Advisory Committee Briefing Document

Celecoxib and Valdecoxib Cardiovascular Safety

Arthritis Advisory Committee

Drug Safety and Risk Management Advisory Committee

16-18 February 2005

Pfizer Inc

12 January 2005

AVAILABLE FOR PUBLIC RELEASE WITHOUT REDACTION

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ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Monitoring
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AD	Alzheimer's Disease
ADAPT	Alzheimer's Disease Anti-Inflammatory Prevention Trial
AERS	Adverse Event Reporting System
APC	Prevention of Sporadic Colorectal Adenomas with Celecoxib Trial
APPROVe	Adenomatous Polyp Prevention on Vioxx Trial
APTC	Antiplatelet Trialists Collaboration
BID	Twice Daily
CABG	Coronary Artery Bypass Graft
CCTR	Corporate Clinical Trials Registry
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLASS	Celecoxib Long-Term Arthritis Safety Study
CMS	Concerned Member State
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CRC	Colorectal Cancer
CRP	C-Reactive Protein
CSC	Cardiovascular Safety Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EMEA	European Agency for the Evaluation of Medicinal Products
EU	European Union
FAP	Familial Adenomatous Polyposis
FDA	Food and Drug Administration
GPRD	General Practice Research Database
HEK	Human Embryonic Kidney
hERG	Human Ether-A-Go-Go
IRG	Independent Research Grant
IV	Intravenous
LDL	Low-Density Lipoprotein

ABBREVIATIONS, continued

MACE	Major Adverse Cardiovascular Event
n	Number of Patients With Events
N	Number of Patients Treated
NA	Not Applicable
NCI	National Cancer Institute
NDA	New Drug Application
NO	Nitric Oxide
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
PG	Prostaglandin
PGE_2	Prostaglandin E_2
PGI_2	Prostaglandin I_2, also known as Prostacyclin
PRESAP	Prevention of Colorectal Sporadic Adenomatous Polyps Trial
QD	Once Daily
RA	Rheumatoid Arthritis
SAP	Spontaneous Adenomatous Polyposis
SPC	Summary of Product Characteristics
SR	Sustained Release
SUCCESS	Successive Celecoxib Efficacy and Safety Study
TDD	Total Daily Dose
TID	Three Times Daily
TXA_2	Thromboxane
TEMC	Treatment Effects Monitoring Committee
US	United States
VIGOR	Vioxx Intestinal Outcomes Research Trial

1. INTRODUCTION AND BACKGROUND

Patients seeking relief in chronic painful conditions such as osteoarthritis (OA) and rheumatoid arthritis (RA) or in acute conditions ranging from dysmenorrhea to post-surgical pain can benefit from effective pain relief using any of a variety of non-opiate analgesics (eg, acetaminophen or analgesic/anti-inflammatory medications, including naproxen, diclofenac, ibuprofen, piroxicam, celecoxib, and valdecoxib). With any of these medications, benefit/risk considerations may vary according to clinical setting (eg, chronic versus acute pain) and according to patient characteristics such as baseline risk for gastrointestinal or cardiovascular adverse effects. Celecoxib and valdecoxib, both diaryl-substituted pyrazoles, are selective inhibitors of the inducible form of the enzyme cyclooxygenase (COX-2), which catalyzes the formation of prostaglandins that act as proinflammatory mediators. As a result of this selective COX-2 inhibitory activity, such medications are believed to provide effective analgesic and anti-inflammatory benefits with less risk of gastrointestinal adverse effects than has been associated with inhibition of both COX-1 and COX-2 using nonselective, non-steroidal anti-inflammatory drugs (NSAIDs). As well as providing effective pain relief, both nonselective NSAIDs and selective COX-2 inhibitors provide a degree of relief from inflammation, making their chronic use necessary for many arthritis sufferers, for whom intermittent use or use of purely analgesic agents like acetaminophen is inadequate. Hence, both nonselective NSAIDs and selective COX-2 inhibitors enjoy extremely widespread use both as prescription arthritis medications and, in the case of some nonselective NSAIDs, as over-the-counter pain relievers.

On 30 September 2004, the selective COX-2 inhibitor rofecoxib (VIOXX®, Merck) was voluntarily withdrawn from worldwide markets after the data safety monitoring board (DSMB) overseeing a long-term, placebo-controlled rofecoxib clinical trial in cancer prevention (the Adenomatous Polyp Prevention on VIOXX [APPROVe] trial; Section 2.4.2) recommended that the trial be suspended because interim data at 18 months indicated that patients treated with rofecoxib had a significantly increased risk of serious cardiovascular events, including myocardial infarction and stroke, compared to patients treated with placebo. On 17 December 2004, the DSMB for the long-term Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC) trial recommended that use of study medication in this trial should be suspended because interim data at 33 months indicated that patients treated with celecoxib had a significantly increased incidence of serious cardiovascular events, including myocardial infarction, stroke, and death compared to patients treated with placebo (Section 2.3.1). In response, the DSMB for another long-term celecoxib sporadic adenomatous polyposis (SAP) prevention trial, the Prevention of Colorectal Sporadic Adenomatous Polyps Trial (PreSAP), recommended suspension of that trial also. However, no increase in cardiovascular risk was observed comparing celecoxib treatment versus placebo treatment in the PreSAP trial at 33 months. Also suspended on 17 December 2004 in response to the finding of increased cardiovascular risk with celecoxib in the APC trial was treatment with study medication in the long-term Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT); however, no

significant difference in cardiovascular risk was observed comparing celecoxib treatment versus placebo treatment in this trial (Section 2.3.2). Rather, interim data at 18 months from the ADAPT trial demonstrated statistically significant increases in risk for myocardial infarction and stroke in patients treated with low-dose naproxen compared to patients treated with placebo.

