due to GI AEs than placebo ($P = 0.037$). In both studies, there were no significant differences between the three treatment groups with respect to discontinuations due to oedema- or hypertension-related AEs, nor were any significant differences observed in the rates of CHF, pulmonary oedema or cardiac failure.

Part II: 26 weeks. The rates of AEs and pre-specified AEs were not significantly different between etoricoxib and celecoxib over the entire 26-week duration in either study (data not shown).

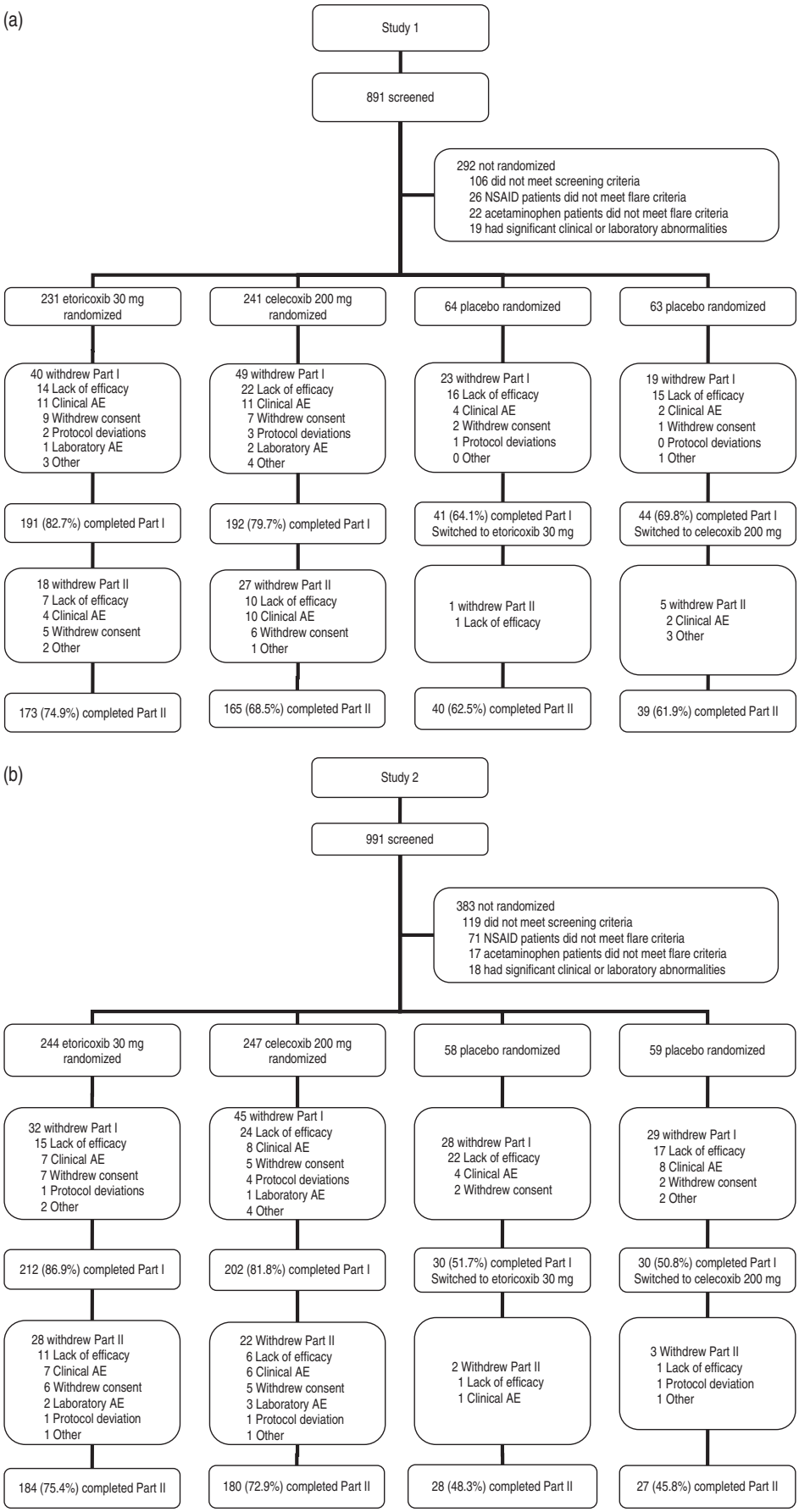

FIG. 2. (a) Study 1: patient disposition and (b) Study 2: patient disposition.

Table 1. Demographics

		Study 1			Study 2		
		Etoricoxib 30 mg ($N=231$) *n* (%)	Celecoxib 200 mg ($N=241$) *n* (%)	Placebo ($N=127$) *n* (%)	Etoricoxib 30 mg ($N=244$) *n* (%)	Celecoxib 200 mg ($N=247$) *n* (%)	Placebo ($N=117$) *n* (%)
Sex	Female	153 (66.2)	168 (69.7)	83 (65.4)	170 (69.7)	153 (61.9)	76 (65.0)
Age (yrs)	Mean (s.d.)	62.1 (10.2)	62.5 (9.3)	62.8 (9.7)	61.9 (9.6)	62.2 (9.5)	60.9 (8.6)
Race	Asian	1 (0.4)	1 (0.4)	1 (0.8)	3 (1.2)	2 (0.8)	1 (0.9)
	Black	15 (6.5)	26 (10.8)	13 (10.2)	18 (7.4)	14 (5.7)	9 (7.7)
	Hispanic	4 (1.7)	5 (2.1)	4 (3.1)	9 (3.7)	10 (4.0)	4 (3.4)
	White	210 (90.9)	208 (86.3)	108 (85.0)	213 (87.3)	219 (88.7)	101 (86.3)
	Other	1 (0.4)	1 (0.4)	1 (0.8)	1 (0.4)	2 (0.8)	2 (1.7)
Prior medicine use	Acetaminophen	27 (11.7)	47 (19.5)	25 (19.7)	31 (12.7)	33 (13.4)	15 (12.8)
	NSAID/COX-2 inhibitor	204 (88.3)	194 (80.5)	102 (80.3)	213 (87.3)	214 (86.6)	102 (87.2)
ARA function class	Class I	42 (18.2)	45 (18.7)	21 (16.5)	49 (20.1)	54 (21.9)	22 (18.8)
	Class II	131 (56.7)	145 (60.2)	80 (63.0)	126 (51.6)	130 (52.6)	68 (58.1)
	Class III	58 (25.1)	51 (21.2)	26 (20.5)	69 (28.3)	63 (25.5)	27 (23.1)
Low-dose aspirin use		62 (26.8)	62 (25.7)	39 (30.7)	79 (32.4)	73 (29.6)	40 (34.2)
Primary OA joint	Knee	185 (80.1)	193 (80.1)	104 (81.9)	182 (74.6)	192 (77.7)	98 (83.8)
	Hip	46 (19.9)	48 (19.9)	23 (18.1)	62 (25.4)	55 (22.3)	19 (16.2)

Discontinuations due to drug-related AEs were similar for etoricoxib and celecoxib in both studies.

Blood pressure change

Mean changes in BP from baseline (randomization) and the percentage of patients exceeding pre-defined BP limits are shown in Tables 4 and 5. Results were generally similar between the treatment groups for either category.

Adjudicated PUBs and thrombotic cardiovascular AEs

No patients in study 1 experienced a PUB. In study 2, one etoricoxib patient experienced an investigator-reported duodenal ulcer, which was confirmed by the adjudication committee, and one celecoxib patient experienced a duodenal and a gastric ulcer, which were confirmed by the adjudication committee.

In study 1, there was one investigator-reported thrombotic CV AE (cerebrovascular accident) in a celecoxib patient, which was confirmed by the adjudication committee and met APTC criteria as a thrombotic CV AE. In study 2, one patient in each treatment group had an investigator-reported thrombotic CV AE. Coronary artery disease in a patient receiving placebo did not meet adjudication committee or APTC criteria for confirmation. A transient ischaemic attack in a patient receiving etoricoxib was reclassified by the adjudication committee as stroke/transient ischaemic attack, which was confirmed by the adjudication committee and fulfilled APTC criteria. A celecoxib patient had an investigator-reported myocardial infarction that was confirmed as a non-thromboembolic event by the adjudication committee and APTC criteria.

Discussion

Several clinical trials have demonstrated that OA pain can be effectively treated in many patients with lower doses of COX-2 inhibitors. A plateau effect observed with increasing doses suggests that prostaglandin-mediated pain is saturable [12, 24, 27, 29–33]. The current studies were designed to determine whether etoricoxib 30 mg daily was as effective as the recommended dose of celecoxib 200 mg daily in patients with OA of the knee or hip. For each co-primary end point, etoricoxib met the definition for non-inferiority compared with the maximum recommended dose of celecoxib over 12 weeks and 26 weeks. Both active treatments were superior to placebo during the 12-week placebo-controlled portion of the study. In both studies, a placebo benefit was observed, but in neither did pain decrease to the pre-flare level of control.

Our studies differ from some OA trials by the use of TWA rather than a landmark assessment to measure efficacy. In a landmark assessment, the outcome is measured only by the final time point value. The TWA takes into account not only the value at a given time point, but also the duration of those values over the entire study period. As the name suggests, it represents the average treatment effect through the trial duration, and is closely related to the area under the curve (AUC) measurement. This difference is of crucial importance in evaluating the response to treatment in a condition such as OA. Patients with OA experience periods of exacerbation during which onset of relief is of great importance. A landmark assessment does not account for differences in onset, nor does it account for any variations or trends in response prior to the landmark time point, making it a less precise estimate of overall treatment effect during the study period. It has been suggested that TWA is a more important consideration in chronic analgesia trials, while landmark measurement is better suited for acute analgesia trials [34].

For the two trials presented here, the ANCOVA-adjusted TWA and landmark values for etoricoxib at 12 weeks were generally similar, with the TWA change being slightly smaller than the landmark measurement for each of the three primary end points in both studies (Table 2a and b, Figs 3–5). The similarities of these two measurements in our studies suggest that there was little variation in treatment effect and that onset was similar. A larger difference in favour of a TWA value might be anticipated if the comparator were, for example, etoricoxib 60 mg, which has been shown to be superior to etoricoxib 30 mg in WOMAC Pain Subscale and patient global assessment of response to therapy (PGART) scores at 6 weeks in OA, with a more pronounced, sustained analgesia [24].

Because the studies presented here represent the first time etoricoxib has been directly compared with another selective COX-2 inhibitor in a prospective OA trial, it is impossible to directly compare our results to those from similar studies. However, some investigators have advocated the use of effect size (ES) to indirectly compare consistency and efficacy across trials. ES is a measure of treatment magnitude independent of sample size. There are several different methods to calculate ES, but in general it is determined by dividing the mean change in efficacy for an active agent compared with placebo by the pooled

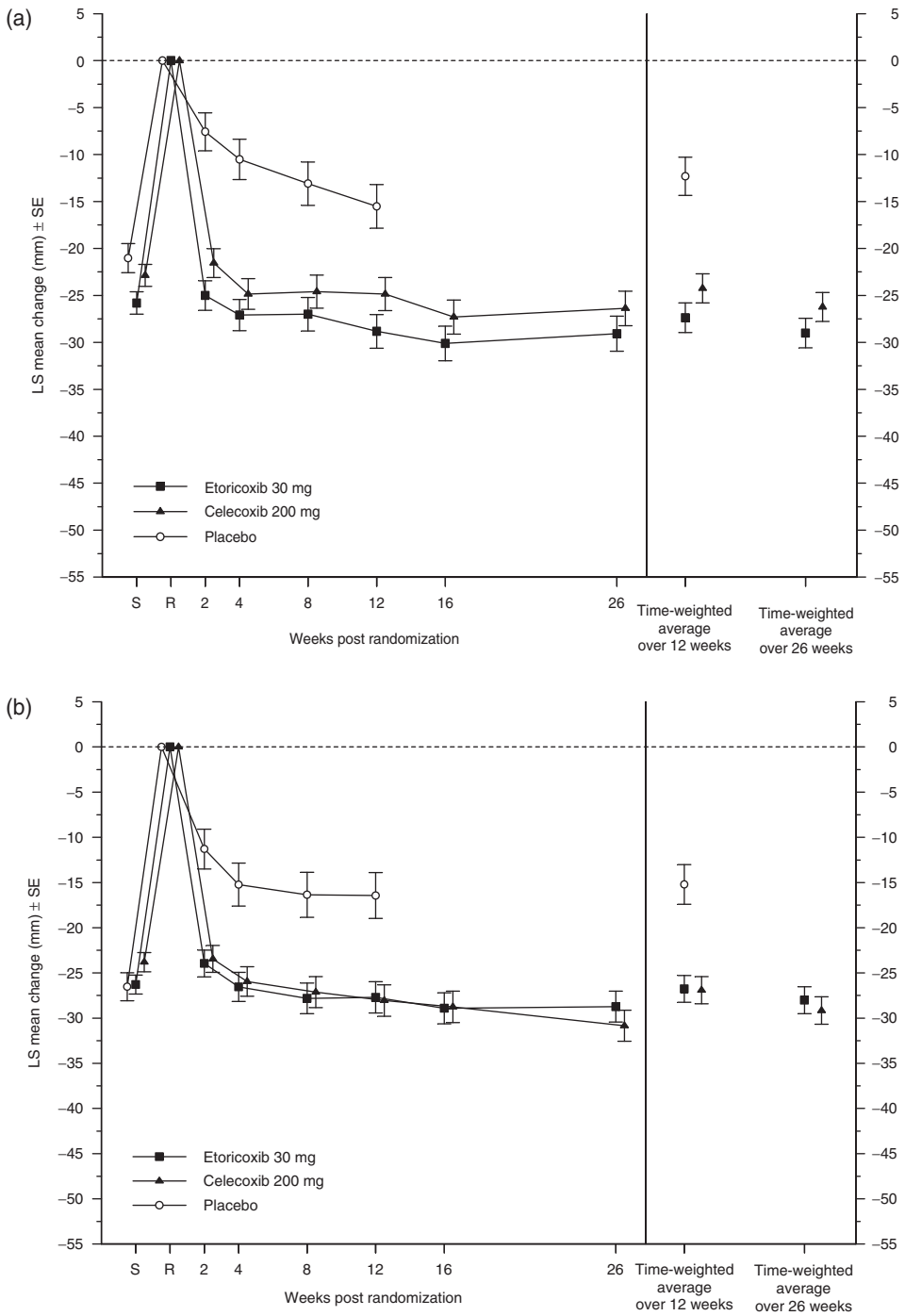

FIG. 3. (a) Study 1: pain subscale change from flare visit (least squares means) measured on a 0–100 mm VAS. (b) Study 2: pain subscale change from flare visit (least squares means) measured on a 0–100 mm VAS. S, screening visit; R, randomization visit.

standard deviation ($M_1 - M_2/\sigma_{POOLED}$) [35, 36]. Although there are no absolute ES efficacy cut-offs, it has been estimated that an ES of 0.2 represents a small change, 0.5 a moderate change and 0.8 a large change [35]. In our studies, ES (calculated for the WOMAC Pain Subscale) for etoricoxib was 0.71 in study 1 and 0.53 in study 2; ES for celecoxib was 0.56 in study 1 and 0.54 in study 2. These results are generally consistent with previously published studies. A recent meta-analysis performed by Lee *et al.* [36] calculated ES of COX-2 inhibitors and NSAIDs in 15 OA trials, all of which employed a flare design. Although none of the trials included the 30 mg dose of etoricoxib, the average ES of etoricoxib 60 mg for three trials was 0.73 [36]. An earlier dose-ranging study of etoricoxib in OA found that the ES for etoricoxib 30 mg was approximately one-half to two-thirds that observed for etoricoxib 60 or 90 mg [24], suggesting that our results are consistent with the meta-analysis. The average ES of celecoxib 200 mg qd over four trials in the meta-analysis was 0.26, which is considerably lower than our average of 0.55. The authors suggest that pre-randomization (i.e. pre-flare) pain severity may explain discrepancies, but this information is typically not reported, and was not available, thus making it difficult to compare these studies with ours. It should be noted, however, that the authors calculated the overall ES for all coxibs to be 0.44 (95% CI; 0.33, 0.55), slightly lower than our results [36].

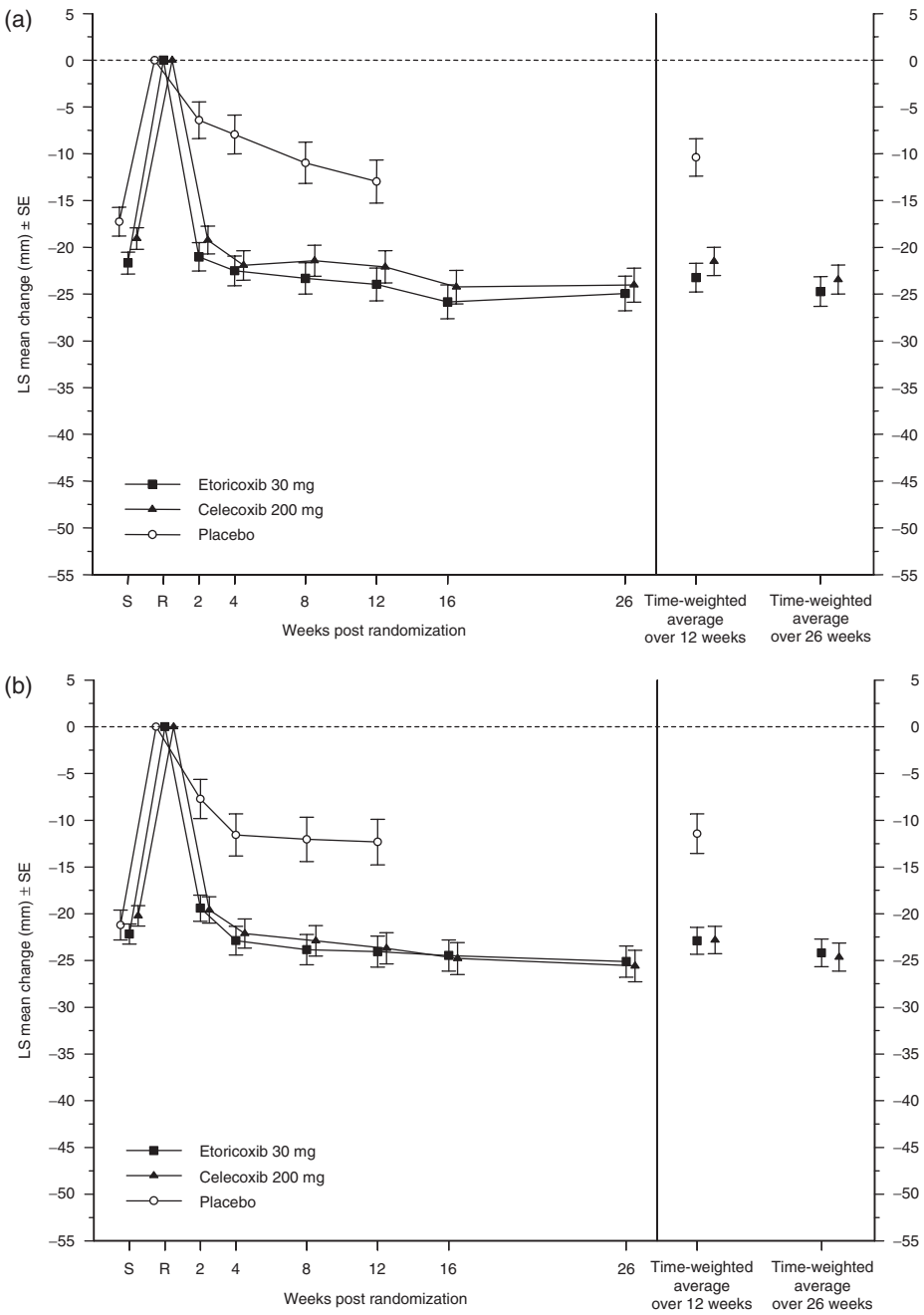

FIG. 4. (a) Study 1: physical function subscale change from flare visit (least squares means) measured on a 0–100 mm VAS. (b) Study 2: physical function subscale change from flare visit (least squares means) measured on a 0–100 mm VAS. S, screening visit; R, randomization visit.

Bjordal *et al.* [35] performed a similar meta-analysis of 23 randomized, double-blind, placebo-controlled NSAID and coxib trials of OA of the knee and/or hip. The combined ES for all NSAIDs (selective and non-selective) was 0.32 (95% CI; 0.24, 0.39) for pain reduction and 0.29 (95% CI; 0.18, 0.40) for functional disability reduction. The authors performed a subanalysis that excluded trials requiring a minimum flare, and determined the ES for all NSAIDs and coxibs to be 0.23 (95% CI; 0.16, 0.31) for pain, and 0.20 (95% CI; 0.09, 0.30) for functional disability, which is substantially lower than our findings. This may be due both to the fact that the meta-analysis pooled selective COX-2 inhibitors and NSAIDs together, as well as the exclusion of flare designs in the latter calculations.

The currently recommended dose of etoricoxib for OA in countries where it is approved, 60 mg, has been compared with etoricoxib 30 mg in OA in a 2-part, multi-extension trial. In part I of the base study, doses of 5, 10, 30, 60 and 90 mg were evaluated over 6 weeks. Dose-dependent efficacy was observed over the 5–60 mg dose range [24], with etoricoxib 60 mg demonstrating significantly more efficacy than etoricoxib 30 mg for the co-primary end points of WOMAC Pain Subscale, PGART and IGADS ($P < 0.01$ for all). Importantly, etoricoxib 30 mg was the lowest dose to consistently meet or exceed the study's pre-defined minimal clinically relevant changes (10 mm on VAS or 0.5 Likert units), confirming the clinical utility of the dosage. In Part II (8 weeks), which was designed to evaluate the consistency of treatment effect of etoricoxib over 14 weeks and

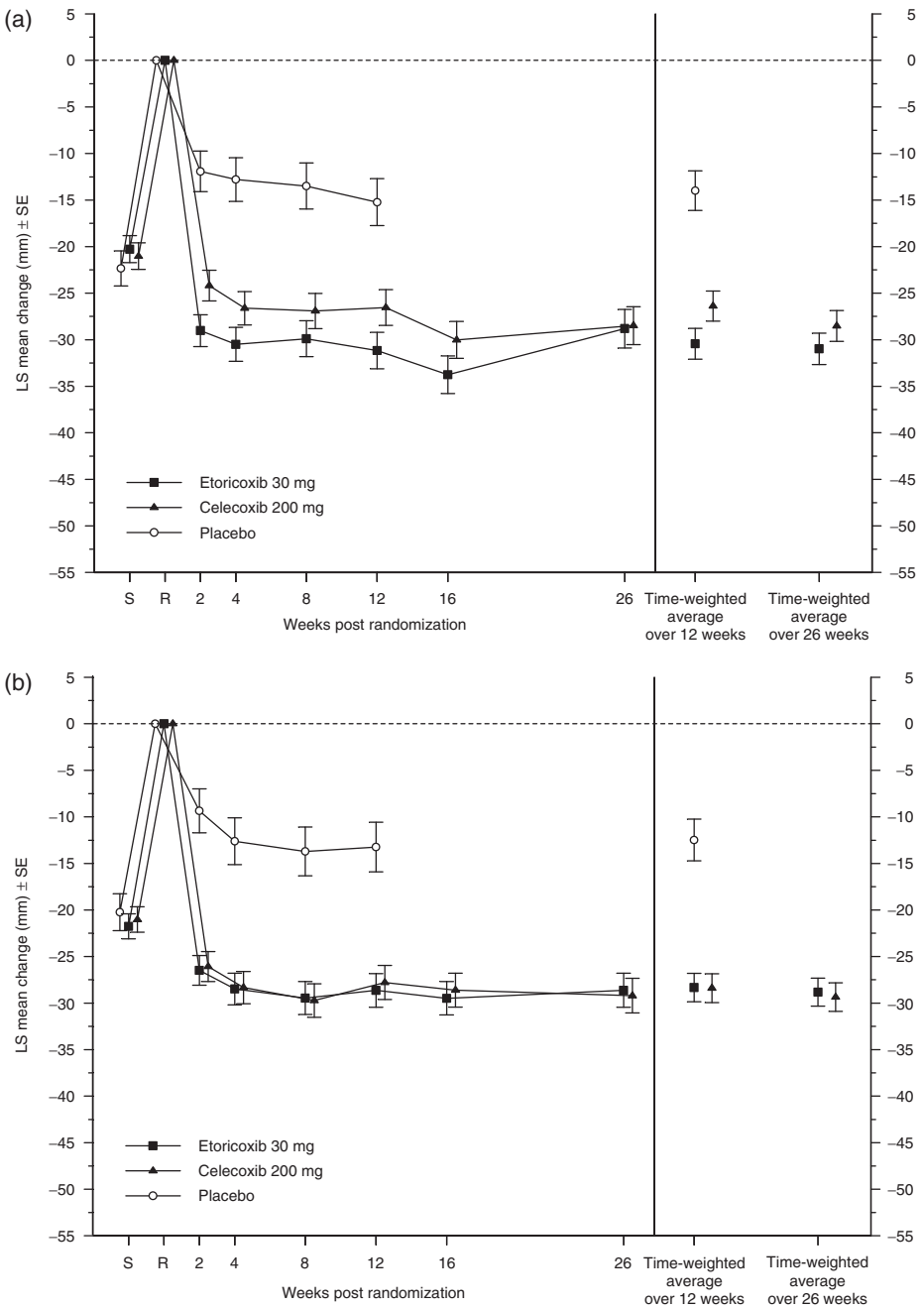

FIG. 5. (a) Study 1: patient global assessment of disease status (least squares means) measured on a 0–100 mm VAS. (b) Study 2: patient global assessment of disease status (least squares means) measured on a 0–100 mm VAS. S, screening visit; R, randomization visit.

to compare the treatment effect of etoricoxib versus diclofenac, patients from the placebo, etoricoxib 5 and 10 mg groups were reallocated to etoricoxib 30, 60, or 90 mg qd or diclofenac 50 mg tid. The improvements seen in the first 6 weeks with etoricoxib 30, 60, and 90 mg were sustained through 14 weeks, and the three etoricoxib doses appeared similar to each other and to diclofenac. It should be noted that Part II was not designed to compare the relative efficacy of the etoricoxib groups, and formal statistical testing was not performed. In the consecutive 12 and 26 week extensions of this study [37], the three etoricoxib doses (30, 60 and 90 mg) maintained clinical efficacy through 52 weeks, and were similar to diclofenac. Thus it appears that while etoricoxib 60 mg showed some early efficacy advantages, etoricoxib 30 mg demonstrated a clinically important degree of efficacy over 6 weeks which was maintained over 52 weeks.

The observation, that long-term, unopposed selective COX-2 inhibition may be associated with thrombotic CV and cerebrovascular side effects greater than placebo has raised concerns about the safety and future use of these agents in spite of their efficacy and improved GI tolerability compared with traditional NSAIDs [22, 38, 39]. On 30 September, 2004, Merck & Co., Inc. voluntarily withdrew rofecoxib from the worldwide market after reports from a large study showed an increased risk of thrombotic events beginning after 18 months of therapy in patients taking rofecoxib as compared with placebo [38]. In February 2005, the Food and Drug Administration (FDA) convened a joint advisory committee to further evaluate NSAIDs and coxibs [40], and concluded that the CV findings should be treated as a class effect that involves both COX-2 inhibitors and non-selective NSAIDs [41]. In April 2005, valdecoxib was withdrawn from the market at

TABLE 2a. Primary end points: analysis of TWA change from baseline (flare/randomization visit) averaged over weeks 2, 4, 8 and 12 (mITT Population), study 1

		Baseline		Treatment		*vs* Celecoxib 200 mg[a]			*vs* Placebo		
	N	Mean	S.D.	Mean	S.D.	Difference	95% CI	*P*	Difference	95% CI	*P*
WOMAC Pain Subscale											
Etoricoxib 30 mg	228	67.4	16.2	39.6	22.9	−3.12	(−7.02, 0.77)	0.116	−15.07	(−19.72, −10.41)	<0.001
Celecoxib 200 mg	236	67.5	16.3	42.8	22.9				−11.95	(−16.57, −7.32)	<0.001
Placebo	126	66.6	16.2	54.2	24.6						
WOMAC Physical Function Subscale											
Etoricoxib 30 mg	228	65.5	17.6	42.2	22.9	−1.74	(−5.53, 2.05)	0.367	−12.86	(−17.40, −8.31)	<0.001
Celecoxib 200 mg	236	66.6	17.9	44.6	23.2				−11.11	(−15.63, −6.59)	<0.001
Placebo	125	64.7	18.0	54.6	23.9						
Patient Global Assessment of Disease Status (PGADS)											
Etoricoxib 30 mg	228	72.2	17.6	41.3	22.7	−4.05	(−8.11, 0.02)	0.051	−16.44	(−21.31, −11.57)	<0.001
Celecoxib 200 mg	236	71.2	16.3	45.0	23.1				−12.39	(−17.23, −7.56)	<0.001
Placebo	126	69.1	18.1	56.7	23.6						

[a]Comparability was defined by the upper bound not exceeding 10 mm.
A negative difference favours etoricoxib.
vs Celecoxib 200 mg: difference is the estimated difference of treatment etoricoxib 30 mg – celecoxib 200 mg.
vs Placebo: difference is the estimated difference of treatment (etoricoxib 30 mg or celecoxib 200 mg) – placebo.
P-value: significance level resulting from the ANCOVA model including terms for treatment, primary OA joint and baseline covariate.

TABLE 2b. Primary end points: analysis of TWA change from baseline (flare/randomization visit) averaged over weeks 2, 4, 8 and 12 (mITT population), study 2

		Baseline		Treatment		*vs* Celecoxib 200 mg[a]			*vs* Placebo		
	N	Mean	S.D.	Mean	S.D.	Difference	95% CI	*P*	Difference	95% CI	*P*
WOMAC Pain Subscale											
Etoricoxib 30 mg	243	68.7	16.4	41.6	23.7	0.14	(−3.72, 4.00)	0.943	−11.56	(−16.45, −6.67)	<0.001
Celecoxib 200 mg	246	67.3	18.7	40.6	24.1				−11.70	(−16.56, −6.83)	<0.001
Placebo	112	66.4	16.9	51.8	24.8						
WOMAC Physical Function Subscale											
Etoricoxib 30 mg	243	67.7	17.9	44.2	24.1	−0.08	(−3.83, 3.67)	0.967	−11.46	(−16.22, −6.71)	<0.001
Celecoxib 200 mg	246	65.8	19.7	43.0	24.6				−11.38	(−16.11, −6.65)	<0.001
Placebo	112	65.2	18.7	53.9	24.2						
Patient Global Assessment of Disease Status (PGADS)											
Etoricoxib 30 mg	243	73.0	16.6	43.8	22.9	0.06	(−3.90, 4.02)	0.977	−15.86	(−20.88, −10.83)	<0.001
Celecoxib 200 mg	246	70.1	19.1	42.6	23.5				−15.91	(−20.92, −10.91)	<0.001
Placebo	111	72.3	17.2	59.4	24.4						

[a]Comparability was defined by the upper bound not exceeding 10 mm.
A negative difference favours etoricoxib.
vs Celecoxib 200 mg: difference is the estimated difference of treatment etoricoxib 30 mg – celecoxib 200 mg.
vs Placebo: difference is the estimated difference of treatment (etoricoxib 30 mg or celecoxib 200 mg) – placebo.
P-value: significance level resulting from the ANCOVA model including terms for treatment, primary OA joint and baseline covariate.

the request of the FDA due to concerns about reports of Stevens–Johnson syndrome and of increased CV risk in patients receiving valdecoxib immediately following coronary artery bypass grafting [41]. Based on the current efficacy and safety evidence, a number of regulatory authorities, including the FDA and European Medicines Agency, recommended that NSAIDs or coxibs be used at the lowest possible dose for the shortest time possible [41, 42]. Thus, determining doses of medications with similar efficacy is important in making comparisons of safety. In this study, etoricoxib 30 mg/day was as effective as celecoxib 200 mg/day. A number of safety end points were assessed in this study including pre-determined evaluations of BP along with a careful adjudication of GI and cardiac events. Importantly, there was no significant difference in treatment-related AEs over the first 12 weeks compared with placebo for either of the active treatments, nor were there any significant differences in AEs for celecoxib compared with etoricoxib over the 26-week study. Hypertension was assessed carefully in this study in all patients with three measurements at each visit. At 26 weeks, both the active treatments showed similar mean increases in SBP and DBP, with etoricoxib trending numerically higher than celecoxib for both measures. These increases are consistent with previous studies that have shown small increases in BP with the use of NSAIDs and COX-2 selective inhibitors [43]. However, in our studies, discontinuations from hypertension- or oedema-related AEs were few and not significantly different across groups, nor was there evidence of increased AEs related to CHF, pulmonary oedema or cardiac failure. Furthermore, the incidence of serious thrombotic CV events in these studies was also low. It is important to note that this was a relatively short trial and was not designed as a safety trial. Although the studies' 26-week duration has regulatory precedent for demonstrating tolerance for long-term therapy, the study was not designed either by size, duration or pre-specified end point or outcome to compare the incidence of rare events such as GI or CV AEs of these two COX-2 selective inhibitors. The numbers of patients and duration of therapy were

Table 3. Summary of clinical adverse experiences over 12 weeks

	Study 1			Study 2		
Adverse experiences (AEs)	Etoricoxib 30 mg ($N=231$) *n* (%)	Celecoxib 200 mg ($N=241$) *n* (%)	Placebo ($N=127$) *n* (%)	Etoricoxib 30 mg ($N=243$) *n* (%)	Celecoxib 200 mg ($N=247$) *n* (%)	Placebo ($N=117$) *n* (%)
Any AE	88 (38.1)	101 (41.9)	42 (33.1)	127 (52.3)	121 (49.0)	61 (52.1)
Drug-related AEs[a]	28 (12.1)	31 (12.9)	7 (5.5)	46 (18.9)	35 (14.2)	20 (17.1)
Serious AE	2 (0.9)	8 (3.3)	3 (2.4)	1 (0.4)	3 (1.2)	5 (4.3)
Discontinued due to drug-related AE[a]	6 (2.6)	7 (2.9)	1 (0.8)	6 (2.5)	6 (2.4)	7 (6.0)
AEs of interest						
Discontinued due to AE	10 (4.3)	12 (5.0)	6 (4.7)	9 (3.7)*	8 (3.2)*	12 (10.3)
Discontinued due to GI AE	3 (1.3)	2 (0.8)	0 (0.0)	3 (1.2)	2 (0.8)*	5 (4.3)
Discontinued due to oedema-related AE	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Discontinued due to hypertension-related AE	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE of congestive heart failure, pulmonary oedema or cardiac failure	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)

In study 1, $P=$ NS for all pre-specified between-treatment comparisons for 'AEs of interest'.
[a]Determined by the investigator to be possibly, probably or definitely drug related.
*$P<0.05$ compared with placebo.

Table 4. Mean change in blood pressure (mmHg)

	Study 1			Study 2		
	Etoricoxib 30 mg	Celecoxib 200 mg	Placebo[a]	Etoricoxib 30 mg	Celecoxib 200 mg	Placebo[a]
SBP (SE)						
12 weeks	−0.7 (0.9)	−0.7 (0.9)	−0.5 (1.3)	0.5 (0.9)	−0.2 (0.9)	1.1 (1.6)
26 weeks	1.9 (1.0)	0.9 (1.0)	–	2.4 (0.9)	1.8 (0.9)	–
DBP (SE)						
12 weeks	−0.8 (0.5)	−0.5 (0.6)	0.6 (0.9)	0.5 (0.6)	−0.2 (0.6)	−0.4 (1.1)
26 weeks	0.6 (0.6)	0.1 (0.6)	–	0.7 (0.7)	0.1 (0.6)	–

[a]Placebo values for 12 weeks only.
SBP, systolic blood pressure; DBP, diastolic blood pressure; SE, standard error.

Table 5. Number of patients exceeding pre-defined limits of change in blood pressure (n/m)[a]

	Study 1			Study 2		
	Etoricoxib 30 mg	Celecoxib 200 mg	Placebo[b]	Etoricoxib 30 mg	Celecoxib 200 mg	Placebo[b]
SBP (%)						
12 weeks	1/229 (0.4)	2/237 (0.8)	1/126 (0.8)	3/243 (1.2)	1/245 (0.4)	1/115 (0.9)
26 weeks	6/229 (2.6)	5/237 (2.1)	–	9/243 (3.7)	4/245 (1.6)	–
DBP (%)						
12 weeks	0/229 (0.0)	0/237 (0.0)	0/126 (0.0)	1/243 (0.4)	0/245 (0.0)	1/115 (0.9)
26 weeks	0/229 (0.0)	0/237 (0.0)	–	1/243 (0.4)	0/245 (0.0)	–

[a]Pre-defined SBP limits of change: consecutive values >140 mmHg and increases from baseline >20 mmHg; pre-defined DBP limits of change: consecutive values >90 mmHg and increases from baseline >15 mmHg.
[b]Placebo values for 12 weeks only.
SBP, systolic blood pressure; DBP, diastolic blood pressure.

not sufficient to make long-term conclusions concerning the chronic administration of either etoricoxib at 30 mg/day or celecoxib at 200 mg/day. To further address safety with chronic administration of etoricoxib, long-term studies are ongoing to precisely compare the CV safety of etoricoxib 60 and 90 mg to the most widely prescribed traditional NSAID in the world, diclofenac.

Conclusion

Defining the therapeutic window is important in determining the use of medications for OA pain. These studies demonstrated that etoricoxib 30 mg qd is at least as effective as celecoxib 200 mg qd in the treatment of OA of the knee and hip over 26 weeks based on reduction of pain, and improvement in physical function and global health status. Both active treatments provided superior efficacy compared with placebo over 12 weeks. The safety profiles of etoricoxib and celecoxib were similar over 26 weeks, including pre-defined AEs, with no safety risks noted compared with placebo over 12 weeks. Both active treatments had increased mean SBP and DBP from baseline over 26 weeks. Etoricoxib administered at 30 mg qd is efficacious in the treatment of OA.

Rheumatology	Key message
	• Etoricoxib 30 mg is comparable with celecoxib 200 mg in osteoarthritis.

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Efficacy and Tolerability Profile of Etoricoxib in Patients with Osteoarthritis: A Randomized, Double-blind, Placebo and Active-comparator Controlled 12-Week Efficacy Trial

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Key words: **Etoricoxib – Naproxen – Non-steroidal anti-inflammatory drugs – Cyclo-oxygenase – Osteoarthritis**

SUMMARY

Objective: To evaluate the efficacy of 12 weeks of treatment with etoricoxib, a selective COX-2 inhibitor, in patients with osteoarthritis (OA) of the knee or hip.

Methods: In the 12-week placebo- and active comparator-controlled period of a randomized, double-blind study, eligible patients were treated with etoricoxib 60 mg once daily (n = 224), naproxen 500 mg twice daily (n = 221), or placebo (n = 56). Western Ontario McMaster's Osteoarthritis Index (WOMAC) pain and physical function subscales and patient's global assessment of disease status were primary end points. Key secondary and other end points were patient's and investigator's global assessment of response to therapy, WOMAC stiffness subscale, investigator's global assessment of disease status, rescue paracetamol use, proportion of patients discontinuing due to lack of efficacy, and study joint tenderness.

Results: Etoricoxib 60 mg demonstrated efficacy significantly superior to placebo ($p \leq 0.005$) and comparable to naproxen 500 mg twice daily as assessed by the primary efficacy end points. Secondary and other end points confirmed these results. Treatment effects were evident by day 2, maximal by week 2, and sustained over the entire 12 weeks. Etoricoxib was well tolerated for 12 weeks.

Conclusions: Etoricoxib showed rapid and durable treatment effects in patients with OA of the knee or hip. Etoricoxib was generally well tolerated.

Introduction

Osteoarthritis (OA), the most common joint disorder, affects at least 25 million people in the United States and millions of others worldwide[1]. It affects the knees, hips, spine, hands, and feet, and generally progresses steadily over time, causing pain, joint stiffness, and loss of physical function[2]. Up to

33% of older adults have OA of the knee, which is a leading cause of knee replacement surgery[3,4].

Both selective cyclooxygenase (COX)-2 inhibitors and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended with other measures for the management of symptomatic OA[4,5]. Nonselective COX inhibition is associated with untoward gastrointestinal (GI) side-effects, particularly gastropathy, which may occur even with short-term use[6]. Selective COX-2 inhibitors, such as rofecoxib and celecoxib, have demonstrated clinical benefits in patients with arthritis and an improved GI tolerability profile[7–10]. The known variability of clinical response in individual patients to NSAIDs and to selective COX-2 inhibitors[11] and the suggested potential for greater benefits with increased selectivity of COX-2 inhibition[12] have further prompted the development of a second generation of selective COX-2 inhibitors, such as etoricoxib.

Etoricoxib (MK-0663 or 5-chloro-2-{6-methyl-pyridine-3-yl}-3-{4-methylsulfonylphenyl} pyridine) is a novel, orally active, selective COX-2 inhibitor, structurally unrelated to rofecoxib or celecoxib[13]. Previous *in vitro* and *ex vivo* human whole blood studies have indicated that etoricoxib is more highly selective than any other COX-2 inhibitor currently available, even at doses above those anticipated to be recommended for clinical use[13]. In a dose-ranging study, once-daily etoricoxib 60 mg showed maximal efficacy in patients with OA of the knee[14,15]. We present the results of a phase III trial conducted in over 500 patients with OA of the knee or hip.

Methods

The primary objective was to assess the efficacy and tolerability of etoricoxib compared with placebo in the treatment of patients with OA of the knee or hip over a 12-week period. The protocol and informed consent were approved by appropriate ethical review committees and investigational review boards for each participating center. The study was conducted in accordance with ethical standards for the treatment of human subjects outlined in the Declaration of Helsinki as written at the time of study initiation. Each patient gave written informed consent before undergoing any study procedure.