As a result of the observations described above, significant concern has arisen regarding the cardiovascular safety of both selective COX-2 inhibitors and nonselective NSAIDs. Though the cardioprotective effect of aspirin is well-established in medical practice, this effect is attributable to a biochemical activity in platelets (irreversible acetylation of COX-1) that is not shared with other nonselective NSAIDs.[1] There is little evidence that other nonselective NSAIDs are cardioprotective, and cardiorenal effects including increased blood pressure in NSAID users are well known.[2-12] Moreover, in some settings the cardioprotective antiplatelet effect of COX-1 inhibition with aspirin can be offset by increased risk of cerebrovascular hemorrhage: the use of aspirin for primary cardiovascular prevention in low risk subjects is not recommended due to this increase in risk, as established in an Antiplatelet Trialists' Collaboration (APTC) overview of randomized trials in antiplatelet therapy, because for these subjects the benefit/risk balance is not favorable.[13] Conversely, in post-stroke patients, antiplatelet therapy has minor impact on risk of myocardial infarction (reduction of 2 events per 1000 patients) but a large benefit in reduction of risk for ischemic stroke (reduction of 25 events per 1000 patients).[14]

For the reasons described above, the APTC has recommended that cardiovascular and cerebrovascular risk should be evaluated using a composite endpoint that comprises a variety of serious clinical outcomes including myocardial infarction, stroke, pulmonary embolism, and intracerebral or extracerebral hemorrhage.[14] Thus, studies that use only myocardial infarction as the primary endpoint, as most epidemiology studies of nonselective NSAIDs and selective COX-2 inhibitors have done (Section 2.5.1.1), may characterize cardiovascular safety in a manner that is incomplete. However, because of the very large numbers of patients and cardiovascular events available for analysis, epidemiology studies can be powerful adjuncts to randomized clinical trials in evaluation of the safety of NSAIDs and COX-2 inhibitors. In this document we will review the available epidemiology and clinical trial data on NSAIDs in the medical literature and in comparison with celecoxib and valdecoxib. We conclude that not enough is currently known about the relative cardiovascular risks of selective COX-2 inhibitors versus nonselective NSAIDs to make fully informed benefit/risk decisions, because cardiovascular risks with nonselective NSAID use have never been adequately studied. Accordingly, at present the assumption that all nonselective NSAIDs are safer with respect to cardiovascular events than all selective COX-2 inhibitors is not supported by objective data: existing cardiovascular safety data fail to distinguish between nonselective NSAIDs and selective COX-2 inhibitors, with the exception of rofecoxib. .

This Briefing Document presents a critical evaluation of the cardiovascular safety of celecoxib and valdecoxib, including comparisons to placebo and, more importantly, to nonselective NSAIDs, the primary therapeutic alternative.

- It will be shown that where celecoxib and nonselective NSAIDs have been studied together in the same setting, including both epidemiology studies and extensive clinical trials up to 1 year in duration in patients with chronic conditions, celecoxib consistently demonstrates no increase in cardiovascular risk compared to nonselective NSAIDs.

Where possible, these comparisons are evaluated in terms of the entire spectrum of APTC cardiovascular events.

- While limited, preliminary safety data from long-term (>1 year) celecoxib prevention trials made available recently will also be presented. These data must be understood in the context of what little is known about the cardiovascular risks of nonselective NSAIDs in similar settings.

- Comparability between valdecoxib cardiovascular safety and that of nonselective NSAIDs will be demonstrated in data from clinical trials up to 1 year in duration. Cardiovascular safety with valdecoxib in the unique, high-risk setting of coronary artery bypass graft (CABG) surgery will be discussed.

- The cardiovascular safety of both celecoxib and valdecoxib will be contrasted with that of rofecoxib, which has shown significant cardiovascular risk in direct comparison to nonselective NSAIDs both in clinical trials and in epidemiology studies.

- The possibility is explored that differences in molecular structure and pharmacology between rofecoxib on the one hand and celecoxib or valdecoxib on the other may explain differences in cardiovascular risk that have been observed with these agents.