Patients

Eligible patients were men and women ≥ 40 years of age with a diagnosis of OA of the knee or hip, based on clinical and radiographic criteria, including joint space narrowing of the primary study joint; American Rheumatism Association (ARA) functional class I, II, or III; symptoms for at least 6 months; in otherwise good general health. Women were either postmenopausal or demonstrably nongravid. In addition, all patients were required to be regular users (for 25 of the 30 days prior to screening) of NSAIDs, selective COX-2 inhibitors, or paracetamol, and to demonstrate a minimum level of disease activity at screening, and < 80 mm on the Western Ontario and McMaster Universities OA Index (WOMAC) question 1 (pain walking on a flat surface; 100 mm visual analog scale {VAS})[16]. Users of NSAIDs or selective COX-2 inhibitors were required to demonstrate worsening of pain (flare) after a prespecified washout period based on the half-life of the drug. The flare criteria were: ≥ 40 mm and an increase of ≥ 15 mm compared with screening values on question 1 of WOMAC questionnaire and a worsening on the investigator's global assessment of disease status by ≥ 1 point on a 5-point Likert scale. Prestudy paracetamol (acetaminophen) users had to demonstrate reproducible symptoms on the screening and randomization visits: of ≥ 40 mm pain while walking on a flat surface and patient's global assessment of disease status. The investigator's global assessment of disease status was to be fair, poor, or very poor.

Patients with a past history of coronary atherosclerotic disease with active angina or congestive heart failure were excluded as were those with uncontrolled hypertension or a history of stroke, transient ischemic attack or hepatitis in the previous two years. Patients with any medical condition which, in the opinion of the investigator, could confound study results or cause undue risk to the patient (e.g. co-morbid conditions for which NSAIDs are contraindicated) were not allowed to participate. Patients using concomitant warfarin, anti-epileptics, ticlopidine, clopidrogel or digoxin were also excluded. Patients who had received intra-articular steroids or immunosuppressant therapy within three months, or systemic steroids, misoprostol, or sucralfate within one month prior to study entry were excluded, as were regular users (defined as > 6 of the 30 days prior to randomization) of proton pump inhibitors or H_2-blockers. Proton pump inhibitors and H_2-blockers were permitted at over-the-counter and prescription doses, as needed, after randomization to therapy.

Study Design

In this 12-week double-blind, placebo-controlled, primary efficacy period, eligible patients were randomized, according to a computer-generated allocation schedule, to receive placebo, etoricoxib 60 mg once daily or naproxen 500 mg twice daily, in a 1:4:4 ratio. Patients returned to the clinic for

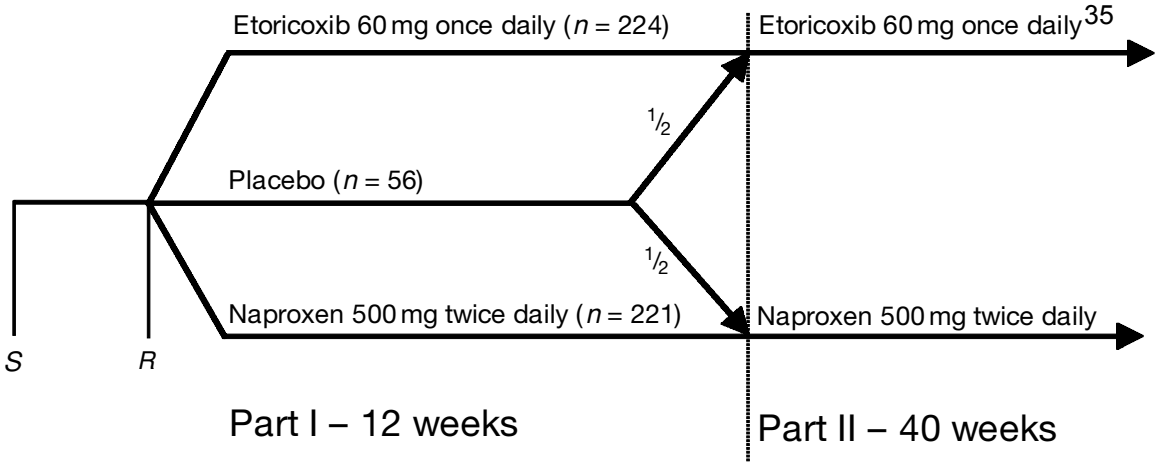

Figure 1. *Study design*

assessments at 2, 4, 8, and 12 weeks. A 40-week active-comparator controlled continuation period followed (data not reported) (Figure 1). Study blinding was maintained by using matching placebo tablets; patients took two tablets in the morning (etoricoxib 60 mg or matching placebo and naproxen 500 mg or matching placebo) and one tablet in the evening (naproxen 500 mg or matching placebo). Patients were permitted to use open-label paracetamol (up to 2600 mg/day) for OA pain of the study joint not adequately controlled by study medication; the number of tablets used was recorded.

Efficacy Assessments

Efficacy was assessed for multiple manifestations of OA using measurements recommended by Outcomes Measures in Rheumatology Clinical Trials (OMERACT), a world-wide consensus group of clinicians, researchers, regulatory agency officials and health policy experts[17,18]. Evaluations were made by patients and investigators at regular clinic visits, at 2, 4, 8, and 12 weeks. In addition, patients provided data for the evaluation of the onset and duration of early efficacy. Patients recorded their global assessment of response to therapy and pain walking on a flat surface (WOMAC)[16] at 4 and 24 hours after dosing on Days 1 through 6 on take-home forms.

The primary efficacy end points were: WOMAC pain and physical function subscales (100 mm VAS; 0 = none, to 100 = extreme, assessing pain and disability in performing specific activities of daily living, respectively), and patient's global assessment of disease status (100 mm VAS; 0 = 'very well' to 100 = 'very poor', assessing patient's overall well-being). The secondary efficacy end points included the patient's and investigator's global assessment of response to therapy (5-point Likert scale, 0 = excellent, 4 = no response), WOMAC stiffness subscale (100 mm VAS; 0 = no stiffness, to 100 = extreme stiffness, assessing the level of stiffness in specific activities of daily living), investigator's global assessment of disease status (5-point Likert scale; 0 = patient doing very well, to 4 = patient doing very poorly), rescue paracetamol use (tablets per day), percentage of patients discontinuing due to lack of efficacy, and study joint tenderness (scale of 0 = no pain, to 3 = patient states there is pain, winces, and withdraws).

Two exploratory end points were used to assess the duration of efficacy at the end of the dosing period in the primary study joint – WOMAC night pain and stiffness on awakening, questions from the pain and stiffness subscales (100 mm VAS; 0 = no pain or stiffness, to 100 = extreme pain or stiffness), which rated pain at night or joint stiffness on awakening over the previous two days.

Safety Assessments

Patients were closely monitored throughout the study for clinical or laboratory adverse events by physical examinations, vital signs, electrocardiograms, and routine hematology, blood chemistry, and urinalysis. All investigator-reported clinical adverse experiences were recorded at each visit and evaluated by the investigator, while blinded to study therapy, for intensity, seriousness, and relation to study medication. Investigators were instructed to report all adverse experiences occurring between patients' given consent and for 14 days after study drug discontinuation.

All potential upper GI perforations, ulcers, and bleeding, and potential thrombotic cardiovascular events were reviewed and adjudicated by external blinded committees using prespecified case definitions[7]. GI nuisance symptoms were defined as abdominal pain, acid reflex, dyspepsia, epigstric discomfort, heartburn, nausea, and vomiting.

Any event meeting a regulatory definition of 'serious' (life-threatening, resulting in or prolonging

hospitalization, causing permanent incapacity (including birth defects), or requiring significant medical intervention to prevent hospitalization, incapacity or death, or a malignancy)[19] was identified as such by the investigators.

Adverse events associated with NSAIDs or selective COX-2 inhibitors (e.g. hypertension and lower extremity edema), and percentage of patients who discontinued due to adverse experiences, were examined carefully.

Statistical Analysis

The primary analysis for each end point was the time-weighted average response over the 12-week treatment period. Analysis of covariance (ANCOVA) was used to assess time-weighted average changes from baseline for each efficacy end point, with treatment and primary study joint as the main effects and baseline as covariate. Analysis of variance (ANOVA) with terms for treatment and primary study joint was employed for end points without relevant baseline measurements.

Power was computed based on the variability seen in the etoricoxib Phase IIb dose-ranging study in patients with OA. With 200 patients in each active treatment group and 50 in the placebo group, the detectable differences vs. placebo (with 95% power, $\alpha = 0.05$, two-tailed) ranged from 12.8 mm to 14.1 mm for the three primary end points. Prespecified clinical comparability between etoricoxib 60 mg and naproxen 500 mg twice daily was demonstrated if the 95% confidence interval (CI) for the mean differences between the two groups in the time-weighted average response fell within ± 10 mm on a 100 mm VAS for all three primary end points; these comparability bounds were based on those used in previous studies with rofecoxib and etoricoxib[14,20–22]. For all evaluations, lower values were consistent with improvement.

All statistical tests for differences were two-tailed with $\alpha = 0.05$; $p \leq 0.05$ was considered statistically significant.

Results

Six hundred and seventy-seven (677) patients were screened and 501 were randomized to placebo ($n = 56$), etoricoxib 60 mg ($n = 224$), or naproxen 500 mg twice daily ($n = 221$) at 48 study sites (university clinics, rheumatology and general practice clinics) in 19 countries in North and South America, Europe, Africa, and Australia. The most common reasons for exclusion were not fulfilling OA disease or other criteria at screening (70 patients) and not fulfilling flare criteria at randomization (20 patients). At randomization, patients in all treatment groups had similar demographic and disease characteristics and baseline values for primary, secondary, and other efficacy end points. Most patients were prior NSAID users (approx. 92%) and had OA of the knee (approx. 75%) (Table 1).

Of the 501 patients enrolled, 337 (approx. 78%) completed the 12-week placebo-controlled period. The percentage of patients discontinuing due to clinical or laboratory adverse experiences was similar in the placebo, etoricoxib, and naproxen groups. However, significantly fewer patients discontinued due to lack of efficacy in the etoricoxib and naproxen groups compared with placebo ($p \leq 0.028$) (see Figure 2 and Table 2).

Efficacy

Over 12 weeks, etoricoxib 60 mg and naproxen 500 mg twice daily each demonstrated significantly greater improvements in clinical efficacy parameters compared with placebo, as assessed by all primary, secondary, and other efficacy end points ($p < 0.05$), except the use of rescue medicine for etoricoxib vs. placebo ($p = 0.063$). For the primary end points, only four patients, two on each of the active treatments, were excluded from one or more analysis due to missing baseline or on-treatment values. Treatment effects were comparable between the active treatment groups for all primary end points (see Table 2). No significant differences in treatment effects were observed between centers.

The onset of efficacy with etoricoxib was rapid; by day 2 differences from placebo were statistically significant. Efficacy was sustained at a relatively constant level for the days data were collected from take-home forms (days 2–6). For each active treatment, maximal treatment effects vs. placebo were evident by the first clinical evaluation (week 2) and persisted at approximately the same magnitude throughout the 12-week study period (Figure 3).

The efficacy of etoricoxib 60 mg at the end of the dosing interval, an indicator of the duration of treatment over the 24-hour dosing interval, as assessed by the WOMAC night pain and stiffness upon first awakening, was superior to placebo ($p = 0.009$) and similar to naproxen.

Safety and Tolerability

Both etoricoxib and naproxen had a generally favorable safety profile and were generally well tolerated by OA patients over the 12-week period. The most common adverse experiences over the 12 weeks of treatment are shown in Table 3(a). The percentage of patients discontinuing for adverse

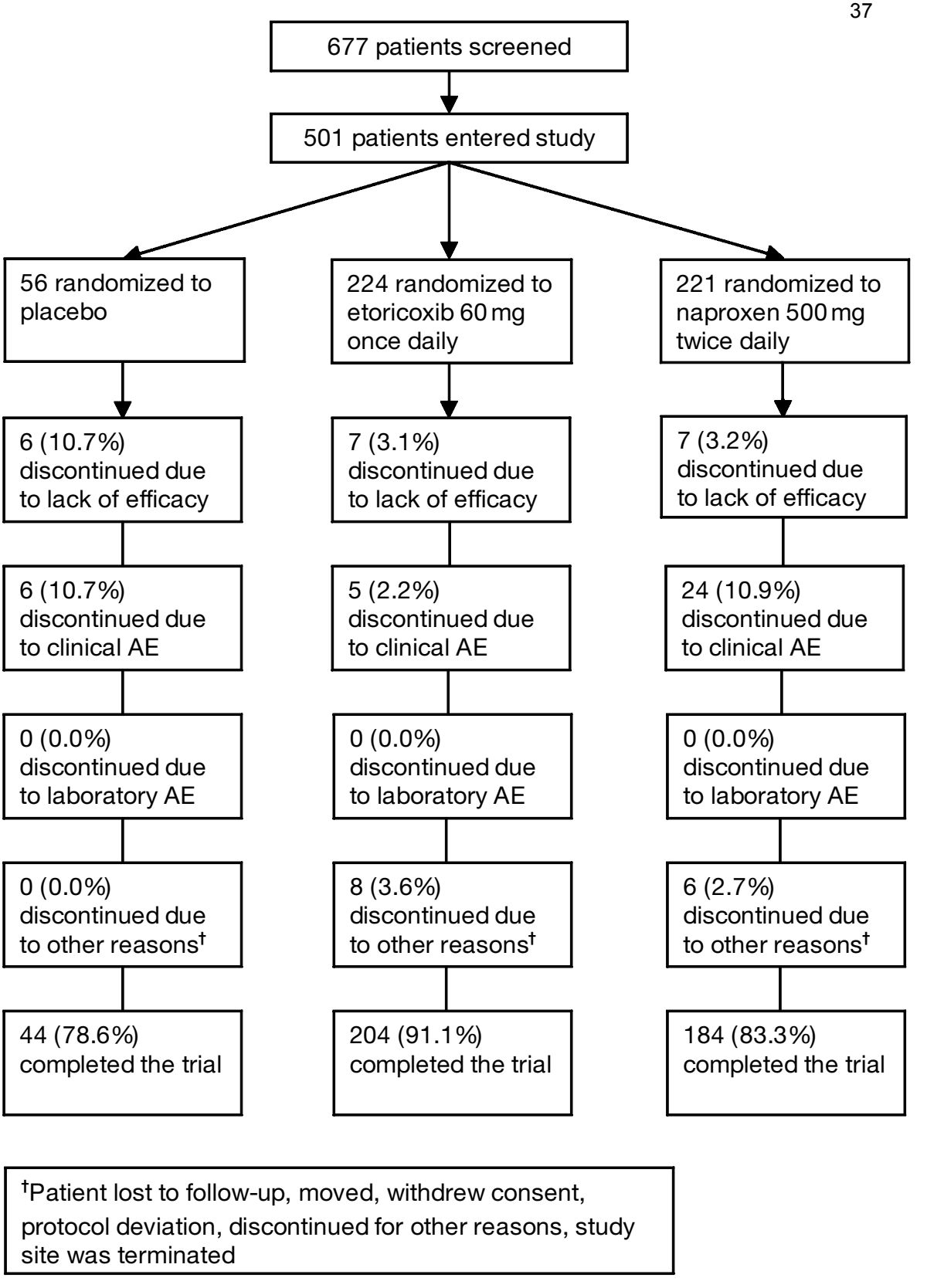

Figure 2. *Study flowchart*

experiences was relatively small in all treatment groups, but was lowest in the etoricoxib group (see Table 3(b)). Few serious adverse experiences were reported (Table 3(a)).

The incidence of 'nuisance' GI symptoms, such as nausea, epigastric discomfort or dyspepsia, was similar in the placebo and etoricoxib groups, and higher in the naproxen group (Table 3(b)). Five

Table 1. *Number (%) of patients with specific baseline characteristics at randomization*

	Placebo (*N* = 56)		Etoricoxib 60 mg (*N* = 224)		Naproxen 500 mg bid (*N* = 221)		Total (*N* = 501)	
Number and percentage of patients by:								
Gender:								
Women	46	(82.1)	173	(77.2)	173	(78.3)	392	(78.2)
Men	10	(17.9)	51	(22.8)	48	(21.7)	109	(21.8)
Race:								
Asian	0	(0.0)	1	(0.4)	2	(0.9)	3	(0.6)
Black	0	(0.0)	5	(2.2)	4	(1.8)	9	(1.8)
Multiracial	5	(8.9)	24	(10.7)	20	(9.0)	49	(9.8)
Other	7	(12.5)	38	(17.0)	33	(14.9)	78	(15.6)
White	44	(78.6)	156	(69.6)	162	(73.3)	362	(72.3)
Primary joint:								
Hip	12	(21.4)	54	(24.1)	58	(26.2)	124	(24.8)
Knee	44	(78.6)	170	(75.9)	163	(73.8)	377	(75.2)
Prior therapy:								
Paracetamol	4	(7.1)	12	(5.4)	22	(10.0)	38	(7.6)
NSAID user	52	(92.9)	212	(94.6)	199	(90.0)	463	(92.4)
ARA functional class:								
I	10	(17.9)	43	(19.2)	43	(19.5)	96	(19.2)
II	36	(64.3)	127	(56.7)	132	(59.7)	295	(58.9)
III	10	(17.9)	54	(24.1)	46	(20.8)	110	(22.0)
Mean baseline values with standard deviations:								
Age	64.09 (8.91)		62.93 (9.23)		63.16 (9.25)		63.16 (9.19)	
Body weight (kg)	83.35 (18.58)		79.58 (15.06)		78.09 (14.97)		79.34 (15.50)	
OA duration (years)	6.30 (6.35)		5.88 (6.04)		6.25 (6.46)		6.09 (6.25)	
WOMAC Pain Subscale†	68.70 (15.67)		64.91 (16.76)		65.64 (17.13)		65.65 (16.82)	
WOMAC Physical Function Subscale†	68.95 (14.38)		64.03 (18.82)		63.71 (18.01)		64.44 (18.05)	
Patient global assessment of disease status†	73.55 (16.73)		66.90 (19.96)		67.81 (19.08)		68.05 (19.31)	

†0–100 mm visual analog scale.

Table 2*. Efficacy end points: mean change from baseline with 95% confidence interval; time-weighted average response over 12 weeks*

	Placebo	Etoricoxib 60 mg	Naproxen 500 mg bid
Primary end points			
WOMAC pain subscale (VAS)	–15.33 (–20.70, –9.96)	–25.76 (–28.58, –22.94)	–25.32 (–28.13, –22.50)
WOMAC physical function subscale (VAS)	–12.46 (–17.80, –7.12)	–20.88 (–23.69, –18.08)	–20.73 (–23.53, –17.93)
Patient global assessment of disease status (VAS)	–16.59 (–22.26, –10.92)	–25.93 (–28.90, –22.95)	–24.18 (–27.15, –21.21)
Key secondary end points			
Patient global assessment of response to therapy (Likert)†	2.40 (2.15, 2.65)	1.78 (1.65, 1.91)	1.85 (1.72, 1.98)
Investigator global assessment of disease status (Likert)	–0.81 (–1.01, –0.61)	–1.35 (–1.46, –1.24)	–1.32 (–1.43, –1.21)
WOMAC stiffness subscale (VAS)	–14.94 (–20.72, –9.17)	–24.37 (–27.41, –21.34)	–23.41 (–26.44, –20.37)
Other end points			
Investigator global assessment of response to therapy (Likert)†	2.31 (2.07, 2.56)	1.66 (1.53, 1.79)	1.74 (1.62, 1.87)
Percentage of patients discontinued due to lack of efficacy‡	10.7 (2.6, 18.8)	3.1 (0.8, 5.4)	3.2 (0.9, 5.5)
Study joint tenderness§	–0.63 (–0.82, –0.44)	–0.91 (–1.01, –0.81)	–0.87 (–0.97, –0.77)
Paracetamol tablet count per day (for rescue)†	0.96 (0.68, 1.24)	0.67 (0.52, 0.81)	0.60 (0.46, 0.75)
WOMAC pain walking on a flat surface (VAS)	–23.64 (–29.51,–17.77)	–35.10 (–38.19, –32.01)	–33.30 (–36.39, –30.21)

Likert = 0–4-point scale; VAS = 0–100 mm scale
Lower values are consistent with improvement for all end points
$p < 0.001$ for all end points for etoricoxib and naproxen vs. placebo; except naproxen for study joint tenderness ($p < 0.05$)
†No baseline values available. For the response to therapy end points, primary assessment of improvement was based on difference from placebo
‡Percentages and confidence intervals were calculated from sample proportions; improvement is based on difference from placebo
§0–3-point scale

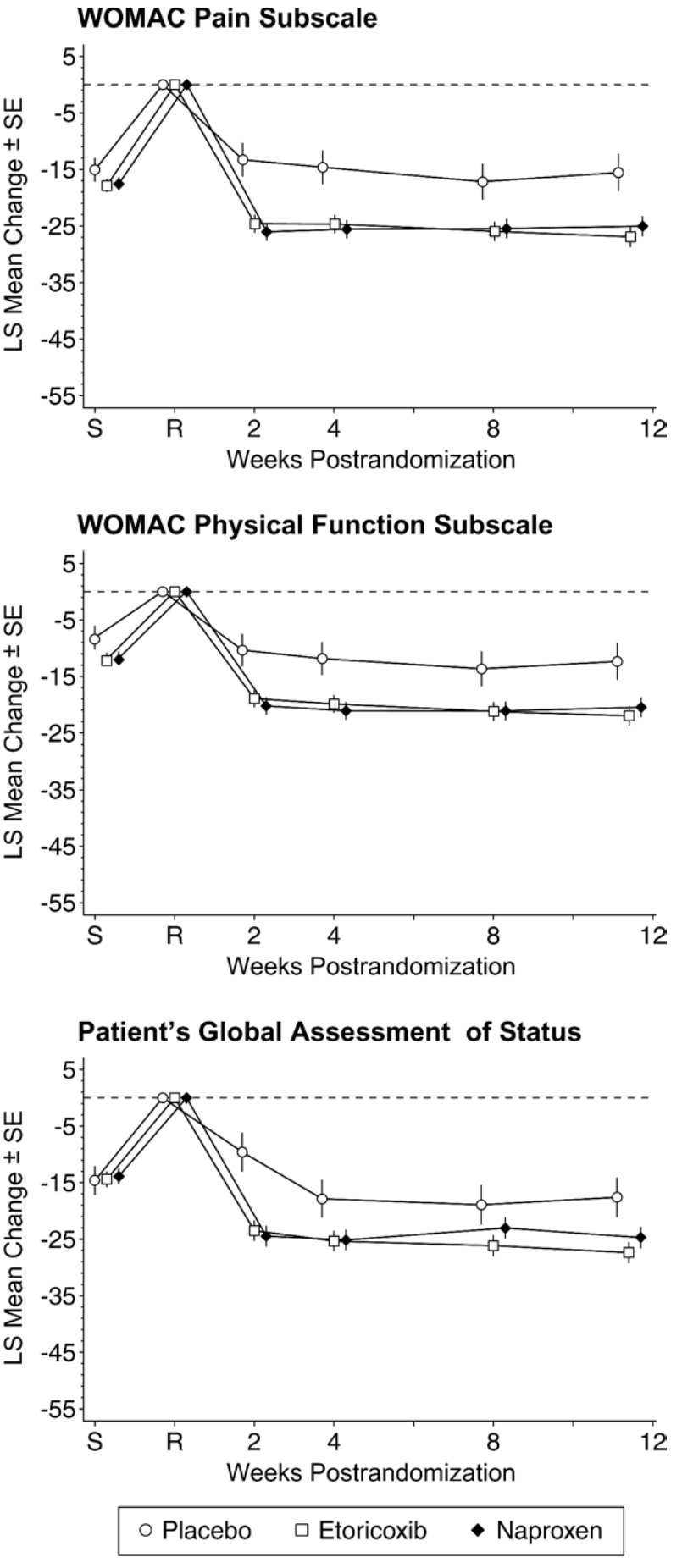

***Figure* 3.** *Change from baseline (R) for the primary efficacy end points over 12 weeks, by treatment group (placebo, etoricoxib 60 mg once daily, and naproxen 500 mg twice daily). Each end point was measured in millimeters on a 0–100 mm visual analog scale (VAS). Screening (S) values are also provided*

Table 3(a). *Summary of placebo-controlled safety data*

	Placebo (*N* = 56)		Etoricoxib 60 mg (*N* = 224)		Naproxen 500 mg bid (*N* = 221)	
	n	(%)	*n*	(%)	*n*	(%)
Number (%) of patients:						
with drug-related adverse experiences†	14	(25.0)	57	(25.4)	69	(31.2)
with serious adverse experiences	0	(0.0)	1	(0.4)	7	(3.2)
discontinued due to adverse experiences	6	(10.7)	5	(2.2)	24	(10.9)
Most common adverse experiences‡:						
abdominal pain	1	(1.8)	4	(1.8)	12	(5.4)
back pain	3	(5.4)	3	(1.3)	5	(2.3)
diarrhea	3	(5.4)	10	(4.5)	7	(3.2)
dyspepsia	1	(1.8)	6	(2.7)	11	(5.0)
epigastric discomfort	3	(5.4)	11	(4.9)	18	(8.1)
heartburn	4	(7.1)	9	(4.0)	14	(6.3)
hypertension	5	(8.9)	17	(7.6)	7	(3.2)
nausea	2	(3.6)	9	(4.0)	12	(5.4)
upper respiratory infection	1	(1.8)	11	(4.9)	12	(5.4)

†Determined by the investigator to be possibly, probably, or definitely, drug related while blinded to study treatment
‡Observed in 5% or more of patients in any treatment group

Table 3(b). *Adverse experiences of interest with discontinuations*

	Placebo (*N* = 56)		Etoricoxib 60 mg (*N* = 224)		Naproxen 500 mg bid (*N* = 221)	
	n	(%)	*n*	(%)	*n*	(%)
Renovascular:						
hypertension	5	(8.9)	17	(7.6)	7	(3.2)
discontinued	0	(0.0)	0	(0.0)	1	(0.5)
lower extremity edema	1	(1.8)	6	(2.7)	6	(2.7)
discontinued	0	(0.0)	0	(0.0)	0	(0.0)
congestive heart failure	0	(0.0)	0	(0.0)	1	(0.5)
discontinued	0	(0.0)	0	(0.0)	1	(0.5)
Gastrointestinal nuisance symptoms†:						
overall	11	(19.6)	45	(20.1)	73	(33.0)
discontinuations	1	(1.8)	3	(1.3)	10	(4.5)
Confirmed PUBs§:	0	(0.0)	0	(0.0)	5	(2.3)
discontinuations	0	(0.0)	0	(0.0)	5	(2.3)

†Including abdominal pain, acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea, and vomiting
§Upper GI perforation, ulcer, obstruction, or bleeding events

patients had confirmed upper GI perforations, ulcers or bleeding events; all were receiving naproxen.

Overall, the percentage of patients with lower extremity edema was similar for the active treatments and higher than for placebo. The percentage of patients in the placebo and etoricoxib groups who had adverse experiences of hypertension was similar; a numerically smaller percentage of patients receiving naproxen had hypertension compared with placebo or etoricoxib. The severity of lower extremity edema and hypertension adverse experiences were generally mild to moderate with few patients in any treatment group needing to discontinue the study drug. One patient had congestive heart failure (on naproxen). No thrombotic cardiovascular events were reported in any group (Table 3(b)).

Laboratory abnormalities occurred in similar proportions in all treatment groups. No patient discontinued study therapy specifically as a result of an abnormal laboratory value.

Discussion

In this pivotal phase III study, etoricoxib 60 mg once daily demonstrated clinically meaningful efficacy in treating the signs and symptoms of OA, confirming the results of a dose-ranging study[14,15]. Patients receiving etoricoxib 60 mg demonstrated significantly superior clinical improvements compared with those receiving placebo. These improvements were comparable to those seen with naproxen 500 mg twice daily. Etoricoxib was generally well-tolerated.

The methodology used in this trial is similar to that in previous trials comparing COX-2 selective agents to nonselective NSAIDs[14–15,20–22] and employed validated instruments and end points for the clinical evaluation of therapies for OA[16–19]. In keeping with recommendations by experts[17], the primary end points used in this study evaluated a broad range of domains, including pain, stiffness, and physical function, and thus provided a comprehensive evaluation of treatment effect. Key secondary measures were used to confirm these measurements. The end points used have been previously shown to be highly correlated and to provide adequate information to assess therapeutic efficacy[23]. Etoricoxib showed improvements for end points in each domain.

The active comparator, naproxen, is approved for use in treating the signs and symptoms of OA at the dose used in the current study (500 mg twice daily). Of note, unlike ibuprofen or diclofenac comparators used in other trials in OA patients[20–22], naproxen can be taken twice, rather than three times, daily, which simplified the dosing regimen. In the current study, naproxen at an approved dose and etoricoxib 60 mg had generally similar effects as measured by the primary end points.

A rapid onset of pain relief and durable efficacy throughout the dosing interval are beneficial in managing painful conditions. The pharmacokinetic profile of etoricoxib (half-life of approx. 22 h; time to peak plasma concentration of approx. 1 h) suggests that early onset and sustained effects might be seen with this compound in clinical practice[13]. In this trial, therapeutic response was prompt, observed in the first two days following initiation of treatment. Therapeutic responses were sustained over the 24 h dosing interval.

In this study, etoricoxib showed a generally favorable safety and tolerability profile over 12 weeks. In addition to standard observations of clinical and laboratory data, areas of particular interest (e.g. GI tolerability, upper GI ulceration, renovascular events, thrombotic cardiovascular events) based on COX-2 expression and distribution[24] and previous studies of selective COX-2 inhibitors[7,25–27] were emphasized. In the current study, etoricoxib exhibited a safety profile to be expected with a selective COX-2 inhibitor, with no new or unique toxicities noted. While these results are generally consistent with previous observations of selective COX-2 inhibitors[7,8,25,28], more conclusive assessments of the profile of etoricoxib, specifically in terms of GI, and cardiovascular safety, await the accumulation and analysis of larger clinical safety datasets.

In summary, results from this trial indicate that patients with OA of the knee or hip receiving etoricoxib 60 mg once daily showed treatment effects that were clinically superior to placebo and comparable to naproxen 500 mg twice daily. All treatments were generally well tolerated for 12 weeks. Thus, etoricoxib, a selective COX-2 inhibitor, may be an important new treatment option for the symptomatic management of OA.

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Evaluation of the efficacy and safety of etoricoxib compared with naproxen in two, 138-week randomized studies of osteoarthritis patients

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Evaluation of the efficacy and safety of etoricoxib compared with naproxen in two, 138-week randomized studies of osteoarthritis patients

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Word count: 3,498

Abstract

Objectives: To assess the efficacy and safety of etoricoxib 60 mg once daily and naproxen 500 mg twice daily over a 138-week treatment period in patients with osteoarthritis (OA).

Methods: Two 1-year randomized, double-blind, parallel-group 2-part base studies (Part I 12 weeks; Part II 40 weeks), followed by an 86-week extension, in OA (hip or knee) patients were conducted at 80 clinical centers (19 countries). The studies had identical designs. Patients taking placebo in Part I received etoricoxib or naproxen (1:1 ratio) in Part II and the Extension; patients taking etoricoxib or naproxen in Part I remained on the same treatment throughout the entire length of the studies. Co-primary efficacy endpoints were Patient Global Assessment of Disease Status, and WOMAC questionnaire Pain Subscale and Physical Function Subscale (100mm VAS). Efficacy over 138-weeks was assessed by graphical analysis. Safety was assessed by observation of adverse experiences and laboratory and physical evaluations.

Results: There were 997 patients who entered (615 completed) the Base studies. Of these patients, 463 patients entered the Extensions. A total of 161 and 151 patients in the etoricoxib and naproxen groups, respectively, completed 138-treatment weeks. Etoricoxib and naproxen showed similar efficacy throughout the 138 weeks of therapy. For etoricoxib and naproxen, respectively, WOMAC Pain assessments were: 67 and 67 mm (baseline); 28 and 29 mm (1-year), and 34 and 33mm (138-weeks). Results for the other efficacy endpoints were similar to those seen with the WOMAC Pain assessments. Both etoricoxib and naproxen were generally well tolerated.

Conclusion: Both etoricoxib and naproxen demonstrated long-term clinical efficacy for the treatment of OA. Etoricoxib and naproxen were generally well tolerated.

Introduction

Osteoarthritis (OA) is a condition that is characterized by loss of articular cartilage in synovial joints, osteophyte formation, subchondral bone change and synovitis.[1,2] Patients with OA experience symptoms such as pain, loss of physical function, and, in advanced stages, disability. [1,3,4] The goal of treatment is to increase joint function and improve quality-of-life. Non-pharmacologic approaches, such as diet and exercise, as well as use of paracetamol for the reduction of pain are recommended for patients with mild to moderate OA. For patients who require greater efficacy, NSAIDs or selective COX-2 inhibitors are often prescribed. While there are many treatment options available, selection of a therapeutic approach for patients is often difficult and involves weighing benefits of a particular therapy against its potential risks on an individual basis.

Traditional, nonselective NSAIDs inhibit both isoforms of cyclooxygenase (COX): COX-1 and COX-2. These analgesic agents have demonstrated their value in the treatment of pain from osteoarthritis, however, their use is associated with gastrointestinal (GI) adverse experiences (AEs) such as ulcers and GI bleeding because of their potent inhibition of the gastro-protective COX-1 isoform.[5,6] Selective COX-2 inhibitors have demonstrated comparable efficacy in chronic and acute pain settings with significantly improved GI tolerability compared with traditional NSAIDs.[7]

Etoricoxib is a COX-2 selective inhibitor that has demonstrated efficacy in patients with OA.[8] The objective of the current analysis was to assess the maintenance of efficacy and tolerability of etoricoxib 60 mg once daily and naproxen 500 mg twice daily in patients with OA in a combined analysis of two studies over 138 weeks of therapy. Recent studies have suggested that COX-2 selective inhibitors are associated with an increased risk of thrombotic cardiovascular (CV) events as compared to placebo.[9,10] Data are also available that suggest traditional NSAIDs are associated with increased CV risk.[11] In this analysis, data on CV AEs were collected and adjudicated by an external safety monitoring committee; however, these studies were not powered or designed to specifically evaluate the CV safety profile of etoricoxib.

Methods

Two studies, Protocol 018 and Protocol 019, were conducted at 47 centers in the United States and 33 centers internationally (United States, Europe, Canada, and Australia), respectively. The protocol and consent forms were approved by Institutional Review Boards or Ethics Review Committees for each study site. Each patient provided written informed consent prior to entering the base studies and before starting the extension studies.

Patient Inclusion/Exclusion

Patients who entered the base studies were > 40 years of age and had clinical symptoms or a clinical diagnosis of OA of the knee or hip, based on clinical and radiographic criteria, for greater than 6 months prior to the beginning of the studies. Patients who entered the extension studies were required to have fulfilled eligibility requirements for the base studies and to have tolerated treatment during the previous treatment period. Patients were classified as American Rheumatism Association (ARA) functional Class I, II, or III. Other than OA, the patients were in general good health. Female patients of child-bearing potential were instructed to use contraception and were excluded if they were pregnant. Patients included in the studies were regular users of either NSAIDs or paracetamol (i.e. patients used these analgesics for at least 25 of the previous 30 days prior to study enrollment). The number of paracetamol users enrolled at each study site was limited to 20%. Recent sustained use (i.e. 6 consecutive days during the month prior to enrollment) of H_2 receptor antagonists or proton pump inhibitors was not permitted. Proton pump inhibitors and H_2 receptor antagonists were permitted at over-the-counter and prescription doses, as needed, after randomization. Up to one-third of patients were allowed to take low-dose aspirin($\leq$100 mg/day). Paracetamol (325 mg tablets) was available as rescue medication; rescue medication use was restricted (i.e., it was not permitted during the initial 2 weeks of therapy) and recorded. All other analgesic medications were not permitted. The following medications were also not permitted during the studies: warfarin, ticlopidine, clopidogrel, anti-epileptics, digoxin, rifampin, dexamethasone, or lithium.

Prestudy NSAID users were required to demonstrate worsening of pain (flare) after a prespecified washout period based on the half-life of the drug. The length of the washout period was based on the individual medication, but was at least 3 days and as much as 15 days. They were required to meet two flare criteria: 1) $\geq$40 mm and an increase of 15 mm compared with screening values on question 1 of the Western Ontario and McMaster Universities OA Index (WOMAC),[17] Pain While Walking on a Flat Surface (100-mm visual analog scale [VAS]) and 2) a worsening on the Investigator's Global Assessment of Disease Status by $\geq$1 point on a 0- to 4- point Likert scale. At the flare visit, prestudy paracetamol users were required to have a response on the Investigator's Global Assessment of Disease Status as fair, poor, or very poor and had to demonstrate reproducible disease activity compared with the screening visit: $\geq$40 mm Pain While Walking on a Flat Surface (WOMAC 100 mm VAS) and the Patient's Global Assessment of Disease Status (100 mm VAS).

Study Design

The initial base studies, which had replicate study designs, randomized patients to receive placebo, etoricoxib 60 mg, or naproxen 500 mg twice daily. Each base study consisted of a 12-week placebo- and active-comparator-controlled period (Part I) followed by a 40-week active-comparator controlled period (Part II); this was followed by an 86-week active-comparator controlled extension period. In Part I, patients were randomly allocated (according to a computer-generated allocation schedule) to once-daily etoricoxib 60 mg or matching placebo or naproxen 1000 mg (500 mg twice daily, or matching placebo twice daily) in a blinded, double-dummy fashion. In Part II and the extensions, patients took etoricoxib 60 mg or naproxen 1000 mg (500 mg twice daily) in a blinded, double-dummy fashion. Patients taking placebo in Part I were randomly assigned to take etoricoxib 60mg (50%) or naproxen 1000mg (50%) in Part II and the extensions. Patients taking etoricoxib 60mg or naproxen 1000mg in Part I remained on the same regimen throughout the Base study and Extension.

Study visits occurred at Weeks 2, 4, 8, 12, 19, 26, 33, 39, 45, and 52 during the base studies. During the extension studies, study visits occurred at Weeks 69, 86, 104, 121, and 138. If a patient discontinued, then a discontinuation visit was scheduled.

Efficacy Measures

The primary efficacy endpoints were: Western Ontario and McMaster Universities (WOMAC) pain subscale (100-mm VAS; 0 = no pain to 100 = extreme pain); the WOMAC physical function subscale (100-mm VAS; 0 = no difficulty to 100 = extreme difficult); and the patient's global assessment of disease status (100-mm VAS; 0 = "very well" to 100 = "very poor," assessing the patient's overall well-being).

Safety Measures

Patients were monitored for clinical or laboratory adverse events (AEs) by physical examinations, vital signs, electrocardiograms, and routine hematology, blood chemistry, and urinalysis at each study visit. Investigators were instructed to report all AEs occurring while patients received therapy and for 14 days after study drug discontinuation. Serious AEs (life-threatening experiences, those resulting in or prolonging hospitalization, those causing permanent incapacity, those requiring significant medical intervention to prevent hospitalization, incapacity or death, or a malignancy) were identified by investigators. Additionally, prior to initiation of the studies, blinded, external adjudication committees were organized to evaluate any potential serious thrombotic CV or upper GI perforations, ulcers, or bleeding events (PUBs) that occurred during the trial.

Safety was evaluated by various means, including an examination of patients exceeding predefined limits for laboratory values of interest (e.g. consecutive decreases in hemoglobin and hematocrit, increased aminotransferase values, or increases in serum creatinine), common events associated with NSAIDs or selective COX-2 inhibitors (e.g., hypertension and lower extremity edema), and clinical review of tabulated data.

Power and Determination of Sample Size

Power and sample size were calculated for the efficacy evaluation during Part I of the base study based on the variability seen in a previous etoricoxib dose-ranging study.[12] With 200 patients in each active treatment group and 50 in the placebo group, the detectable differences vs. placebo (with 95% power, alpha=0.05, two-tailed) ranged from 12.8 to 14.1 mm for the primary endpoints. Prespecified clinical comparability between etoricoxib 60 mg and naproxen 1000 mg was demonstrated if the 95% confidence interval (CI) for the mean differences between the two groups in the time-weighted average response fell within ±10 mm on a 100-mm VAS for all three primary endpoints (primary variables). Using this equivalence range, the sample size of 200 patients per treatment group has greater than 95% power to demonstrate equivalence if the true (not observed) mean difference between the etoricoxib group and the naproxen group is 0 for all 3 primary end points. For all evaluations, lower values were consistent with improvement. All statistical tests for differences were 2-tailed with $\alpha = 0.05$; $p \leq 0.05$ was considered statistically significant.

Statistical Analysis

In Part I, the primary analysis for each end point was the time-weighted average response over the 12-week treatment period. The time-weighted average response is calculated by taking the time between adjacent observations divided by the time from the randomization visit to the last observation in the treatment period, and using it as the weight for computation of the average. Analysis of covariance (ANCOVA) was used to assess time-weighted average changes from baseline for each efficacy endpoint, with treatment and primary study joint as the main effect and baseline as covariate. Analysis of variance (ANOVA) with terms for treatment and primary study joint was employed for most endpoints without relevant baseline measurements. For the Patient and Investigator Global Response to Therapy endpoints, the Patient Global Assessment of Disease was used as the covariate.

In Part II and the extensions, the treatment response was assessed through graphical presentation and tabulation of mean change from baseline at each study visit. The comparability of etoricoxib and naproxen was examined by the time-weighed average change from baseline over 52 weeks as described for Part I, and the analysis was limited to patients who received the same treatment in Parts I and II.

For the extensions, efficacy results were assessed over time within each of the treatment groups by least squares means changes from baseline obtained from an ANCOVA model similar to that used for Part I, with appropriate 95% Confidence Intervals (CIs). No formal hypothesis testing was carried out due to the non-randomized, self-selected nature of the patient population in the extension studies. Only visual examination of the summary statistics through tables and graphs was performed.

Results

Patient Demographics

Of the 997 patients randomized into Part I, 838 entered Part II and 463 entered the 86-week extension studies (Figure 1). The baseline characteristics were similar among patients receiving placebo, etoricoxib, and naproxen; baseline patient characteristics from Part I are representative of the patients in the extension, and remained similar among the etoricoxib and naproxen groups (Table 1). The most common reasons for discontinuations in Part I were clinical AEs and a lack of efficacy. In Part II, patients discontinued due to clinical AEs, lack of efficacy, and patients withdrew consent. Most common reasons for discontinuation during the 86-week extension were clinical AEs, patients withdrew consent, and lack of efficacy (Figure 1).

Efficacy Results

Efficacy over 52 weeks

Etoricoxib 60 mg and naproxen 1000 mg demonstrated significantly greater improvements than placebo over the 12-week treatment period for all efficacy endpoints. For the three co-primary efficacy endpoints, etoricoxib was comparable to naproxen 1000 mg, as evidenced by the 95% confidence intervals for the between-group mean differences being contained within the ±10 mm equivalence bound. The placebo group had a statistically significantly higher discontinuation rate due to lack of efficacy than both the etoricoxib ($p<0.001$) and naproxen 1000 mg groups ($p<0.001$) (Figure 1). Efficacy responses in the etoricoxib and naproxen groups was not significantly different. Furthermore, differences between the active treatments and placebo were observed at the earliest time point of measurement (2 weeks after the commencement of study medication) and persisted at approximately the same magnitude across the 12 weeks. Onset of treatment effect, as assessed by the WOMAC pain walking on flat surface and patient global assessment of response to therapy recorded at 4-hours post dose, was seen as early as Day 1. Duration of treatment effect following treatment with etoricoxib or naproxen, as assessed by the WOMAC pain walking on flat surface and patients global assessment of response to therapy recorded at 24-hours post dose, was significantly different relative to placebo from Day 2 onwards.

For patients who remained on the same treatment (etoricoxib or naproxen) during Part I and II of the studies, treatment effects, as measured by the time-weighted average change from baseline over the entire 52 weeks of the studies, were similar between etoricoxib and naproxen 1000 mg. Efficacy was maintained at a consistent level over the 52 weeks of the studies for both the etoricoxib and naproxen 1000-mg treatment groups.

Efficacy over 138 weeks

Graphical examination of the adjusted mean changes from baseline for the 3 primary endpoints (WOMAC Pain Subscale, WOMAC Physical Function Subscale, and Patient Global Assessment of Disease) demonstrated relatively constant treatment effect over the entire 138-week extension period; results were similar for the etoricoxib and naproxen groups (Figure 2). Clinically important treatment effects from etoricoxib and naproxen were observed from the first treatment period at Week 2; these treatment effects were significantly superior to that of placebo during Part I (Table 2; Figure 2)

Safety Results

All treatments were generally well tolerated in all periods of the studies. The percentage of patients with any AEs and serious AEs was similar among all treatment groups. In each study period, the naproxen group had a numerically greater percentage of patients discontinuing due to an AE as well as the greatest percentage of patients with drug-related AEs. Regardless of treatment group, the most common AEs in the three study periods overall was upper respiratory infection and hypertension (Table 3).

Hypertension occurred in 6.3% (placebo), 5.2% (etoricoxib), and 3.0% (naproxen) of patients during the placebo-controlled Part I; 7.4% (etoricoxib) and 4.2% (naproxen) during Part II of the base period; and 11% (etoricoxib) and 10.6% (naproxen) during the 86-week extension period. The observed increase in incidence over time in all treatment groups is not unexpected as these results represent a cumulative incidence of AEs over time. Other renovascular AEs such as lower extremity edema and congestive heart failure occurred at a lower frequency relative to that observed with hypertension AEs and with similar frequency among the treatment groups in all three treatment periods. Discontinuations from renovascular AEs were rare in all treatment groups (Table 4).

In Part I, the incidence of gastrointestinal (GI) nuisance AEs (i.e. abdominal pain, acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea, and vomiting) was similar for etoricoxib and placebo; GI nuisance AEs were more frequent in the naproxen group. In Part II, the etoricoxib and naproxen groups had a similar proportion of patients with GI nuisance AEs, whereas they occurred with greater frequency in the naproxen group compared with the etoricoxib group during the extension period (Table 4).

Upper GI PUB events (confirmed by an external adjudication committee) did not occur in patients on etoricoxib during the Part I of the base period while 7 (1.6%) patients receiving naproxen experienced a GI PUB. In Part II of the base period, 5 (1.2%) patients receiving etoricoxib experienced a GI PUB while 11 (2.7%) patients receiving naproxen experienced a GI PUB. GI PUB events occurred in 2 (0.8%) patients in the etoricoxib group and 13 (5.9%) patients in the naproxen group during the 86-week extension period. The following specific PUB events occurred in the etoricoxib group: duodenal ulcer and upper GI hemorrhage. In the naproxen group, duodenal ulcers, gastric ulcers, and upper GI hemorrhages occurred.

During Part I, 1(0.2%) patient in the etoricoxib group had a confirmed serious CV AE compared with none in the naproxen group. In Part II, 10 (2.3%) etoricoxib patients had thrombotic CV events compared with 2 (0.5%) naproxen patients. Confirmed thrombotic CV events occurred in 2 (0.8 %) etoricoxib patients and 4 (1.8 %) naproxen patients in the 86-week extension period; these thrombotic CV events included acute myocardial infarction and ischemic stroke in the etoricoxib group, and, in the naproxen group, acute myocardial infarction, transient ischemic attack, and a pulmonary embolism. All patients with confirmed thrombotic CV events recovered.

Discussion

The present report provides data from a combined analysis of two, long-term studies of identical design comparing the efficacy and safety of etoricoxib 60 mg and naproxen 1000 mg in patients with OA. The 12-week, placebo-controlled period of the international study from the present analysis was previously reported; the efficacy of etoricoxib was superior to that of placebo and similar to that of naproxen; both etoricoxib and naproxen were also generally well tolerated.[13] (1) The base period of the U.S. study demonstrated similar results [14] In the present, combined analysis of both studies, the efficacy of etoricoxib and naproxen were comparable; clinical improvements, as assessed by the primary efficacy endpoints, were observed by the first treatment visit, 2 weeks after randomization, and maintained for up to 138 weeks. Both treatments were generally well tolerated. Although a similar proportion of patients in each treatment group experienced an AE over the entire course of these studies, the specific types of AEs that occurred in each treatment group differed to some degree.

Hyptertension is a common comorbidity in patients with OA and is also a condition that may be associated with the use of both selective and traditional NSAIDs due to their effects on renal prostaglandins.[15,16] In a pooled analysis of studies in the etoricoxib development program, etoricoxib demonstrated a shallow dose response with a generally similar incidence of hypertension compared with traditional NSAIDs. In comparisons to ibuprofen, the incidence was slightly lower with etoricoxib whereas in comparisons to naproxen the incidence was slightly higher with etoricoxib; none of these differences were interpreted as clinically meaningful.[17] In a large, randomized, controlled trial in OA patients comparing etoricoxib 90 mg, (1.5 times the recommended OA dose) versus the traditional NSAID, diclofenac 150 mg, etoricoxib 90 mg demonstrated a significantly higher incidence of hypertension.[18] In the current studies, hypertension was among the most common AEs to occur for both etoricoxib and naproxen. The incidence of hypertension was numerically greater with etoricoxib compared with naproxen, which is consistent with what is observed in previous analyses.[17] The medical signficance of these observations likely remains limited however, as discontinuations from hypertension were infrequent and generally similar among both groups. Furthermore, the occurrence of other renovascular AEs such as lower extremity edema and congestive heart failure were generally similar among patients that received etoricoxib and naproxen throughout the 138-week treatment period. These data demonstrate the importance of monitoring the blood pressure of all patients that are treated with any NSAID, including etoricoxib.

Previous studies have suggested that etoricoxib is associated with a lower frequency of gastrointestinal AEs in comparison to patients receiving chronic treatment with traditional, nonselective NSAIDs.[19,20] The present analysis supports the outcomes from these previous studies; patients on etoricoxib experienced GI AEs with a reduced frequency compared with patients on naproxen during Part I of the study. Due to the self-selected nature of the study population beyond Part I of the study, the lack of a demonstrable difference in GI tolerability among the treatment groups was not unexpected. However, there was an observable difference in GI tolerability during the extension period in favor of etoricoxib, although the extension data should be viewed with caution since it also is not representative of a randomized patient population.

Additionally, the proportion of patients with GI perforations, ulcers, or bleeding was smaller in the etoricoxib group compared with the proportion in the naproxen group.

Although these studies were not powered to specifically address CV risk, this report presents the available data from these studies. In the current studies, the incidence of thrombotic CV events was low in each treatment group with a greater proportion of patients experiencing a thrombotic CV event in the etoricoxib group compared with naproxen. These results are consistent with a previous analysis of CV data from the etoricoxib development program, in which confirmed thrombotic CV events occurred at a similar rate among patients treated with etoricoxib and traditional NSAIDs with the exception of naproxen. In comparisons to naproxen, the rate of confirmed thrombotic CV events was higher for etoricoxib.[21] These results are also consistent with CV safety data observed in randomized trials of other COX-2 selective inhibitors in which a lower incidence of thrombotic CV events was observed with naproxen.[22,7,23]

Conclusions

In summary, etoricoxib 60 mg and naproxen 1000 mg had similar efficacy for the treatment of OA that was maintained over 138 weeks. Both agents were generally well tolerated. Although these studies were not powered to evaluate the relative risk of GI or CV events, the safety data from these studies suggest that etoricoxib has a more favorable GI safety and tolerability profile as compared to naproxen, whereas naproxen is associated with a numerically lower incidence of thrombotic CV events.

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Figure Legend

Figure 1: Patient Accounting and Study Design displaying Part I (weeks 0-12), Part II (weeks 12-52), and the Extension (weeks 52-138)

Figure 2: Mean change from baseline (+/- SE) over time in patients remaining on the same treatment from baseline to Week 121 for the primary endpoints: WOMAC Pain Subscale (100-mm Visual Analog Scale); WOMAC Physical Function Subscale (100-mm Visual Analog Scale); Patient and Investigator Global assessments of Disease Status (100-mm Visual Analog Scale)

Tables

Table 1 – Baseline Patient Characteristics

	Baseline Patient Characteristics for All Enrolled Patients			Baseline Patient Characteristics for Patients That Entered the Extension Study	
	Placebo (N=112)	**Etoricoxib 60 mg (N=446)**	**Naproxen (N=439)**	**Etoricoxib 60 mg (N=246)**	**Naproxen (N=217)**
Gender [n (%)]					
Female	82 (73.2)	322 (72.2)	314 (71.5)	191 (77.6)	156 (71.9)
Male	30 (26.8)	124 (27.8)	125 (28.5)	55 (22.4)	61 (28.1)
Race [n (%)]					
Asian	1 (0.9)	2 (0.4)	3 (0.7)	1 (0.4)	1 (0.5)
Black	6 (5.4)	18 (4.0)	19 (4.3)	10 (4.1)	5 (2.3)
Multi-racial	6 (5.4)	24 (5.4)	20 (4.6)	26 (10.6)	19 (8.8)
Other	10 (8.9)	42 (9.4)	35 (8.0)	31 (12.6)	22 (10.1)
White	89 (79.5)	360 (80.7)	362 (82.5)	178 (72.4)	170 (78.3)
Age					
Mean (SD)	63.8 (10.2)	62.59 (9.8)	62.7 (9.7)	62.19 (9.0)	61.51 (9.4)
Range (in years)	40 to 87	35 to 92	40 to 87	40 to 84	40 to 87
Body Weight (kg)					
Mean (SD)	86.4 (18.5)	84.28 (18.9)	85.09 (18.9)	83.90 (18.67)	86.03 (18.44)
Range	51.3 to 138.0	44.8 to 176.9	48.00 to 158.8	47.6 to 176.9	48.0 to 142.9
Primary OA Joint [n (%)]					
Hip	20 (17.9)	100 (22.4)	99 (22.6)	40 (16.3)	38 (17.5)
Knee	92 (82.1)	346 (77.6)	340 (77.4)	206 (83.7)	179 (82.5)
ARA Function Class [n (%)]					
Class I	24 (21.4)	99 (22.2)	90 (20.5)	48 (19.5)	48 (22.1)
Class II	69 (61.6)	246 (55.2)	269 (61.3)	144 (58.5)	126 (58.1)
Class III	19 (17.0)	101 (22.6)	80 (18.2)	54 (22.0)	43 (19.8)

Table 2

LS mean changes (95% CI) from baseline in the 52-week base studies (analysis of time-weighted average response to therapy)

Treatment Group	WOMAC Pain Subscale (VAS†)			WOMAC Physical Function Subscale (VAS†)			Patient Global Assessment of Disease Status (VAS†)		
Part I (12-week Treatment Period)									
Placebo	-15.31	(-19.25,	-11.37)	-10.27	(-14.19,	-6.35)	-13.38	(-17.51,	-9.26)
Etoricoxib 60 mg	-27.94	(-30.03,	-25.85)	-22.81	(-24.89,	-20.74)	-26.39	(-28.57,	-24.21)
Naproxen 1000 mg	-28.57	(-30.68,	-26.47)	-23.70	(-25.78,	-21.61)	-26.46	(-28.66,	-24.26)
Parts I & II (52-week Treatment Period; in patients on the same therapy for 52 weeks)									
60 mg	-31.03	(-33.19,	-28.86)	-25.96	(-28.24,	-23.69)	-27.58	(-29.83,	-25.32)
Naproxen	-30.60	(-32.82,	-28.39)	-26.06	(-28.39,	-23.73)	-27.82	(-30.14,	-25.51)

† 0- to 100-mm scale

Table 3 – Incidence of Clinical Adverse Experiences (AEs), by Study Period.

	12-Week Part I of Base Studies			40-week Part II of Base Studies		86-week Extension Period	
	Placebo	**Etoricoxib**	**Naproxen**	**Etoricoxib**	**Naproxen**	**Etoricoxib**	**Naproxen**
	N=112	**N=446**	**N=439**	**N=434**	**N=404**	**N=246**	**N=217**
	n(%)	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Any AE	57 (50.9)	262 (58.7)	279 (63.6)	301 (69.4)	276 (68.3)	179 (72.8)	181 (83.4)
Serious AEs	1 (0.9)	6 (1.3)	9 (2.1)	32 (7.4)	30 (7.4)	26(10.6)	33 (15.2)
Discontinuations due to AEs	9 (8.0)	24 (5.4)	44 (10.0)	37 (8.5)	46 (11.4)	24(9.8)	28 (12.9)
Drug Related AEs	19 (17.0)	96 (21.5)	128 (29.2)	76 (17.5)	91 (22.5)	42 (17.1)	58 (26.7)
Most Common AEs (≥ 5.0% in any treatment group)							
Abdominal Pain	2 (1.8)	7 (1.6)	22 (5.0)	8 (1.8)	10 (2.5)	2 (0.8)	11 (5.1)
Influenza-like disease	2 (1.8)	13 (2.9)	13 (3.0)	27 (6.2)	13 (3.2)	5 (2.0)	11 (5.1)
Upper Respiratory Infection	6 (5.4)	34 (7.6)	35 (8.0)	47 (10.8)	43 (10.6)	33 (13.4)	18 (8.3)
Hypertension	7 (6.3)	23 (5.2)	13 (3.0)	32 (7.4)	17 (4.2)	27 (11.0)	23 (10.6)
Dyspepsia	2 (1.8)	9 (2.0)	22 (5.0)	11 (2.5)	11 (2.7)	6 (2.4)	5 (2.3)
Epigastric Discomfort	3 (2.7)	13 (2.9)	24 (5.5)	13 (3.0)	17 (4.2)	6 (2.4)	9 (4.1)
Heartburn	4 (3.6)	12 (2.7)	23 (5.2)	10 (2.3)	10 (2.5)	4 (1.6)	4 (1.8)
Nausea	4 (3.6)	14 (3.1)	23 (5.2)	8 (1.8)	4 (1.0)	3 (1.2)	4 (1.8)
Sinusitis	2 (1.8)	9 (2.0)	7 (1.6)	8 (1.8)	15 (3.7)	13 (5.3)	12 (5.5)
Back Pain	6 (5.4)	3 (0.7)	6 (1.4)	21 (4.8)	12 (3.0)	15 (6.1)	13 (6.0)
Bronchitis	1 (0.9)	9 (2.0)	6 (1.4)	14 (3.2)	12 (3.0)	11 (4.5)	12 (5.5)
Urinary Tract Infection	0 (0.0)	14 (3.1)	11 (2.5)	21 (4.8)	20 (5.0)	13 (5.3)	18 (8.3)

Table 4 – AEs of Special Interest

	12-Week Part I of Base Studies			40-week Part II of Base Studies		86-week Extension Period	
	Placebo	Etoricoxib	Naproxen	Etoricoxib	Naproxen	Etoricoxib	Naproxen
	N=112	N=446	N=439	N=434	N=404	N=246	N=217
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
GI Nuisance Symptoms							
GI Nuisance AEs	14 (12.5)	50 (11.2)	102 (23.2)	54 (12.4)	51(12.6)	19 (7.7)	31 (14.3)
Discontinuations	2 (1.8)	5 (1.1)	18 (4.1)	6 (1.4)	8 (2.0)	0 (0.0)	3 (1.4)
Renovascular AEs							
Hypertension	7 (6.3)	23 (5.2)	13 (3.0)	32 (7.4)	17 (4.2)	27 (11.0)	23 (10.6)
Discontinuations	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)
Lower Extremity Edema	2 (1.8)	10 (2.2)	9 (2.1)	10 (2.3)	13 (3.2)	8 (3.3)	7 (3.2)
Discontinuations	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)
Congestive Heart Failure	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.9)
Discontinuations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Confirmed serious thrombotic CV AEs and Upper GI Bleeding AEs							
Confirmed serious thrombotic CV AEs	0 (0.0)	1 (0.2)	0 (0.0)	10 (2.3)	2 (0.5)	2 (0.8)	4 (1.8)
Confirmed Upper GI Bleeding AEs	0 (0.0)	0 (0.0)	7 (1.6)	5 (1.2)	11 (2.7)	2 (0.8)	13 (5.9)

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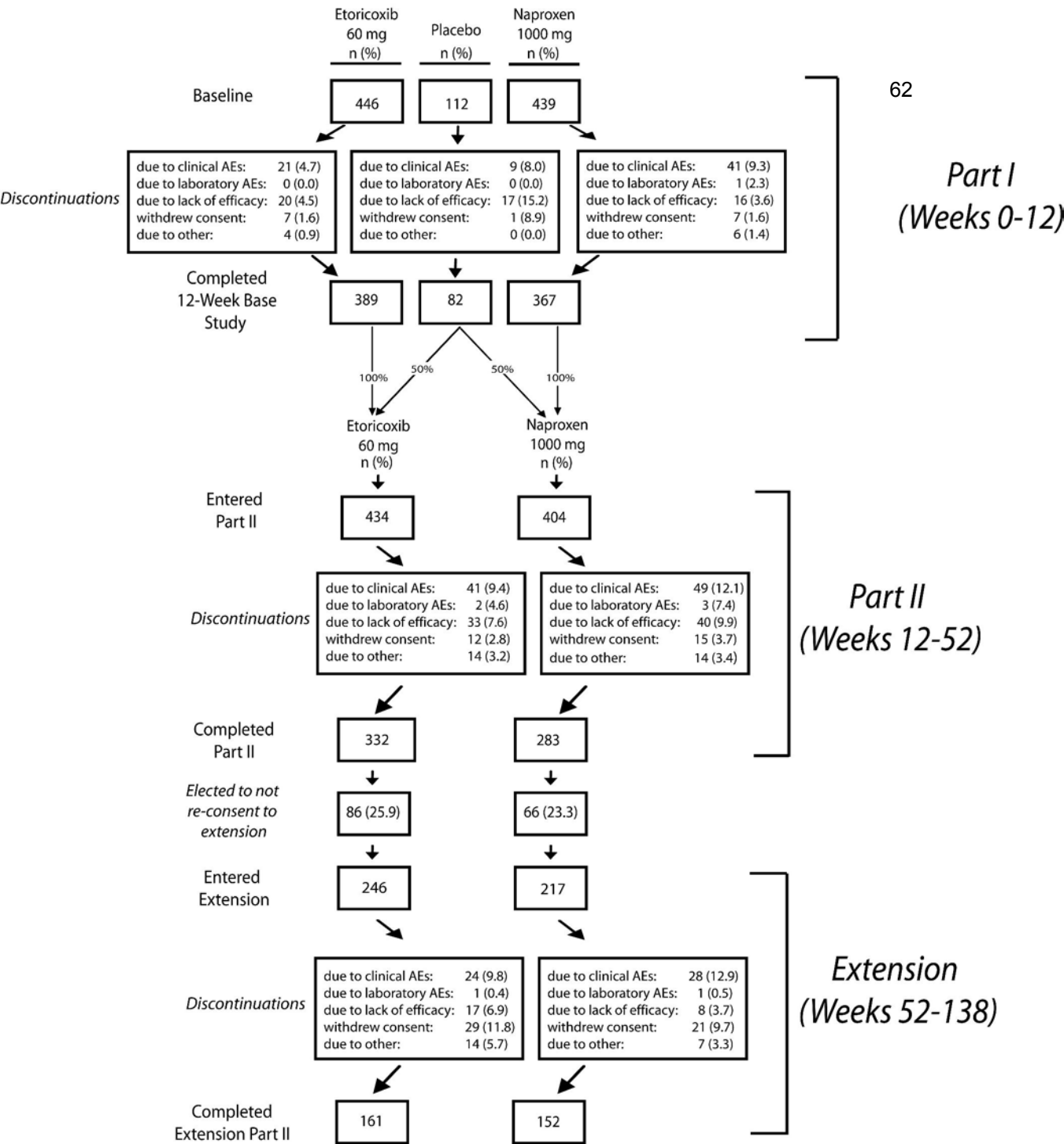
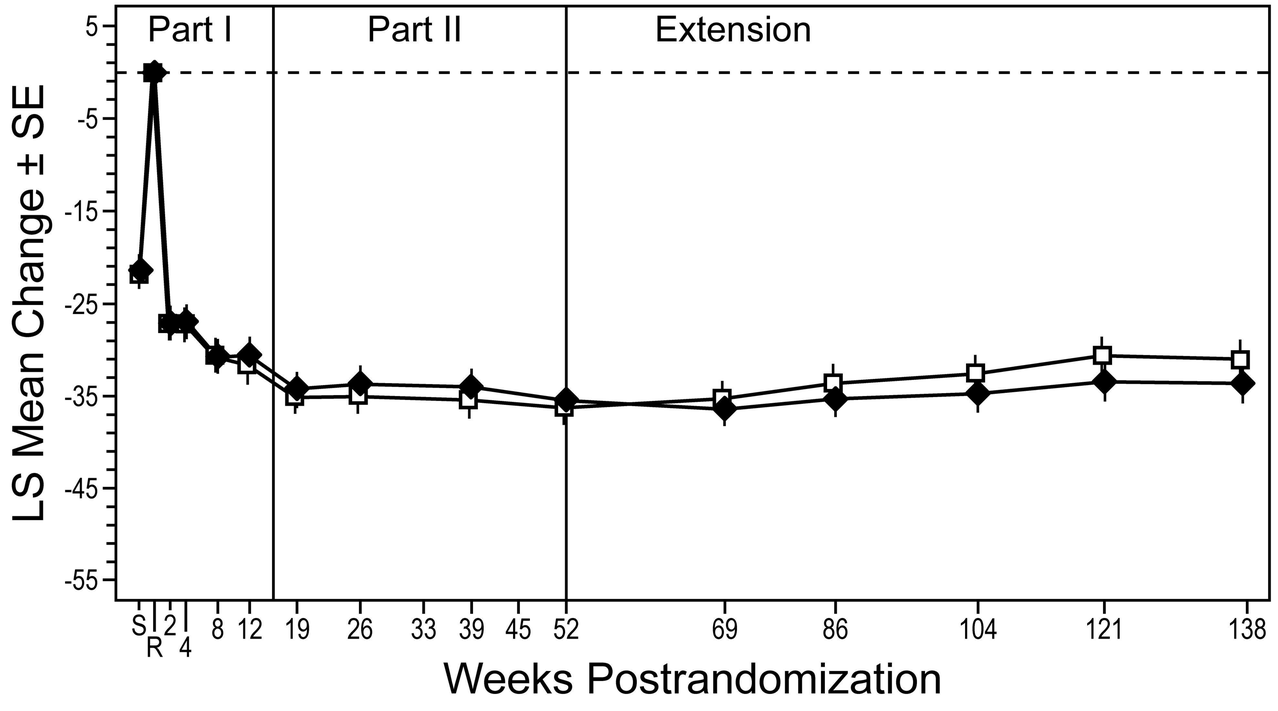
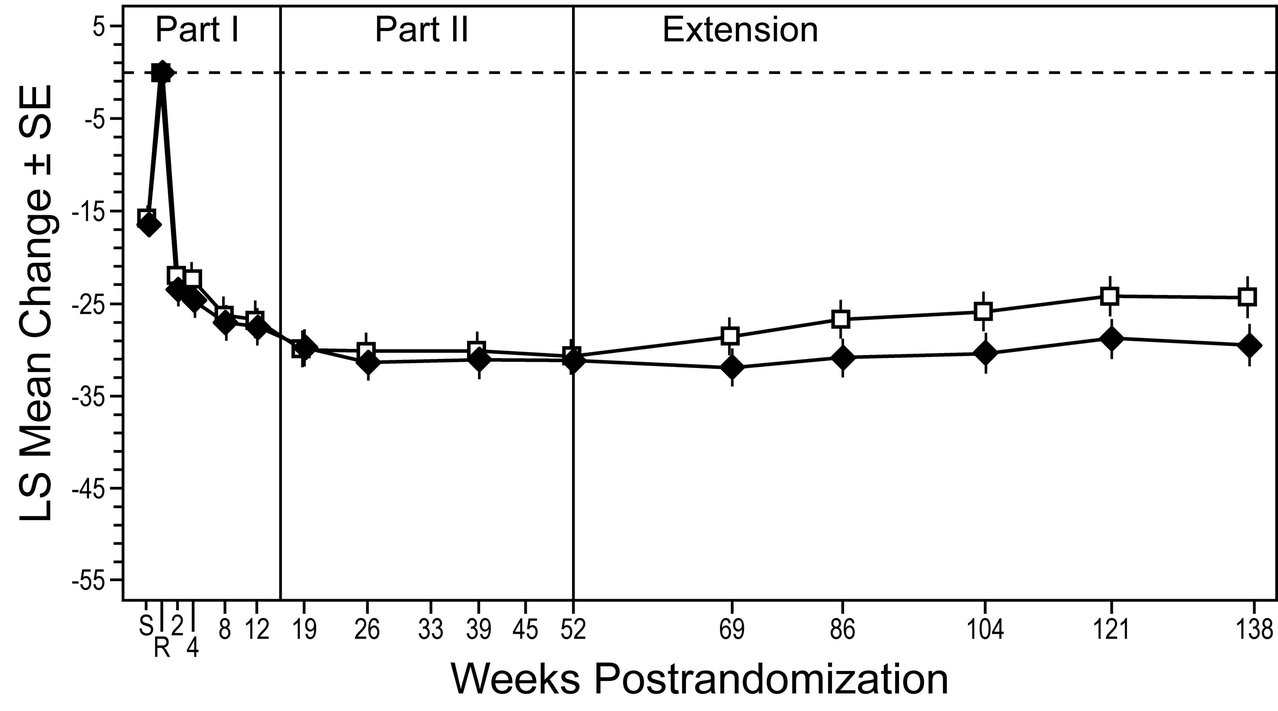

Etoricoxib 60 mg n (%)
Placebo n (%)
Naproxen 1000 mg n (%)
Baseline
446
112
439
Discontinuations
due to clinical AEs: 21 (4.7)
due to laboratory AEs: 0 (0.0)
due to lack of efficacy: 20 (4.5)
withdrew consent: 7 (1.6)
due to other: 4 (0.9)
due to clinical AEs: 9 (8.0)
due to laboratory AEs: 0 (0.0)
due to lack of efficacy: 17 (15.2)
withdrew consent: 1 (8.9)
due to other: 0 (0.0)
due to clinical AEs: 41 (9.3)
due to laboratory AEs: 1 (2.3)
due to lack of efficacy: 16 (3.6)
withdrew consent: 7 (1.6)
due to other: 6 (1.4)
Part I (Weeks 0-12)
Completed 12-Week Base Study
389
82
367
100%
50%
50%
100%
Etoricoxib 60 mg n (%)
Naproxen 1000 mg n (%)
Entered Part II
434
404
Discontinuations
due to clinical AEs: 41 (9.4)
due to laboratory AEs: 2 (4.6)
due to lack of efficacy: 33 (7.6)
withdrew consent: 12 (2.8)
due to other: 14 (3.2)
due to clinical AEs: 49 (12.1)
due to laboratory AEs: 3 (7.4)
due to lack of efficacy: 40 (9.9)
withdrew consent: 15 (3.7)
due to other: 14 (3.4)
Part II (Weeks 12-52)
Completed Part II
332
283
Elected to not re-consent to extension
86 (25.9)
66 (23.3)
Entered Extension
246
217
Discontinuations
due to clinical AEs: 24 (9.8)
due to laboratory AEs: 1 (0.4)
due to lack of efficacy: 17 (6.9)
withdrew consent: 29 (11.8)
due to other: 14 (5.7)
due to clinical AEs: 28 (12.9)
due to laboratory AEs: 1 (0.5)
due to lack of efficacy: 8 (3.7)
withdrew consent: 21 (9.7)
due to other: 7 (3.3)
Extension (Weeks 52-138)
Completed Extension Part II
161
152

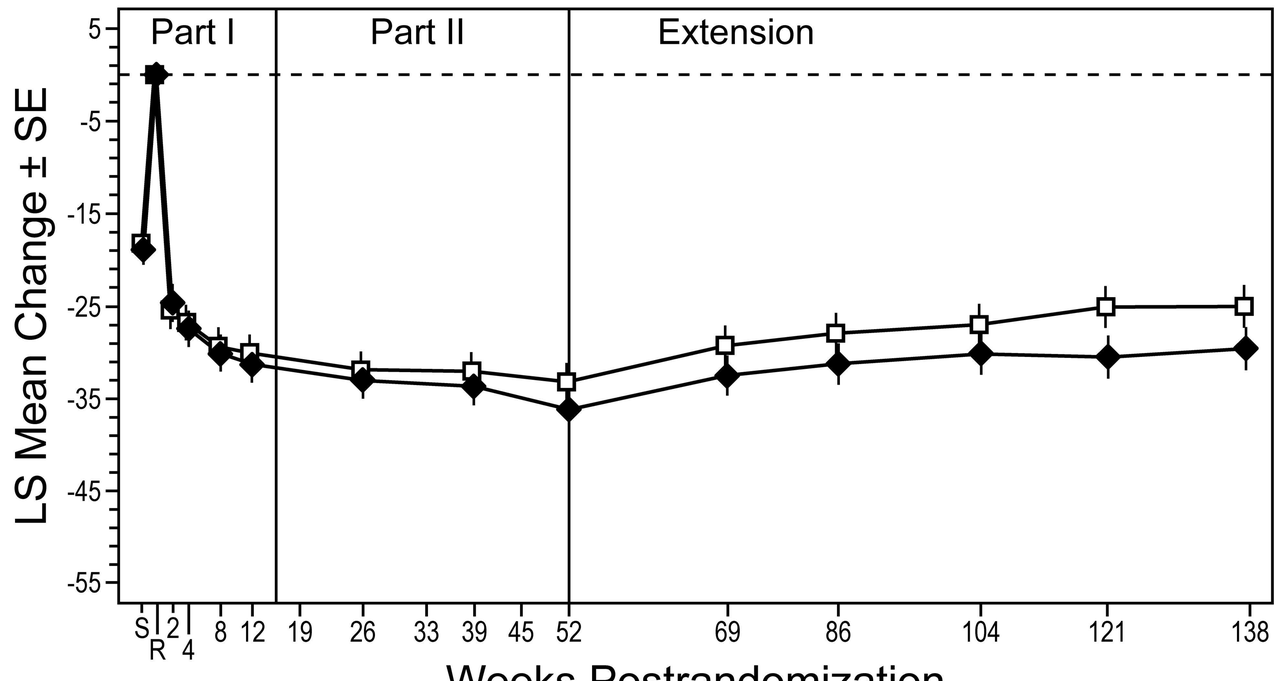
A. WOMAC Pain Subscale (100-mm VAS)

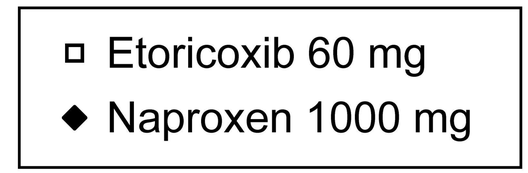


B. WOMAC Physical Function Subscale (100-mm VAS)



C. Patient Global Assessment of Disease Status (100-mm VAS)





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ORIGINAL ARTICLE

Pooled analysis of thrombotic cardiovascular events in clinical trials of the COX-2 selective Inhibitor etoricoxib*

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Key words: **Cardiovascular – Diclofenac – Etoricoxib – Ibuprofen – Naproxen**

ABSTRACT

Background: A pooled analysis of randomized clinical trials data was performed to compare the rate of thrombotic cardiovascular events (thrombotic events) in patients taking the COX-2 selective inhibitor (coxib) etoricoxib, a traditional NSAID, or placebo.

Methods: Data collected during all phase IIb/III etoricoxib clinical trials ≥ 4 weeks in duration were evaluated. The pooled data set includes clinical information from ≈ 6500 patient-years (PYs) of drug exposure in patients diagnosed with rheumatoid arthritis (RA), osteoarthritis (OA), ankylosing spondylitis (AS), or chronic low back pain (CLBP). Patients were treated with either etoricoxib (≥ 60 mg/day), the traditional NSAIDs naproxen (1000 mg/day), ibuprofen (2400 mg/day), diclofenac (150 mg/day), or placebo. The Relative risks (RRs) based on time to first occurrence of a thrombotic event in the etoricoxib group versus the comparator traditional NSAIDs or versus placebo were determined using patient-level data.

Results: In the pooled dataset, a total of 74 thrombotic events occurred in 69 patients. The RRs for thrombotic events were 1.11 (95%CI: 0.32, 3.81) for etoricoxib ($N = 2818$) versus placebo ($N = 1767$); 0.83 (95%CI: 0.26, 2.64) for etoricoxib ($N = 1266$) versus the combined non-naproxen traditional NSAID group (ibuprofen and diclofenac; $N = 718$); and 1.70 (95%CI: 0.91, 3.18) for etoricoxib ($N = 1960$) versus naproxen ($N = 1497$).

Conclusions: There was no discernible difference in the incidence of thrombotic events in patients treated with etoricoxib versus non-naproxen traditional NSAIDs in this limited dataset. A trend toward more events with etoricoxib versus naproxen was observed. Despite the limited dataset available for this pooled analysis, these results are consistent with findings for other coxibs.

Introduction

The coxibs were specifically developed to provide analgesic and anti-inflammatory efficacy comparable to traditional NSAIDs and with improved GI safety and tolerability. Results from randomized controlled clinical trials have demonstrated improved upper GI safety and tolerability of the coxibs compared to traditional NSAIDs[1,2]. In the APPROVe study (rofecoxib) and the APC study (celecoxib), however, there was an increased risk of thrombotic cardiovascular (CV) events following long-term use with the coxibs as compared to placebo[3,4].

To more precisely assess the cardiovascular safety profile of coxibs, a thrombotic event adjudication standard operating procedure was established for the clinical development program prior to initiation of phase IIb studies for etoricoxib. Using adjudicated

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pooled patient level thrombotic event data, the current analysis was performed to estimate the RR of thrombotic events in OA, RA, AS, or CLBP patients receiving chronic treatment (≥ 4 weeks) with etoricoxib compared to placebo and traditional NSAIDs.

Methods

Clinical trials examined

This pooled analysis only considered etoricoxib studies that were at least 4 weeks in duration and referred to as chronic exposure studies. These clinical trials enrolled patients with OA, RA, AS, or CLBP. Data from short-term analgesia studies were available but not included because the majority of these studies administered only a single dose of study medication and were thus felt to be too short in duration to combine with the chronic exposure studies. Comparisons of etoricoxib to placebo were based on data from the placebo-controlled portions of chronic-exposure studies and were limited in duration to a maximum of 12 weeks. Comparisons to the traditional NSAIDs were based on data from the active-comparator-controlled portions of the chronic-exposure studies, which extended to greater than 2.5 years in duration. Twelve studies met the criteria and were included in the pooled analyses (Table 1). A two-part study examining the efficacy and safety of etoricoxib 90 mg compared to placebo and rofecoxib 25 mg* in patients with hemophilic arthropathy was not included in the analysis because of the difference in the patient population in this study (i.e., hemophiliacs) compared to all the other studies. Of note, there were no reported thrombotic events in that trial[5].

All clinical protocols examined in this analysis were approved by institutional review boards and all patients provided written informed consent prior to their participation. These studies were conducted from September 1998 to December 2002.

Primary endpoint

The primary endpoint used in the current analysis was a confirmed thrombotic CV event endpoint referred to in this manuscript as 'thrombotic events'. The thrombotic event endpoint represents a composite of all investigator-reported CV serious adverse experiences, which were confirmed to be thrombotic based on a prespecified adjudication process. This endpoint includes cardiac, cerebrovascular, and peripheral vascular events such as unstable angina, myocardial infarction, ischemic stroke and transient ischemic attacks, but does not include fatal hemorrhagic deaths or hemorrhagic stroke (Table 2). This was chosen as the primary endpoint because it represents the largest amount of adjudicated data for etoricoxib, and at this time allows for the most precise estimate of thrombotic event rates. Analyses using the Antiplatelet Trialists' Collaboration (APTC) combined endpoint were also performed to confirm the primary analysis[6,7].

To improve the precision of the estimates of the occurrence of thrombotic events, which typically occur infrequently, a pooled analysis of patient-level data across the etoricoxib development program was performed.

Table 1. *Studies included in the etoricoxib pooled CV analysis*

Indication for therapy	Protocol No.	Short study title	Comparator	Maximum exposure, mean (weeks)	Ref.
Rheumatoid arthritis	010	Phase IIb dose finding	Placebo, diclofenac	174	–
	024	Phase III pivotal US	Placebo, naproxen	121	20
	025	Phase III pivotal international	Placebo, naproxen	121	21
	026*	Endoscopy	Placebo, naproxen	12	22
Osteoarthritis	007	Phase IIb dose ranging study	Placebo, diclofenac	190	23
	018	Phase III pivotal international	Placebo, naproxen	138	–
	019	Phase III pivotal US	Placebo, naproxen	138	24
	026*	Endoscopy	Diclofenac	12	22
	029	Endoscopy	Ibuprofen, placebo	12	25
	805	Phase III international	Diclofenac	6	26
Other	032	Phase III AS	Placebo, naproxen	52	12
	041	Phase III chronic low back pain	Placebo	12	27
	042	Phase III chronic low back pain	Placebo	12	28

*Protocol number 026 included OA and RA patients and appears twice

* On September 30, 2004, Merck announced the voluntary, worldwide withdrawal of rofecoxib from the market

Table 2. *Serious adverse events included in the thrombotic event and APTC* combined endpoints*

Adjudication committee categories for cardiovascular events	Confirmed thrombotic cardiovascular event	APTC* combined endpoint
Thrombotic events		
Cardiac events		
Acute MI	√	√
Fatal: acute MI	√	√
Unstable angina pectoris	√	
Sudden and/or unexplained death	√	√
Resuscitated cardiac arrest	√	√
Cardiac thrombus	√	
Peripheral vascular events		
Pulmonary embolism	√	
Fatal: pulmonary embolism	√	
Peripheral arterial thrombosis	√	
Fatal: peripheral arterial thrombosis	√	√
Peripheral venous thrombosis	√	
Cerebrovascular events		
Ischemic cerebrovascular stroke	√	√
Fatal: ischemic cerebrovascular stroke	√	√
Cerebrovascular venous thrombosis	√	
Fatal: cerebrovascular venous thrombosis	√	√
Transient ischemic attack	√	
Hemorrhagic events		
Hemorrhagic cerebrovascular stroke†		√
Fatal: hemorrhagic cerebrovascular stroke†		√
Fatal: hemorrhagic deaths of any cause		√

*APTC = Anti-platelet Trialists' Collaboration
†These events are included as investigator-reported events but not confirmed thrombotic events

Thrombotic event adjudication procedure

The adjudication procedure was carried out in a prespecified manner by external panels of experts in cardiovascular medicine who were blinded to treatment assignments. All deaths reported during the etoricoxib clinical development program were also adjudicated in a blinded manner to determine the specific cause of death.

Thrombotic event categories

Thrombotic event rates per 100 PYs of exposure by event category (i.e., cardiac, cerebrovascular, and peripheral vascular events) and treatment group occurring on therapy or within 14 days after study therapy discontinuation were also compared across the entire data set to explore and compare the distribution of events.