Separate executive summaries precede the various sections of this Briefing Document that present data from meta-analyses (celecoxib chronic conditions or valdecoxib chronic pain) or from integrated analysis (valdecoxib acute pain) of results from clinical trials; preliminary results of long-term prevention studies; and reviews of published clinical trials, of published epidemiology studies, and of mechanistic and clinical data regarding the possibility of a class effect for selective COX-2 inhibitors. In addition, separate summaries of overall cardiovascular safety results for celecoxib (Sections 2.7) and valdecoxib (Sections 3.6) follow the respective data presentations, and benefit/risk considerations are discussed at the end of the document (Section 6).

2. CELECOXIB CARDIOVASCULAR SAFETY

Data presented and reviewed in this evaluation of celecoxib cardiovascular safety include a new Pfizer meta-analysis of data from clinical trials of up to 1 year duration in patients with chronic conditions (Section 2.2); recently available results from long-term celecoxib prevention studies (Section 2.3), a review of prospective clinical trials (Section 2.4) and epidemiology studies (Section 2.5) published to date, and an analysis of celecoxib postmarketing safety data (Section 2.6).

2.1. Celecoxib Clinical Development Program

In December 1998, celecoxib was approved by the United States (US) Food and Drug Administration (FDA; NDA 20-998) to be marketed as CELEBREX® for relief of the signs and symptoms of osteoarthritis (OA) with a recommend dose of 100 to 200 mg TDD, and for relief of the signs and symptoms of rheumatoid arthritis (RA) in adults with a recommend dose of 200 to 400 mg daily (200 mg BID). In December 1999, celecoxib was approved for the symptomatic relief of OA and RA in Sweden, which acted as the Reference Member State for a Mutual Recognition procedure in the European Union (EU). Also in December 1999, the FDA approved an additional celecoxib indication at 800 mg TDD (400 mg BID) to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis as an adjunct to usual care (eg, endoscopic surveillance and/or surgery), and in October 2001 FDA approved CELEBREX for the management of acute pain in adults and treatment of primary dysmenorrhea at doses of 600 mg TDD day 1, followed by 400 mg TDD thereafter. In October 2004, Pfizer submitted to FDA a supplemental New Drug Application (NDA) in support of a CELEBREX indication for management of the signs and symptoms of ankylosing spondylitis (AS).

Celecoxib clinical programs have been conducted for the following indications: symptomatic relief of OA, RA, AS, and chronic low back pain (ie, studies in chronic pain indications); acute pain; primary dysmenorrhea; and reduction of intestinal polyps in patients with familial adenomatous polyposis FAP. Long-term SAP prevention (PreSAP) and Alzheimer's disease progression (ADAPT) trials have recently been suspended, while other investigational programs in cancer treatment and cancer prevention are currently ongoing. Patients in completed chronic pain studies, together with patients in a completed 1-year Alzheimer's disease study, constitute the clinical study population with the greatest celecoxib exposure to date for which comprehensive safety data are available. The acute pain and primary dysmenorrhea studies have included over 3000 patients treated with celecoxib in over 25 studies; few cardiovascular adverse events occurred in these short term studies, and events were balanced across treatment groups. The chronic pain and Alzheimer's disease studies therefore better represent a population with baseline risk for cardiovascular events compared to patients in the acute pain or primary dysmenorrhea studies. In these studies in chronic indications, patients have been treated with daily doses of celecoxib for treatment durations ranging from 2 weeks up to 1 year, at doses ranging from 25 mg BID up to 400 mg BID.

2.2. Meta-Analysis of Data From Studies in Chronic Indications: Summary

To evaluate the cardiovascular safety of celecoxib, 41 completed clinical studies, representing a total of >44,000 unique patients with chronic conditions, were identified for meta-analysis. Patients in the 41 completed studies selected for meta-analysis were treated with celecoxib at doses ranging from 40 to 800 mg TDD for durations ranging from 2 weeks to 12 months; all studies had randomized, parallel-group designs with placebo and/or active comparators (naproxen, diclofenac, ibuprofen, ketoprofen, acetaminophen, loxoprofen [a nonselective NSAID prodrug approved in some countries outside the US], or rofecoxib). Not included were open label studies, studies with treatment durations ≤2 weeks, studies that did not have completed study reports as of 31 October 2004, and studies by independent investigators or other sponsors. Results for all 41 studies that met criteria for meta-analysis either have been published in the medical literature or have been published or otherwise addressed as part of the Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database, available at www.clinicalstudyresults.org.

Endpoints selected for meta-analysis were composites of serious cardiovascular thromboembolic adverse events, myocardial thromboembolic events, cerebrovascular events, peripheral vascular events, and the individual adverse events myocardial infarction and stroke. Data were integrated across studies for summarization and comparison of cardiorenal adverse events categorized as follows: hypertension/hypertension aggravated; edema/edema generalized/edema peripheral; and cardiac failure/cardiac failure left/cardiac failure right.

The results of this meta-analysis of cardiovascular thromboembolic and cardiorenal adverse events support the following conclusions:

- The risk of serious cardiovascular thromboembolic events, myocardial thromboembolic events, myocardial infarction, cerebrovascular events, stroke, and peripheral vascular events in patients with chronic painful conditions treated with celecoxib (all patients, all events) is comparable to that observed in patients treated with placebo or nonselective NSAIDs (all nonselective NSAIDs combined, any dose).

- For the all-patients cohort, the overall incidence of myocardial infarction tended to be higher for celecoxib compared to combined nonselective NSAIDs (not statistically significant); this increase was offset by a significantly reduced risk of stroke. Analyses of patient subgroups for individual adverse events were not useful for the statistical evaluation of cardiovascular risk due to small numbers of events. Emphasis is therefore given to the all-patients cohort and to the composite endpoint of serious cardiovascular thromboembolic adverse events.

- As expected, percentages of patients with cardiorenal adverse events were greater among patients treated with celecoxib compared to patients treated with placebo. Percentages of patients with cardiorenal adverse events were smaller in patients treated with celecoxib (differences were statistically significant for hypertension and edema) compared to patients treated with nonselective NSAIDs.

2.2.1. Studies in Chronic Indications Included in Meta-Analysis

The criteria for selection of studies in chronic indications to be included in this meta-analysis were as follows:

- Randomized, parallel-group study design;
- At least one treatment group with celecoxib TDD ≥200 mg;
- At least one placebo, nonselective NSAID, or rofecoxib comparator group;
- Planned duration ≥2 weeks; and
- Study completed and study report finalized by a cutoff date of 31 October 2004.

A search of the Pfizer Corporate Clinical Trials Registry using these criteria identified 41 studies in chronic indications for meta-analysis (Table 1) in which a total of 44,308 unique patients were treated with celecoxib (24,933 patients), placebo (4057 patients), or active comparators (15,318 patients). In these 41 chronic pain studies, celecoxib doses ranged from 50 to 800 mg TDD, and doses of active comparator medications were consistent with the current standard of care for OA and RA (naproxen 1000 mg TDD, diclofenac 100 to 150 mg TDD, ibuprofen 2400 mg TDD, ketoprofen 200 mg TDD, acetaminophen 4000 mg TDD, loxoprofen 180 mg TDD, and rofecoxib 25 mg TDD). The predominant exposure to celecoxib was in the range of 200 to 400 mg TDD, and the predominant nonselective NSAID exposure was to diclofenac.

Nineteen of the 41 studies included in the meta-analysis were 3 months or longer in duration, and 3 studies were 1 year or longer in duration. For comparisons of celecoxib versus placebo, 76% of patient exposure to celecoxib was in studies with planned duration ≥3 months, and 22% of patient exposure to celecoxib was in studies with planned duration ≥1 year. For comparisons of celecoxib versus nonselective NSAIDs, 97% of patient exposure to celecoxib was in studies with planned duration ≥3 months, and 48% of patient exposure to celecoxib was in studies with planned duration ≥1 year.

Table 1. Celecoxib Studies in Chronic Indications Included in Meta-Analysis

(Page 1 of 2)

Indication Protocol ID	Duration of Treatment	Treatment Groups
Osteoarthritis and/or Rheumatoid Arthritis		
N49-96-02-012	4 weeks	Placebo, Celecoxib 40 mg BID, 200 mg BID, 400 mg BID
N49-96-02-013	2 weeks	Placebo, Celecoxib 40 mg BID, 100 mg BID, 200 mg BID
N49-96-02-020	12 weeks	Placebo, Celecoxib 50 mg BID, 100 mg BID, 200 mg BID, Naproxen 500 mg BID
N49-96-02-021	12 weeks	Placebo, Celecoxib 50 mg BID, 100 mg BID, 200 mg BID, Naproxen 500 mg BID
N49-96-02-022	12 weeks	Placebo, Celecoxib 100 mg BID, 200 mg BID, 400 mg BID, Naproxen 500 mg BID
N49-96-02-023	12 weeks	Placebo, Celecoxib 100 mg BID, 200 mg BID, 400 mg BID, Naproxen 500 mg BID
I49-96-02-041	24 weeks	Celecoxib 200 mg BID, Diclofenac SR 75 mg BID
I49-96-02-042	6 weeks	Celecoxib 100 mg BID, Diclofenac 50 mg BID
N49-96-02-047	4 weeks	Placebo, Celecoxib 25 mg BID, 100 mg BID, 400 mg BID
N49-96-02-054	12 weeks	Placebo, Celecoxib 50 mg BID, 100 mg BID, 200 mg BID, Naproxen 500 mg BID
N49-96-02-060	6 weeks	Placebo, Celecoxib 100 mg BID, 200 mg QD
N49-97-02-062	12 weeks	Celecoxib 200 mg BID, Naproxen 500 mg BID
N49-97-02-071	12 weeks	Celecoxib 200 mg BID, Diclofenac 75 mg BID, Ibuprofen 800 mg TID
N49-98-02-087	6 weeks	Placebo, Celecoxib 100 mg BID, 200 mg QD
I49-98-02-096 (the SUCCESS trial)	12 weeks	Celecoxib 100 mg BID, 200 mg BID, Diclofenac 50 mg BID, Naproxen 500 mg BID
N49-98-02-035/102 (the CLASS trial)	15 Months	Celecoxib 400 mg BID, Ibuprofen 800 mg TID, diclofenac 75 BID
I49-98-02-105	12 weeks	Celecoxib 100 mg BID, Diclofenac 50 mg BID
I49-98-02-106	12 weeks	Celecoxib 100 mg BID, Diclofenac 50 mg BID
I49-98-02-107	12 weeks	Celecoxib 100 mg BID, Diclofenac 50 mg BID
N49-98-02-118	6 weeks	Placebo, Celecoxib 100 mg BID, Diclofenac 50 mg TID
N49-99-02-149	6 weeks	Celecoxib 200 mg QD, Rofecoxib 25 mg QD
N49-99-02-152	6 weeks	Placebo, Celecoxib 200 mg QD, Rofecoxib 25 mg QD