Treatment groups

The comparator traditional NSAID treatments included naproxen 500 mg b.i.d., diclofenac 50 mg t.i.d., and ibuprofen 800 mg t.i.d. The comparator traditional NSAIDs were divided into two groups for purposes of comparison. Comparator group definitions took into account the differing anti-platelet effects of the agents, specifically singling out naproxen based on its potent and sustained anti-platelet effects across its dosing interval[8,9]. Additional rationale for keeping comparisons to naproxen separate from other traditional NSAIDs included the qualitative difference in thrombotic CV event rates observed in the comparison of etoricoxib to naproxen versus the comparison of etoricoxib to the other traditional NSAIDs (ibuprofen and diclofenac combined).

Patient subgroups: comparisons of different underlying disease populations

To explore potential effects of conditional pharmacology between patients with OA and RA, thrombotic events were analyzed by disease indication using the naproxen-controlled data set, since this is the largest data set and thus the most suitable for subgroup analysis. In this data set, the OA and the RA populations both included two Phase III studies and the relevant portion

of data from a Phase III OA/RA surveillance endoscopy study. Since there were too few events observed in the single study in patients with ankylosing spondylitis and the two studies of patients with low back pain, no comparisons to other disease cohorts were made using those data.

Patients at an increased baseline thrombotic risk

Only the naproxen-controlled data was set large enough to examine thrombotic risk in patients at risk at baseline. In the naproxen-controlled data set, two subgroups were identified which met the criteria of being at increased baseline thrombotic risk. The first subgroup included patients at increased baseline thrombotic risk, defined as having two or more of four primary cardiac risk factors (i.e., tobacco use, diabetes mellitus, hypertension, or hypercholesterolemia), or a history of symptomatic atherosclerotic CV disease (ASCVD) that included; myocardial infarction, angina pectoris, cerebral vascular accident, transient ischemic attack, angioplasty, or coronary artery bypass surgery. The second subgroup was defined as patients on anti-platelet therapy for cardioprophylaxis, indicating a subgroup of patients presumably enriched with patients having existing CV disease and thus at increased risk for an event. For this analysis, a patient on anti-platelet therapy was defined as anyone who took any dose of aspirin, clopidogrel, clopidogrel bisulfate, ticlopidine, or ticlopidine hydrochloride for at least 50% of the time while on study therapy, although the majority of these patients were taking aspirin only.

Statistical methodology

This pooled analysis used individual patient data and was conducted using a modified intent-to-treat approach. The modified intent-to-treat population included all patients randomized who received at least one dose of study medication. Analyses were performed using SAS for Windows version 8.2. Adverse experiences were collected until 14 days after either study completion or patient discontinuation of study medication. The statistical analysis plan stipulated that patients receiving etoricoxib doses ≥ 60 mg would be combined into a single etoricoxib treatment group to increase statistical precision. Data from treatment periods when patients were on lower doses of etoricoxib (< 60 mg) were excluded as they do not represent maximally efficacious doses[10].

The data sets were thus defined in order to allow for the following comparisons: (1) a placebo-controlled data set which compared etoricoxib to placebo, (2) a non-naproxen traditional NSAID-controlled data set which compared etoricoxib to all traditional NSAID comparators pooled other than naproxen (i.e., diclofenac, ibuprofen), (3) a naproxen-controlled data set which compared etoricoxib to naproxen.

Standard survival analysis techniques were used to analyze time to first event within patients. Event rates per 100 PYs and RRs (with 95% CIs) for thrombotic events for each data set were determined. Relative risks were determined using a Cox proportional hazards model stratified by disease block where the number of cases was at least 11. Otherwise, the ratio of the rates was provided. Kaplan–Meier plots for cumulative incidence rates of thrombotic events for all three data sets were constructed. As recommended, Kaplan–Meier curves were truncated when there were ≈ 10–20% of patients remaining at risk in any treatment group (or ≈ 150–200 patients)[11]. Such a truncation was just for the plot; any events occurring after the truncation time point were still retained in the analyses of crude proportions, PY-adjusted incidence rates and RRs. Treatment by subgroup interaction was evaluated using the Cox proportional hazards model by adding terms for the subgroup factor and treatment-by-subgroup factor interaction to the model.

The presence of a dose-response for thrombotic events was explored by analyzing event rates by dose across all studies included in the thrombotic event pooled analysis, using two different analytical approaches. The primary approach involved a pair-wise analysis, including data from only those studies which contained two of the three doses being analyzed (i.e., both 60 and 90 mg, or both 90 and 120 mg) since only one study (a phase II OA study) contained 60, 90, and 120 mg doses of etoricoxib. A secondary analysis included rates by individual doses (60, 90, and 120 mg) combined across all of the studies included in the thrombotic event pooled analysis. While this approach was more comprehensive, doses were partially confounded by differences in patient populations across protocols.

Results

This pooled analysis utilized data from 12 chronic exposure studies representing ≈ 6500 PYs of drug exposure. A total of 124 investigator-reported thrombotic CV serious adverse experiences in 116 patients were adjudicated. Of these, 74 confirmed thrombotic events occurred in 69 patients.

The comparison to placebo treatment extends to a maximum of 12 weeks, with no placebo-controlled data beyond that time point. Compared to placebo (N = 1767), the RR of thrombotic events for etoricoxib (N = 2818) was 1.11 (95% CI: 0.32, 3.81; Table 3; Figure 1). Compared to non-naproxen NSAIDs

Table 3. *Absolute rate and RRs (95% CI) of thrombotic events from the pooled analysis*

Comparisons	*N*	Cases/PYR*	Rate† (95% CI)	RR‡ (95% CI)
Thrombotic cardiovascular adverse experiences				
Etoricoxib§	2818	7/560	1.25 (0.50, 2.58)	1.11 (0.32, 3.81)
Placebo	1767	4/335	1.19 (0.33, 3.06)	–
Etoricoxib	1266	12/1522	0.79 (0.41, 1.38)	0.83 (0.26, 2.64)
Non-naproxen NSAIDs¶	718	4/501	0.80 (0.22, 2.04)	–
Etoricoxib	1960	34/2480	1.37 (0.95, 1.92)	1.70 (0.91, 3.18)
Naproxen 1000 mg	1497	14/1727	0.81 (0.44, 1.36)	–

*PYs at risk
†Per 100 PYR
‡RR using Cox model stratified by therapeutic block where the number of cases is at least 11, otherwise RR is ratio of rates
§≥ 60 mg etoricoxib
¶Ibuprofen and diclofenac
APTC = Antiplatelet Trialists' Collaboration; CI = confidence interval; PYR = PYs at risk

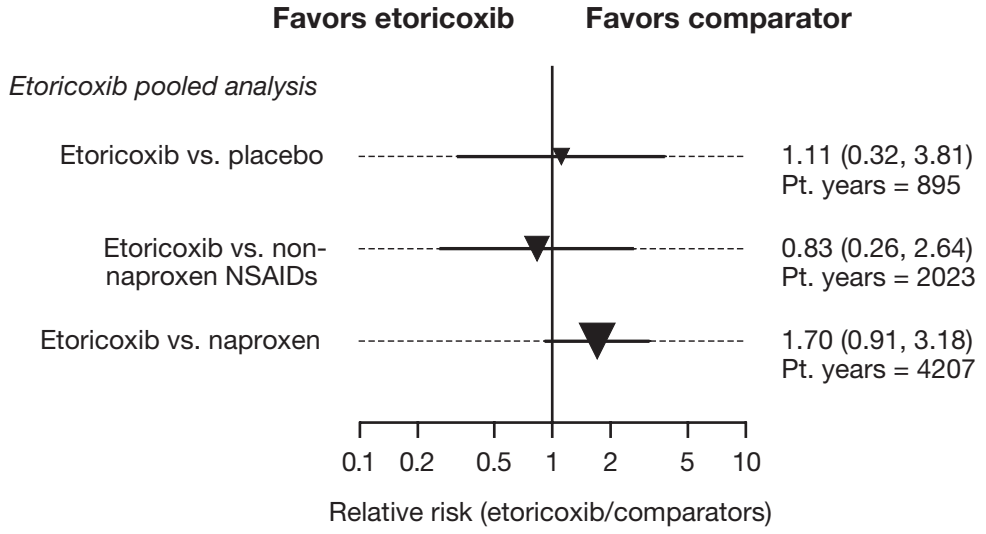


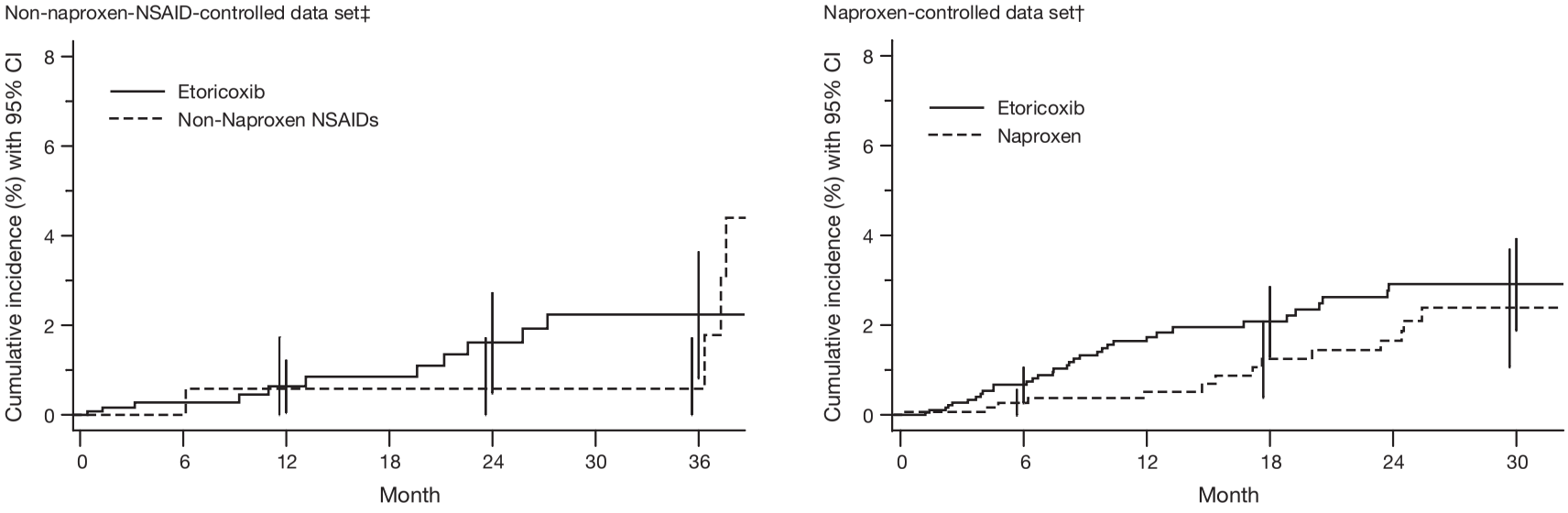
Figure 1. *Relative risk (95% CIs) of confirmed thrombotic events from the pooled analysis*

(*N* = 718), the RR for etoricoxib (*N* = 1266) was 0.83 (95% CI: 0.26, 2.64) suggesting no apparent difference in risk between etoricoxib and these traditional NSAIDs. Compared to naproxen (*N* = 1497), the RR for etoricoxib (*N* = 1960) was 1.70 (95% CI: 0.91, 3.18) suggesting a difference between treatment groups for risk of thrombotic events favoring naproxen (Table 3). Kaplan–Meier plots showing the cumulative estimates for the incidence of thrombotic events in the naproxen and non-naproxen-controlled data sets are shown in Figure 2. In the naproxen-controlled data set the cumulative incidence of thrombotic events separates early with a lower cumulative incidence of thrombotic events in the naproxen group. Overall, results using the APTC combined clinical endpoints were generally consistent with these results.

There was no evidence of a dose–response relationship for the incidence of thrombotic events across the 60, 90, and 120 mg doses of etoricoxib (Figure 3). The estimated rates for thrombotic events for etoricoxib 60 mg were generally similar to 90 mg and the estimated rates for etoricoxib 90 mg were similar to 120 mg. The rates per 100 PYs for the secondary analysis of dose across all studies for the thrombotic event endpoint were consistent with the analyses provided above, supporting the lack of a dose–response relationship across the 60–120 mg dose range of etoricoxib.

Thrombotic events were categorized by the CV adjudication committee by vascular bed (cardiac, cerebrovascular, or peripheral vascular) and by specific event type. Overall, there was no clear pattern to the specific thrombotic events by vascular bed or event type (Tables 4 and 5), however, the amount of data is limited, precluding a robust analysis.

Thrombotic events were reported in all three vascular beds, with more cardiac events than cerebro-



Number of patients at risk							
Etoricoxib	1266	604	524	415	352	295	236
Non-naproxen NSAIDs	718	174	133	116	94	85	83

(A)

Number of patients at risk						
Etoricoxib	1960	1411	1124	749	668	145
Naproxen	1497	942	721	523	468	143

(B)

†No events occurred after the last shown time on the axis
‡One event (in etoricoxib) occurred after the last shown time on the axis. All events are included in the analysis
Error bars are ± 95% CIs of cumulative incidence (%) at the indicated time points
Plots were truncated when the risk size in any arm is < 50

Figure 2 (A and B). *Kaplan–Meier estimates of cumulative incidence of thrombotic events in the naproxen and non-naproxen NSAID-controlled data sets*

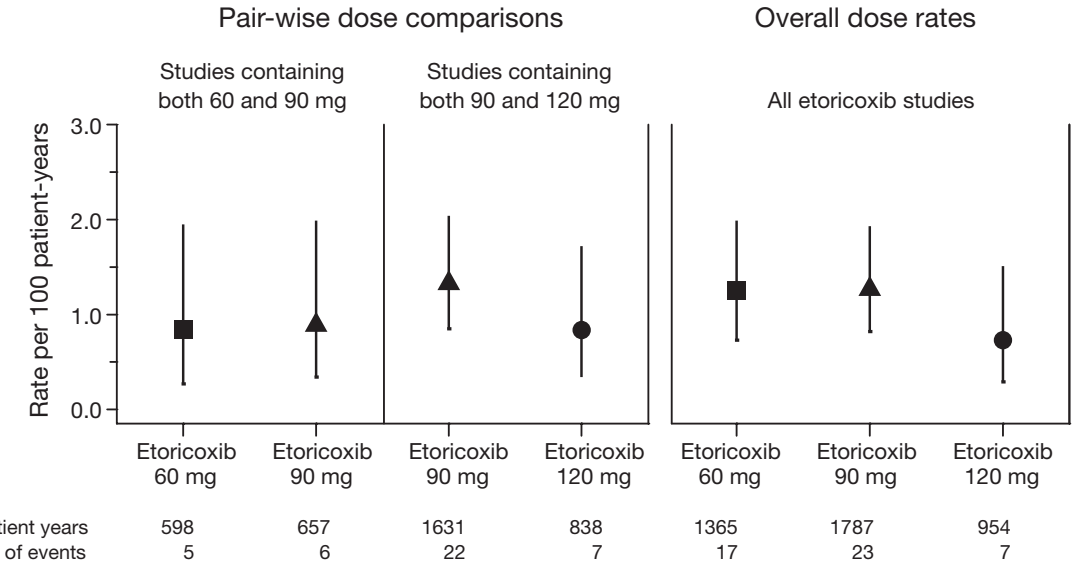


Figure 3. *Rates per 100-PYs (95% CIs) of thrombotic events stratified by etoricoxib dose*

Table 4. *Summary of patients with confirmed thrombotic events by class of terms in the naproxen-controlled data set*

Endpoint terms	Etoricoxib (N = 1960) (PYR = 2480)		Naproxen (N = 1497) (PYR = 1727)	
	n (%)*	Rate†	n (%)*	Rate†
Patients with one or more confirmed thrombotic cardiovascular adverse experiences	34 (1.73)	1.37	14 (0.94)	0.81
Cardiac events	21 (1.07)	0.85	7 (0.47)	0.41
Acute myocardial infarction	10 (0.51)	0.40	5 (0.33)	0.29
Fatal acute myocardial infarction	2 (0.10)	0.08	1 (0.07)	0.06
Unstable angina pectoris	6 (0.31)	0.24	3 (0.20)	0.17
Sudden/unknown cause of death	3 (0.15)	0.12	0 (0.00)	0.00
Cerebrovascular events	12 (0.61)	0.48	2 (0.13)	0.12
Ischemic cerebrovascular stroke	10 (0.51)	0.40	0 (0.00)	0.00
Fatal ischemic cerebrovascular stroke	0 (0.00)	0.00	1 (0.07)	0.06
Transient ischemic attack	2 (0.10)	0.08	1 (0.07)	0.06
Peripheral vascular events	2 (0.10)	0.08	5 (0.33)	0.29
Pulmonary embolism	2 (0.10)	0.08	2 (0.13)	0.12
Peripheral arterial thrombosis	0 (0.00)	0.00	1 (0.07)	0.06
Peripheral venous thrombosis	0 (0.00)	0.00	2 (0.13)	0.12

*Crude incident ($n/N \times 100$)
†Events per 100 PYs
Note: patients with multiple events may be counted more than once under different terms but only once in the 'one or more' category

vascular or peripheral vascular events regardless of treatment group. In considering the difference between the naproxen and etoricoxib groups, no single type of thrombotic event predominates, although a higher incidence of ischemic cerebrovascular stroke was observed with etoricoxib compared to naproxen.

Thrombotic events were analyzed by disease indication (OA, RA) using the naproxen-controlled data set. The rates per 100 PYs at risk for thrombotic events in OA patients were 1.48 (95% CI: 0.74, 2.65) and 0.89 (95% CI: 0.33, 1.95) in the etoricoxib (N = 558) and naproxen (N = 531) groups, respectively. In RA patients, the rates per 100 PYs at risk for thrombotic events were 1.18 (95% CI: 0.70, 1.87) and 0.84 (95% CI: 0.36, 1.65) in the etoricoxib (N = 1149) and naproxen (N = 839) groups, respectively. The RRs compared to naproxen were similar for OA [RR 1.66 (95% CI: 0.61, 4.49)] and RA patients [RR 1.41 (95% CI: 0.61, 3.25)], and the treatment-by-disease-subgroup interaction was not statistically significant ($p > 0.82$) indicating that the magnitude of the difference between etoricoxib and

Table 5. Summary of patients with confirmed thrombotic events by class of terms in the non-naproxen-NSAID-controlled data set

Endpoint terms	Etoricoxib (*N* = 1266)		Non-naproxen NSAIDs					
			Combined (*N* = 718)		Diclofenac (N = 492)		Ibuprofen (*N* = 226)	
	(PYR = 1522)		(PYR = 501)		(PYR = 447)		(PYR = 54)	
	n (%)*	Rate†	*N* (%)*	Rate†	*n* (%)*	Rate†	*n* (%)*	Rate†
Patients with one or more confirmed thrombotic cardiovascular adverse experiences	12 (0.95)	0.79	4 (0.56)	0.80	4 (0.81)	0.89	0 (0.00)	0.00
Cardiac events	11 (0.87)	0.72	2 (0.28)	0.40	2 (0.41)	0.45	0 (0.00)	0.00
Acute myocardial infarction	3 (0.24)	0.20	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00
Fatal acute myocardial infarction	2 (0.16)	0.13	1 (0.14)	0.20	1 (0.20)	0.22	0 (0.00)	0.00
Unstable angina pectoris	4 (0.32)	0.26	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00
Sudden/unknown cause of death	2 (0.16)	0.13	1 (0.14)	0.20	1 (0.20)	0.22	0 (0.00)	0.00
Cerebrovascular events	1 (0.08)	0.07	2 (0.28)	0.40	2 (0.41)	0.45	0 (0.00)	0.00
Ischemic cerebrovascular stroke	1 (0.08)	0.07	1 (0.14)	0.20	1 (0.20)	0.22	0 (0.00)	0.00
Transient ischemic attack	1 (0.08)	0.07	1 (0.14)	0.20	1 (0.20)	0.22	0 (0.00)	0.00

*Crude incident ($n/N \times 100$)
†Events per 100 PYs
Note: patient with multiple events may be counted more than once under different terms but only once in the 'one or more' category. No peripheral vascular events were observed in this data set

naproxen is generally similar in patients with underlying OA and RA. The number of thrombotic events in the AS study[12] did not differ substantially from what would have been predicted based on the rates observed in the naproxen-controlled data set from the pooled analysis.

As clinical trials data subsequently became available from the etoricoxib development program, establishing 30 mg as an effective dose for the symptomatic treatment of OA[13], post-hoc sensitivity analyses were performed which included the 30-mg dose experience (versus ibuprofen 2400 mg only) in the combined etoricoxib group in the primary pooled analysis. The results including the 30 mg dose were consistent with the primary analysis described in this report which considered doses of etoricoxib ≥ 60 mg.

The RR observed in the total cohort between etoricoxib and naproxen was generally similar in patients with or without two or more CV risk factors. Rates of thrombotic events per 100 PYs of exposure in patients at increased risk were 3.33 (95% CI: 1.87, 5.50) and 1.76 (95% CI: 0.65, 3.83) for etoricoxib and naproxen, respectively, with a RR of 1.87 (95% CI: 0.73, 4.82). For patients without two or more CV risk factors, rates for thrombotic events were 0.94 (95% CI: 0.56, 1.46) and 0.58 (95% CI: 0.25, 1.14) for etoricoxib and naproxen, respectively, with a RR of 1.58 (95% CI: 0.69, 3.61). Treatment-by-subgroup interaction analyses indicated the observed treatment differences, between subgroups with or without two or more CV risk factors, were not significantly different ($p = 0.81$).

The naproxen-controlled data set was also used to explore thrombotic CV event rates in aspirin users ($n = 195$) and non-users ($n = 3262$). Due to the small number (5.6%) of patients using concomitant aspirin, these limited data should be interpreted with caution. The event rate per 100 PYs in users of anti-platelet therapies was 1.92 (95% CI: 0.40, 5.61) and 1.82 (95% CI: 0.22, 6.56) for etoricoxib and naproxen, respectively, with a RR of 1.06 (95% CI: 0.12, 12.65). For non-users of anti-platelet therapies, the event rates were slightly lower; 1.33 (95% CI: 0.91, 1.89) and 0.74 (95% CI: 0.38, 1.30), with a RR for etoricoxib compared to naproxen of 1.77 (95% CI: 0.91, 3.45). The higher rate of thrombotic events in users of anti-platelet therapies is consistent with the notion that these patients were presumably taking these medications to mitigate a higher underlying CV risk. Treatment-by-subgroup interaction analyses indicated the treatment differences in thrombotic events observed between anti-platelet users and non-users were not significantly different ($p = 0.57$).

Discussion

This pooled analysis suggests that the RR of thrombotic events following the use of etoricoxib at daily doses of 60–120 mg is similar to non-naproxen traditional NSAIDs but higher than naproxen. Although the 95% CI for the RR compared to naproxen includes 1, this likely represents a real difference given the contrast in the point estimates for the RR compared to the results from the non-naproxen-controlled data sets. This pooled analysis also suggests a difference from naproxen that begins shortly after the start of

treatment. Compared to naproxen or non-naproxen traditional NSAIDs, our findings with etoricoxib are also qualitatively similar to published data from the rofecoxib VIGOR study and the lumiracoxib TARGET study[1,14,15]. Our results, using patient-level data, are also consistent with results for other coxibs from a meta-analysis of study-level data from 138 published and unpublished randomized trials that compared coxibs (i.e., rofecoxib, celecoxib, valdecoxib, lumiracoxib, and etoricoxib) to placebo or to traditional NSAIDs (i.e., naproxen and the non-naproxen traditional NSAIDs ibuprofen and diclofenac)[14]. In that meta-analysis, high dose regimens of diclofenac or ibuprofen, but not high-dose naproxen, were associated with a similar risk of CV events compared to the coxib comparator group.

Although there was a limited data set, the comparison of thrombotic event rates in anti-platelet therapy users and non-users taking etoricoxib or naproxen was explored. Event rates for thrombotic events were similar between etoricoxib and naproxen in the cohort of anti-platelet users, whereas the event rates were different between etoricoxib and naproxen in the cohort of non-anti-platelet users. This also appears to be consistent with the hypothesis that anti-platelet effects of naproxen can confer a difference in thrombotic event rates in comparison to other agents[9]. The anti-platelet user cohort, however, was quite small and, therefore, this needs to be explored further in larger clinical datasets when available.

Evaluation of individual types of thrombotic events indicated small numeric differences between treatments for certain event types; some occurring at a higher rate on etoricoxib and some occurring at a lower rate, as expected for two treatments with similar overall rates. Although, none of these differences were statistically significant, the absolute number of any of these individual events was small, and results at the level of individual events cannot be appropriately interpreted further.

Our pooled analysis has several limitations. In the APPROVe and APC trials, there was a time-dependent increased risk of thrombotic events associated with the use of the coxibs, rofecoxib and celecoxib, in comparison to placebo[3,4,16]. The duration of placebo-controlled data for etoricoxib in the pooled analysis is only up to 12 weeks and there is not a large quantity of long-term active comparator-controlled data available at this time. The ability to estimate the magnitude of any potential difference between treatment with etoricoxib and placebo, using these data, is also limited due to the small numbers of events, as reflected in the width of the 95% CIs. Specifically, these limited data on etoricoxib are insufficient to conclude that the increased risk of thrombotic events observed in patients with a history of colorectal adenomas following long term treatment of rofecoxib and celecoxib compared to placebo would not be observed with etoricoxib.[72]

Determination of the CV risk of traditional NSAIDs versus no therapy (or placebo) and the RR of non-naproxen traditional NSAIDs versus coxibs in studies large enough to support definitive conclusions are currently unanswered questions of great clinical importance, especially in patients who are heavily reliant on these therapies. To directly compare the CV safety of etoricoxib to a traditional NSAID, a long-term non-inferiority comparison in arthritis patients, the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term Study) Program was designed. This clinical trials program will precisely estimate the relative CV safety of etoricoxib compared to diclofenac; the most widely prescribed traditional NSAID on a worldwide basis[17]. The MEDAL Program has enrolled over 34 000 OA and RA patients who have a range of risk factors, including those with pre-existing CV disease for whom low-dose aspirin was prescribed per treatment guidelines for cardioprophylaxis[18,19].

Comparison of the size of this pooled analysis to the MEDAL Program is illustrative of this analysis' limitations. As previously discussed[17], given a true underlying hazard ratio of 1.0 between etoricoxib and a traditional NSAID, such as diclofenac, 635 confirmed thrombotic CV events would be needed for 91% power to yield an upper bound of the 95% CI for a hazard ratio of < 1.30. This number of required events is approximately 9-fold larger than the total number of confirmed thrombotic CV events that occurred in the etoricoxib phase IIb/III clinical development program. The maximum event rate for etoricoxib that would meet the non-inferiority bound set in the MEDAL Program was ≈ 1.46% with 635 observed events and ≈ 40 000 patient-years of exposure. This would translate into an absolute difference in events of < 2 per 1000 patient-years of exposure. The baseline demographics of patients enrolled in the program closely simulates the variety of patient profiles encountered in clinical practice. The MEDAL Program will provide CV safety data collected from ≈ 50 000 total PYs of exposure with > 10 000 patients having ≥ 24 months of active treatment, and a maximum exposure of ≈ 40 months.

Conclusion

Based on the results of this pooled analysis, there appears to be no evidence at this time of a discernible difference in thrombotic event rates among patients taking etoricoxib or non-naproxen traditional NSAIDs. The etoricoxib MEDAL Program[17] will further define the long-term risk to benefit ratio of etoricoxib compared to the traditional NSAID diclofenac.

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Declaration of interest: S. P. Curtis, A. T. Ko, J. A. Bolognese, P. F. Cavanaugh, and A. S. Reicin are employees of Merck & Co., Inc., and own stock and/or hold stock options in the Company.

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ORIGINAL ARTICLE

The incidence of upper gastrointestinal adverse events in clinical trials of etoricoxib vs. non-selective NSAIDs: an updated combined analysis*

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Key words: **Adverse effects – Clinical trials – COX-2 inhibitors – Etoricoxib – Gastrointestinal – Non-steroidal anti-inflammatory drugs**

ABSTRACT

Objective: In spite of numerous studies demonstrating the serious gastrointestinal (GI) toxicity associated with non-selective non-steroidal anti-inflammatory drugs (NSAIDs), many patients at high GI risk continue to receive prescriptions for these drugs, often without gastroprotective agents. Etoricoxib, a COX-2 specific inhibitor, was developed to provide similar efficacy and less GI toxicity than non-selective NSAIDs. We compared the incidence of upper GI Perforations, symptomatic gastroduodenal Ulcers, and upper GI Bleeding (PUBs) in a combined analysis of all randomized, double-blind, clinical trials of chronic treatment with etoricoxib versus NSAIDs completed by June 2003.

Research design and methods: Data for 5441 individual subjects with osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis were pooled from all 10 multinational etoricoxib trials completed by June 2003. Information on suspected PUBs was prospectively collected in all protocols, and all investigator-reported PUBs were judged by a blinded, external adjudication committee using pre-specified criteria. PUBs were analyzed using Cox proportional hazards models using terms for treatment and known PUB risk factors.

Main outcome measure: The incidence of confirmed PUBs among patients treated with etoricoxib 60 mg, 90 mg, or 120 mg (combined $N = 3226$) was compared to that among patients treated with ibuprofen, diclofenac, or naproxen (combined $N = 2215$).

Results: The incidence of PUBs over 44.3 months was significantly lower with etoricoxib vs. NSAIDs [cumulative incidence 1.24% vs. 2.48%, $p < 0.001$; rate/100 patient-years 1.00 vs. 2.47; relative risk 0.48, 95% Confidence Interval (CI) 0.32, 0.73]. Results of analysis of events occurring during the first year of treatment and subgroup analyses were consistent with the primary result.

Conclusions: Treatment with etoricoxib was associated with a significantly lower incidence of PUBs than was treatment with non-selective NSAIDs. The difference was consistent in subgroups of patients defined by a variety of known risk factors.

* Some of the material included in this manuscript was presented at the American College of Rheumatology 2003 Annual Meeting (Orlando, FL, 23–26 November 2003) and at the 2004 European League Against Rheumatism meeting (Berlin, Germany, 9–12 June 2004)

Introduction

Many patients with musculoskeletal diseases requiring treatment with non-steroidal anti-inflammatory drugs are at risk for serious gastrointestinal (GI) adverse events (AEs) due to advanced age, previous history of a serious GI AE, use of aspirin or other anti-platelet drugs, or use of corticosteroids. COX-2 selective inhibitors were developed based on the hypothesis that by sparing the COX-1 isoform, they would provide anti-inflammatory activity with reduced GI toxicity when compared with non-selective NSAIDs, and this has been borne out in studies of rofecoxib, celecoxib, etoricoxib, and other COX-2 selective inhibitors[1–17].

The GI safety profile of etoricoxib has been demonstrated at doses of 120 mg once daily based on fecal red blood cell loss[9] and by endoscopic assessment of gastroduodenal mucosal injury in osteoarthritis and rheumatoid arthritis patients (at 120 mg once daily)[9,10]. Etoricoxib has also demonstrated a lower incidence of GI-related clinical outcomes relative to non-selective NSAIDs in a prior combined analysis[10].

Despite the evidence of the relative GI benefit of COX-2 selective NSAIDs, many high risk patients continue to receive prescriptions for non-selective NSAIDs, often without gastroprotection. To further demonstrate the GI safety of etoricoxib, we conducted a prespecified combined analysis of all ten randomized, double-blind, clinical trials of chronic etoricoxib use completed by June 2003. The objective was to determine the incidence of upper GI Perforations, symptomatic gastroduodenal Ulcers, and upper GI Bleeding (collectively termed PUBs) with etoricoxib compared with non-selective NSAIDs. We hypothesized that the incidence of PUBs would be lower with etoricoxib (all doses combined) than with non-selective NSAIDs (diclofenac, ibuprofen, and naproxen combined). The additional accrued patient exposure in the ten trials also allowed us to examine the incidence of PUBs in subgroups of patients. The current analysis includes 31% more reported events and 58% more patient years than the previously published study[10].

Patients and methods

This analysis used individual patient data pooled from the 10 Merck-sponsored randomized, double-blind clinical trials of etoricoxib including all study extensions completed by June 2003[9–12,18–24]. Of the 10 trials, 2 were dose ranging studies [1 each in osteoarthritis (OA) and rheumatoid arthritis (RA) patients], 6 were safety and efficacy studies: 3 in patients with OA, 2 in patients with RA, and 1 in patients with ankylosing spondylitis (AS). There were also 2 endoscopy studies, 1 in OA patients, and 1 in OA and RA patients (Table 1). The analytic methods closely followed the previously published combined analysis[10] and the analyses of PUB events in rofecoxib trials[4,25]. Data from studies or phases of studies in which there was an active NSAID comparator were utilized.

A standard operating procedure for the reporting and adjudication of events in clinical trials of etoricoxib was in effect before the initiation of any of the trials. This standard procedure and the adjudication criteria have been described previously[4]. Investigators were instructed to report suspected upper GI PUBs that occurred from the date study medication was started until 14 days after study drug discontinuation. Clinical source documentation for suspected PUBs was reviewed by a blinded, external adjudication committee. The committee made separate determinations as to whether a suspected PUB was confirmed and whether it was complicated (due to serious bleeding, obstruction, or perforation), using pre-defined criteria.

Two of the studies included scheduled endoscopic evaluations[9,10]. Asymptomatic non-bleeding ulcers diagnosed during scheduled endoscopies were not eligible for adjudication because these procedures do not reflect symptomatic clinical events that would have been diagnosed in regular clinical practice. Investigators were instructed to report only events diagnosed during unscheduled endoscopic evaluations that were done for clinical reasons. These events were sent for adjudication and included in the analysis.

The primary endpoint was the incidence of confirmed PUBs. Suspected events adjudicated as 'not an upper GI event' were excluded from the primary analysis. This category was used for events which represented lower GI pathology, or where the event was determined by the adjudication committee to be of no clinical relevance.

We compared the incidence of confirmed PUBs in patients treated with etoricoxib (60 mg, 90 mg, or 120 mg daily, combined) in all non-selective NSAID controlled treatment periods with that in patients treated with one of the non-selective NSAIDs shown in Table 1 (all groups combined). Patients taking doses of etoricoxib less than 60 mg daily (n = 998) were excluded from the analyses. The comparator NSAIDs used in the trials were all within the approved dose range and similarly effective to etoricoxib in each of the indications studied. Individual patient data were combined across etoricoxib doses and across the comparator NSAIDs to enhance precision, since too little data would be available to meaningfully assess events for each etoricoxib dose or individual NSAID separately.

We also analyzed all investigator-reported PUBs (whether confirmed by the adjudication committee or not), as well as the subsets of confirmed and complicated PUBs, and all investigator-reported complicated PUBs

to corroborate the analysis of the primary endpoint, confirmed PUBs. All analyses were conducted according to a modified intention-to-treat principle, without imputation of missing data after discontinuation. Patients were included in the treatment group to which they were randomized, and all patients who received the study drug were included in the analyses.

Event rates were presented as the number of PUBs per 100 person-years of follow-up, along with 95% confidence intervals. Modified Kaplan–Meier survival plots (one minus the Kaplan–Meier estimate of the survival rate) were used to display the event occurrence over time. Only the first event for each individual patient that occurred between the start of the study drug and censoring date was included in the time-to-event analysis. Patients were censored at the time of an event or 14 days after their last dose of study medication. Because Kaplan–Meier estimates can be unstable or imprecise when the number of patients at risk becomes small (as occurs toward the end of a study), graphic displays of cumulative incidence of events were truncated at the last time point at which

Table 1. *Features of studies included in the combined analysis**

Reference	Design	Duration†	Etoricoxib daily dose(s)	NSAID comparator and daily dose	No. of patients‡
	Osteoarthritis trials				
11	Active comparator- and placebo-controlled dose ranging study in patients with knee or hip osteoarthritis	Up to 190 weeks	5, 10, 30, 60, or 90 mg	Diclofenac 150 mg	467
18, 19	Active comparator- and placebo-controlled safety and efficacy in patients with knee or hip osteoarthritis (US)	Up to 138 weeks	60 mg	Naproxen 1000 mg	478
20	Active comparator- and placebo-controlled safety and efficacy in patients with knee or hip osteoarthritis (multinational)	Up to 138 weeks	60 mg	Naproxen 1000 mg	489
21	Active-comparator-controlled safety and efficacy in patients with knee or hip osteoarthritis	6 weeks	60 mg	Diclofenac 150 mg	516
	Rheumatoid arthritis trials				
22	Active comparator- and placebo-controlled dose ranging study in patients with rheumatoid arthritis	Up to 174 weeks	10, 60, 90, or 120 mg	Diclofenac 150 mg	554
12	Active comparator- and placebo-controlled safety and efficacy in patients with rheumatoid arthritis (US)	Up to 121 weeks	90 mg	Naproxen 1000 mg	765
23	Active comparator- and placebo-controlled safety and efficacy in patients with rheumatoid arthritis (multinational)	Up to 121 weeks	90 mg	Naproxen 1000 mg	850
	Ankylosing spondylitis trial				
24	Active comparator- and placebo-controlled safety and efficacy in patients with ankylosing spondylitis	Up to 52 weeks	90 or 120 mg	Naproxen 1000 mg	380
	Endoscopy trials				
9	Active comparator- and placebo-controlled study to determine the incidence of gastroduodenal ulcers in patients with osteoarthritis or rheumatoid arthritis	12 weeks	120 mg	Naproxen 1000 mg	495 (124 OA, 371 RA)
10	Active comparator- and placebo-controlled study to determine the incidence of gastroduodenal ulcers in patients with osteoarthritis	12 weeks	120 mg	Ibuprofen 2400 mg	447

*All studies were randomized, double-blind, controlled trials

†Some trials had initial placebo-controlled phases followed by active comparator-controlled phases or extensions. Duration shown is that of the active-comparator phases or extensions

‡Shown are the numbers of patients from each trial that were included in the analysis. Patients treated with placebo, and patients in multi-part studies who were started on placebo or etoricoxib < 30 mg and who did not continue into active controlled period or extension were not included in the analysis

there were still at least 200 patients left at risk in each treatment group[26]. This truncation does not affect the statistical analyses, estimates of rates, or the Cox model results which account for all events and all patient time data. Relative risk (RR) estimates and associated 95% confidence intervals (CIs) and *p*-values were obtained using a Cox model which included terms for treatment and known risk factors for PUB, including history of clinically important GI AE (yes/no), age (< 65, ≥ 65 years), and corticosteroid use (based on baseline therapy records). Tests of the model's hazard proportionality assumption were performed using a *p*-value of 0.05 as the critical value.

A second analysis was performed that was restricted to events occurring during the first year of treatment to mitigate potential bias due to self-selection of patients who continued in the study extensions. Subgroup analyses were also carried out, including some subgroups at high risk of PUBs (history of clinically important GI AE, age (< 65, ≥ 65 years) and baseline corticosteroid use). The analysis plan specified that where there was a small number of events (< 11) and/or limited patient exposure in the subgroups, rate ratios (and associated confidence intervals) would be computed rather than using a Cox model for the subgroup analyses.

Results

Individual data for 5441 patients from 10 studies were included in the analysis; 3226 patients were treated with etoricoxib (950, 885, and 716 received 60 mg, 90 mg, and 120 mg, respectively; another 675 patients received more than one dose of etoricoxib in a given study due to dose switching by design) and 2215 patients were treated with NSAIDs (226 received ibuprofen 800 mg three times daily, 492 diclofenac 50 mg three times daily, and 1497 naproxen 500 mg twice daily). The average dose of etoricoxib was 87.3 mg once daily. Total-patient years of exposure were 4001.65 and 2225.46; median patient months of exposure were 12.4 and 6.3 in the etoricoxib and NSAID groups respectively, and maximum follow-up was 46.4 months and 44.3 months, respectively.

There were no clinically meaningful differences in baseline characteristics between groups (Table 2). Mean age overall was 56.7 years (range 17–99 years), 29% were age 65 years or older, and 74% were female. Approximately 7% of the patients in each group had a history of a serious GI adverse experience, and 4% used aspirin during at least 50% of the treatment period.

Etoricoxib was generally well tolerated. Sixty-four per cent of patients treated with etoricoxib and 62% treated with NSAIDs completed the study. The incidence of discontinuation due to a clinical AE was 9.7 and 13.3 per 100 patient-years for etoricoxib and NSAIDs, respectively (RR 0.73, 95% CI 0.63–0.85).

One hundred and twenty potential upper GI PUBs were submitted by investigators and adjudicated; 7 were ineligible for analysis because they occurred > 14 days after study drug discontinuation. Of the remaining 113 reported events, 2 were classified as 'not an upper-GI event' by the adjudication committee [one was considered a lower-GI event (small bowel perforation) and one was considered clinically insignificant (hemorrhoids)]. Of the remaining 111 patients, 95

Table 2. *Baseline patient characteristics from combined studies. Data displayed are number (%) unless otherwise indicated*

	Etoricoxib (*N* = 3226)	NSAIDs (*N* = 2215)	Total (*N* = 5441)
Study indication			
OA	1401 (43.4)	1120 (50.6)	2521 (46.3)
RA	1572 (48.7)	968 (43.7)	2540 (46.7)
AS	253 (7.8)	127 (5.7)	380 (7.0)
Mean age (years)	56.2	57.4	56.7
Age ≥ 65	881 (27.3)	684 (30.9)	1565 (28.8)
Female	2360 (73.2)	1645 (74.3)	4005 (73.6)
Race			
Caucasian	2380 (73.8)	1662 (75.0)	4042 (74.3)
Hispanic	434 (13.5)	272 (12.3)	706 (13.0)
Black	113 (3.5)	87 (3.9)	200 (3.7)
Other	299 (9.3)	194 (8.8)	493 (9.1)
Baseline corticosteroid user	882 (27.3)	591 (26.7)	1473 (27.1)
History of PUB	211 (6.6)	153 (6.9)	364 (6.7)
Aspirin user	123 (3.8)	100 (4.5)	223 (4.1)
Concomitant GPA user	318 (11.5)	227 (13.0)	545 (12.1)

OA: osteoarthritis; RA: rheumatoid arthritis; AS: ankylosing spondylitis; PUB: gastrointestinal (GI) perforation, symptomatic ulcer, or upper GI bleeding; GPA: gastroprotective agent; NSAIDs: nonsteroidal anti-inflammatory drugs

had events confirmed by the adjudication committee (40 etoricoxib and 55 NSAIDs) and 16 patients had unconfirmed events (7 etoricoxib and 9 NSAIDs). Forty-two patients had events adjudicated as confirmed clinically complicated events (19 etoricoxib and 23 NSAIDs) and 8 patients had unconfirmed complicated events (3 etoricoxib and 5 NSAIDs). Forty-five patients had more than one reported PUB (21 etoricoxib and 24 with NSAIDs). Only the first PUB in a given patient was included in the analysis.