N = Number of treated patients; QD = Once daily; BID = Twice daily; TID = Three times daily; TDD = Total daily dose.

Table 1. Celecoxib Studies in Chronic Indications Included in Meta-Analysis

(Page 2 of 2)

Indication Protocol ID	Duration of Treatment	Treatment Groups
Osteoarthritis and/or Rheumatoid Arthritis, continued		
N49-00-02-181	6 weeks	Celecoxib 200 mg QD, Rofecoxib 25 mg QD
J49-01-02-216	4 weeks	Placebo, Celecoxib 100 mg BID, Loxoprofen 60 mg TID
635-IFL-0508-002	12 weeks	Celecoxib 200 mg QD, Rofecoxib 25 mg QD, Naproxen 500 mg BID
635-IFL-0508-003	6 weeks	Placebo, Celecoxib 200 mg QD, Rofecoxib 25 mg QD
635-IFL-0508-010	6 weeks	Placebo, Celecoxib 200 mg QD, Acetaminophen 1000 QID
A3191006 (the CAESAR trial)	52 weeks	Celecoxib 200 mg QD, Diclofenac 50 mg BID
A3191051	6 weeks	Placebo, Celecoxib 200 mg QD, Naproxen 500 mg BID
A3191052	6 weeks	Placebo, Celecoxib 200 mg QD, Naproxen 500 mg BID
A3191053	6 weeks	Placebo, Celecoxib 200 mg QD, Naproxen 500 mg BID
A3191063	6 weeks	Placebo, Celecoxib 200 mg QD, Ibuprofen 800 mg TID
COXA –0508-249	4 weeks	Placebo, Celecoxib 200 mg QD, Acetaminophen 1000 mg QID
Ankylosing Spondylitis		
F49-98-02-137	6 weeks	Placebo, Celecoxib 100 mg BID, Ketoprofen 100 mg BID
N49-01-02-193	12 weeks	Placebo, Celecoxib 200 mg QD, 400 mg QD, Naproxen 500 mg BID
Chronic Low Back Pain		
J49-01-02-217	4 weeks	Celecoxib 100 mg BID, Loxoprofen 60 TID
COXA-0508-244	12 weeks	Placebo, Celecoxib 200 mg QD
COXA-0508-245	12 weeks	Placebo, Celecoxib 200 mg QD
COXA-0508-269	12 weeks	Placebo, Celecoxib 200 mg QD, 200 mg BID
Alzheimer's Disease		
IQ5-97-02-001	52 weeks	Placebo, Celecoxib 200 mg BID
EQ5-98-02-002	3 years[a]	Placebo, Celecoxib 200 mg BID

N = Number of treated patients; QD = Once daily; BID = Twice daily; TID = Three times daily; QID = Four times daily; TDD = Total daily dose.

[a] Terminated early when the results of Study IQ5-97-02-001 failed to show attenuation of the symptomatic progression of Alzheimer's disease

2.2.2. Methodology for Meta-Analysis

2.2.2.1. Categorization of Adverse Events

Overall risk of serious cardiovascular thromboembolic adverse events was evaluated using a composite endpoint, serious cardiovascular thromboembolic adverse events (Table 2), that though wider in scope, approximates as closely as possible the Antiplatelet Trialists Collaboration (APTC) composite endpoint of deaths from any cause plus cardiac events plus cerebrovascular events, a well-accepted endpoint that appropriately takes into account risk for a variety of serious cardiovascular adverse events.[13] However, serious cardiovascular thromboembolic adverse events were not adjudicated in any of these studies. In addition, cardiorenal adverse events were categorized for summarization and comparison across integrated treatment groups as follows: hypertension/hypertension aggravated; edema/edema generalized/edema peripheral; and cardiac failure/cardiac failure left/cardiac failure right.

Table 2. Definition of Serious Cardiovascular Thromboembolic Adverse Events Selected as Endpoints for Meta-Analysis

Cardiovascular Thromboembolic		
Myocardial Thromboembolic	**Cerebrovascular**	**Peripheral Vascular**
Angina pectoris aggravated	Cerebrovascular Accident	Embolism
Cardiac arrest	Cerebrovascular Disorder	Embolism Pulmonary
Circulatory Failure	Cerebral Hemorrhage	Peripheral Ischemia
Myocardial Infarction	**Stroke**	Thrombophlebitis Leg
Myocardial Ischemia	Transient Ischemic Attack	Deep Thrombophlebitis Leg
Myocardial Rupture (Post-Infarction)		
Tachycardia Ventricular		
Thrombosis Coronary		
Unstable Angina		

Event categories (headings) and adverse events indicated in **bold font** were selected as endpoints; **Stroke** comprised the individual adverse events cerebrovascular accident, cerebrovascular disorder, and cerebral hemorrhage.

2.2.2.2. Statistical Methods

For evaluation of cardiovascular risk associated with celecoxib treatment, the most important analyses are those comparing all patients in the celecoxib ≥200 mg TDD treatment group versus the placebo treatment group or the combined NSAIDs treatment group, since these comparisons involve celecoxib exposure at or above the celecoxib doses indicated for OA or RA, including the 400 mg BID dose indicated for FAP and similar doses used in the very large CLASS trial for GI safety. For all comparisons, the combined nonselective NSAIDs treatment group comprises patients treated with any dose of naproxen, diclofenac, ibuprofen, ketoprofen, or loxoprofen, but not patients treated with rofecoxib. For cardiovascular thromboembolic adverse events, the Cochran-Mantel-Haenszel test, stratified by study, was used to analyze differences in incidence rates (numbers of events per patient-year of treatment) between treatment groups. For cardiorenal adverse events, differences between treatment groups were analyzed using Fisher's exact test with no adjustments for multiple comparisons.

2.2.3. Results: Meta-Analysis of Studies in Chronic Indications

Baseline characteristics were generally balanced across integrated treatment groups (Table 3). Mean patient age ranged from 58 to 61 years across treatment groups, and women in each treatment group outnumbered men by approximately 2:1. A large majority of patients in each treatment group, ranging from 75% for placebo up to 95% for nonselective NSAIDs, were contributed by OA/RA studies. Use of aspirin for cardioprotection was also balanced across treatment groups (12 to 13% of patients). Baseline characteristics were also balanced across celecoxib dose groups; however, none of these studies were designed to evaluate cardiovascular risk, and randomization was not stratified for cardiovascular risk factors; as a result there were often imbalances in baseline risk factors and aspirin use in individual studies.

Altogether, this meta-analysis of data from completed clinical trials in chronic conditions represents a total of 44,308 unique patients treated for up to 1 year, including 7462 patients exposed to celecoxib ≥200 mg TDD for 1268 patient-years compared to 4057 patients treated with placebo for 585 patient-years, and 19,773 patients treated with celecoxib ≥200 mg TDD for 5651 patient-years compared to 13,990 patients treated with nonselective NSAIDs (all nonselective NSAIDs combined, any dose) for 4386 patient-years.

Table 3. Baseline Patient Characteristics, Studies in Chronic Indications

Category Characteristic	Treatment Group Placebo N = 4057	 Celecoxib (Any Dose) N = 24,933	 Combined NSAIDs N = 13,990
Age (years)			
Mean	58.3	60.8	60.0
≥ 65 years	1447 (35.7)	10,452 (41.9)	5357 (38.3)
≥ 75 years	424 (10.5)	3255 (13.1)	1582 (11.3)
Gender, n (%)			
Male	1450 (35.7)	7505 (30.1)	4201 (30.0)
Female	2607 (64.3)	17,428 (69.9)	9789 (70.0)
Indication			
OA/RA	3040 (74.9)	22915 (91.9)	13303 (95.1)
Chronic Low Back Pain	632 (15.6)	1333 (5.3)	440 (3.1)
Ankylosing Spondylitis	232 (5.7)	377 (1.5)	247 (1.8)
Alzheimer's Disease	153 (3.8)	308 (1.2)	0 (0.0)
Aspirin Use, n (%)	530 (13.1)	3167 (12.7)	1635 (11.7)

OA = osteoarthritis; RA = rheumatoid arthritis; NSAIDs = Non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, ibuprofen, ketoprofen, and loxoprofen (combined totals).

2.2.3.1. Serious Cardiovascular Thromboembolic Adverse Events

The relative risk for serious cardiovascular thromboembolic adverse events, comparing the celecoxib ≥200 mg TDD treatment group and the placebo treatment group, was not statistically significant for the all-patients cohort, for non-users of aspirin, or for aspirin users (Table 4). There also were no statistically significant differences between these treatment groups for any of the subcategories of adverse events or individual adverse events prespecified for analysis. For individual adverse events (myocardial infarction, stroke) comparisons between treatment groups

are based on very few events and are not useful for the statistical evaluation of cardiovascular risk.

When normalized for patient exposure to study medication in placebo-controlled studies, more serious cardiovascular thromboembolic adverse events occurred among aspirin users (5.4 events per 100 patient-years in the celecoxib ≥200 mg TDD treatment group and 3.3 events per 100 patient-years in the placebo treatment group) compared to non-users of aspirin (1.1 events per 100 patient-years in the celecoxib ≥200 mg TDD treatment group, 1.4 events per 100 patient-years in the placebo treatment group). This difference probably reflects differences in baseline cardiovascular risk for aspirin users versus non-users of aspirin.