The rates per 100 patient-years were 1.00 and 2.47 for etoricoxib and NSAIDs, respectively. The overall relative risk for etoricoxib vs. NSAIDs was 0.48 (95% CI 0.32, 0.73) (Table 3). Similar results were seen with all investigator-reported PUBs (whether confirmed by adjudication or not), and the subsets of confirmed complicated PUBs, and all investigator-reported complicated PUBs, although the difference was not significant for confirmed complicated PUBs due to the small number of events (Table 3). Tests of the proportional hazards assumption did not reject the assumption at the $\alpha = 0.05$ level. Kaplan–Meier curves for the confirmed PUB events for etoricoxib and comparator NSAIDs are shown in Figure 1. The curves appear to separate early and remain separated through the 30-month time point. The analysis of all four endpoints for the events within the first year of treatment yielded similar results, although because of the smaller numbers of events, the confidence intervals were larger. Specifically, the estimated relative risk of the etoricoxib group versus the non-selective NSAID group were 0.47 (95% CI 0.29, 0.77), 0.50 (95% CI 0.32, 0.79), 0.69 (95% CI 0.31, 1.53), and 0.73 (95% CI 0.35, 1.52) for the confirmed PUBs, all investigator-reported PUBs, confirmed complicated PUBs, and all investigator-reported complicated PUBs, respectively.

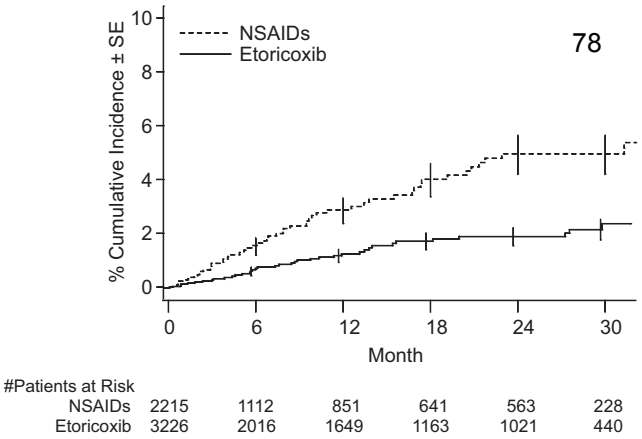

Figure 1. *Survival analysis of confirmed upper GI perforations, symptomatic ulcers, and upper GI bleeding, by combined treatment groups. Relative risk with etoricoxib vs. NSAIDs: 0.48 (95% CI 0.32, 0.73). Cumulative incidence display truncated at the last time point at which there were still at least 200 patients left at risk in each of the treatment groups*

The relative advantage of etoricoxib over non-selective NSAIDs in reducing PUBs was generally maintained in all subgroups analyzed (Figure 2), and none of the treatment-by-subgroup interactions was found to be significant. In some subgroups (patients with a history of PUBs, GPA users, and men), the precision of the rate ratio estimates was low due to low numbers of events (≤ 11) and/or limited patient years of exposure. Of note, the risk reductions were similar for those with and without known risk factors for PUBs (history of clinically

Table 3. *Incidence rates and relative risk of PUBs with etoricoxib compared with NSAIDs*

Treatment	No. of events/ total *N* (%)	Person-years	Rate* (95% CI)	Relative risk† (95% CI)	*p*-value‡
Confirmed PUBs					
Etoricoxib	40/3226 (1.24)	4001.65	1.00 (0.71, 1.36)	0.48 (0.32, 0.73)	< 0.001
NSAIDs	55/2215 (2.48)	2225.46	2.47 (1.86, 3.22)		
All investigator-reported PUBs					
Etoricoxib	47/3226 (1.46)	4001.37	1.17 (0.86, 1.56)	0.49 (0.33, 0.72)	< 0.001
NSAIDs	64/2215 (2.89)	2224.50	2.88 (2.22, 3.67)		
Confirmed complicated PUBs					
Etoricoxib	19/3226 (0.59)	4007.24	0.47 (0.29, 0.74)	0.59 (0.32, 1.09)	0.09
NSAIDs	23/2215 (1.04)	2229.66	1.03 (0.65, 1.55)		
All investigator-reported complicated PUBs					
Etoricoxib	22/3226 (0.68)	4007.15	0.55 (0.34, 0.83)	0.55 (0.31, 0.98)	0.41
NSAIDs	28/2215 (1.26)	2229.41	1.26 (0.83, 1.82)		

*Events per 100 person-years. CI = confidence interval
†Relative risk for an event with etoricoxib compared with NSAIDs estimated with Cox proportional hazards model
‡Based on the Cox proportional hazards model
NSAIDs: non-steroidal anti-inflammatory drugs
PUB: gastrointestinal (GI) perforation, symptomatic ulcer, or GI bleeding

significant GI event, age > 65 years, and concomitant corticosteroid use). The effect of etoricoxib was also consistent in those taking gastroprotective agents (GPAs) as well as those not using GPAs (rate ratios 0.42 and 0.25, respectively). Although concomitant aspirin use was allowed in some of the trials, overall use was only 4.1% and there were too few events (6 with etoricoxib and 2 with NSAIDs) for meaningful analysis.

Discussion

This study was an updated combined analysis of the incidence of clinically significant GI events with etoricoxib compared with non-selective NSAIDs using data from ten randomized, double-blind, clinical trials in patients with OA, RA, and AS. The combined population included patients at high risk of PUBs (e.g., those with a history of PUB, using steroids, and/or age ≥ 65 years). The analysis demonstrated a significantly lower incidence of confirmed PUBs with etoricoxib than with NSAIDs for treatment durations up to 44.3 months, during which the overall risk with etoricoxib was half that of NSAIDs. The risk reduction with etoricoxib was evident early and was maintained over time (Figure 1). Similar results were obtained when the outcome studied was PUBs complicated by perforation, obstruction, or serious bleeding. The overall rates of discontinuation due to clinical adverse experiences were similar with etoricoxib and NSAIDs. The doses of etoricoxib in the studies comprising this analysis have been shown to be therapeutically equivalent or superior to, in terms of symptom relief, the doses of the main comparator NSAIDs[11,12,18–24].

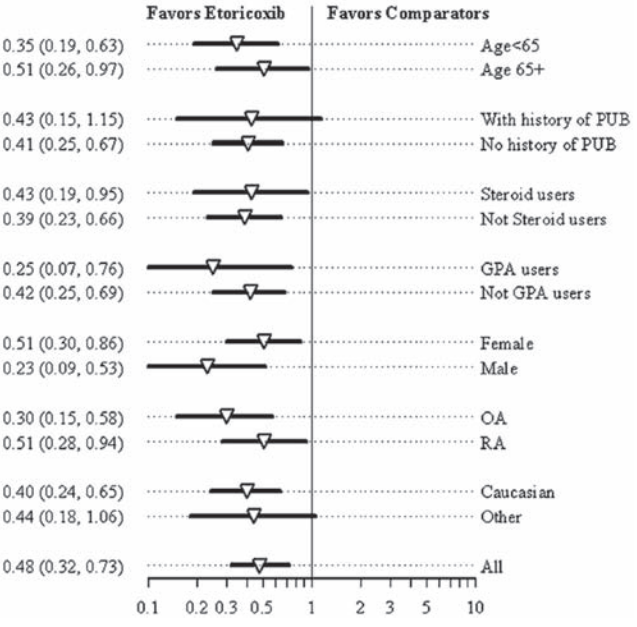

Figure 2. *Rate ratios and 95% confidence intervals for confirmed PUBs in subgroups from analysis of combined studies*

This study expands on the results of the previous analysis of PUBs in patients treated with etoricoxib and non-selective NSAIDs[10]. These results are also consistent with the results of similar combined analyses of clinical trials with rofecoxib vs. non-selective NSAIDs in OA and RA patients[25] and those of a large GI outcomes trial of 50 mg rofecoxib daily vs. naproxen in RA patients[4]; in both previous analyses the risk reduction for confirmed PUBs was approximately 50%[4,25]. The results are also consistent with reductions in the primary endpoint of gastrointestinal ulcer complications reported for celecoxib[16,17].

This analysis has particular strengths. There were sufficient numbers of patients to examine subgroups at risk of PUBs. In these subgroup analyses, results were generally consistent with the primary result, although in a few subgroups the precision of the analyses was low. The classification of endpoints was based on pre-specified adjudication criteria, and an external, blinded committee adjudicated all reported PUBs. The population studied included a large number and a broad range of patients, including those with known risk factors for PUBs. The doses of NSAID comparators for the included studies were chosen to be within the clinical dose range for treatment of OA, RA, and AS, while doses of etoricoxib included those at and above the clinical dose range for these indications. The average dose of etoricoxib in this study was 87.3 mg daily; the recommended daily dose for RA and AS is 90 mg while that for OA is 30 mg or 60 mg. The time-to-event analytic methods took account of the varying lengths of the included studies. To control for potential differences in PUB risk by treatment, the relative risk estimates were adjusted by including known risk factors for PUB (history of clinically important GI AE, age (< 65, ≥ 65 years), and baseline corticosteroid use) in the Cox models.

This analysis could not, however, effectively evaluate differences among doses of etoricoxib because of too few events per dose and because of confounding between doses, study designs, and disease. In addition, because of small sample sizes for diclofenac and ibuprofen, the NSAID results are largely driven by naproxen, and comparisons to the individual NSAIDs were not possible. It was also not possible to compare event rates in aspirin users and non-users because of the small number of patients taking aspirin in these studies.

Inclusion of studies with scheduled endoscopies mandated in their protocols may have caused a bias against etoricoxib. Patients in these studies were systematically discontinued from treatment when they developed endoscopically-evident gastroduodenal

ulcers ≥ 3 mm in diameter, and a much higher rate of endoscopically-detected ulceration was observed with NSAID comparators than with etoricoxib[9,10]. If discontinued patients had excess potential to develop a PUB (e.g. because of their endoscopic ulcer or a history of PUB, which is a strong risk factor for both endoscopic ulcer and clinical PUB), then the inclusion of these two studies may have reduced the incidence of clinically-evident PUBs in the non-selective NSAID group. In spite of this source of bias against etoricoxib, its advantage over NSAIDs was readily apparent.

In light of the recent findings of increased cardiovascular risk associated with rofecoxib[27], celecoxib[28], and valdecoxib[29], it should be noted that this likely represents a class effect applicable to all COX-2 selective NSAIDs and possibly to many non-selective NSAIDs as well. A recent combined analysis of confirmed thrombotic cardiovascular events in the etoricoxib development program that was presented at an FDA advisory committee meeting on the cardiovascular safety of COX-2 selective inhibitors, indicated that the event rate for etoricoxib was similar to that of non-naproxen NSAIDs (ibuprofen and diclofenac) (RR: 0.83, 95% CI: 0.26, 2.64); however, the event rate for etoricoxib was numerically higher than that for naproxen (RR: 1.70, 95% CI: 0.91, 3.18)[30]. The Etoricoxib vs. Diclofenac in Gastrointestinal Tolerability and Efficacy in Osteoarthritis (EDGE) study showed no difference in confirmed thrombotic cardiovascular events between etoricoxib (90 mg qid) and diclofenac (50 mg tid) in 7111 patients studied over a mean duration of 9 months (RR 1.07, 95% CI 0.65, 1.74)[30]. Limited data are available for patients taking etoricoxib beyond 18 months, although long-term cardiovascular outcome studies are ongoing. Cardiovascular risk will need to be taken into account in determining the most appropriate NSAID treatment for a given patient.

Conclusions

This study demonstrates that COX-2 specific inhibition with etoricoxib is associated with a significantly lower risk of PUBs relative to non-selective NSAIDs. These findings are consistent with the results of studies of fecal red blood cell loss[9] and upper endoscopy[9,10] with etoricoxib, and indicate that the risk of GI toxicity associated with NSAIDs can be reduced by COX-2 specific inhibition with etoricoxib. Moreover, in this study, the risk reduction with etoricoxib pertained to important subgroups of patients with and without risk factors for PUB and in patients using concomitant gastroprotective therapy. Etoricoxib may provide a safe and effective alternative for patients at high risk of gastrointestinal complications with non-selective NSAIDs.

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Clinical trial design and patient demographics of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Study Program: Cardiovascular outcomes with etoricoxib versus diclofenac in patients with osteoarthritis and rheumatoid arthritis

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently needed for the treatment of patients with arthritis. However, long-term use of such drugs that are cyclooxygenase-2 (COX-2) selective inhibitors has been reported to increase cardiovascular risk as compared with placebo, whereas long-term, randomized controlled trials assessing the risk of traditional NSAIDs versus placebo are lacking. The MEDAL program is designed to provide a precise estimate of the relative cardiovascular event rates with the COX-2 selective inhibitor etoricoxib in comparison to the traditional NSAID diclofenac in patients with osteoarthritis and rheumatoid arthritis. The MEDAL program consists of 3 multinational, randomized, double-blind trials in patients with osteoarthritis and rheumatoid arthritis comparing etoricoxib (60 or 90 mg daily) to diclofenac (150 mg daily). All investigator-reported thrombotic cardiovascular events will be adjudicated by an independent panel of experts blinded to treatment assignment. The primary analysis is a noninferiority comparison of etoricoxib versus diclofenac for confirmed thrombotic cardiovascular events, defined as an upper bound of the 95% CI for a hazard ratio of <1.30. With the planned 635 observed events from approximately 40 000 patient-years of exposure, using an estimated annual event rate of 1.30% in the control arm, the maximum annual event rate for etoricoxib that would meet the noninferiority criteria would be approximately 1.46%, yielding a hazard ratio of 1.12. A total of 34 701 patients have been enrolled in the MEDAL program. Roughly 13 000 and 10 000 patients will, respectively, have had ≥18 or ≥24 months of exposure, with maximum exposure of ~40 months. The MEDAL program will help to better define the risk-to-benefit ratio of 2 NSAIDs, that differ in their selectivity for COX-2, notably diclofenac and etoricoxib. (Am Heart J 2006;152:237-45.)

Selective inhibitors of COX-2 (coxibs) were developed to provide analgesic and anti-inflammatory efficacy comparable to traditional NSAIDs with improved gastrointestinal safety. Several randomized trials have provided clinical evidence that the use of coxibs is associated with a significantly decreased relative risk of upper gastrointestinal ulcers, complications (eg, bleeding), and symptoms as compared with traditional NSAIDs.[1] Coxib use also appears to decrease the risk of lower gastrointestinal mucosal damage and clinical events.[2]

Recent long-term, randomized placebo-controlled trials provide evidence that coxibs are associated with an increased risk of thrombotic cardiovascular events as compared with placebo.[3,4] However, long-term, placebo-controlled cardiovascular safety data are lacking for traditional NSAIDs, and clinical trials directly comparing the risk of cardiovascular events to a coxib are limited to approximately 1 year of drug exposure.[5] After a review of currently available data, the US Food and Drug Administration recently concluded that there is no clear evidence that coxibs confer a greater risk of cardiovascular events compared with traditional NSAIDs.[6] In addition, they concluded that all NSAIDs, except aspirin, may carry an increased risk of cardiovascular events after long-term use and that this should be stated in their product labels.[7]

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Table I. Summary and description of the 3 etoricoxib studies comprising the prospectively designed MEDAL program

	MEDAL program component trials		
	EDGE	**EDGE II**	**MEDAL**
Primary objective	Compare gastrointestinal tolerability of etoricoxib to diclofenac in patients with osteoarthritis	Compare gastrointestinal tolerability of etoricoxib to diclofenac in patients with rheumatoid arthritis	1. Compare cardiovascular events with etoricoxib versus diclofenac, based on data combined from 3 component studies (EDGE, EDGE II, MEDAL) 2. Compare cardiovascular events with etoricoxib versus diclofenac, based on data from the MEDAL study alone
Sponsor protocol no.	061	072	066
Clinical trial registry no.	NCT00092703	NCT00092742	NCT00250445
Study size	7111	4086	23504; 17804 osteoarthritis, 5700 rheumatoid arthritis
Patient population	Osteoarthritis	Rheumatoid arthritis	Osteoarthritis and rheumatoid arthritis
Study therapy	Etoricoxib 90 mg/d versus diclofenac 50 mg three times a day (1:1)	Etoricoxib 90 mg/d versus diclofenac 75 mg twice a day (1:1)	Etoricoxib (60 or 90 mg/d in osteoarthritis, 90 mg in rheumatoid arthritis) versus diclofenac 75 mg twice a day (1:1)*
Duration of therapy in months [mean (max)]	9 (16)	19 (34)†‡	20 (40)§
Data available	Study complete	2006	2006

*In the MEDAL Study, the first 4000 patients with osteoarthritis were randomized to etoricoxib 90 mg or diclofenac 75 mg twice a day. The remaining patients with osteoarthritis were randomized to etoricoxib 60 mg or diclofenac 75 mg twice a day.
†The duration of EDGE II was defined as 2 years from the last patient randomized.
‡Because the study is ongoing the duration of therapy provided represents a prediction.
§The MEDAL study is end point–driven and will be complete when the prespecified number of confirmed cardiovascular events is reached.

The MEDAL program addresses an important clinical (and public health) question: for patients with osteoarthritis and rheumatoid arthritis who require use of an anti-inflammatory drug, what is the risk and benefit of a coxib as compared with a traditional NSAID? The MEDAL program was specifically designed to estimate precisely the relative risk of thrombotic cardiovascular events with the COX-2 selective inhibitor etoricoxib compared with the widely used traditional NSAID diclofenac using a noninferiority trial design. Patients in the MEDAL program will have a range of cardiovascular risk, including those with preexisting cardiovascular disease, and will be allowed to use low-dose aspirin for cardioprophylaxis to closely simulate real-world conditions. Here we present the clinical study design, baseline characteristics of the study population, and current status of the MEDAL program.

Methods

MEDAL program design

The MEDAL program was designed to provide a noninferiority analysis of thrombotic events after daily treatment with etoricoxib (60 and 90 mg combined) compared with diclofenac 150 mg. The program is composed of 3 randomized, double-blind trials conducted in 38 countries in academic medical centers and private practice–based research centers (Table I).

Study eligibility

Patients with osteoarthritis or rheumatoid arthritis were eligible if they were ≥50 years of age with a clinical diagnosis of osteoarthritis of the knee, hip, hand, or spine, or a clinical diagnosis of rheumatoid arthritis that satisfied at least 4 of 7 of the American Rheumatism Association 1987 revised criteria,[8] and in the judgment of the investigator, would require long-term therapy with a traditional NSAID or coxib. These patients were not candidates for acetaminophen first-line therapy because of the severity of their symptoms. Patients with a history of myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention >6 months preceding enrollment in the study could participate.

Patients who had any of the following were excluded: morbid obesity; significantly impaired renal function (creatinine clearance <30 mL/min or serum creatinine >2.0 mg/dL); uncontrolled hypertension (sitting diastolic blood pressure >95 mm Hg or sitting systolic blood pressure >165 mm Hg); stroke or transient ischemic attack within the previous 6 months; gastrointestinal malabsorption; active hepatitis or hepatic disease; congestive heart failure with symptoms at rest or with minimal activity; unstable angina; bleeding diathesis; inflammatory bowel disease; evidence of active gastrointestinal bleeding; history of leukemia, lymphoma, melanoma, or myeloproliferative disease, or other malignancy within the past 5 years that had not been successfully treated; American College of Rheumatology functional class IV rheumatoid arthritis; required therapy with warfarin, heparin, high-dose aspirin (>100 mg/d), nonstudy NSAID or coxib, or the combination of ticlopidine or clopidogrel plus low-dose

Table II. Serious adverse events included in the cardiovascular thrombotic event, arterial event, and APTC combined end points

Adjudication committee categories for cardiovascular events	Thrombotic cardiovascular event	Arterial events	APTC combined end point
Thrombotic events			
Cardiac events			
Acute MI	✓	✓	✓
Fatal: acute MI	✓	✓	✓
Unstable angina pectoris	✓	✓	
Sudden and/or unexplained death	✓	✓	✓
Resuscitated cardiac arrest	✓	✓	✓
Cardiac thrombus	✓		
Peripheral vascular events			
Pulmonary embolism	✓		
Fatal: pulmonary embolism	✓		✓
Peripheral arterial thrombosis	✓	✓	
Fatal: peripheral arterial thrombosis	✓	✓	✓
Peripheral venous thrombosis	✓		
Cerebrovascular events			
Ischemic cerebrovascular stroke	✓	✓	✓
Fatal: ischemic cerebrovascular stroke	✓	✓	✓
Cerebrovascular venous thrombosis	✓		
Fatal: cerebrovascular venous thrombosis	✓		✓
Transient ischemic attack	✓	✓	
Hemorrhagic events			
Hemorrhagic cerebrovascular stroke*			✓
Fatal: hemorrhagic cerebrovascular stroke*			✓
Fatal: hemorrhagic deaths of any cause			✓

APTC, Antiplatelet Trialists' Collaboration; *MI*, myocardial infarction.
*These events are included as investigator-reported events, but not confirmed thrombotic cardiovascular serious adverse experiences.

aspirin; or allergy or hypersensitivity to aspirin, other traditional NSAIDs, or coxibs.

Study treatments

In countries where it is approved, the highest recommended daily dose of etoricoxib for long-term use is 60 mg for osteoarthritis and 90 mg for rheumatoid arthritis. Etoricoxib 90 mg was evaluated in both the EDGE and EDGE II studies. In the MEDAL study, 90 mg was evaluated in patients with rheumatoid arthritis; in patients with osteoarthritis, the etoricoxib dose was amended from 90 to 60 mg after an initial period of enrollment to reflect the current osteoarthritis dosing recommendation for etoricoxib. We chose a daily dose of diclofenac, 150 mg, which is at the upper end of the indicated daily dose range (100-150 mg) for the treatment osteoarthritis and at the lower end of the indicated daily dose range (150-200 mg) for the treatment of rheumatoid arthritis.[9]

Patients meeting screening criteria were randomized with concealed allocation to treatment in equal proportions within study site using a different computer-generated randomization schedule for each of the 3-component trials (Table I). The first 4000 patients with osteoarthritis and all patients with rheumatoid arthritis in the MEDAL study were randomized to receive etoricoxib 90 mg/d or diclofenac 75 mg twice a day. The remaining patients with osteoarthritis in the MEDAL study were randomized to receive etoricoxib 60 mg/d or diclofenac 75 mg twice a day. Patients in the EDGE and EDGE II studies were randomized to receive etoricoxib 90 mg/d, diclofenac 50 mg three times a day (EDGE), or diclofenac 75 mg twice a day (EDGE II). A double-dummy design along with coded study medications was used to maintain blinding to treatment assignment.

Concomitant medication use

Low-dose aspirin (<100 mg/d) was recommended for cardiovascular prophylaxis in patients with established cardiovascular, peripheral arterial, or cerebrovascular disease as per current treatment guidelines.[10] In addition, low-dose aspirin use was strongly encouraged for patients with diabetes.[11] All patients had a worksheet completed by the investigator to determine if low-dose aspirin therapy was appropriate, and aspirin was provided free of charge. If aspirin was not provided to patients meeting established guidelines, investigators were contacted again and required to state their reasons for not providing it. Concomitant use of clopidogrel or ticlopidine with low-dose aspirin was allowed for up to 1 month in patients who had undergone coronary stent implantation.

The use of agents documented to reduce upper gastrointestinal ulcers and complications such as proton-pump inhibitors and misoprostol was also recommended per current guidelines in patients with risk factors for gastrointestinal complications (age >65 years, prior upper gastrointestinal clinical event, use of corticosteroid or anticoagulant, use of low-dose aspirin).[12,13] Omeprazole was provided free of charge to patients in the MEDAL study if proton-pump inhibitor therapy was recommended by the investigator. If a gastroprotective agent (eg, proton pump inhibitor or misoprostol) was not given to patients with risk factors, investigators were again contacted and were required to state their reasons for not using it.

In an effort to ensure that blood pressure is adequately controlled in the MEDAL study, regular weekly reviews of the blinded database were instituted during the course of the study to identify patients with systolic blood pressure of >140 mm Hg. For these patients, investigators were encouraged to follow current treatment guidelines.[14]

Acetaminophen was provided for treatment of breakthrough arthritis pain. If the maximum dose of 650 mg every 6 hours failed to relieve pain, use of heat, physical therapy, or capsaicin was suggested, and investigators could prescribe non-aspirin, non-NSAID analgesics.

Primary end point

The primary end point is the occurrence of confirmed adjudicated thrombotic events. This composite end point of arterial and venous disease includes the following events: myocardial infarction (including silent infarction), unstable angina pectoris, intracardiac thrombus, resuscitated cardiac arrest, thrombotic stroke, cerebrovascular thrombosis, transient ischemic attack, peripheral venous thrombosis, pulmonary embolism, peripheral arterial thrombosis, and sudden and/or unexplained death (Table II). A secondary prespecified thrombotic cardiovascular end point is the subset of confirmed adjudicated arterial events (Table II).

Electrocardiograms performed on all patients at study randomization, along with any electrocardiograms performed during the trial, will be compared with an electrocardiogram at study end to assess for evidence of intercurrent cardiac injury that was not detected clinically (eg, silent myocardial infarction). Patients are routinely seen every 4 months with telephone contact between visits. Patients discontinued from the study are contacted every 6 months by telephone through the end of the study. All reported thrombotic events from the 3 component trials of the MEDAL program are adjudicated by a common adjudication committee composed of clinical experts for adjudication of cardiac, neurologic, and peripheral vascular events. Reported cardiovascular events will also be adjudicated using the Anti-Platelet Trialists' Collaboration end point for comparison (Table II).[15] In addition, cases of congestive heart failure will be adjudicated and analyzed separately.

Study duration

The MEDAL program is end point–driven and will continue until the total number of confirmed thrombotic events reaches at least 635 with at least 490 confirmed events in the MEDAL Study alone. The EDGE and EDGE II studies were designed with specific study start and stop times allowing some patients to reach a maximum duration of therapy of 16 and 34 months, respectively (Table I).

Sample size and data analysis

The primary hypothesis for the MEDAL program is that treatment with etoricoxib for patients who have osteoarthritis and rheumatoid arthritis will be noninferior to treatment with diclofenac with regard to the incidence of confirmed thrombotic events. The primary analysis will consider the events from all 3 component studies combined. A secondary hypothesis is that etoricoxib will be noninferior to diclofenac when only confirmed thrombotic event data from the MEDAL study are analyzed.

We chose a noninferiority bound of 1.30, below which the 95% CI for the hazard ratios must fall, for the MEDAL program. Estimates of power were obtained using a proportional hazards assumption. Given a true underlying hazard ratio of 1.00, approximately 635 confirmed thrombotic events need to be observed across the 3 component studies to provide 91% power (81% power for the arterial end point) to yield the upper limit of the 95% CI for hazard ratios of <1.30 for the primary end point. The required number of events was calculated using the Lachin-Foulkes[16] method.

The primary method of analysis will follow a per-protocol approach to determine noninferiority of etoricoxib compared to diclofenac for the primary end point. Supporting analyses will also be performed using a modified intent-to-treat population, which includes all patients who received at least 1 dose of study medication and will consider all events observed within 14 days (and another sensitivity analysis within 28 days) of the last dose of study medication. In addition, a supportive intent-to-treat analysis based on ascertainment of confirmed thrombotic events from all patients through the end of each respective trial will be carried out. Analysis of the 3 populations is aimed at demonstrating robustness of results; heterogeneity will be examined and explained.

The time frame for the per-protocol and modified intent-to-treat analyses will be from day 1 of therapy to 14 days after the last dose of study therapy for each patient. Patients excluded from the per-protocol analysis will include subjects with <75% compliance for usage of study medication (while taking study medication) or those who took nonstudy NSAIDs or coxibs >10% of the time on study. The 75% compliance figure is consistent with criteria used in other large, longer-term arthritis studies.[5] Studies have shown that >95% of subjects are compliant by this definition [17]; thus, only a small proportion of patients are expected to be excluded from the per-protocol analysis with this definition of compliance. The time frame for the supportive intent-to-treat analysis is the first day of medication through 28 days after the date of the last dose in the last patient.

The hazard ratio for confirmed thrombotic events for etoricoxib versus diclofenac will be calculated using Cox proportional hazards model. Treatment will be used as an explanatory factor, and low-dose aspirin use will be used as a stratification factor. Kaplan-Meier time-to-event curves will be shown. The proportional hazards assumption will be assessed by testing a log(time)-by-treatment interaction term added to the Cox model; if this assumption is not supported by the data, additional analyses by time interval will be performed as appropriate.

The MEDAL program is sufficiently large so that effects of other factors on relative risk of thrombotic events can be assessed across a range of subgroup factors including disease (osteoarthritis and rheumatoid arthritis), cardiovascular risk, aspirin use, etoricoxib dose (60 vs 90 mg), study (EDGE, EDGE II, MEDAL), and exposure >18 months. These analyses are aimed at demonstrating robustness of results adjusted for various subgroup factors and consistency of results across the subgroups. Any heterogeneity found will be explored and explained. In addition to cardiovascular events, investigator-reported upper and lower gastrointestinal events will be adjudicated as previously described.[2,17]

Table III. Baseline patient demographics (overall population) in the MEDAL program

Baseline characteristics	EDGE I N = 7111	EDGE II* N = 4086	MEDAL study* N = 23504	Program total* N = 34701
Sex, n (%)				
Female	5099 (71.7)	3261 (79.8)	17386 (74.0)	25746 (74.2)
Male	2012 (28.3)	825 (20.2)	6118 (26.0)	8955 (25.8)
Ethnic group, n (%)				
White	6051 (85.1)	2595 (63.5)	18595 (79.1)	27241 (78.5)
Black	267 (3.8)	110 (2.7)	890 (3.8)	1267 (3.6)
Hispanic	410 (5.8)	465 (11.4)	1991 (8.5)	2866 (8.3)
Asian	226 (3.2)	184 (4.5)	921 (3.9)	1331 (3.8)
Native American	22 (0.3)	10 (0.2)	40 (0.2)	72 (0.2)
Other	135 (1.9)	722 (17.7)	1067 (4.5)	1924 (5.5)
Mean age (SD) (y)	63.7 (8.6)	60.8 (7.7)	63.4 (8.5)	63.2 (8.5)
Patients ≥65 y, n (%)	3152 (44.3)	1245 (30.5)	10000 (42.6)	14397 (41.5)
Disease indication, n (%)				
Osteoarthritis	7111 (100)	0	17804 (75.8)	24915 (71.8)
Rheumatoid Arthritis	0	4086 (100)	5700 (24.2)	9786 (28.2)
Study region, n (%)				
USA	5265 (74.0)	993 (24.3)	9693 (41.2)	15951 (46.0)
Ex-USA	1846 (26.0)	3093 (75.7)	13811 (58.8)	18750 (54.0)
Diabetic patients	709 (10.0)	344 (8.4)	2608 (11.1)	3661 (10.6)
Current smokers	661 (9.3)	662 (16.2)	2748 (11.7)	4071 (11.7)
Hypertension	3236 (45.5)	1540 (37.7)	11543 (49.1)	16319 (47.0)
History of symptomatic atherosclerotic cardiovascular disease	673 (9.5)	312 (7.6)	2889 (12.3)	3874 (11.2)

*Preliminary data.

Data and safety monitoring board

An independent data and safety monitoring board monitored data throughout the course of the MEDAL program and could recommend modification of the protocols or early termination if emerging data show a safety advantage for 1 of the 2 treatment groups. There are no plans to stop the MEDAL program because of noninferiority of etoricoxib in comparison to diclofenac with respect to confirmed cardiovascular events. The specific stopping criterion for inferiority is hazard ratio of >1.30 and for superiority it is hazard ratio of <0.77. The O'Brien-Fleming–type stopping bounds are defined at an overall 1-sided α level of .025 for inferiority and overall 1-sided α level of .001 for superiority.

Independent confirmation of study analyses

In addition to the analyses performed by the MEDAL program Sponsor, analyses will also be performed independent of the Sponsor to confirm the primary results of the MEDAL program.

Results

Current program status and baseline demographics

The clinical trials that are part of the MEDAL program were each approved by the institutional review boards of each study center. All patients provided written informed consent before their participation in the component studies. During the course of the EDGE II and MEDAL studies, patients were asked to provide written informed consent again, after being informed of new regulatory guidance information on the risk and benefit aspects of traditional NSAID and coxib use.

Enrollment in all 3 component trials of the MEDAL program has been completed (Table III). Program-wide, a total of 39949 patients were screened: EDGE 8711 patients, EDGE II 4724 patients, and MEDAL study 26514 patients. The leading reasons for exclusion from the component studies upon screening were clinical or laboratory abnormalities; positive fecal occult blood test result; history of or current illness that could confound the study results or pose a risk to patient safety; uncontrolled hypertension; and recent sustained use of gastroprotective agents (EDGE and EDGE II only) before study. A total of 34701 patients were randomized to treatment (Table III). This includes 24915 and 9786 patients with osteoarthritis and rheumatoid arthritis, respectively. Projections indicate ~13000 and ~10000 patients will have ≥18 or ≥24 months of exposure, respectively. Maximum duration of exposure is projected to be ~40 months. In addition, all patients regardless of discontinuation status will be followed until the end of each component trial and their data included in the intent-to-treat analysis.

Discussion

In light of the recent evidence of a cardiovascular risk with coxibs compared with placebo, their relative safety compared with traditional NSAIDs and the absolute safety of the traditional agents themselves are issues of great clinical importance.[3,4,6,7] Direct comparison of coxibs or traditional NSAIDS to placebo is the definitive

method to assess absolute risk; however, in patients with arthritis, long-term placebo-controlled trials of either type of agent are not possible because patients would have breakthrough symptoms on placebo and thus require some type of anti-inflammatory therapy. Placebo-controlled trials in other populations (eg, in chemoprevention) have been conducted and have demonstrated increased risk versus placebo.[3,4] The clinically relevant question for patients with arthritis, who require anti-inflammatory therapy, is to assess the relative cardiovascular risk among different active anti-inflammatory therapies required by these patients. The MEDAL program directly addresses this question and evaluates one of the newer coxibs, etoricoxib.

Numerous traditional NSAIDs were considered when selecting the active comparator for the MEDAL program. The 3 traditional NSAIDs given primary consideration were diclofenac, naproxen, and ibuprofen. We chose diclofenac for the following reasons. It is the most widely used prescription NSAID on a worldwide basis and is effective for the treatment of both osteoarthritis and rheumatoid arthritis.[18] Compared with ibuprofen, diclofenac is administered twice a day rather then 3 times a day, an important factor to enhance compliance for a study that is intended to assess safety over a prolonged period of use. Importantly, diclofenac does not interfere with the antiplatelet effects of low-dose aspirin (used by ~30% of patients in the MEDAL program), whereas both naproxen and ibuprofen have been shown to interfere with aspirin on the basis of platelet function assays.[19-21] Therefore, the use of diclofenac avoids the potential confounding of the primary cardiovascular end point that may result with either naproxen or ibuprofen.

From the perspective of ease of clinical use and lack of confounding, diclofenac was selected as the comparator in this trial. However, questions may be asked as to how different is diclofenac pharmacodynamically from the coxibs. Although in vitro assays suggest some COX-1 sparing (ie, modest COX-2 selectivity) with diclofenac,[22,23] results from ex vivo assays in patients receiving therapeutic doses demonstrate that diclofenac does substantially inhibit COX-1, whereas celecoxib, rofecoxib, and etoricoxib do not.[24-26] From the perspective of clinically important gastrointestinal outcomes, diclofenac was not statistically significantly different from celecoxib in the CLASS trial.[27] Endoscopic trials, however, indicate that diclofenac behaves similarly to a traditional NSAID at therapeutic doses, significantly increasing the incidence of gastroduodenal ulcers compared with celecoxib and valdecoxib with rates not unlike another traditional NSAID, ibuprofen.[28-30]

Given the emerging evidence (including data from observational studies) that traditional NSAIDs may increase cardiovascular risk,[6] diclofenac should not be viewed as a putative placebo from the perspective of cardiovascular safety. As such, an assessment of absolute cardiovascular risk for etoricoxib cannot, and should not, be inferred from MEDAL program studies, nor can the results of the MEDAL study necessarily be extrapolated to other coxibs or traditional NSAIDs. However, one can draw conclusions as to the cardiovascular safety of etoricoxib relative to the most widely used NSAID in the world, an assessment of paramount importance to the millions of patients who require long-term NSAID treatment for relief of arthritic symptoms.

The primary end point in the MEDAL program is a composite of both arterial and venous thrombotic events. Arterial events, such as myocardial infarction and stroke, have become the clinical events of greatest interest in the ongoing cardiovascular safety evaluation of COX-inhibiting therapies, primarily because of their clinical significance and the fact that imbalances in these events have been observed relatively consistently in the major data sets in which a coxib was associated with an increase in cardiovascular events, either compared with placebo[3,4] or naproxen.[17] It should be noted however that in the VIGOR study, the overall imbalance in cardiovascular events between rofecoxib and naproxen included venous events as well as arterial events.[17] With the scientific debate on mechanistic hypotheses for cardiovascular risk ongoing, we elected to designate as primary an end point inclusive of all thrombotic cardiovascular events, both venous and arterial, to be as comprehensive as possible. Along with the primary end point, analyses will be presented using only arterial events as an end point as well as the Antiplatelet Trialists combined end point[15] to provide a complete view of the data. With respect to arterial thrombotic events only, the MEDAL program as designed is anticipated to observe >500 such events and have >80% power to establish noninferiority based on the same boundary as defined for the primary end point. The incidence of congestive heart failure will also be evaluated using blindly adjudicated event data, but will be tabulated separately because the etiology of congestive heart failure likely involves different pathophysiologic processes related primarily to salt and water retention.[31,32]

The selection of the noninferiority bound is a major issue in designing a noninferiority trial.[33] Determining this noninferiority bound is a clinical rather than a statistical decision. This upper bound should represent the highest value that could still be considered clinically noninferior. Because safety differences between the 2 treatments are of clinical interest, it is desirable for the noninferiority bound to be as small as possible. However, even if the 2 treatments being studied have the same true underlying risk, it is impossible to design a trial to rule out any difference; there always is a 50% chance that the estimated relative risk will be >1.0. Consequently, the noninferiority bound for the CI must be >1.0. For reference, noninferiority bounds for 95%

Table IV. Representative upper noninferiority bounds considered with the number of required cardiovascular events, sample size, maximum HR, and CI for each upper bound, and width of the CI if the HR is 1.0

Noninferiority bound	No. of cardiovascular events required*	No. of patient-years exposure†	Maximum HR for upper bound considered‡	95% CI if observed HR = 1.0
1.4	372	28615	1.13 (0.91-1.39)	(0.81-1.23)
1.3	611	47000	1.10 (0.93-1.29)	(0.85-1.18)
1.2	1265	97308	1.07 (0.96-1.198)	(0.89-1.12)
1.1	4627	355923	1.03 (0.97-1.096)	(0.94-1.06)

HR, Hazard ratio.
*Number of events required for a 2-treatment study to have 90% probability (power) that the resultant 95% CI for HR is less than the noninferiority bound.
†Number of patient-years of exposure required to yield the indicated number of events if the underlying event rate is 1.3%/y.
‡Maximum observed HR with associated 95% CI that is less than the noninferiority bound.

CIs for hazard ratios of 1.1, 1.2, 1.3, and 1.4 along with simulated hazard ratios and CIs are shown in Table IV.

At an assumed event rate of 1.3% per year for diclofenac[34] the maximum annual event rate for etoricoxib that would meet the noninferiority criteria would be approximately 1.46% with 635 observed events and approximately 40 000 patient-years of exposure from the combined studies. This represents an absolute difference in events of <2 per 1000 patient-years.

Per-protocol analyses are recommended for noninferiority trials by statisticians, regulatory agencies, and the CONSORT statement[35-37] because they provide a more conservative approach to equivalence or noninferiority trials than an intent-to-treat analysis because the use of the intent-to-treat population can predispose the event rates of the 2 groups toward similarity.[33] For example, event rates for discontinued patients from either study group would trend toward an equal event rate for each group after discontinuation because these patients would be treated with other nonstudy medications in a random fashion. This would make the 2 treatment groups appear to be more similar. The greater the number, and the longer the time patients were off study therapy (but still being counted in an intention-to-treat analysis), the greater the chances of equivalence or noninferiority being identified. Conversely, evaluating study medications only during (and for 2-4 weeks after) treatment would allow a direct pharmacologic comparison of risk. However, in the MEDAL program, both analytical approaches will be used and examined for consistency.

The MEDAL program is the first clinical program specifically designed to assess noninferiority for thrombotic cardiovascular events between a coxib and a traditional NSAID with adequate power. Other studies[5,27,38] have assessed the relative risk of thrombotic events in smaller numbers of patients followed for shorter duration. However, those studies were not designed as noninferiority trials.[33] Therefore, a lack of significant difference between a coxib and traditional NSAID in those trials[5,27,38] cannot be interpreted as demonstrating noninferiority, particularly given the wide 95% CIs reported in those trials.