Table 4. Serious Cardiovascular Thromboembolic Events, Studies in Chronic Indications: Celecoxib ≥200 mg Total Daily Dose Versus Placebo

	Celecoxib		Placebo			
Event Category or Adverse Event Population	n/N	Exposure (pt-years)	n/N	Exposure (pt-years)	Relative Risk (95%CI)	p-Value[a]
Any Cardiovascular Thromboembolic						
All Patients	23/7462	1268.3	10/4057	584.5	1.02 (0.49, 2.13)	0.957
Non-Users of Aspirin	11/6466	1047.0	7/3527	494.0	0.76 (0.30, 1.98)	0.580
Aspirin Users	12/996	221.3	3/530	90.8	1.46 (0.43, 5.01)	0.544
Any Myocardial Thromboembolic						
All Patients	13/7462	1268.3	3/4057	584.5	1.77 (0.53, 5.85)	0.350
Non-Users of Aspirin	5/6466	1047.0	2/3527	494.0	1.07 (0.20, 5.62)	0.933
Aspirin Users	8/996	221.3	1/530	90.8	2.92 (0.46, 18.39)	0.254
Myocardial Infarction						
All Patients	9/7462	1268.3	2/4057	584.5	1.65 (0.38, 7.21)	0.508
Non-Users of Aspirin	4/6466	1047.0	1/3527	494.0	1.64 (0.17, 15.33)	0.666
Aspirin Users	5/996	221.3	1/530	90.8	1.63 (0.21, 12.48)	0.640
Any Cerebrovascular						
All Patients	9/7462	1268.3	6/4057	584.5	0.71 (0.26, 1.97)	0.511
Non-Users of Aspirin	4/6466	1047.0	4/3527	494.0	0.54 (0.14, 2.08)	0.373
Aspirin Users	5/996	221.3	2/530	90.8	0.84 (0.15, 4.64)	0.842
Stroke						
All Patients	8/7462	1268.3	4/4057	584.5	0.96 (0.29, 3.17)	0.942
Non-Users of Aspirin	4/6466	1047.0	3/3527	494.0	0.72 (0.17, 3.07)	0.654
Aspirin Users	4/996	221.3	1/530	90.8	1.28 (0.14, 11.71)	0.830
Any Peripheral Vascular						
All Patients	2/7462	1268.3	1/4057	584.5	0.95 (0.08, 11.38)	0.966
Non-Users of Aspirin	2/6466	1047.0	1/3527	494.0	1.01 (0.09, 11.48)	0.996
Aspirin Users	0/996	221.3	0/530	90.8	NA	NA

N = Number of patients treated with study medication; n = number of patients with events; CI = Confidence interval; TDD = Total daily dose.

[a] Relative risks and p-values based on Cochran-Mantel-Haenszel test stratified by study; p-values ≤0.05 are indicated in **bold font**.

The relative risk for serious cardiovascular thromboembolic adverse events, comparing the celecoxib ≥200 mg TDD treatment group and the combined nonselective NSAIDs treatment group, was not statistically significant for the all patients cohort, for non-users of aspirin, or for aspirin users (Table 5). There also were no significant differences between these treatment

groups for adverse events in the myocardial thromboembolic and peripheral vascular subcategories, or for myocardial infarction; however, the risk of cerebrovascular events and of stroke was significantly reduced in the celecoxib ≥200 mg TDD treatment group compared to the combined nonselective NSAIDs treatment group.

When normalized for patient exposure to study medication in nonselective NSAID-controlled studies, more serious cardiovascular thromboembolic adverse events occurred among aspirin users (6.0 events per 100 patient-years in the celecoxib ≥200 mg TDD treatment group and 6.0 events per 100 patient-years in the combined nonselective NSAIDs treatment group) compared to non-users of aspirin (0.96 events per 100 patient-years in the celecoxib ≥200 mg TDD treatment group, 1.3 events per 100 patient-years in the combined nonselective NSAIDs treatment group). This difference likely reflects differences in baseline cardiovascular risk for aspirin users versus non-users of aspirin.

Table 5. Serious Cardiovascular Thromboembolic Events, Studies in Chronic Indications: Celecoxib ≥200 mg Total Daily Dose Versus Nonselective NSAIDs