In summary, the MEDAL program will yield a precise estimate of the long-term incidence of thrombotic cardiovascular events with the coxib etoricoxib and the traditional NSAID diclofenac, the most widely used prescription NSAID in the world. It is expected that results from this clinical trials program will provide information helpful to physicians treating arthritic patients reliant on the therapeutic benefits of these agents.

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Appendix A
MEDAL Program Steering Committee

Christopher P. Cannon, MD (Co-Chair), Brigham and Women's Hospital, Boston, MA; Loren Laine, MD (Co-Chair), USC School of Medicine, Los Angeles, CA; Claire Bombardier, MD, Institute for Work & Health, Toronto, Canada; Craig Brater, MD, Indiana University School of Medicine, Indianapolis, IN; Alain Castaigne, MD*, Hopital Henri Mondor, Creteil, France; Byron Cryer, MD, UT Southwestern, Dallas, TX; David DeMets, PhD, University of Wisconsin, Madison, WI; Paul Emery, MD, Leeds General Infirmary, Leeds, UK; Erland Erdmann, MD, Medical Clinic III of the University of Cologne, Koeln, Germany; Garret FitzGerald, MD,

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Cardiovascular Event Adjudication Committee

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Gastrointestinal Event Adjudication Committee

Marie Griffin, MD, Vanderbilt University, Nashville, TN; Prof Michael Langman, University of Birmingham, Birmingham, UK; Dennis Jensen, MD, UCLA, Los Angeles, CA.

Independent Confirmation of Study Analysis

Independent confirmation of study analyses will be carried out by the Frontier Science Foundation, under the supervision of C Morton Hawkins, ScD, and David DeMets, PhD.

Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison

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Summary

Background **Cyclo-oxygenase-2 (COX-2) selective inhibitors have been associated with an increased risk of thrombotic cardiovascular events in placebo-controlled trials, but no clinical trial has been reported with the primary aim of assessing relative cardiovascular risk of these drugs compared with traditional non-steroidal anti-inflammatory drugs (NSAIDs). The MEDAL programme was designed to provide a precise estimate of thrombotic cardiovascular events with the COX-2 selective inhibitor etoricoxib versus the traditional NSAID diclofenac.**

Methods **We designed a prespecified pooled analysis of data from three trials in which patients with osteoarthritis or rheumatoid arthritis were randomly assigned to etoricoxib (60 mg or 90 mg daily) or diclofenac (150 mg daily). The primary hypothesis stated that etoricoxib is not inferior to diclofenac, defined as an upper boundary of less than 1·30 for the 95% CI of the hazard ratio for thrombotic cardiovascular events in the per-protocol analysis. Intention-to-treat analyses were also done to assess consistency of results. These trials are registered at http://www.clinicaltrials.gov with the numbers NCT00092703, NCT00092742, and NCT00250445.**

Findings **34 701 patients (24 913 with osteoarthritis and 9787 with rheumatoid arthritis) were enrolled. Average treatment duration was 18 months (SD 11·8). 320 patients in the etoricoxib group and 323 in the diclofenac group had thrombotic cardiovascular events, yielding event rates of 1·24 and 1·30 per 100 patient-years and a hazard ratio of 0·95 (95% CI 0·81–1·11) for etoricoxib compared with diclofenac. Rates of upper gastrointestinal clinical events (perforation, bleeding, obstruction, ulcer) were lower with etoricoxib than with diclofenac (0·67 *vs* 0·97 per 100 patient-years; hazard ratio 0·69 [0·57–0·83]), but the rates of complicated upper gastrointestinal events were similar for etoricoxib (0·30) and diclofenac (0·32).**

Interpretation **Rates of thrombotic cardiovascular events in patients with arthritis on etoricoxib are similar to those in patients on diclofenac with long-term use of these drugs.**

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See also Comment page 1745

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications in the world and are often taken long term by patients with osteoarthritis and rheumatoid arthritis. A major factor limiting use of NSAIDs is concern for the development of gastrointestinal complications such as bleeding. Cyclo-oxygenase-2 (COX-2) selective inhibitors were developed to decrease the risk of gastrointestinal tract injury and avoid the anti-platelet effect of traditional NSAIDs, and large outcome trials have shown a decrease in upper gastrointestinal complications with COX-2 selective inhibitors as compared with traditional NSAIDs.[1–3] However, randomised trials have shown an increased risk of thrombotic cardiovascular events with COX-2 selective inhibitors compared with placebo.[4–8] Comparable long-term, placebo-controlled trials in patients with arthritis assessing the risk of thrombotic cardiovascular events with traditional NSAIDs are not available, although results of observational studies suggest that some traditional NSAIDs (eg, diclofenac, ibuprofen) also increase cardiovascular risk compared with no NSAID therapy.[9–11] These safety data for COX-2 selective inhibitors and traditional NSAIDs raise concerns for patients with arthritis taking NSAIDs long term, and add a new element to decisions about the choice of therapy in these patients. Large, long-term prospective trials specifically designed to assess the cardiovascular risk with different agents have been called for to help inform these choices.[12,13] We designed the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long Term) programme to assess the relative cardiovascular safety of two long-term anti-inflammatory treatments for patients with osteoarthritis and rheumatoid arthritis.[14] The aim was to estimate precisely the relative risk of thrombotic cardiovascular events with etoricoxib compared with the widely used traditional NSAID diclofenac, using a non-inferiority trial design. We sought to study a broad range of patients to simulate the general population of individuals with arthritis, enrolling patients with a range of cardiovascular risk factors (including pre-existing cardiovascular disease) and gastrointestinal risk factors.

Methods

Study design and patients

The design of the MEDAL programme has been presented in detail elsewhere.[14] In brief, this study was done between June, 2002, and May, 2006, at 1380 sites in 46 countries. The MEDAL programme was prospectively designed to pool data from three randomised, double-blind clinical trials: the MEDAL study, the Etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) study, and the EDGE II study. Similar entry criteria, including the same diseases and doses, across these three long-term studies made them suitable for pooling. The ethics committee for each study site approved the trial at that site and all patients provided written informed consent before participation. Worldwide regulatory agency review of the safety profile of COX-2 selective inhibitors and traditional NSAIDs occurred during the course of the EDGE II and MEDAL studies, resulting in changes in product labelling to point out the potential increased cardiovascular risk with use of these drugs. Hence, the written informed consent forms for MEDAL programme trials in progress at that time (EDGE II and MEDAL studies) were revised with reference to this potential increased risk, and patients resupplied consent.

The MEDAL programme's primary objective was to compare thrombotic cardiovascular events with etoricoxib and diclofenac during the long-term treatment of patients with osteoarthritis and rheumatoid arthritis. The prespecified primary analysis was based on pooling events from all three trials (91% power) and the prespecified secondary analysis was based on thrombotic cardiovascular events from the MEDAL study alone (83% power).[14]

Patients with osteoarthritis or rheumatoid arthitis aged 50 years or older were eligible for enrolment if they had a clinical diagnosis of osteoarthritis of the knee, hip, hand, or spine, or a clinical diagnosis of rheumatoid arthritis that satisfied at least four of seven of the American Rheumatism Association 1987 revised criteria,[15] and in the judgment of the investigator, would need chronic treatment with an NSAID. These patients were not candidates for paracetamol as first-line therapy because of the severity of their symptoms. Patients with a history of myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention more than 6 months preceding enrolment were allowed to participate.

Procedures

Patients meeting entry criteria were randomly assigned with concealed allocation to treatment in equal proportions in each study site, using a different computer generated randomisation schedule for each of the three-component trials. In the MEDAL study, the first 4333 patients with osteoarthritis and all patients with rheumatoid arthritis received etoricoxib 90 mg once a day or diclofenac 75 mg twice a day. Subsequent patients with osteoarthritis enrolled in this study received etoricoxib 60 mg once a day or diclofenac 75 mg twice a day. In EDGE and EDGE II, patients received etoricoxib 90 mg once a day, diclofenac 50 mg three times a day (EDGE), or diclofenac 75 mg twice a day (EDGE II). A matching placebo design along with coded study medications provided blinding to treatment assignment.

Low-dose aspirin (≤100 mg per day) was recommended for prophylaxis in patients with established cardiovascular, peripheral arterial, or cerebrovascular disease.[16] Use of low-dose aspirin was also strongly encouraged for patients with diabetes.[17] Use of anti-ulcer medication (proton pump inhibitors or misoprostol) was recommended for patients at high risk of upper gastrointestinal clinical events (age >65 years; history of gastrointestinal ulcer or haemorrhage; concurrent use of corticosteroid, anticoagulant, or antiplatelet therapy).[18,19] Antihypertensive drugs were recommended as per the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure guidelines in the MEDAL study.[20] For the MEDAL study, omeprazole and low-dose aspirin were prescribed free of charge; low-dose aspirin alone was provided free of charge in the EDGE and EDGE II trials.

Patients returned for visits every 4 months and a scheduled telephone contact was made between visits. Compliance with study medication was assessed by pill count. Patients who did not continue in the study were contacted every 6 months by telephone until the end of the study they had been enrolled in. All potential thrombotic cardiovascular events from the three trials were identified through active surveillance of reported adverse events, and were adjudicated by an independent blinded committee of clinical experts in cardiology, neurology, and peripheral vascular disease. Electrocardiograms done on all patients at randomisation, along with any electrocardiograms done during the trial, were compared to the electrocardiogram at the end of the study to look for evidence of silent myocardial infarction; these cases were also adjudicated.

The primary composite thrombotic cardiovascular endpoint was the first occurrence of the following fatal and non-fatal events: myocardial infarction (including silent infarction), unstable angina pectoris, intracardiac thrombus, resuscitated cardiac arrest, thrombotic stroke, cerebrovascular thrombosis, transient ischaemic attack, peripheral venous thrombosis, pulmonary embolism, peripheral arterial thrombosis, and sudden or unexplained death. This composite primary endpoint[14] was inclusive of all thrombotic cardiovascular events, both venous and arterial, to be as comprehensive as possible. Myocardial infarction and ischaemic stroke are clinical events of great interest in this context[21,22] and accordingly, we prespecified secondary cardiovascular endpoints consisting of the subset of confirmed arterial events only and the Anti-Platelet Trialists' Collaboration endpoint (APTC; myocardial infarction, stroke, vascular death).[14,23]

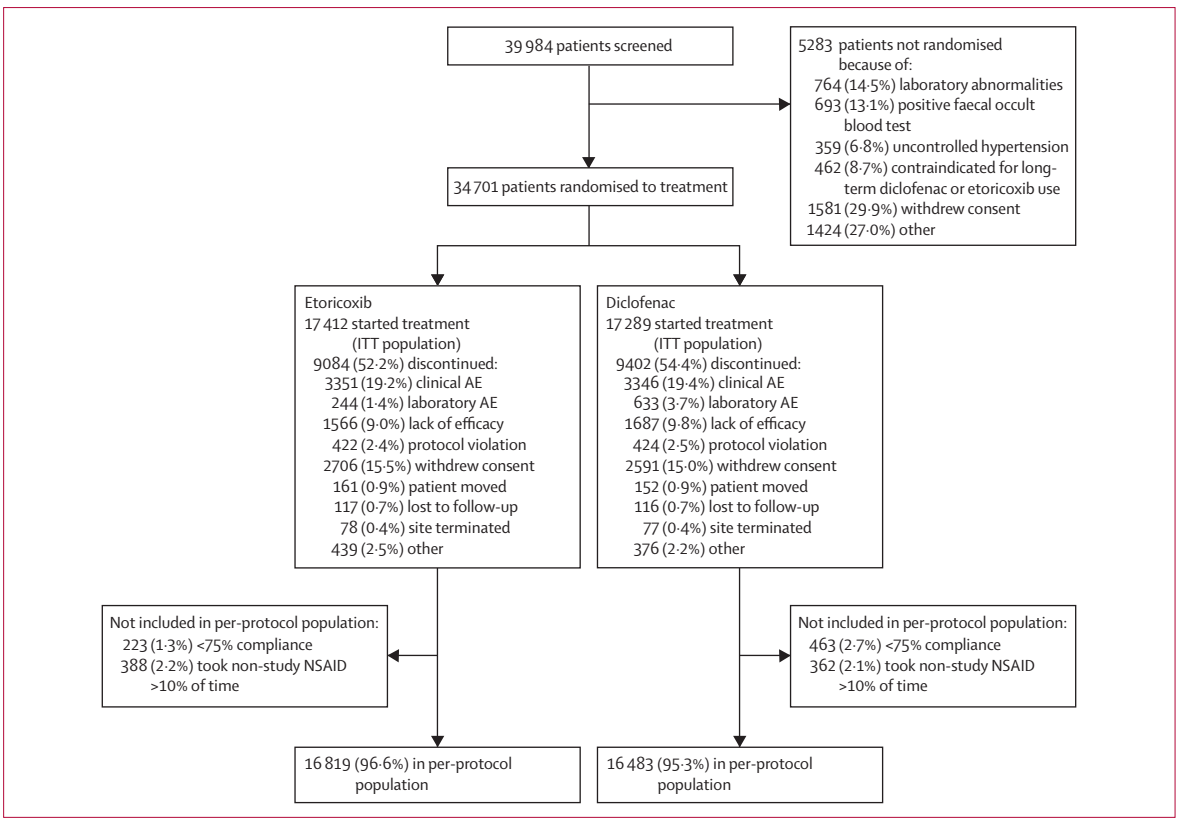

Figure 1: **Distribution of patients**
AE=adverse event.

In addition to cardiovascular events, prespecified safety endpoints also included discontinuations due to hypertension, oedema, renal dysfunction, gastrointestinal adverse events, and liver test abnormalities or other hepatic events. The cardiology adjudication subcommittee used prespecified criteria to adjudicate all episodes of congestive heart failure resulting in admission or emergency room visits. Results for these prespecified safety endpoints are presented by trial (ie, MEDAL study, EDGE, EDGE II). At all visits, patients were asked to rate their overall arthritis disease status (patient-reported global assessment of disease status) on a five-point scale (0=very well to 4=very poor) to assess the efficacy of the study medications.

Potential upper gastrointestinal clinical events were identified through active surveillance of reported adverse events, and were adjudicated by an independent blinded committee as previously described.[1,24] These events included bleeding from the oesophagus, stomach, or duodenum; perforation or obstruction from a non-malignant gastric or duodenal ulcer; or an ulcer documented on clinically indicated workup. They were confirmed by endoscopy, contrast radiography, surgery, or autopsy. Perforation, obstruction, and witnessed ulcer or significant bleeding were categorised as complicated events.[1] Potential lower gastrointestinal clinical events (bleeding, perforation, obstruction) were also identified through active surveillance of reported adverse events, and were adjudicated by the same independent blinded committee.[24] An independent data and safety monitoring board monitored emerging safety data from all three trials at regular intervals.[14]

Sample size and data analysis

The prespecified primary analysis was a comparison of all thrombotic cardiovascular events confirmed by the adjudication committee in the etoricoxib and diclofenac groups from the per-protocol populations of the three component studies combined. The definition of non-inferiority was an upper limit of the 95% CI of the hazard ratio (HR) for etoricoxib versus diclofenac of less than 1·30. As prespecified, to account for the interim analysis, the CI was adjusted to 95·87% to preserve the overall type I error of 0·05.[25] Assuming a true underlying HR of 1·0, 635 confirmed thrombotic cardiovascular events were needed to provide 91% power to yield the 95% CI upper limit of less than 1·30 for the primary endpoint HR. The Lachin-Foulkes method was used to calculate the number of events needed.[26]

The per-protocol population was used for the primary analysis, as recommended, to provide the more conservative approach for this non-inferiority assessment.[27–29]

	Etoricoxib (n=17 412)	Diclofenac (n=17 289)
Age, mean (SD)	63·2 (8·5)	63·2 (8·5)
<65 years	10 178 (58·5%)	10 127 (58·6%)
≥65 to <75 years	5201 (29·9%)	5261 (30·4%)
≥75 years	2033 (11·7%)	1901 (11·0%)
Sex		
Women	12 925 (74·2%)	12 823 (74·2%)
Arthritis type*		
Osteoarthritis	12 533 (72·0%)	12 380 (71·6%)
Rheumatoid arthritis	4878 (28·0%)	4909 (28·4%)
Weight in kg, mean (SD)	78·9 (18·6)	78·9 (18·5)
BMI in kg/m^2, mean (SD)	29·5 (6·1)	29·5 (6·0)
Ethnic group		
Asian	669 (3·8%)	662 (3·8%)
Black	646 (3·7%)	620 (3·6%)
Hispanic American	1441 (8·3%)	1425 (8·2%)
Multiracial	945 (5·4%)	909 (5·3%)
White	13 633 (78·3%)	13 609 (78·7%)
Other†	78 (0·5%)	64 (0·4%)
Diabetes	1810 (10·4%)	1855 (10·7%)
Hypertension‡	8109 (46·6%)	8221 (47·6%)
Dyslipidaemia‡	5097 (29·3%)	5034 (29·1%)
Current cigarette smoker	2034 (11·7%)	2037 (11·8%)
Established atherosclerotic CV disease§	2014 (11·6%)	2010 (11·6%)
≥2 CV risk factors¶ or established atherosclerotic CV disease	6586 (37·8%)	6639 (38·4%)
Low-dose aspirin use	6030 (34·6%)	5976 (34·6%)
Cardiac mediations		
β blocker	2806 (16·1%)	2837 (16·4%)
ACE inhibitor or ARB	4571 (26·3%)	4535 (26·2%)
Calcium channel blocker	2096 (12·0%)	2149 (12·4%)
Statin	2859 (16·4%)	2890 (16·7%)
Diuretic	3129 (18·0%)	3147 (18·2%)
Anti-arthritic medications		
COX-2 selective NSAID	4873 (28·0%)	4939 (28·6%)
Traditional NSAID	14 209 (81·6%)	14 174 (82·0%)
Paracetamol	10 852 (62·3%)	10 765 (62·3%)
High-dose aspirin	173 (1·0%)	185 (1·1%)
Glucocorticoid	2758 (15·8%)	2762 (16·0%)
DMARD‖	2246 (12·9%)	2208 (12·8%)

Data are number (%) unless otherwise specified. BMI=body-mass index. CV=cardiovascular. ACE=angiotension-converting enzyme. ARB=angiotensin-receptor blocker. *Data missing for one patient. †Includes Australoid, European, Indian, Melanesian, Native American, and Polynesian. ‡Clinical history at time of screening. §Includes clinical history of myocardial infarction, angina pectoris, cerebral vascular accident, transient ischaemic attack, angioplasty, carotid artery disease, peripheral vascular disease, or coronary artery bypass surgery. ¶Includes two or more of the following risk factors: history of hypertension, diabetes, dyslipidaemia, family history of CV disease, current cigarette smoking. ‖Disease-modifying antirheumatic drug.

Table 1: **Baseline characteristics**

It included observations for individual patients from the first day of therapy to 14 days after the last dose of study drug, and excluded patients if they took less than 75% of their study medication or took non-study NSAIDs more than 10% of the time while on study medication. As also recommended,[21,27] to evaluate the consistency of the results and provide greater confidence in the conclusions, we prespecified three supporting analyses for the primary endpoint. These included two modified intention-to-treat (ITT) analyses (all randomised patients who received at least one dose of study medication); one included all events that occurred from the first day of study treatment to 14 days after the last dose; the second included all events until 28 days after the last dose of study drug; the third was an ITT analysis that included all events from all patients from the first day of therapy until the end of each trial, including events in patients who discontinued study drug early and who might have been exposed to non-study interventions following discontinuation. The eligibility date for a thrombotic cardiovascular event to be included in this ITT analysis was 28 days after the last patient's last dose of study medication for each respective trial. The ascertainment date for potential thrombotic cardiovascular events to be submitted to the adjudication committee in order to be included in the ITT analysis was 42 days after the last patient's last dose of study drug.

The HR for confirmed thrombotic events for etoricoxib compared with diclofenac was calculated with a Cox proportional hazards model.[30] Treatment served as an explanatory factor and low-dose aspirin use at baseline as a stratification factor. Kaplan-Meier time-to-event curves were generated. Kaplan-Meier curves[31,32] were truncated when the number of patients remaining at risk was less than 500. This truncation did not affect statistical analysis or the Cox model results. The HR of thrombotic events was also assessed across a range of prespecified subgroup factors, which were checked for consistency of HR by testing the subgroup factor-by-treatment interaction with the Cox proportional hazards model. Subgroup analyses might have less power than an analysis based on the full dataset.

For analyses of discontinuations due to hypertension, oedema, renal dysfunction, gastrointestinal adverse events, and liver test abnormalities or other hepatic events, and for confirmed congestive heart failure, pair-wise comparisons by dose and disease (osteoarthritis or rheumatoid arthritis) were computed using Fisher's exact test, and the associated 95% CIs for the differences were calculated by Wilson's score method. Comparisons for the MEDAL study osteoarthritis data were made between the patients randomised to 60 mg etoricoxib and the group of patients randomised to diclofenac during the same period, and between patients randomised to 90 mg etoricoxib and its time-coincident diclofenac group, to account for the time and location of randomisation.

The rates of clinical upper gastrointestinal events, complicated upper gastrointestinal events, and lower gastrointestinal clinical events based on the MEDAL programme were prespecified endpoints, with post-hoc Cox model applied to clinical upper gastrointestinal events. In each individual study, anti-arthritic efficacy was expressed as the average change from baseline in

patient global assessment of disease status (scale 0–4), using an analysis of covariance model.[33,34]

This trial is registered at http://www.clinicaltrials.gov with the numbers NCT00092703 (EDGE), NCT00092742 (EDGE II), and NCT00250445 (MEDAL study).

Role of the funding source

The MEDAL programme was designed cooperatively by the sponsor (Merck Research Laboratories) and the programme steering committee, which consisted of experts in cardiovascular medicine, gastroenterology, rheumatology, pharmacology, statistical sciences, and epidemiology. The sponsor monitored the study, collected data, and did statistical analysis. An independent confirmation of the statistical analyses was done by Frontier Science Foundation (Madison, WI, USA), under the supervision of C Morton Hawkins and David DeMets (MEDAL programme steering committee member). The authors had full access to data and statistical analyses and drafted the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the overall trial profile for the 34701 patients in the MEDAL programme. 23504 patients were randomised in the MEDAL study, 7111 in EDGE, and 4086 in EDGE II, including 24913 (72%) patients with osteoarthritis and 9787 (28%) with rheumatoid arthritis. Baseline characteristics were similar in both treatment groups (table 1). 14396 (41%) patients were aged 65 years or older; 3665 (11%) had diabetes; 10131 (29%) had dyslipidaemia; 16330 (47%) had hypertension; 4024 (12%) had established atherosclerotic cardiovascular disease, and 13225 (38%) had established atherosclerotic cardiovascular disease or two or more cardiovascular risk factors (hypertension, diabetes, dyslipidaemia, family history of cardiovascular disease, smoking); 12006 (35%) patients were using low-dose aspirin at baseline.

6769 patients were assigned to etoricoxib 60 mg once a day, 10643 to etoricoxib 90 mg once a day, and 3518 to diclofenac 50 mg three times a day, and 13771 to diclofenac 75 mg twice daily. The mean (SD) duration of exposure to study drug was 18·2 (11·7) months for etoricoxib and 17·7 (11·9) months for diclofenac; 21395 patients took the drug for 12 months or longer and 12854 for 24 months or longer. All patients randomised to treatment received at least one dose of study medication, so the predefined modified ITT population included all patients randomised (ie, a true ITT population). Overall mean treatment compliance was 98% (SD 7·4) for etoricoxib, and 96% (8·2) for diclofenac; compliance was less than 75% for 223 (1%) patients in the etoricoxib group and 463 (3%) in the diclofenac group. 1399 (4%) patients were excluded from the per-protocol population (figure 1), but included in all other analyses.

	Treatment	n	n/PYR	Rate (95% CI)*	HR (95% CI)
Thrombotic events					
Per-protocol	Etoricoxib	16819	320/25836	1·24 (1·11–1·38)	0·95 (0·81–1·11)
	Diclofenac	16483	323/24766	1·30 (1·17–1·45)	
ITT (within 14 days)	Etoricoxib	17412	345/26384	1·31 (1·17–1·45)	0·96 (0·83–1·11)
	Diclofenac	17289	345/25394	1·36 (1·22–1·51)	
ITT (within 28 days)	Etoricoxib	17412	366/27036	1·35 (1·22–1·50)	0·98 (0·85–1·14)
	Diclofenac	17289	357/26042	1·37 (1·23–1·52)	
ITT (to end of studies)	Etoricoxib	17412	495/39654	1·25 (1·14–1·36)	1·05 (0·93–1·19)
	Diclofenac	17289	468/39413	1·19 (1·08–1·30)	
Arterial thrombotic events					
Per-protocol	Etoricoxib	16819	272/25839	1·05 (0·93–1·19)	0·96 (0·81–1·13)
	Diclofenac	16483	272/24771	1·10 (0·97–1·24)	
ITT (within 14 days)	Etoricoxib	17412	297/26386	1·13 (1·00–1·26)	0·97 (0·83–1·14)
	Diclofenac	17289	293/25399	1·15 (1·03–1·29)	
ITT (within 28 days)	Etoricoxib	17412	305/27040	1·13 (1·00–1·26)	0·98 (0·83–1·15)
	Diclofenac	17289	300/26049	1·15 (1·03–1·29)	
ITT (to end of studies)	Etoricoxib	17412	407/39767	1·02 (0·93–1·13)	1·03 (0·89–1·18)
	Diclofenac	17289	394/39513	1·00 (0·90–1·10)	
APTC events					
Per-protocol	Etoricoxib	16819	216/25851	0·84 (0·73–0·95)	0·96 (0·79–1·16)
	Diclofenac	16483	216/24787	0·87 (0·76–1·00)	
ITT (within 14 days)	Etoricoxib	17412	231/26402	0·87 (0·77–1·00)	0·96 (0·80–1·15)
	Diclofenac	17289	232/25416	0·91 (0·80–1·04)	
ITT (within 28 days)	Etoricoxib	17412	237/27059	0·88 (0·77–0·99)	0·95 (0·80–1·14)
	Diclofenac	17289	239/26068	0·92 (0·80–1·04)	
ITT (to end of studies)	Etoricoxib	17412	332/39894	0·83 (0·75–0·93)	1·02 (0·87–1·18)
	Diclofenac	17289	325/39623	0·82 (0·73–0·91)	

PYR=patient-years at risk. *Per 100 PYR.

Table 2: **Incidence of thrombotic cardiovascular events**

Numbers and rates of thrombotic cardiovascular events, with HRs, are shown in table 2. The HR for the per-protocol comparison of thrombotic events in the two groups was 0·95 (95% CI 0·81–1·11), showing non-inferiority of etoricoxib to diclofenac according to the prespecified criterion (table 2). We noted consistency across the three different prespecified endpoints and across the per-protocol and ITT analyses. The prespecified secondary analysis, assessing confirmed thrombotic cardiovascular events in the per-protocol population of the MEDAL study alone, gave an HR of 0·96 (95% CI 0·81–1·15).

The Kaplan-Meier estimates over 36 months are shown in figure 2. The cumulative incidence of primary and secondary endpoints with etoricoxib compared with diclofenac satisfied the proportional hazard assumption, indicating a constant HR over time.

The HR for etoricoxib versus diclofenac for cardiac events, cerebrovascular events, and peripheral vascular events did not show any discernible difference between treatment groups (table 3). The most common thrombotic cardiovascular event was non-fatal or fatal myocardial infarction, with rates of 0·43 per 100 patient-years

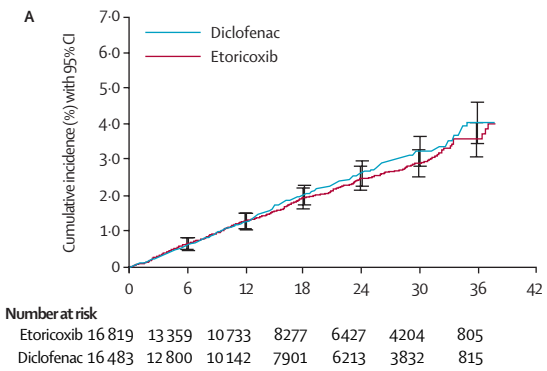

Figure 2: **Time-to-event per-protocol analysis**
(A) Cumulative incidence of thrombotic cardiovascular events. (B) Cumulative incidence of arterial thrombotic events. (C) Cumulative incidence of APTC[23] events (myocardial infarction, stroke, or vascular death).

in the etoricoxib group and 0·49 per 100 patient-years in the diclofenac group (per-protocol analysis). Rates of fatal thrombotic cardiovascular events were similar between the groups (0·17 per 100 patient-years in both groups). All-cause mortality rates were 0·48 per 100 patient-years for etoricoxib and 0·50 per 100 patient-years for diclofenac in the ITT population through 14 days after study drug discontinuation.

Analyses of thrombotic cardiovascular events by subgroups in the per-protocol population are shown in figure 3. We noted no significant treatment-by-subgroup interactions, including study, suggesting that the thrombotic cardiovascular risk of etoricoxib versus diclofenac did not differ across the subgroups analysed, including varying baseline cardiovascular risk and etoricoxib dose. Additionally, HRs were similar in patients with (HR 0·85, 95% CI 0·64–1·12) and without (1·00, 95% CI 0·83–1·20) previous use of COX-2 selective NSAID (treatment-by-subgroup interaction, p=0·344). Cardiovascular event rates varied on the basis of cardiovascular risk. For example, rates ranged from less than one event per 100 patient-years for patients with no established atherosclerotic cardiovascular disease and one or no cardiovascular risk factors, to more than three events per 100 patient-years in patients with established atherosclerotic cardiovascular disease.

Incidences of congestive heart failure and discontinuations for pre-specified adverse events are shown in figure 4 by study, etoricoxib dose, and disease (ITT analyses including events within 14 days of last dose of study drug). In the MEDAL study, a higher rate of congestive heart failure was seen with etoricoxib 90 mg than with diclofenac, but the difference was not significant; no difference was seen with etoricoxib 60 mg. Discontinuations because of oedema were significantly more frequent with 90 mg of etoricoxib than with diclofenac, but rates were similar for 60 mg of etoricoxib and diclofenac. Discontinuations because of hypertension were more frequent with both doses of etoricoxib than with diclofenac. Discontinuations due to gastrointestinal adverse events were significantly less frequent with etoricoxib than diclofenac, as were discontinuations due to liver test abnormalities or other hepatic events. Results for EDGE and EDGE II were consistent with the results of the MEDAL study (figure 4).

Rates of upper gastrointestinal clinical events were 0·67 (95% CI 0·57–0·77) per 100 patient-years with etoricoxib and 0·97 (0·85–1·10) per 100 patient-years with diclofenac, yielding an HR of 0·69 (0·57–0·83). However, rates of complicated upper gastrointestinal clinical events did not differ between the groups (0·30 etoricoxib *vs* 0·32 diclofenac per 100 patient-years). The rates of lower gastrointestinal clinical events were 0·32 per 100 patient-years (95% CI 0·25–0·39) for etoricoxib and 0·38 per 100 patient-years (0·31, 0·46) for diclofenac, yielding an HR of 0·84 (0·63–1·13).

Etoricoxib and diclofenac showed similar efficacy for treatment of arthritis. In the MEDAL study, the average changes from baseline (Likert units) in patient-reported global assessment of disease status were –0·67 (SD 1·02) for etoricoxib and –0·61 (1·02) for diclofenac. Efficacy results for EDGE and EDGE II were similar (data not shown). Discontinuations because of lack of efficacy were also similar between the groups (figure 1).

	Etoricoxib (N=16 819, 25 836 PY)*		Diclofenac (N=16 483, 24 766 PY)		HR (95% CI)
	n (%)†	Rate‡	n (%)†	Rate‡	
Patients with fatal thrombotic cardiovascular events	43 (0·26)	0·17 (0·12–0·22)	43 (0·26)	0·17 (0·13–0·23)	0·96 (0·63–1·46)
Patients with cardiac events	183 (1·09)	0·71 (0·61–0·82)	194 (1·18)	0·78 (0·68–0·90)	0·90 (0·74–1·10)
Non-fatal myocardial infarction	105 (0·62)	0·41 (0·33–0·49)	105 (0·64)	0·42 (0·35–0·51)	
Fatal myocardial infarction	6 (0·04)	0·02 (0·01–0·05)	17 (0·10)	0·07 (0·04–0·11)	
Sudden cardiac death	29 (0·17)	0·11 (0·08–0·16)	23 (0·14)	0·09 (0·06–0·14)	
Unstable angina pectoris	42 (0·25)	0·16 (0·12–0·22)	51 (0·31)	0·21 (0·15–0·27)	
Resuscitated cardiac arrest	2 (0·01)	0·01 (0·00–0·03)	1 (0·01)	0·00 (0·00–0·02)	
Cardiac thrombus	4 (0·02)	0·02 (0·00–0·04)	3 (0·02)	0·01 (0·00–0·04)	
Patients with cerebrovascular events	89 (0·53)	0·34 (0·28–0·42)	79 (0·48)	0·32 (0·25–0·40)	1·08 (0·80–1·46)
Non-fatal ischaemic cerebrovascular stroke	53 (0·32)	0·21 (0·15–0·27)	55 (0·33)	0·22 (0·17–0·29)	
Fatal ischaemic cerebrovascular stroke	6 (0·04)	0·02 (0·01–0·05)	2 (0·01)	0·01 (0·00–0·03)	
Cerebrovascular venous thrombosis	1 (0·01)	0·00 (0·00–0·02)	1 (0·01)	0·00 (0·00–0·02)	
Transient ischaemic attack	31 (0·18)	0·12 (0·08–0·17)	22 (0·13)	0·09 (0·06–0·13)	
Patients with peripheral vascular events	53 (0·32)	0·20 (0·15–0·27)	55 (0·33)	0·22 (0·17–0·29)	0·92 (0·63–1·35)
Non-fatal pulmonary embolism	17 (0·10)	0·07 (0·04–0·11)	25 (0·15)	0·10 (0·07–0·15)	
Fatal pulmonary embolism	1 (0·01)	0·00 (0·00–0·02)	0 (0·00)	0·00	
Non-fatal peripheral arterial thrombosis	5 (0·03)	0·02 (0·01–0·05)	4 (0·02)	0·02 (0·00–0·04)	
Fatal peripheral arterial thrombosis	1 (0·01)	0·00 (0·00–0·02)	1 (0·01)	0·00 (0·00–0·02)	
Peripheral venous thrombosis	29 (0·17)	0·11 (0·08–0·16)	27 (0·16)	0·11 (0·07–0·16)	

Patients with several events were listed for each of their specific diagnoses. PY=patient-years. *Etoricoxib combined 60 mg and 90 mg. †Crude incidence (n/Nx100); ‡Events per 100 patient-years.

Table 3: **Incidence of thrombotic cardiovascular event types in per-protocol population**

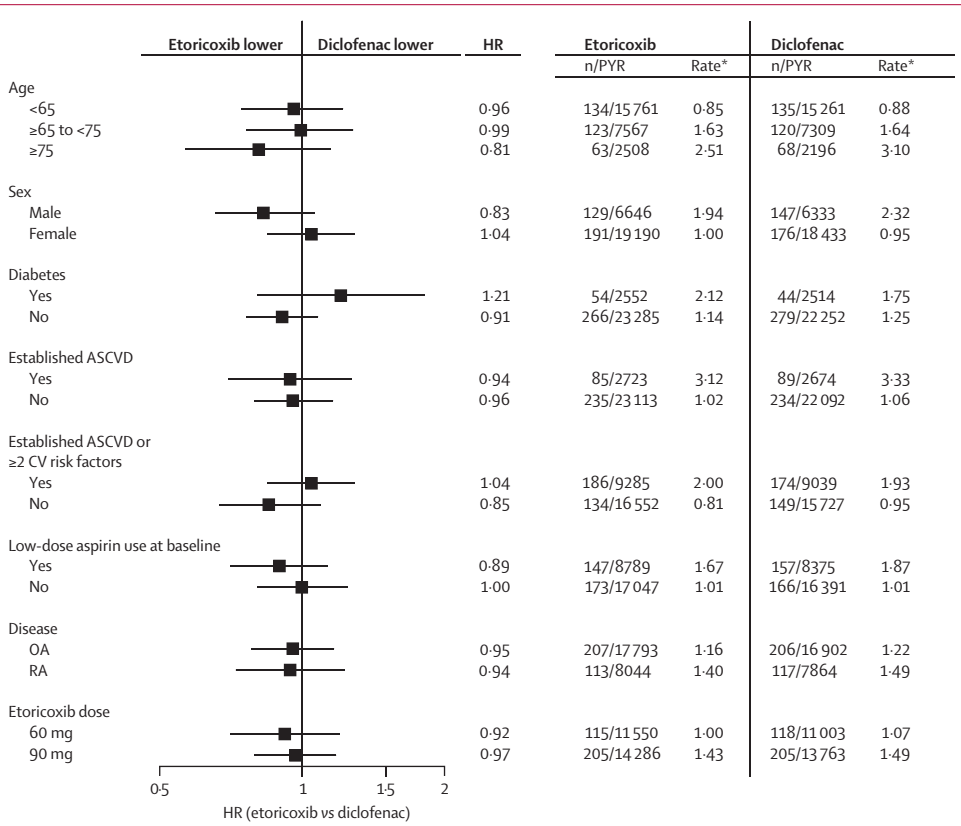

Figure 3: **Incidence of thrombotic cardiovascular (CV) events in prespecified subgroups, per-protocol population**
ASCVD=atherosclerotic cardiovascular disease. PYR=patient-years at risk. *Events per 100 patient-years.

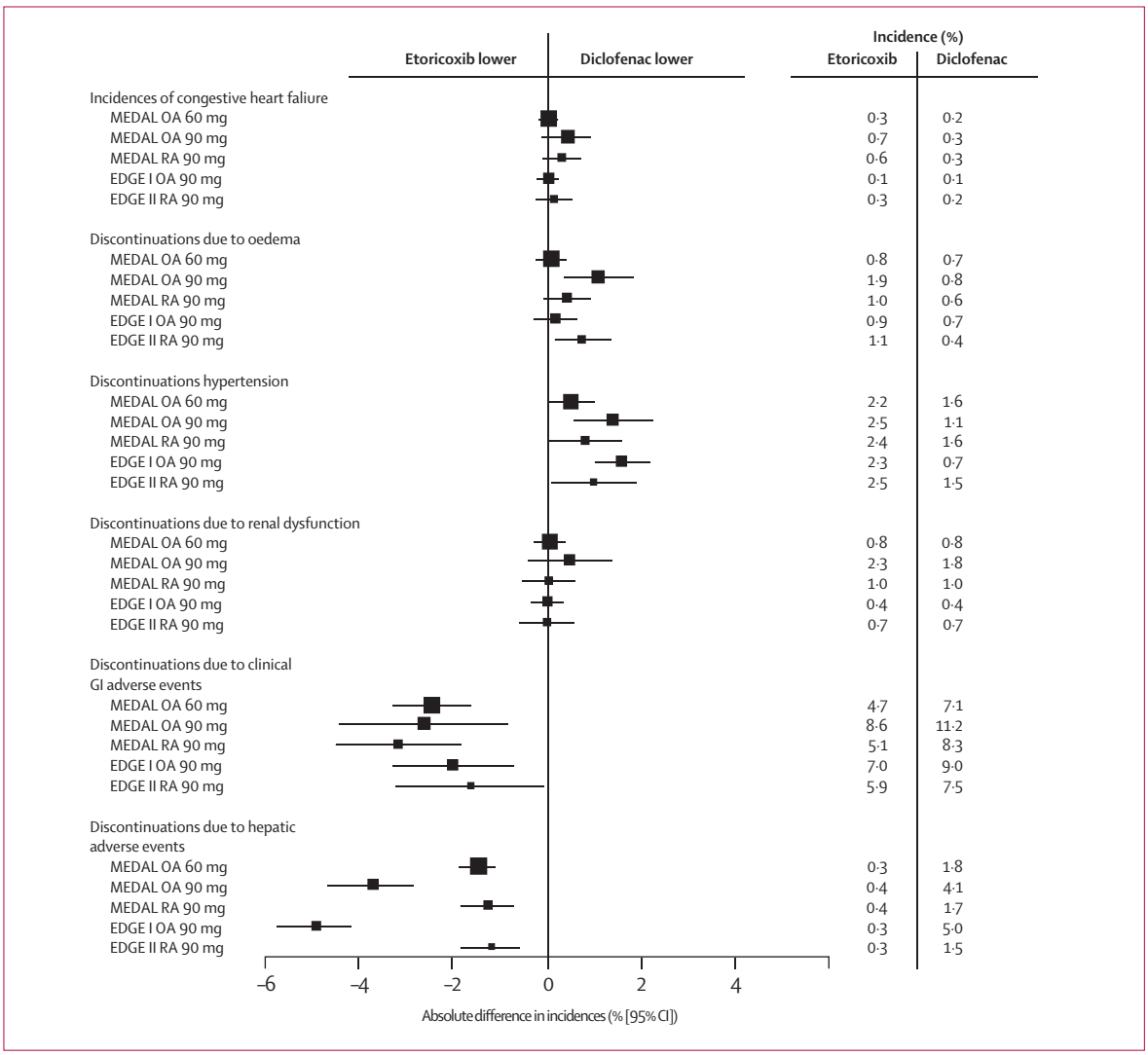

Figure 4: **Difference in incidences of prespecified renovascular and gastrointestinal (GI) endpoints from MEDAL study, EDGE, and EDGE II, by dose and disease**
Symbol areas represent the relative size of each group. OA=osteoarthritis. RA=rheumatoid arthritis.

Discussion

Our results show that patients with arthritis treated with the COX-2 selective NSAID etoricoxib and those given the traditional NSAID diclofenac have nearly identical rates of thrombotic cardiovascular events. The robustness of this finding was supported by consistency of results across several prespecified analyses. Furthermore, the similarity in rates was consistent across all subgroups assessed. The results of subgroup analyses suggest that cardiovascular risk factors and low-dose aspirin use do not affect the absence of difference in the relative risk of cardiovascular events for etoricoxib and diclofenac.

The MEDAL programme was designed with the primary aim of assessing thrombotic cardiovascular events with a COX-2 selective NSAID compared with a traditional NSAID. Enrolment of 34701 patients with treatment duration up to 3·5 years (mean duration 18 months, SD 11·8) allowed us to provide estimates of thrombotic cardiovascular events in patients with arthritis taking chronic NSAID therapy with greater precision than previous clinical trials. In addition to the large size, the worldwide distribution of patients and the inclusion of patients with a broad range of cardiovascular risk factors should simulate a real-world population of patients with arthritis. The annual incidence of thrombotic cardiovascular events in the overall MEDAL programme population was about 1·25%, and the absolute difference in event rates between treatments was less than one patient per 1000 treated for a year (–0·07 events per 100 patient years; 95% CI –0·26 to 0·13). On the basis of the 95% CI for this difference in the primary analysis, etoricoxib could be associated with at most an increase of 1·3 events (or a decrease of 2·6 events) per 1000 patients treated for a year compared with diclofenac.

The question of the relative cardiovascular and gastrointestinal safety of long-term treatment with COX-2 selective and traditional NSAIDs is important to patients, doctors, public-health officials, and regulatory agencies. The evidence that treatment with COX-2 selective NSAIDs is associated with an increased risk of cardiovascular events compared with placebo,[4–7] and the suggestion from observational studies and a meta-analysis of randomised clinical trials[8,10,35] of possible differences among traditional NSAIDs with respect to cardiovascular risk, raise the clinical issue of the different risk between COX-2 selective and traditional NSAIDs. Although randomised clinical trials have established that COX-2 selective NSAIDs reduce the risk of upper gastrointestinal clinical events,[1,3] large long-term outcome studies, such as the MEDAL programme, are needed to ascertain the relative risk of cardiovascular and gastrointestinal events of different agents in the NSAID class.

We chose to compare the COX-2 selective inhibitor etoricoxib and the traditional NSAID diclofenac. Etoricoxib is a highly selective COX-2 inhibitor, which does not inhibit COX-1 at clinical doses, causes significantly fewer gastroduodenal ulcers than traditional NSAIDs, is effective for the treatment of osteoarthritis and rheumatoid arthritis, and is currently approved in over 60 countries.[36–39] Diclofenac was selected as the traditional NSAID comparator in the MEDAL programme for several reasons.[14] First, diclofenac is the most widely prescribed NSAID in the world.[40] Additionally, unlike ibuprofen and naproxen,[41–45] diclofenac does not interfere with the antiplatelet effects of low-dose aspirin, which was used by about a third of patients in the MEDAL programme. Thus, diclofenac should not inhibit the cardioprotective effect of aspirin, although this notion has not been assessed in randomised clinical trials. Unlike etoricoxib or celecoxib, diclofenac inhibits COX-1 at clinical doses, although to a lesser degree than ibuprofen and naproxen.[36] Clinical evidence for COX-1 inhibition by diclofenac in the gastrointestinal tract is provided by endoscopic studies showing that diclofenac is associated with gastroduodenal ulcers at rates similar to those seen with ibuprofen and higher than those with COX-2 selective inhibitors.[46–48]

Diclofenac, like many traditional NSAIDs, does not provide sustained inhibition of COX-1 derived thromboxane-dependent platelet function.[42] Greater than 95% inhibition of thromboxane is necessary to affect platelet function.[49] Diclofenac achieves 87% inhibition of thromboxane at 2 h (time of peak plasma concentration), which decreases to 55% 6 h after dosing.[42] Etoricoxib, a COX-2 selective NSAID, produces no inhibition of thromboxane and thus has no effect on platelet aggregation over its clinical dose range.[38] Daily low-dose aspirin, by contrast, achieves long-term inhibition of thromboxane due to irreversible binding to COX-1,[42] making it an effective cardioprotective agent.[16,17]

Prostacyclin is a prostanoid that acts as a restraint on mediators of platelet activation, hypertension, and atherogenesis, including thromboxane A_2, which is generated in the platelet by COX-1.[50] Suppression of prostacyclin (and prostaglandin E_2) is the most thoroughly developed explanation for the cardiovascular hazard associated with NSAIDs.[50] Coincident inhibition of platelet COX-1-derived thromboxane would be expected to mitigate this hazard,[50,51] although clinical trials to directly address this question are not available.

Although the degree of COX-1 inhibition with diclofenac may not be enough to inhibit platelet aggregation, results of endoscopic studies suggest that it is sufficient to inhibit the gastrointestinal tract mucosal prostaglandins that protect the mucosa.[46–48] The difference in the extent of COX-1 inhibition[52] between etoricoxib and diclofenac presumably explains our finding of a significant difference in rates of upper gastrointestinal clinical events between the groups (even with 50% of patients receiving gastroprotective agents)—although this finding was driven by a difference in uncomplicated upper gastrointestinal events, not complicated gastrointestinal events. By contrast, the difference in COX-1 mediated thromboxane inhibition between diclofenac and etoricoxib is unlikely to translate into a difference in effective inhibition of platelet aggregation, and was not associated with a difference in rates of thrombotic cardiovascular events.

In clinical practice, the choice of anti-inflammatory agent needs to take into consideration the risk for thrombotic cardiovascular and gastrointestinal events, as well as congestive heart failure and other renovascular effects (eg, blood pressure, fluid retention), gastrointestinal tolerability (eg, dyspepsia), and efficacy. As shown in figure 4, the incidence of clinically important renovascular endpoints such as congestive heart failure (90 mg) and discontinuations because of hypertension (60 mg and 90 mg) was higher with etoricoxib than with diclofenac. We noted no difference in the incidence of discontinuation due to renal dysfunction, and a lower incidence of discontinuations due to gastrointestinal and hepatic adverse events was observed with etoricoxib than with diclofenac.

The MEDAL programme had some limitations. For example, it did not include a placebo group; long-term placebo-controlled trials in arthritic patients are not possible, because many patients in the placebo group would have breakthrough symptoms on placebo, and thus would require some type of anti-inflammatory treatment. Therefore, the absolute cardiovascular risks associated with etoricoxib and diclofenac cannot be ascertained from this trial. Another limitation is that the results observed with these two drugs cannot necessarily be extrapolated to other COX-2 selective or traditional NSAIDs. Only studies that directly compare drugs can provide definitive information on differences in cardiovascular and gastrointestinal outcomes. Such studies are

needed because an idiosyncratic absence or loss of NSAID effectiveness is a leading cause of patients switching treatment from one NSAID to another.[53]

The data from this large randomised clinical trial should help clinicians and patients, and will hopefully encourage guideline committees to continue developing recommendations for optimum treatment of patients with arthritis.

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See Online for webappendix

For the full list of participating investagators see webappendix.

Contributors

All authors read and approved the manuscript and contributed to its design, analysis or interpretation of data, and drafting and revision of the manuscript. H Krum joined the Steering Committee after the design of the programme but contributed to all other subsequent aspects as stated above. S P Curtis was the clinical leader of the programme and A Kaur was the programme's statistical science leader.

Conflict of interest statement

C P Cannon receives research grant support from Accumetrics, AstraZeneca, Merck, Merck/Schering-Plough Partnership, and Schering-Plough, and has spoken at symposia sponsored by and served on scientific advisory boards for Alnylam, AstraZeneca, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Merck, Merck/Schering-Plough Partnership, Pfizer, Sanofi-Aventis, Schering-Plough, and Vertex. G A FitzGerald receives financial support for investigator-initiated research from Bayer, Boehringer Ingelheim, and Merck, and serves as a consultant for Bayer, Boehringer Ingelheim, Cardiovascular Therapeutics, Genentech, Genome Institute of the Novartis Foundation, GlaxoSmithKline, Logical Therapeutics, Merck, NicOx, Novartis, Portala, and VIA Pharmaceuticals. H Krum has received research grant support, spoken at symposia, and served on scientific advisory boards for Merck, Pfizer, and Novartis in the area of COX-2 selective inhibitors. C Bombardier has received research support from Abbott, Amgen, Bristol-Myers Squibb, and Schering Canada, and served as a consultant for AstraZeneca, Hoffmann LaRoche, Merck, and Pfizer, and served on an advisory board for Merck. M E Weinblatt has received research support from Amgen, Abbott, Bristol-Myers Squibb, Genentech, and Millennium Pharmaceuticals, and served as a consultant for Abbott, Alza, Amgen, AstraZeneca, Biogen, Bristol-Myers Squibb, Canfite, Celgene, Centocor, Critical Therapeutics, Entremed, Human Genome Sciences, Genetech, Gilead, Eli Lilly, Merrimack, Merck, Millennium Pharmaceuticals, Novartis, Pfizer, Praecis, Rigel, Hoffmann LaRoche, Sanofi-Aventis, Serona, Scios, Synta, Wyeth, and VBL. D van der Heijde has received research support from Wyeth and served as a consultant for Abbott, Amgen, Centocor, Merck, Schering-Plough, and Wyeth. E Erdmann has received research support from Bayer and has served as a speaker, consultant, or advisory board member for Bayer, E Merck Germany, Merck, and Takeda. L Laine has received research support and served as a consultant for Pfizer, Novartis, Bayer, and Merck. S P Curtis, A Kaur, J A Bolognese, and A S Reicin are employees of Merck and own stock and/or hold stock options in the company.

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Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison

Loren Laine, Sean P Curtis, Byron Cryer, Amarjot Kaur, Christopher P Cannon, for the MEDAL Steering Committee

Summary

Background **Upper gastrointestinal safety of cyclo-oxygenase (COX)-2 selective inhibitors versus traditional non-steroidal anti-inflammatory drugs (NSAIDs) has not been assessed in trials that simulate standard clinical practice. Our aim was to assess the effects of these drugs on gastrointestinal outcomes in a population that includes patients taking gastrointestinal protective therapy.**

Methods **A prespecified pooled intent-to-treat analysis of three double-blind randomised comparisons of etoricoxib (60 or 90 mg daily) and diclofenac (150 mg daily) in 34 701 patients with osteoarthritis or rheumatoid arthritis was done for upper gastrointestinal clinical events (bleeding, perforation, obstruction, or ulcer) and the subset of complicated events (perforation, obstruction, witnessed ulcer bleeding, or significant bleeding). We also assessed such outcomes in patients who were taking concomitant proton pump inhibitors (PPIs) or low-dose aspirin. These trials are registered with ClinicalTrials.gov, with the numbers NCT00092703, NCT00092742, and NCT00250445.**

Findings **Overall upper gastrointestinal clinical events were significantly less common with etoricoxib than with diclofenac (hazard ratio [HR] 0·69, 95% CI 0·57–0·83; p=0·0001). There were significantly fewer uncomplicated gastrointestinal events with etoricoxib than there were with diclofenac (0·57, 0·45–0·74; p<0·0001); there was no difference in complicated events (0·91, 0·67–1·24; p=0·561). PPIs were used concomitantly for at least 75% of the study period by 13 862 (40%) and low-dose aspirin by 11 418 (33%) patients; treatment effects did not differ significantly in these individuals.**

Interpretation **There were significantly fewer upper gastrointestinal clinical events with the COX-2 selective inhibitor etoricoxib than with the traditional NSAID diclofenac due to a decrease in uncomplicated events, but not in the more serious complicated events. The reduction in uncomplicated events with etoricoxib is maintained in patients treated with PPIs and is also observed with regular low-dose aspirin use.**

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See **Comment** page 439

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Introduction

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) significantly increase the risk of upper gastrointestinal clinical events such as bleeding ulcers by about two to five times compared with no NSAID therapy.[1] Strategies used to decrease the risk of NSAID-associated upper gastrointestinal clinical events include medical co-therapy with misoprostol or proton pump inhibitors (PPIs), or the use of cyclo-oxygenase (COX)-2 selective inhibitors.

PPIs are most frequently used as co-therapy with traditional NSAIDs,[2] although no large clinical outcome studies have assessed this strategy. However, randomised trials in patients with complicated ulcers indicate that PPIs significantly decrease recurrent ulcer complications compared with *Helicobacter pylori* therapy in *H pylori*-positive patients taking naproxen[3] and compared with placebo in patients taking low-dose aspirin.[4]

The incidences of upper gastrointestinal clinical events have been shown to be significantly less with COX-2 selective inhibitors than traditional NSAIDs in randomised gastrointestinal outcomes trials of 12 weeks to 12 months duration.[5–8] However, none of these trials simulated real-world practice because gastrointestinal protective therapies—eg, PPIs—were not allowed. Thus, the effect of COX-2 selective inhibitors versus traditional NSAIDs in patients taking PPIs is unknown.

Another area of controversy relates to the use of COX-2 selective inhibitors plus low-dose aspirin. Endoscopic trials indicate that the combination of a COX-2 selective NSAID and low-dose aspirin has an ulcer incidence comparable with a traditional NSAID,[9] but still lower than the rate with a traditional NSAID plus low-dose aspirin.[10,11] An observational cohort study reported a significantly lower rate of upper gastrointestinal complications with COX-2 selective inhibitors than with traditional NSAIDs in low-dose aspirin users.[12] However, subgroup analyses from randomised outcomes trials of COX-2 selective inhibitors versus traditional NSAIDs have not identified

significant reductions in upper gastrointestinal clinical events with low-dose aspirin use.[5,7,8]

Although upper gastrointestinal clinical events raise greater concern among physicians, upper gastrointestinal symptoms such as dyspepsia are the most common side-effects that occur with NSAID use. Dyspepsia is reported weekly in up to about 30% of patients taking NSAIDs regularly, and in up to 15% daily.[13] Furthermore, dyspepsia is the most common reason for discontinuation of NSAID therapy.[14] Among patients without ulcers, PPIs have shown significant benefit in relief or prevention of NSAID-associated upper gastrointestinal symptoms.[15–17] COX-2 selective inhibitors have also been reported to induce less dyspepsia than traditional NSAIDs.[18–22] However, the relative benefit of traditional NSAIDs versus COX-2 selective inhibitors on upper gastrointestinal symptoms in PPI users has not been studied in a clinical trial.

The MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) programme provides a randomised comparison of the COX-2 selective inhibitor etoricoxib and the traditional NSAID diclofenac in 34701 osteoarthritis and rheumatoid arthritis patients followed for a mean duration of 18 months.[23,24] The primary endpoint was thrombotic cardiovascular events, but upper gastrointestinal clinical events were also a predefined endpoint. Our aim was to assess upper gastrointestinal outcomes in a setting that simulated real-world practice, in which patients with gastrointestinal risk factors were encouraged to use protective PPI therapy and those with cardiovascular risk were encouraged to use low-dose aspirin.

	Criteria
Perforation*	Perforation due to non-malignant gastric or duodenal ulcer confirmed by endoscopy, surgery, radiography (intraperitoneal air or contrast extravasation), or autopsy
Obstruction*	Postprandial nausea and vomiting for ≥24 h and evidence of narrowing of the distal stomach, pylorus, or duodenum due to a non-malignant ulcer documented by endoscopy, surgery, radiography, or autopsy
Complicated bleeding*	1 Health-care provider-witnessed haematemesis, melaena, haematochezia, or nasogastric aspirate with blood or coffee grounds material; 2 Active upper gastrointestinal bleeding documented by endoscopy, angiography, or surgery; 3 Occult blood-positive stool associated with significant bleeding† and with a documented upper gastrointestinal lesion judged by the health-care provider to be the source of the bleeding; or 4 Patient-reported haematemesis, melaena, or haematochezia associated with significant bleeding† and a documented upper gastrointestinal lesion judged by the health-care provider to be the source of the bleeding
Uncomplicated bleeding‡	1 Occult blood-positive stool associated with a documented upper gastrointestinal lesion judged by the health-care provider to be the source of the bleeding and stigmata of recent bleeding (visible vessel, pigmented spot, or clot in ulcer base) at endoscopy but no significant bleeding†; or 2 Patient-reported haematemesis, melaena, or haematochezia associated with a documented upper gastrointestinal lesion judged by the health-care provider to be the source of the bleeding and stigmata of recent bleeding at endoscopy but no significant bleeding†
Uncomplicated ulcer‡	Gastric or duodenal ulcer documented on clinical assessment by endoscopy, surgery, upper gastrointestinal contrast radiography, or autopsy

*Complicated event. †Hypotension, orthostatic changes in heart rate (>20 bpm) or blood pressure (>20 mm Hg systolic or 10 mm Hg diastolic), haemoglobin drop ≥20 g/L, or transfusion. ‡Uncomplicated event.

Table 1: **Prespecified criteria for upper gastrointestinal clinical events**

	Etoricoxib group (n=17 412)	Diclofenac group (n=17 289)
Age (years)	63·2 (8·5)	63·2 (8·5)
<65 years	10 178 (58%)	10 127 (59%)
≥65 to <75 years	5201 (30%)	5261 (30%)
≥75 years	2033 (12%)	1901 (11%)
Sex (female)	12 925 (74%)	12 823 (74%)
Osteoarthritis	12 533 (72%)	12 380 (72%)
Rheumatoid arthritis	4878 (28%)	4909 (28%)
Cigarette smoker	2034 (12%)	2037 (12%)
Low-dose aspirin use	6030 (35%)	5976 (35%)
PPI use	6742 (39%)	6664 (39%)
Traditional NSAID use	14 209 (82%)	14 174 (82%)
COX-2 selective inhibitor use	4873 (28%)	4939 (29%)
Systemic corticosteroid use	2685 (15%)	2705 (16%)
Methotrexate use	2762 (16%)	2831 (16%)
Other DMARD use	2246 (13%)	2208 (13%)
History of upper gastrointestinal event	1127 (6%)	1133 (7%)

Data are mean (SD) or n (%). DMARD=disease modifying antirheumatic drug. NSAID=non-steroidal anti-inflammatory drug. PPI=proton pump inhibitor.

Table 2: **Selected baseline characteristics in intention-to-treat population**

Methods

Study design and patients

The design of the MEDAL programme and the results for cardiovascular outcomes have been presented in detail elsewhere.[23,24] In brief, this study was done between June, 2002, and May, 2006, at 1380 sites in 46 countries. The MEDAL programme was prospectively designed to pool data from three randomised, double-blind clinical trials: the MEDAL study, the Etoricoxib *vs* Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) study, and the EDGE II study. Similar entry criteria and study medications across these three long-term studies made them suitable for pooling. The ethics committee for each study site approved the trial at that site and all patients provided written informed consent before participation.

Eligibility for the MEDAL programme has been described previously.[24] Briefly, patients with osteoarthritis or rheumatoid arthritis aged 50 years or over were eligible for enrolment if they had a clinical diagnosis of osteoarthritis of the knee, hip, hand, or spine, or a clinical diagnosis of rheumatoid arthritis that satisfied at least four of seven of the American Rheumatism Association 1987 revised criteria,[25] and in the judgment of the investigator, would require chronic therapy with an NSAID.

Procedures

Patients that met the entry criteria were randomly assigned to treatment with etoricoxib or diclofenac, as previously described.[23]

Low-dose aspirin (≤100 mg/day) was strongly recommended for cardiovascular prophylaxis in patients with established cardiovascular, peripheral arterial, or

cerebrovascular disease and was also encouraged for patients with diabetes. Use of medical co-therapy (PPIs or misoprostol) was also strongly recommended for patients at high risk of upper gastrointestinal clinical events (ie, age >65 years; history of gastrointestinal ulcer or haemorrhage; concurrent use of corticosteroid, anticoagulant, or antiplatelet therapy). If low-dose aspirin or a PPI or misoprostol was not given to a patient meeting these criteria, investigators were contacted and required to state their reasons for not providing the medication. For the MEDAL study, omeprazole (20 mg) and low-dose aspirin were provided free of charge; low-dose aspirin was provided free of charge in the EDGE and EDGE II trials. Patients returned for visits every 4 months and a scheduled telephone contact was made between visits. Patient compliance with study medication was assessed by pill count. An independent data and safety monitoring board monitored emerging safety data from all three trials at regular intervals.

The primary endpoint for the MEDAL programme was thrombotic cardiovascular events with the primary hypothesis that etoricoxib was non-inferior to diclofenac in thrombotic cardiovascular events in the per-protocol population.[23,24] Upper gastrointestinal clinical and complicated events were prespecified endpoints, but were not the primary endpoint.

Potential upper gastrointestinal clinical events (bleeding, perforation, obstruction, ulcer diagnosed on clinical work-up) were identified through active surveillance of reported adverse events, and were adjudicated by an independent blinded committee by use of predefined criteria (table 1). The subset of complicated events included those with perforation, obstruction, and complicated bleeding, whereas uncomplicated events included uncomplicated bleeding and uncomplicated ulcer (table 1). Patients with both a complicated and uncomplicated event (n=4; bleeding ulcer with synchronous uncomplicated ulcer) were counted in the overall clinical event patient group and the complicated event patient subgroup, but not the uncomplicated event patient subgroup.

Statistical analysis

Rates of upper gastrointestinal clinical events and complications per 100 patient-years with their 95% CI were prespecified determinations. The 95% CI for the rates per 100 patient-years were calculated with the Poisson distribution assumption. To better characterise the observed treatment effects, a post-hoc calculation of the hazard ratios (HR) with 95% CI was done with a Cox model with a term for treatment effect and stratification factor for baseline low-dose aspirin use. The proportional hazard assumption was tested by inclusion of treatment-by-log (time) as a factor in the model. Kaplan-Meier time-to-event curves were generated and truncated when the number of patients remaining at risk was less than 500. The MEDAL programme was event-driven and continued until at least 635 confirmed thrombotic cardiovascular events had occurred; the number of upper gastrointestinal events was not prespecified and was determined by the time required to accrue the necessary cardiovascular events. Hence, no power calculations were done for any of the upper gastrointestinal analyses. All analyses were done in the intention-to-treat population of all patients randomised followed until 14 days after discontinuation of study medication.

Subgroup analyses were done for concomitant use of low-dose aspirin or PPI co-therapy, or both, with both very liberal definitions and more restrictive definitions

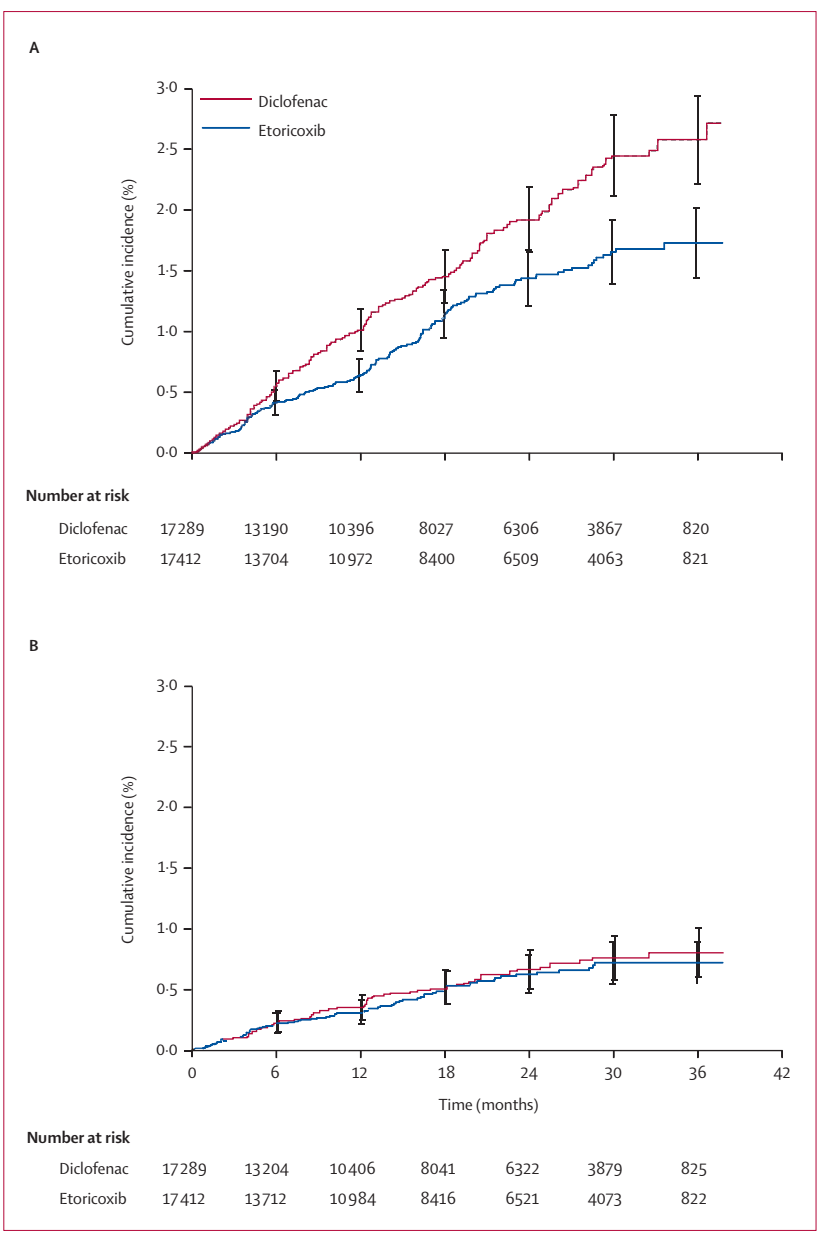

Figure: **Time-to-event analyses in intention-to-treat population**
(A) Cumulative incidence of all upper gastrointestinal clinical events. (B) Cumulative incidence of upper gastrointestinal complicated events. Error bars are 95% CI.

	Etoricoxib (n=17 412)		Diclofenac (n=17 289)		Hazard ratio (95% CI)
	n (%)	Rate*	n (%)	Rate*	
Patients with any clinical event	176 (1·01%)	0·67	246 (1·42%)	0·97	0·69 (0·57–0·83)
Patients with complicated events	78 (0·45%)	0·30	82 (0·47%)	0·32	0·91 (0·67–1·24)
Perforation†	5 (0·03%)	0·02	11 (0·06%)	0·04	
Obstruction	2 (0·01%)	0·01	2 (0·01%)	0·01	
Bleeding	72 (0·41%)	0·27	72 (0·42%)	0·28	
Gastric ulcer	40 (0·23%)	0·15	26 (0·15%)	0·10	
Duodenal ulcer	17 (0·10%)	0·06	23 (0·13%)	0·09	
Gastric and duodenal ulcer	4 (0·02%)	0·02	5 (0·03%)	0·02	
Anastomotic ulcer	1 (0·01%)	0·00	1 (0·01%)	0·00	
Other source	10 (0·06%)	0·04	17 (0·10%)	0·07	
Patients with uncomplicated events	98 (0·56%)	0·37	164 (0·95%)	0·65	0·57 (0·45–0·74)
Bleeding‡	6 (0·03%)	0·02	4 (0·02%)	0·02	
Ulcer	92 (0·53%)	0·35	161 (0·93%)	0·63	
Gastric ulcer	57 (0·33%)	0·22	110 (0·64%)	0·43	
Duodenal ulcer	27 (0·16%)	0·10	35 (0·20%)	0·14	
Gastric and duodenal ulcer	8 (0·05%)	0·03	16 (0·09%)	0·06	

*Events per 100 patient-years. †Four patients with perforation also had bleeding reported. ‡One patient with uncomplicated bleeding from a Mallory-Weiss tear also had an uncomplicated gastric ulcer identified.

Table 3: **Upper gastrointestinal clinical events in intention-to-treat population**

of concomitant therapy. The first definition was prespecified to capture all patients who took even modest amounts of concomitant therapy: use of low-dose aspirin for at least 10% of the study period, and use of US prescription doses of any PPI (omeprazole ≥20 mg, lansoprazole ≥15 mg, rabeprazole ≥20 mg, pantoprazole ≥40 mg, esomeprazole ≥20 mg daily) for more than 20% of the study period consecutively or for 30 consecutive days. The data analysis plan allowed for additional exploratory analyses with regard to co-therapies, and therefore a more restrictive definition was developed after unblinding to better investigate the specific effect of regular aspirin or PPI use on upper gastrointestinal outcomes. This definition of regular use required concomitant therapy for at least 75% of the study period (and for patients with an event, ≥75% in the period before the event); 75% was chosen because it was the prespecified definition of compliance for the study drug in the MEDAL programme. Concomitant use of other anti-ulcer medications (prescription strength histamine$_2$-receptor antagonists, misoprostol, and sucralfate) was also recorded. The subgroup analyses were done by adding terms for the subgroup factor and its interaction with treatment to the Cox model. A p value of 0·05 or less was deemed to be significant. Subgroup analyses do not have the same

	Regular PPI use		No regular PPI use		Regular aspirin use		No regular aspirin use	
	Etoricoxib (n=6951)	Diclofenac (n=6911)	Etoricoxib (n=10 461)	Diclofenac (n=10 378)	Etoricoxib (n=5745)	Diclofenac (n=5673)	Etoricoxib (n=11 667)	Diclofenac (n=11 616)
Age >65 years	2876 (41%)	2808 (41%)	3695 (35%)	3699 (36%)	2735 (48%)	2721 (48%)	3836 (33%)	3786 (33%)
Sex (female)	5311 (76%)	5311 (77%)	7614 (73%)	7512 (72%)	3977 (69%)	3961 (70%)	8948 (77%)	8862 (76%)
History of upper gastrointestinal event	728 (10%)	747 (11%)	399 (4%)	386 (4%)	377 (7%)	388 (7%)	750 (6%)	745 (6%)
Corticosteroid use	1239 (18%)	1257 (18%)	1446 (14%)	1448 (14%)	669 (12%)	674 (12%)	2016 (17%)	2031 (17%)
Aspirin use	3116 (45%)	3081 (45%)	2914 (28%)	2895 (28%)	5546 (97%)	5501 (97%)	484 (4%)	475 (4%)
Established atherosclerotic cardiovascular disease	976 (14%)	991 (14%)	1038 (10%)	1019 (10%)	1449 (25%)	1447 (26%)	565 (5%)	563 (5%)
Diabetes	823 (12%)	836 (12%)	987 (9%)	1019 (10%)	946 (16%)	956 (17%)	864 (7%)	899 (8%)
Cigarette smoker	799 (11%)	809 (12%)	1235 (12%)	1228 (12%)	628 (11%)	629 (11%)	1406 (12%)	1408 (12%)
Hypertension	3613 (52%)	3644 (53%)	4496 (43%)	4577 (44%)	3608 (63%)	3605 (64%)	4501 (39%)	4616 (40%)

Data are n (%).

Table 4: **Baseline risk factors in patients with and without PPI use or low-dose aspirin use for at least 75% of the study period**

power as did the analysis of the primary endpoint and thus should be interpreted with appropriate caution.

Discontinuations due to upper gastrointestinal symptoms consistent with dyspepsia and reflux were assessed for patients in the intent-to-treat population, and subgroup analyses were done related to the use of PPIs as well as to the use of low-dose aspirin. The definition of dyspepsia included pain or discomfort in the upper abdomen (including epigastric or stomach) or nausea, whereas reflux included reports of heartburn, oesophagitis, oesophageal burning or discomfort, gastro-oesophageal reflux disease, and hiatal hernia. Because reports of mild gastrointestinal adverse events are extremely common and might be variably reported from different sites and investigators, we chose to assess discontinuations as a marker of clinically meaningful upper gastrointestinal symptoms—ie, symptoms that were more likely to have adversely affected patient quality of life. Discontinuations due to any gastrointestinal adverse event were also assessed as a prespecified endpoint.

Role of the funding source

The MEDAL programme was designed cooperatively by the sponsor (Merck Research Laboratories) and the programme steering committee, which consists of experts in gastroenterology, cardiovascular medicine, rheumatology, pharmacology, statistical sciences, and epidemiology. The sponsor monitored the study, collected data, and did statistical analysis. An independent confirmation of the statistical analyses was done by Frontier Science Foundation (Madison, WI, USA), under the supervision of C Morton Hawkins and David DeMets (MEDAL programme steering committee member). All authors had full access to data and statistical analyses and wrote the manuscript. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

Results

34 701 patients were enrolled in the MEDAL programme (23 504 in the MEDAL study, 7111 in EDGE, and 4086 in EDGE II), including 24 913 (72%) with osteoarthritis and 9787 (28%) with rheumatoid arthritis. Baseline characteristics were much the same in the two study groups (table 2). Etoricoxib and diclofenac had similar efficacy for treatment of arthritis as measured by global assessment of disease status and discontinuations for lack of efficacy.

The figure shows the Kaplan-Meier estimates for upper gastrointestinal clinical events and complicated events. The cumulative incidence rates with etoricoxib compared with diclofenac satisfied the proportional hazard assumption, indicating a constant hazard ratio over time. The number of patients with upper gastrointestinal clinical events and the rates per 100 patient-years are shown in table 3. Upper gastrointestinal clinical events were significantly less frequent with etoricoxib than they were with diclofenac (HR 0·69, 95% CI 0·57–0·83; p=0·0001), although there was no difference in the subset of complicated events (0·91, 0·67–1·24; p=0·561). The major difference between study groups was in uncomplicated ulcers, with rates of 0·35 (95% CI 0·28–0·43) per 100 patient-years for etoricoxib and 0·63 (0·54–0·74) per 100 patient-years for diclofenac.

A breakdown of the component events is shown in table 3. Perforation (16 patients) and obstruction (four patients) were uncommon. The most common event was an uncomplicated ulcer (253 patients) followed by complicated or uncomplicated upper gastrointestinal bleeding (154 patients). The complication of upper gastrointestinal bleeding was due to gastric or duodenal ulcers in 117 (81%) cases (including two patients with anastomotic ulcers); other sources included erosions (n=11), vascular ectasias (3), cancer (1), Mallory-Weiss tears (2), varices (3), and oesophageal ulcer (1); causes were unknown or there was insufficient work-up in six cases. Gastric ulcers were almost twice as common as duodenal ulcers as a source of bleeding and were over twice as common among the uncomplicated ulcers.

The rate of upper gastrointestinal clinical events was also assessed related to concomitant use of PPIs or low-dose aspirin. Concomitant low-dose aspirin was used during at least 10% of the study by 6454 (37%) individuals in the etoricoxib group and 6367 (37%) in the diclofenac

	Etoricoxib		Diclofenac		Hazard ratio (95% CI)
	n/N (%)	Rate*	n/N (%)	Rate*	
Patients with any clinical event					
Aspirin use (p=0·19†)					
Yes	100/5752 (1·7%)	1·14	124/5680 (2·2%)	1·46	0·78 (0·60–1·01)
No	76/11 660 (0·65%)	0·43	122/11 609 (1·1%)	0·72	0·60 (0·45–0·80)
PPI use (p=0·36†)					
Yes	68/6950 (0·98%)	0·56	106/6906 (1·5%)	0·91	0·62 (0·45–0·83)
No	108/10 462 (1·0%)	0·76	140/10 383 (1·3%)	1·02	0·74 (0·58–0·95)
Patients with complicated events					
Aspirin use (p=0·92†)					
Yes	50/5752 (0·87%)	0·57	52/5680 (0·92%)	0·61	0·93 (0·63–1·36)
No	28/11 660 (0·24%)	0·16	30/11 609 (0·26%)	0·18	0·90 (0·53–1·50)
PPI use (p=0·28†)					
Yes	24/6950 (0·35%)	0·20	32/6906 (0·46%)	0·27	0·72 (0·42–1·22)
No	54/10 462 (0·52%)	0·38	50/10 383 (0·48%)	0·36	1·03 (0·70–1·52)
Patients with uncomplicated events					
Aspirin use (p=0·26†)					
Yes	50/5752 (0·87%)	0·57	72/5680 (1·3%)	0·85	0·67 (0·47–0·96)
No	48/11 660 (0·41%)	0·27	92/11 609 (0·79%)	0·54	0·50 (0·35–0·71)
PPI use (p=0·97†)					
Yes	44/6950 (0·63%)	0·36	74/6906 (1·1%)	0·63	0·57 (0·39–0·83)
No	54/10 462 (0·52%)	0·38	90/10 383 (0·87%)	0·66	0·58 (0·41–0·81)

PPI=proton pump inhibitor. *Events per 100 patient-years. †Treatment-by-subgroup interaction.

Table 5: **Upper gastrointestinal clinical events related to concomitant use of low-dose aspirin or PPIs for at least 75% of the study period in intention-to-treat population**

	Etoricoxib		Diclofenac		Hazard ratio (95% CI)
	n/N (%)	Rate*	n/N (%)	Rate*	
Patients with any clinical event (p=0·30†)					
No aspirin or PPI	52/7754 (0·67%)	0·49	83/7738 (1·1%)	0·80	0·60 (0·43–0·86)
PPI but no aspirin	24/3906 (0·61%)	0·35	39/3871 (1·0%)	0·59	0·59 (0·36–0·98)
Aspirin but no PPI	56/2708 (2·1%)	1·58	57/2645 (2·2%)	1·69	0·93 (0·65–1·35)
Aspirin and PPI	44/3044 (1·4%)	0·84	67/3035 (2·2%)	1·31	0·64 (0·44–0·93)
Patients with complicated events (p=0·74†)					
No aspirin or PPI	20/7754 (0·26%)	0·19	20/7738 (0·26%)	0·19	0·96 (0·52–1·79)
PPI but no aspirin	8/3906 (0·20%)	0·12	10/3871 (0·26%)	0·15	0·77 (0·30–1·95)
Aspirin but no PPI	34/2708 (1·3%)	0·96	30/2645 (1·1%)	0·89	1·09 (0·66–1·77)
Aspirin and PPI	16/3044 (0·53%)	0·30	22/3035 (0·72%)	0·43	0·70 (0·37–1·34)
Patients with uncomplicated events (p=0·63†)					
No aspirin or PPI	32/7754 (0·41%)	0·30	63/7738 (0·81%)	0·61	0·49 (0·32–0·75)
PPI but no aspirin	16/3906 (0·41%)	0·23	29/3871 (0·75%)	0·44	0·53 (0·29–0·98)
Aspirin but no PPI	22/2708 (0·81%)	0·62	27/2645 (1·0%)	0·80	0·77 (0·44–1·34)
Aspirin and PPI	28/3044 (0·92%)	0·53	45/3035 (1·5%)	0·88	0·61 (0·38–0·97)

PPI=proton pump inhibitor. *Events per 100 patient-years. †Treatment-by-subgroup interaction.

Table 6: **Upper gastrointestinal clinical events related to combinations of concomitant PPIs and low-dose aspirin use for at least 75% of the study period in intention-to-treat population**

	Etoricoxib		Diclofenac		Hazard ratio (95% CI)
	n/N (%)	Rate*	n/N (%)	Rate*	
Aspirin use (p=0·89†)					
Yes	109/5745 (1·9%)	1·26	139/5673 (2·5%)	1·66	0·76 (0·59–0·98)
No	218/11 667 (1·9%)	1·25	285/11 616 (2·5%)	1·70	0·75 (0·63–0·89)
PPI use (p=0·27†)					
Yes	111/6951 (1·6%)	0·92	161/6911 (2·3%)	1·39	0·67 (0·53–0·86)
No	216/10 461 (2·1%)	1·54	263/10 378 (2·5%)	1·95	0·80 (0·67–0·96)
Combinations of aspirin and PPI use (p=0·63†)					
No aspirin or PPI	152/7759 (2·0%)	1·44	184/7738 (2·4%)	1·81	0·81 (0·66–1·01)
PPI but no aspirin	66/3908 (1·7%)	0·96	101/3878 (2·6%)	1·54	0·63 (0·46–0·86)
Aspirin but no PPI	64/2702 (2·4%)	1·83	79/2640 (3·0%)	2·39	0·78 (0·56–1·08)
Aspirin and PPI	45/3043 (1·5%)	0·87	60/3033 (2·0%)	1·19	0·73 (0·50–1·08)

PPI=proton pump inhibitor. *Events per 100 patient-years. †Treatment-by-subgroup interaction.

Table 7: **Patient discontinuations due to dyspepsia related to concomitant use of low-dose aspirin and PPIs for at least 75% of the study period in intention-to-treat population**

group. Of these patients, aspirin was used for at least 75% of the study period in 5745 (89%) taking etoricoxib and 5673 (89%) of those taking diclofenac.

17 560 (51%) patients used anti-ulcer medications concomitantly for at least 20% of the study period consecutively (or 30 consecutive days); concomitant PPIs were used by 16 881 patients (96% of all patients taking any anti-ulcer medication concomitantly for at least 20% of the study period consecutively, or 30 consecutive days). Misoprostol was used by only 25 (0·07%) patients. Therefore, the only type of anti-ulcer medical co-therapy we assessed was PPIs. Concomitant PPIs were used for 20% or more of the study consecutively, or for 30 consecutive days, by 8434 (48%) patients in the etoricoxib group and 8447 (49%) in the diclofenac group. Of these patients, PPIs were used for at least 75% of the study period in 6951 (82%) of those taking etoricoxib and 6911 (82%) of those receiving diclofenac.

The proportion of patients with baseline gastrointestinal and cardiovascular risk factors among those with and without PPI use or low-dose aspirin use for at least 75% of the study period was much the same in the etoricoxib and diclofenac groups (table 4). As expected, cardiovascular risk factors were more common in patients using low-dose aspirin regularly than those not using aspirin regularly, and gastrointestinal risk factors were more common in patients using PPIs regularly than in those not using PPIs regularly. At least one gastrointestinal risk factor at baseline (age >65 years, history of upper gastrointestinal event, low-dose aspirin use, systemic corticosteroid use) was present in 11 565 (66%) patients in the etoricoxib group and 11 500 (67%) patients in the diclofenac group; 5292 (46%) of these higher-risk patients in the etoricoxib group and 5277 (46%) in the diclofenac group received PPI therapy for 75% or more of the study period.

For patients who experienced an upper gastrointestinal event to be deemed to be regular PPI or aspirin users, they were required to have taken concomitant therapy for 75% or more of the period before the event (table 5). Thus, the denominators in the aspirin and PPI subgroups for the upper gastrointestinal clinical event analyses are slightly different than the values cited elsewhere. No significant treatment-by-subgroup interactions were seen related to low-dose aspirin or PPI use, indicating that the treatment effect for etoricoxib versus diclofenac was consistent with and without low-dose aspirin and with and without PPI use. When the more liberal definitions of concomitant aspirin use (≥10% of study) and PPI use (≥20% of study consecutively, or 30 consecutive days) were assessed, no differences were seen in the results of the PPI use analyses. However, for the aspirin use analyses, the treatment-by-subgroup interactions were significant for overall upper gastrointestinal clinical events (aspirin: HR 0·83, 95% CI 0·65–1·07 *vs* no aspirin: 0·52, 0·38–0·71; p=0·021) and for uncomplicated events (aspirin: 0·73, 0·52–1·03 *vs* no aspirin: 0·43, 0·30–0·63; p=0·043), indicating that the magnitude of the decrease in overall and uncomplicated events with etoricoxib versus diclofenac was smaller in patients taking low-dose aspirin for at least 10% of the study period than in those without aspirin use.

The rates of upper gastrointestinal clinical events are further broken down into four subgroups based on the presence or absence of both low-dose aspirin and PPI use for 75% of the study period in table 6. The treatment-by-subgroup interactions were not significant for any of these analyses, or in any analyses of the four subgroups when using the more liberal definitions of concomitant therapy.

Patients taking etoricoxib discontinued study medication due to dyspepsia symptoms significantly

less often than did patients taking diclofenac (327 [1·9%] patients, 1·25 per 100 patient-years *vs* 424 [2·5%] patients, 1·69 per 100 patient-years; HR 0·75, 95% CI 0·65–0·87; p=0·0001). By contrast, the rates of patients discontinuing due to reflux symptoms were much the same in the two treatment groups (0·38 *vs* 0·41 per 100 patient-years; HR 0·95, 95% CI 0·72–1·25; p=0·718). When dyspepsia discontinuations were assessed in subgroups on the basis of the use of PPIs, low-dose aspirin, or both, for at least 75% of the study period (table 7), or the more liberal definition of concomitant therapy, no significant treatment-by-subgroup interactions were seen, indicative of no significant difference for the treatment effect based on concomitant PPI or low-dose aspirin use. The rates of discontinuations due to any gastrointestinal adverse event were 3·92 per 100 patient-years for etoricoxib and 5·69 per 100 patient-years with diclofenac (HR 0·69, 95% CI 0·64–0·75; p<0·0001).

Discussion

Our results indicate that the rate of clinically important upper gastrointestinal events was lower with the COX-2 selective inhibitor etoricoxib than it was with the traditional NSAID diclofenac in a broad population including patients taking PPIs for gastrointestinal protection and low-dose aspirin for cardiovascular protection. This result was driven by the lower rate of uncomplicated ulcers in those treated with etoricoxib than in those treated with diclofenac; no significant difference was seen in the more serious complicated events. The lower rate of uncomplicated events with etoricoxib versus diclofenac was consistent in patients taking PPIs and those not taking PPIs concomitantly, and was also maintained in patients taking concomitant low-dose aspirin regularly. Additionally, significantly fewer patients discontinued etoricoxib than they did diclofenac due to dyspepsia.

We strongly encouraged PPI use for patients with increased gastrointestinal risk, and 13 862 (40%) patients took PPIs for at least 75% of the study period. In both treatment groups, the rates of upper gastrointestinal clinical events were not higher in patients taking PPIs than in those not taking PPIs regularly. Presumably PPI use decreased the rate of events in the higher-risk patients given PPIs, approximating the level seen in patients without PPI therapy. Both PPI users and non-users had reductions in the relative risk with etoricoxib versus diclofenac in uncomplicated events of just over 40%, indicating no diminution in the relative benefit of the COX-2 selective inhibitor compared with the traditional NSAID with PPI use.

Patients taking low-dose aspirin have an increased risk of upper gastrointestinal clinical events, as corroborated here. Previous outcome trials have not identified a significant reduction in events with a COX-2 selective inhibitor compared with a traditional NSAID in aspirin users.[5,7,8] The largest subgroup analysis, in 4362 aspirin users, revealed a relative risk of upper gastrointestinal clinical events for lumiracoxib versus ibuprofen or naproxen of 0·73 (95% CI 0·47–1·14).[7] However, previous trials[5,7,8] were shorter in duration and had fewer patients taking low-dose aspirin than did the MEDAL programme. The risk of uncomplicated upper gastrointestinal events was reduced with etoricoxib versus diclofenac both in patients taking aspirin for at least 75% of the study period (HR 0·67, 95% CI 0·47–0·96) and in those using aspirin less often or not at all (0·50, 0·35–0·71). The treatment-by-subgroup interaction for regular aspirin use was not significant, indicating that the reduction in uncomplicated events with etoricoxib was not significantly different with and without regular aspirin use. However, when patients taking aspirin for only 10% of the study were deemed to be aspirin users, the treatment-by-subgroup interaction became significant (0·73, 0·52–1·03 with aspirin vs 0·43, 0·30–0·63 without aspirin; p=0·043). Taken together, these data suggest that the COX-2 selective inhibitor etoricoxib reduces the risk of uncomplicated upper gastrointestinal events compared with the traditional NSAID diclofenac in patients taking low-dose aspirin regularly. However, the magnitude of the gastrointestinal benefit might be decreased with low-dose aspirin use.[5,7,8]

The incidence of upper gastrointestinal clinical events was lower in the MEDAL programme than in other outcome studies. For example, the rates of 0·32 complicated events and 0·97 clinical events per 100 patient-years with the traditional NSAID diclofenac are at least 60% lower than rates with diclofenac or other traditional NSAIDs in other long-term outcomes trials.[5–7,26–28] At least a portion of this difference is presumably due to the MEDAL programme's simulation of real-world practice by allowing (and encouraging) the use of gastrointestinal-protective therapy such as PPIs. Nearly half of the participants in the MEDAL programme used these drugs. However, even in patients not using PPIs, the rates of upper gastrointestinal clinical events were lower than in earlier trials, suggesting that many of the patients enrolled in our studies had a lower gastrointestinal risk. However, there are no notable differences in terms of risk factors (eg, age, history of gastrointestinal events, steroid use, and low-dose aspirin use) between the MEDAL programme and previous outcome trials that would explain this lower risk.

Neither the lower rates of upper gastrointestinal events nor the concomitant use of PPIs and low-dose aspirin in the MEDAL programme seem likely to fully explain the absence of a significant difference in complicated upper gastrointestinal events. Even in the nearly 15 500 patients not using PPIs or low-dose aspirin regularly, no evidence of a decrease in complicated events was seen; by contrast, we noted a 51% reduction in the relative risk of uncomplicated events. We cannot rule out the possibility that PPIs have a differential effect on the prevention of complicated and uncomplicated ulcers. However, the dichotomy between complicated and uncomplicated

events potentially could relate to diclofenac's lack of antiplatelet effect. Patrono and colleagues[29] have suggested that gastroduodenal mucosal lesions develop as a consequence of moderate inhibition of COX-1 activity, whereas upper gastrointestinal bleeding complications occur as a result of high-grade inhibition of platelet COX-1.[29] Greater than 95% inhibition of COX-1 mediated thromboxane is required to affect platelet function.[30,31] Diclofenac's inhibition peaks at a mean of 87%.[32] Although this degree of COX-1 inhibition is sufficient to induce gastrointestinal ulcers,[33–35] it is not sufficient to meaningfully decrease platelet function in most patients.[36] Thus, antiplatelet activity might not have an important role in the induction of gastrointestinal bleeding with diclofenac.

See Online for webappendix

Uncomplicated events accounted for most of the difference seen in the effect of etoricoxib and diclofenac on overall upper gastrointestinal clinical events. The diagnosis of an uncomplicated symptomatic ulcer has important clinical implications for patients. The finding of an uncomplicated ulcer mandates further medical follow-up with the attendant health-care costs and potential additional testing (eg, endoscopy for gastric ulcer[37]). Furthermore, NSAIDs would be discontinued if possible in a patient with a symptomatic ulcer.[38] If NSAIDs were required, long-term medical therapy with a PPI or misoprostol, a COX-2 selective inhibitor, or both, would be started.[38] However, although an uncomplicated ulcer affects quality of life and clinical management, it does not generally require hospitalisation and is not life threatening if a complication does not develop.

Dyspepsia is the most common side-effect that occurs with NSAID use and the most common side-effect leading to discontinuation of NSAID therapy.[13,14] Not only is dyspepsia far more common than upper gastrointestinal clinical events, but medications for gastrointestinal side-effects probably account for most gastrointestinal costs—exceeding the expensive but uncommon hospitalisations for gastrointestinal complications.[39,40] We observed significantly fewer discontinuations due to dyspepsia with etoricoxib than with diclofenac. This decrease was similar in patients who took PPIs, suggesting that the COX-2 selective inhibitor provides symptomatic benefit even in patients already taking a PPI. Additionally, the reduction in dyspepsia discontinuations was not affected by whether or not patients took concomitant low-dose aspirin. The cause of NSAID-associated dyspepsia is unknown. Whether the dyspepsia relates to mucosal injury, changes in motility, or other factors is uncertain, but studies designed to assess the mechanism for the benefits reported with COX-2 selective inhibitors are warranted.

The results of the MEDAL programme provide new information about upper gastrointestinal clinical events and symptoms to assist arthritis patients and their physicians to make decisions regarding NSAID use. In patients taking PPIs, use of the COX-2 selective inhibitor etoricoxib reduced the risk of upper gastrointestinal clinical events and dyspepsia as compared with the traditional NSAID diclofenac. Similarly, in patients taking low-dose aspirin regularly, the risk of upper gastrointestinal clinical events and dyspepsia was reduced with the use of etoricoxib. However, the reductions in risk of these clinical events were seen only in the more common, but less serious uncomplicated events.

Contributors

All authors have read and approved the manuscript and contributed to its design, analysis, or interpretation of data, and drafting and revision of the manuscript. Details of the MEDAL programme steering committee, independent data and safety monitoring board, and the gastrointestinal event adjudication committee can be found in reference 23 and in the webappendix.

Conflict of interest statement

L Laine has received research support from Merck, Pfizer, Novartis, TAP, and Bayer, and has served as a consultant for Merck, Novartis, Bayer, AstraZeneca, Eisai, Altana, J&J, and Santarus. S P Curtis and A Kaur are employees of Merck and own stock and/or hold stock options in the company. B Cryer has served as a consultant for Merck, Pfizer, AstraZeneca, and TAP. C P Cannon has received research grant support from Accumetrics, AstraZeneca, Merck, Merck/Schering Plough Partnership, and Schering Plough through the Department of Medicine of Brigham and Women's Hospital; has served on scientific advisory boards for Alnylam, AstraZeneca, Biosite, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Merck, Merck Schering Plough Partnership, Pfizer, Sanofi-Aventis, Schering Plough, and Tethys; has received lecture fees from Accumetrics, AstraZeneca, Bristol-Myers Squibb, Merck, Merck/Schering Plough Partnership, Pfizer, Sanofi-Aventis, and Schering Plough; has received honoraria for the preparation of educational materials from BGB New York, DIME, and NCME; and has received additional funding for studies and subsidies conducted by the TIMI study group from Merck and Co, Bristol-Myers Squibb Pharmaceutical Research Institute, Sanofi-Aventis, Millennium Pharmaceuticals, Nuvelo, AstraZeneca Pharmaceuticals, CV Therapeutics, Inotek Pharmaceuticals Corporation, Bayer Healthcare LLC, Ortho-Clinical Diagnostics, Sanofi-Synthelabo Recherche, GlaxoSmithKline, Amgen, Beckman Coulter, Biosite Coulter, Biosite Incorporated, Roche Diagnostics Corporation, Roche Diagnostics GmbH, Pfizer, Accumetrics, the National Institutes of Health, and Novartis Pharmaceuticals.

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Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials

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Research

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Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials

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Abstract

Objective To assess the effects of selective cyclo-oxygenase-2 (COX 2) inhibitors and traditional non-steroidal anti-inflammatory drugs (NSAIDs) on the risk of vascular events.

Design Meta-analysis of published and unpublished tabular data from randomised trials, with indirect estimation of the effects of traditional NSAIDs.

Data sources Medline and Embase (January 1966 to April 2005); Food and Drug Administration records; and data on file from Novartis, Pfizer, and Merck.

Review methods Eligible studies were randomised trials that included a comparison of a selective COX 2 inhibitor versus placebo or a selective COX 2 inhibitor versus a traditional NSAID, of at least four weeks' duration, with information on serious vascular events (defined as myocardial infarction, stroke, or vascular death). Individual investigators and manufacturers provided information on the number of patients randomised, numbers of vascular events, and the person time of follow-up for each randomised group.

Results In placebo comparisons, allocation to a selective COX 2 inhibitor was associated with a 42% relative increase in the incidence of serious vascular events (1.2%/year *v* 0.9%/year; rate ratio 1.42, 95% confidence interval 1.13 to 1.78; P = 0.003), with no significant heterogeneity among the different selective COX 2 inhibitors. This was chiefly attributable to an increased risk of myocardial infarction (0.6%/year *v* 0.3%/year; 1.86, 1.33 to 2.59; P = 0.0003), with little apparent difference in other vascular outcomes. Among trials of at least one year's duration (mean 2.7 years), the rate ratio for vascular events was 1.45 (1.12 to 1.89; P = 0.005). Overall, the incidence of serious vascular events was similar between a selective COX 2 inhibitor and any traditional NSAID (1.0%/year *v* 0.9%/year; 1.16, 0.97 to 1.38; P = 0.1). However, statistical heterogeneity (P = 0.001) was found between trials of a selective COX 2 inhibitor versus naproxen (1.57, 1.21 to 2.03) and of a selective COX 2 inhibitor versus non-naproxen NSAIDs (0.88, 0.69 to 1.12). The summary rate ratio for vascular events, compared with placebo, was 0.92 (0.67 to 1.26) for naproxen, 1.51 (0.96 to 2.37) for ibuprofen, and 1.63 (1.12 to 2.37) for diclofenac.

Conclusions Selective COX 2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac, but high dose naproxen is not associated with such an excess.

Introduction

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat pain, but their long term use is limited by serious gastrointestinal side effects. Whereas NSAIDs inhibit the two recognised forms of prostaglandin G/H synthase (also referred to as cyclo-oxygenase), selective cyclo-oxygenase-2 (COX 2) inhibitors are selective inhibitors of the COX 2 isozyme.[1] As the anti-inflammatory effects of NSAIDs were believed to be mediated by inhibition of COX 2, and their gastrointestinal side effects by inhibition of COX 1, people hypothesised that selective COX 2 inhibitors would provide a safer alternative to traditional NSAIDs. However, although some studies have reported a lower incidence of upper gastrointestinal complications with selective COX 2 inhibitors than with traditional NSAIDs,[2 3] recent concerns about the cardiovascular safety of selective COX 2 inhibitors have limited their use.

Although the Vioxx gastrointestinal outcomes research (VIGOR) trial reported a fivefold increase in myocardial infarction among participants allocated to rofecoxib (20 rofecoxib *v* 4 naproxen; P < 0.001),[2] this difference might have occurred, at least in part, because high dose naproxen inhibits platelet aggregation throughout the dosing interval. However, the results of the adenomatous polyp prevention on Vioxx (APPROVe) trial, which was the first relatively large trial comparing a selective COX 2 inhibitor with placebo, indicated that rofecoxib increased the risk of vascular events by about twofold.[4] Soon afterwards, the adenoma prevention with celecoxib (APC) trial, comparing celecoxib with placebo, reported a similar excess.[5]

The accumulating evidence suggests that selective COX 2 inhibitors are associated with an increased risk of vascular events, but several important questions remain unanswered. Firstly, what is the magnitude of any excess risk of myocardial infarction, stroke, and vascular mortality? Secondly, is the excess risk of vascular events dose related, and is the size of this risk different in people who are also taking aspirin (which chiefly inhibits COX 1 at low doses[6])? Thirdly, are traditional NSAIDs (which also inhibit COX 2) associated with an increased risk of vascular events? We did a meta-analysis of randomised trials that compared a selective COX 2 inhibitor with placebo or a selective COX 2 inhibitor with a traditional NSAID in an attempt to answer these questions.

A table, two extra figures, a statistical appendix, and extra references are on bmj.com

Methods

We used three steps to identify prospective randomised controlled trials of a selective COX 2 inhibitor versus placebo, a selective COX 2 inhibitor versus a traditional NSAID, or both. First we approached the manufacturers of each of the selective COX 2 inhibitors—Merck (rofecoxib, etoricoxib), Novartis (lumiracoxib), and Pfizer (celecoxib, valdecoxib). Then we searched the Food and Drug Administration website for data presented at the Cardiorenal Advisory Committee meeting in February 2005. Finally, we used the modified Cochrane strategy[7] combined with the generic names of each of the individual selective COX 2 inhibitors as keywords to search Medline and Embase from January 1966 to April 2005.

Randomised trials involving at least four weeks' scheduled treatment were eligible if they included at least one comparison of a selective COX 2 inhibitor versus placebo or a selective COX 2 inhibitor versus a traditional NSAID and had recorded serious (that is, admitted to hospital or fatal) cardiovascular events. The pre-specified outcomes were "serious vascular event," as defined by the Antiplatelet Trialists' Collaboration (that is, non-fatal myocardial infarction, non-fatal stroke, or vascular death)[8]; fatal or non-fatal myocardial infarction; fatal or non-fatal stroke; and vascular death (including death from myocardial infarction or stroke). The manufacturers and individual investigators provided summary design details for each trial and information on the process (if any) by which vascular events were adjudicated. All of the manufacturers provided written confirmation that the data provided were complete: Pfizer had locked their data at 31 October 2004, whereas Merck and Novartis had locked their databases at the end of January 2005. We requested numbers of events and person time at risk for each trial, where available, but in a few cases we estimated data from published results or the Food and Drug Administration website.[9]

On the basis of the known pharmacokinetic and pharmacodynamic properties of the NSAIDs studied (which raised the hypothesis that naproxen might have aspirin-like antiplatelet effects), we prospectively specified that analyses of a selective COX 2 inhibitor versus NSAID were to be subdivided into those involving naproxen and those concerning other (non-naproxen) NSAIDs.

We derived rate ratios and their confidence intervals for each of the pre-specified comparisons by using the Peto "one step" approximation (see statistical appendix on bmj.com).[10] In figures and in the text, we have used 99% confidence intervals for individual comparisons to allow for the multiplicity of analyses, reserving 95% confidence intervals for subtotals.

Results

Study population

Tabular data were available from 138 randomised trials involving a comparison of a selective COX 2 inhibitor versus placebo or versus a traditional NSAID (or both), in which there were a total of 145 373 participants (see table on bmj.com).[w1-w90]

Comparisons of selective COX 2 inhibitor versus placebo

Figure 1 shows meta-analyses of a selective COX 2 inhibitor versus placebo, subdivided by individual selective COX 2 inhibitor, for each of the primary outcomes. Overall, among 121 placebo controlled trials, 216 vascular events occurred during 18 490 person years of exposure to a selective COX 2 inhibitor (1.2%/year) compared with 112 during 12 639 person years of placebo (0.9%/year), corresponding to a 42% proportional increase in the incidence of a first serious vascular event (rate ratio 1.42, 95% confidence interval 1.13 to 1.78; P = 0.003). We found no evidence that the proportional excess incidence of vascular events varied among the different selective COX 2 inhibitors (heterogeneity $\chi^2 = 0.5$, df = 4; P = 1.0). However, as only two selective COX 2 inhibitors (rofecoxib and celecoxib) had recorded appreciable numbers of such outcomes, the power to identify any real differences that might exist between selective COX 2 inhibitors was limited. In the group of trials analysed, this proportional difference corresponded to an excess of 3 (95% confidence interval 1 to 5) people with a vascular event per 1000 allocated to a selective COX 2 inhibitor per year.

We found an almost twofold proportional increase in myocardial infarction (rate ratio 1.86, 1.33 to 2.59; P = 0.0003) (fig 1), corresponding to an excess of 3 (1 to 4) people with myocardial infarction per 1000 allocated to a selective COX 2 inhibitor per year. We found no significant heterogeneity in the rate ratios for myocardial infarction among individual selective COX 2 inhibitors (heterogeneity $\chi^2 = 1.0$, df = 4; P = 0.9). We found no difference in the incidence of stroke (rate ratio 1.02, 0.71 to 1.47; P = 0.9), corresponding to an absolute difference of 0 (−2 to 1)/1000/year, and the summary rate ratio for vascular death (1.49, 0.97 to 2.29; P = 0.07), although it did not reach statistical significance, corresponded to an absolute excess of 1 (0 to 2)/1000/year.

Duration

Of the 121 placebo controlled trials, nine were long term trials with one year or longer of scheduled treatment (mean 139 weeks) and 112 were shorter trials (mean 11 weeks). Around two thirds of the vascular events had occurred in the nine long term trials. In these long term trials, allocation to a selective COX 2 inhibitor was associated with a 45% increase in the incidence of vascular events (rate ratio 1.45, 1.12 to 1.89; P = 0.005) (fig 2), with no significant heterogeneity between the event rate ratios in the trials (heterogeneity $\chi^2 = 13.4$, df = 8; P = 0.1).

Dose

Too few vascular events were available to allow us to assess dose-response in placebo controlled trials of etoricoxib, lumiracoxib, or valdecoxib. For rofecoxib, 85% of vascular events among patients allocated to a selective COX 2 inhibitor occurred at a dose of 25 mg daily, with few events at lower or higher daily doses, so we could not evaluate dose dependence. For celecoxib, we found a significant trend towards an increased incidence of serious vascular events with higher daily doses (trend P = 0.03) (fig A on bmj.com).

Aspirin

Among the 84 placebo controlled trials that allowed concomitant use of aspirin for which data were available, we found no significant heterogeneity of the summary rate ratios for vascular events among aspirin users and non-users (heterogeneity $\chi^2 = 0.0$, df = 1; P = 0.9) (fig B on bmj.com). We found a similar lack of heterogeneity for myocardial infarction, stroke, and vascular death (data not shown).

Comparisons of selective COX 2 inhibitor versus traditional NSAID

Overall, we found no significant difference in the incidence of a serious vascular event between participants allocated to a selective COX 2 inhibitor and those allocated to a traditional NSAID—340 vascular events during 33 260 person years of exposure to a selective COX 2 inhibitor (1.0%/year) versus 211 vascular events during 23 325 person years with a traditional

NSAID (0.9%/year) (rate ratio 1.16, 0.97 to 1.38; P = 0.1) (fig 3). However, we found marked heterogeneity between the rate ratios for vascular events in trials comparing a selective COX 2 inhibitor with naproxen and those comparing a selective COX 2 inhibitor with a non-naproxen NSAID ($\chi^2 = 10.2$, df = 1; P = 0.001). We found similar heterogeneity for myocardial infarction ($\chi^2 = 4.3$, df = 1; P = 0.04), stroke ($\chi^2 = 3.6$, df = 1; P = 0.06), and vascular death ($\chi^2 = 5.3$, df = 1 P = 0.02).

Any selective COX 2 inhibitor versus naproxen

Overall, compared with naproxen, allocation to a selective COX 2 inhibitor was associated with a highly significant increase in the incidence of a vascular event (rate ratio 1.57, 1.21 to 2.03; P = 0.0006) and a twofold increased risk of a myocardial infarction (2.04, 1.41 to 2.96; P = 0.0002) (fig 3). We found no significant difference in the incidence of stroke (rate ratio 1.10, 0.73 to 1.65; P = 0.7) or of vascular death (1.47, 0.90 to 2.40; P = 0.1).

Any selective COX 2 inhibitor versus a non-naproxen NSAID

Overall, we found no significant difference in the incidence of a vascular event (rate ratio 0.88, 0.69 to 1.12; P = 0.3), myocardial infarction (1.20, 0.85 to 1.68; P = 0.3), or vascular death (0.67, 0.43 to 1.06; P = 0.09), but a selective COX 2 inhibitor was associated with a significantly lower incidence of stroke than any non-naproxen traditional NSAID (rate ratio 0.62, 0.41 to 0.95; P = 0.03) (fig 3). Comparisons of a selective COX 2 inhibitor with ibuprofen (rate ratio 0.85, 99% confidence interval 0.49 to 1.46; P = 0.4), a selective COX 2 inhibitor versus diclofenac (0.85, 0.56

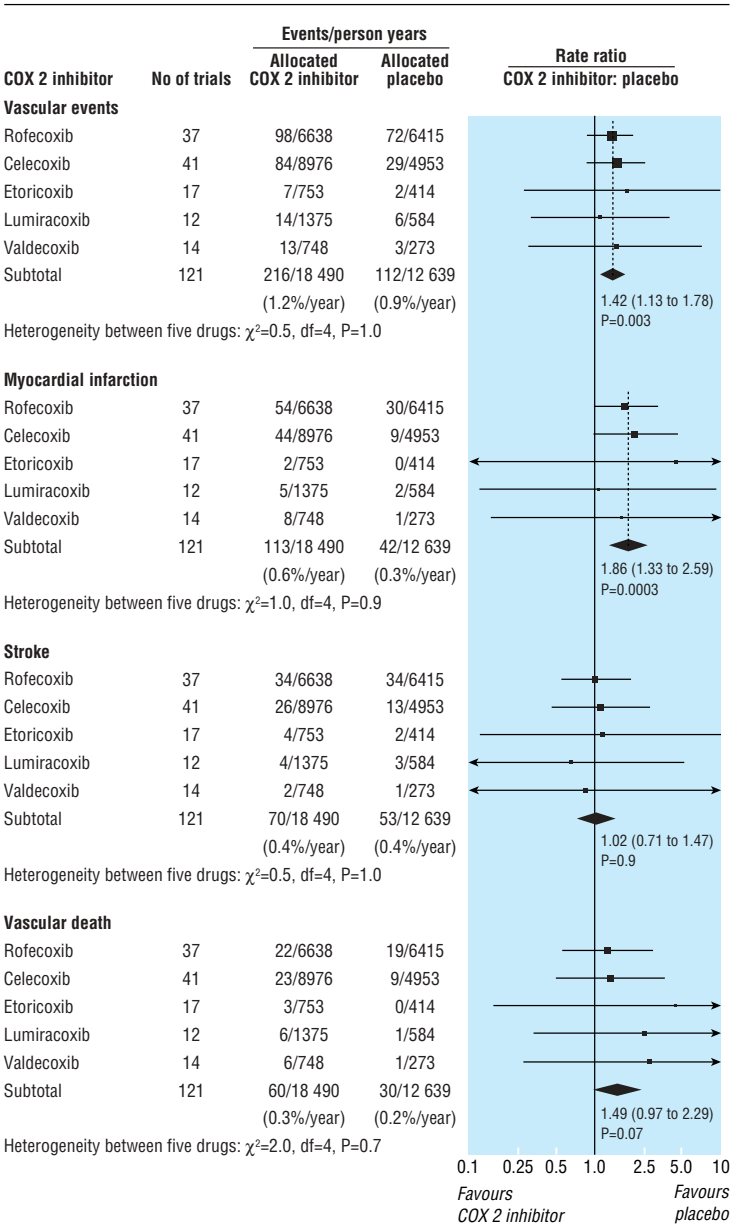

Fig 1 Comparison of effects of different selective COX 2 inhibitors versus placebo on vascular events, myocardial infarction, stroke, and vascular death. Event numbers and person years of exposure, with corresponding mean annual event rates in parenthesis, are presented for patients allocated to selective COX 2 inhibitor and placebo. Event rate ratios for subtotals, with 95% confidence intervals, are indicated by a diamond; rate ratios for individual selective COX 2 inhibitors, with 99% confidence intervals, are indicated by a square and horizontal line. Diamonds to the right of the solid line indicate hazard with a selective COX 2 inhibitor compared with placebo, but this is conventionally significant only if the diamond does not overlap the solid line

to 1.27; P = 0.3), and a selective COX 2 inhibitor versus any other non-naproxen NSAID (2.21, 0.49 to 10.03; P = 0.2) yielded similar rate ratios for vascular events (test for heterogeneity $\chi^2 = 2.6$, df = 2; P = 0.3) (fig 3).

Comparisons of traditional NSAID versus placebo

We combined direct estimates of treatment effect (from trials involving a comparison of an NSAID versus placebo) with indirect information (from a comparison of trials of a selective COX 2 inhibitor versus placebo and a selective COX 2 inhibitor versus NSAID) (see statistical appendix on bmj.com). The summary rate ratio for vascular events, in comparison with placebo, was 0.92 (95% confidence interval 0.67 to 1.26) for naproxen, 1.51 (0.96 to 2.37) for ibuprofen, and 1.63 (1.12 to 2.37) for diclofenac.

Discussion

When we considered all the randomised trial data, selective COX 2 inhibitors were associated with a highly significant 1.4-fold increased risk of serious vascular events, largely due to a twofold increased risk of myocardial infarction. Although we found no significant excesses in the incidence of stroke or vascular death, the confidence intervals for each were wide, so we could not exclude a clinically important excess. If, as some people have suggested (on the basis of the delayed divergence of survival curves), the hazard emerges only after a year or 18 months,[4 5] then combining short term and long term trials might underestimate the effects of long term exposure to a selective COX 2 inhibitor. We were not able to assess time dependent variation in the rate ratio because we sought numbers of events and person time only for the whole period of follow-up in each trial. However, as figure 2 clearly shows, when all the long term trials are considered, the summary rate ratio is similar to that from short term and long term trials combined and somewhat smaller than the twofold to threefold excess suggested by the combined results of the APC and APPROVe studies.[4 5]

Not all of the trials had independent adjudication of vascular events, so a bias towards the null is possible owing to non-differential misclassification of vascular outcomes in those trials without independent adjudication. As more than 70% of the vascular events occurred in trials that were adjudicated, the potential for misclassification is limited. Indeed, the summary rate ratio for a selective COX 2 inhibitor versus placebo among adjudicated trials was 1.45 (95% confidence interval 1.12 to 1.89), which is very similar to the estimate among all trials of 1.42 (1.13 to 1.78). A further potential source of bias was our prospective decision to limit eligibility to trials of at least four weeks' duration, because this resulted in the exclusion of two small short term randomised trials of parecoxib (the intravenously administered pro-drug of valdecoxib) and valdecoxib versus placebo among patients having coronary artery bypass grafting,[11 12] in which the risk of vascular events was increased threefold.[13] If these two trials had been included, the summary rate ratio for a selective COX 2 inhibitor versus placebo would have been 1.49 (1.20 to 1.85). Hence, although we cannot exclude the possibility that, at least in the context of vascular surgery, the proportional increase in risk of a vascular event is higher with parecoxib or valdecoxib than with other selective COX 2 inhibitors, the exclusion of these trials had a small effect on the overall summary rate ratio for a selective COX 2 inhibitor versus placebo.

The available data from placebo controlled trials were inadequate to allow assessment of whether the cardiovascular risks of selective COX 2 inhibitors are dose dependent (fig A on

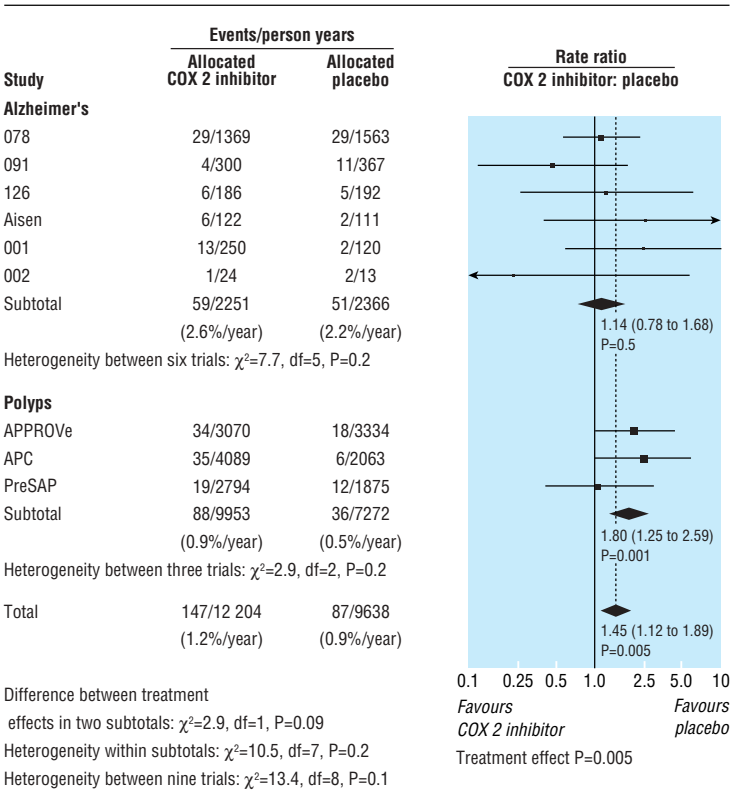

Fig 2 Comparison of effects of selective COX 2 inhibitors versus placebo among trials with scheduled duration of at least one year. Symbols and conventions are as in fig 1

bmj.com). Although we found a weak trend towards larger risks with higher daily doses of celecoxib, this result was driven by the results of one trial.[5] We were also unable to determine reliably whether the cardiovascular effects of selective COX 2 inhibitors might differ among aspirin users and non-users (fig B on bmj.com).

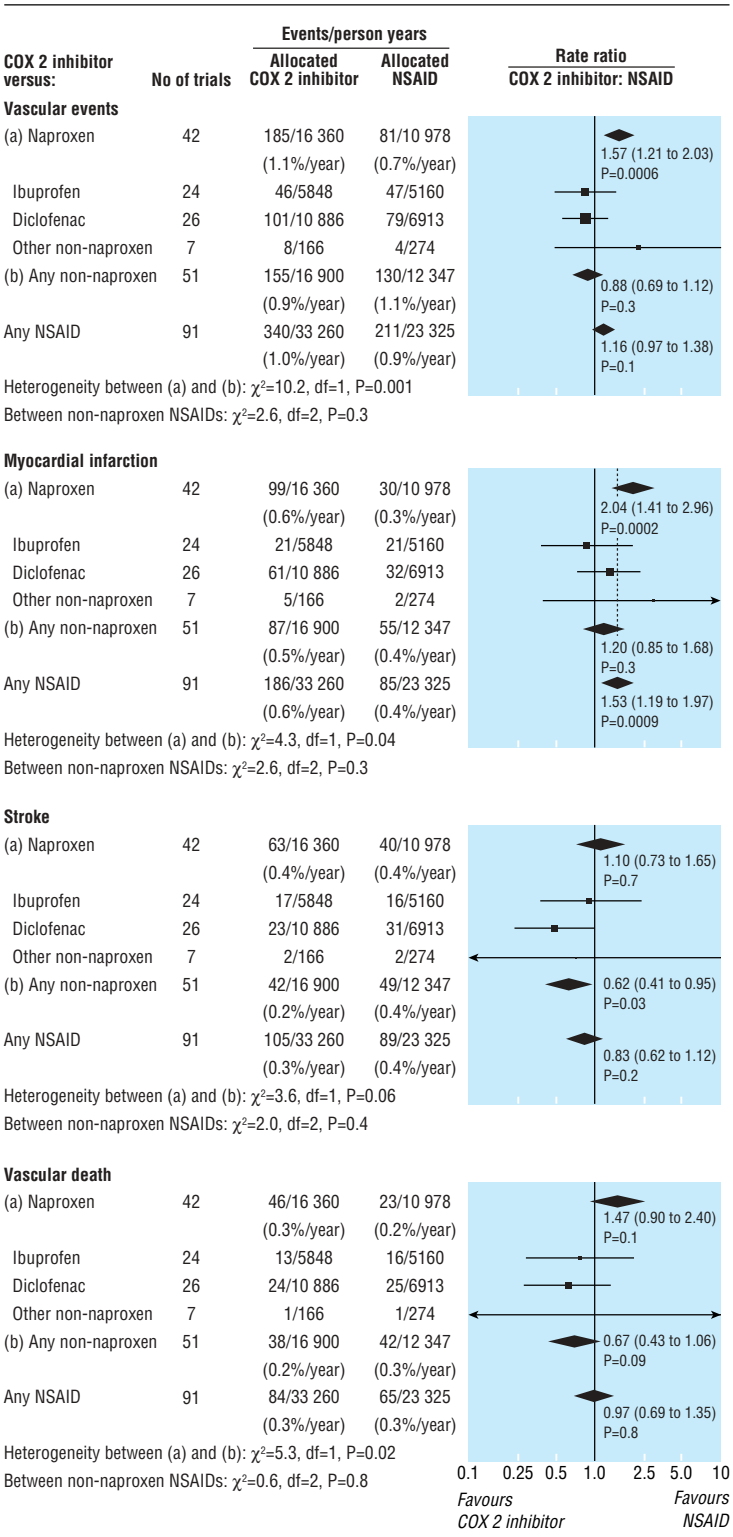

Fig 3 Comparison of effects of selective COX 2 inhibitors versus traditional NSAIDs on vascular events, myocardial infarction, stroke, and vascular death. Symbols and conventions are as in fig 1. Some trials involved more than one NSAID comparator, so numbers of trials in subtotals are not a strict sum of numbers for each NSAID

Cardiovascular effects of traditional NSAIDs

As traditional NSAIDs inhibit the COX 2 enzyme, these drugs might also be associated with an increased risk of vascular events.[14] As NSAIDs were originally developed for the relief of pain, long term placebo controlled trials have not been done. A few traditional NSAIDs with prominent effects on the COX 1 isozyme, such as indobufen and flurbiprofen, have been tested as potential antiplatelet agents in small studies,[15 16] but no adequately powered long term randomised trials have assessed drugs without such antiplatelet effects. As the plasma half life of naproxen is around 14 hours, a regimen of 500 mg twice daily results in sustained inhibition of COX 1 dependent thromboxane biosynthesis, whereas both ibuprofen and diclofenac have much shorter half lives (one to two hours), and standard twice or three times daily regimens have only transient effects. We therefore hypothesised that the cardiovascular effects of naproxen would differ from those of non-naproxen NSAIDs. Our results indicated that high dose ibuprofen (800 mg three times daily) and high dose diclofenac (75 mg twice daily) were each associated with an increased risk of vascular events, but that the risks of high dose naproxen (500 mg twice daily) were substantially smaller. We had insufficient information to determine whether naproxen was protective. Uncertainty remains, however, as to whether the cardiovascular effects of standard (that is, lower) daily doses of these drugs would differ from those identified in this meta-analysis, and this is an important topic for future research.

Estimating absolute risk

In this particular group of trials, allocation to a selective COX 2 inhibitor was associated with around three extra people having a vascular event per 1000 per year, with most of this excess attributable to myocardial infarction. The annual excess incidence associated with full compliance with a selective COX 2 inhibitor would be expected to be larger than this, however. In the APPROVe study, for example, approximately one third of randomised patients discontinued study treatment before the end of the study.[4] If this discontinuation rate was typical, the absolute excess incidence of vascular events produced by full compliance with a selective COX 2 inhibitor might be four or five additional patients having a vascular event per 1000 treated per year overall, with a smaller excess among those at lower than average risk (such as young women with rheumatoid arthritis) and a higher excess in those at above average risk (such as older patients with established atherosclerotic disease).

Study limitations

The chief limitation of this study is the relatively small number of events available for analysis, which limits assessment of the hazards of the various different selective COX 2 inhibitors and traditional NSAIDs in particular clinical circumstances. We were also limited to analysing tabular summaries of data, which prevented us from assessing the timing of the hazard or variation in the rate ratio among particular subgroups of patients. Moreover, we limited attention to cardiovascular hazards, whereas the choice between different anti-inflammatory regimens also needs to take account of differences in their gastrointestinal effects. Some of these outstanding uncertainties may be resolved by a planned meta-analysis of data on individual patients from these trials.

Conclusions

This meta-analysis has shown that selective COX 2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac, but that high dose naproxen is not associated with such an excess. As differences between anti-inflammatory regimens are likely to be small, very large randomised trials will be needed if we are to identify which anti-inflammatory drug regimens minimise the overall burden of adverse gastrointestinal and cardiovascular outcomes.

What is already known on this topic

Some selective cyclo-oxygenase-2 (COX 2) inhibitors have been shown to increase the risk of occlusive vascular events, but important details remain unclear

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the COX 2 enzyme, but their effects on vascular events are unknown

What this study adds

Selective COX 2 inhibitors are associated with a moderately increased risk of vascular events, largely attributable to a twofold increased risk of myocardial infarction

High dose regimens of some traditional NSAIDs, such as diclofenac and ibuprofen, but not high dose naproxen, are associated with a similar excess risk of vascular events

The choice between different anti-inflammatory regimens requires assessment of the individual expected absolute attributable risks of cardiovascular and serious gastrointestinal events

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Competing interests: The Clinical Trial Service Unit has a staff policy of not accepting honorariums or other payments from the drug industry, except for the reimbursement of costs to participate in scientific or advisory committee meetings. CB has had such costs reimbursed for attending meetings arranged by Bayer, Merck, Novartis, GlaxoSmithKline, and Astra-Zeneca. He is the lead investigator of the study of heart and renal protection, a study of cholesterol lowering in chronic kidney disease, which is sponsored by the University of Oxford and supported by an unrestricted grant from Merck. CP has received grant support from Bayer, Merck, and Pfizer. In addition, he has received honorariums for lecturing and consulting from Bayer and NiCox. PMK, JG, HH, and JRE have no competing interests. No funding was provided by any drug company for this project. None of the authors has any stockholdings in pharmaceutical companies, and none is involved in advising any organisation or individual on issues related to litigation.

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