	Celecoxib		Nonselective NSAIDs			
Event Category or Adverse Event Population	n/N	Exposure (pt-years)	n/N	Exposure (pt-years)	Relative Risk (95%CI)	p-Value[a]
Any Cardiovascular Thromboembolic						
All Patients	93/19773	5651.2	85/13990	4386.4	0.88 (0.65, 1.19)	0.403
Non-Users of Aspirin	47/17599	4888.9	47/12355	3750.9	0.81 (0.54, 1.23)	0.327
Aspirin Users	46/2174	762.7	38/1635	635.7	0.95 (0.61, 1.48)	0.827
Any Myocardial Thromboembolic						
All Patients	60/19773	5651.2	38/13990	4386.4	1.31 (0.86, 1.99)	0.213
Non-Users of Aspirin	24/17599	4888.9	17/12355	3750.9	1.16 (0.61, 2.20)	0.651
Aspirin Users	36/2174	762.7	21/1635	635.7	1.42 (0.81, 2.49)	0.219
Myocardial Infarction						
All Patients	42/19773	5651.2	22/13990	4386.4	1.58 (0.92, 2.72)	0.096
Non-Users of Aspirin	17/17599	4888.9	10/12355	3750.9	1.40 (0.61, 3.21)	0.429
Aspirin Users	25/2174	762.7	12/1635	635.7	1.75 (0.85, 3.62)	0.132
Any Cerebrovascular						
All Patients	14/19773	5651.2	29/13990	4386.4	0.35 (0.19, 0.67)	**0.001**
Non-Users of Aspirin	9/17599	4888.9	17/12355	3750.9	0.39 (0.17, 0.87)	**0.022**
Aspirin Users	5/2174	762.7	12/1635	635.7	0.30 (0.11, 0.85)	**0.023**
Stroke						
All Patients	11/19773	5651.2	27/13990	4386.4	0.31 (0.16, 0.61)	**0.001**
Non-Users of Aspirin	8/17599	4888.9	16/12355	3750.9	0.37 (0.16, 0.86)	**0.021**
Aspirin Users	3/2174	762.7	11/1635	635.7	0.22 (0.07, 0.71)	**0.011**
Any Peripheral Vascular						
All Patients	20/19973	5651.2	19/13990	4386.4	0.88 (0.47, 1.63)	0.679
Non-Users of Aspirin	15/17599	4888.9	13/12355	3750.9	1.02 (0.49, 2.12)	0.968
Aspirin Users	5/2174	762.7	6/1635	635.7	0.59 (0.19, 1.84)	0.362

N = Number of patients treated with study medication; n = number of patients with events; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, naproxen, diclofenac, ibuprofen, ketoprofen, and loxoprofen (combined totals); CI = Confidence interval; TDD = Total daily dose.

[a] Relative risks and p-values based on Cochran-Mantel-Haenszel test stratified by study; p-values ≤0.05 are indicated in **bold font**.

Additional analyses of cardiovascular thromboembolic events stratified according to celecoxib dose, comparison versus individual nonselective NSAIDs, age, and gender were not useful for the statistical evaluation of cardiovascular risk due to small numbers of events.

2.2.3.2. Cardiorenal Adverse Events

As expected, percentages of patients with cardiorenal adverse events in the hypertension/hypertension aggravated subcategory, the edema/edema generalized/edema peripheral subcategory, and the cardiac failure/cardiac failure left/cardiac failure right subcategory were significantly greater in the integrated celecoxib (any dose) treatment group compared to the integrated placebo treatment group (Table 6). This observation is consistent with published reports in the medical literature indicating that NSAIDs, including selective COX-2 inhibitors, can be associated with cardiorenal effects.[2-312]

Percentages of patients with adverse events in the hypertension/hypertension aggravated subcategory and the edema/edema generalized/edema peripheral subcategory were significantly greater in the combined nonselective NSAIDs treatment group compared to the celecoxib (any dose) treatment group. Additional analyses of cardiorenal events stratified according to celecoxib dose and comparison versus individual nonselective NSAIDs were not useful for the statistical evaluation of cardiovascular risk due to small numbers of events.

Table 6. Cardiorenal Adverse Events: Studies in Chronic Indications

(Number [%] of Patients)

Comparison Adverse Event Subcategory	Celecoxib	Comparator	p-Value[a]
Celecoxib (any dose) Versus Placebo, N[b]	**8405**	**4057**	
Hypertension/Hypertension Aggravated	91 (1.1)	27 (0.7)	**0.023**
Edema/Edema Generalized/Edema Peripheral	171 (2.0)	35 (0.9)	**<0.001**
Cardiac Failure/Cardiac Failure Left/Cardiac Failure Right	13 (0.2)	1 (<0.1)	**0.046**
Celecoxib (any dose) Versus NSAIDs, N[c]	**20463**	**13990**	
Hypertension/Hypertension Aggravated	317 (1.5)	280 (2.0)	**0.002**
Edema/Edema Generalized/Edema Peripheral	497 (2.4)	420 (3.0)	**0.001**
Cardiac Failure/Cardiac Failure Left/Cardiac Failure Right	26 (0.1)	30 (0.2)	0.056

N = Number of patients treated with study medication; n = number of patients with events;
NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, ibuprofen, ketoprofen, and loxoprofen (combined totals).

[a] P-values based on Fisher's exact test; p-values ≤0.05 are indicated in **bold font**; -- indicates p-value >0.20.

[b] Includes only data from studies with placebo comparators.

[c] Includes only data from studies with NSAID comparators.

2.2.3.3. Serious Cardiovascular Thromboembolic Adverse Events in Individual Celecoxib Clinical Trials

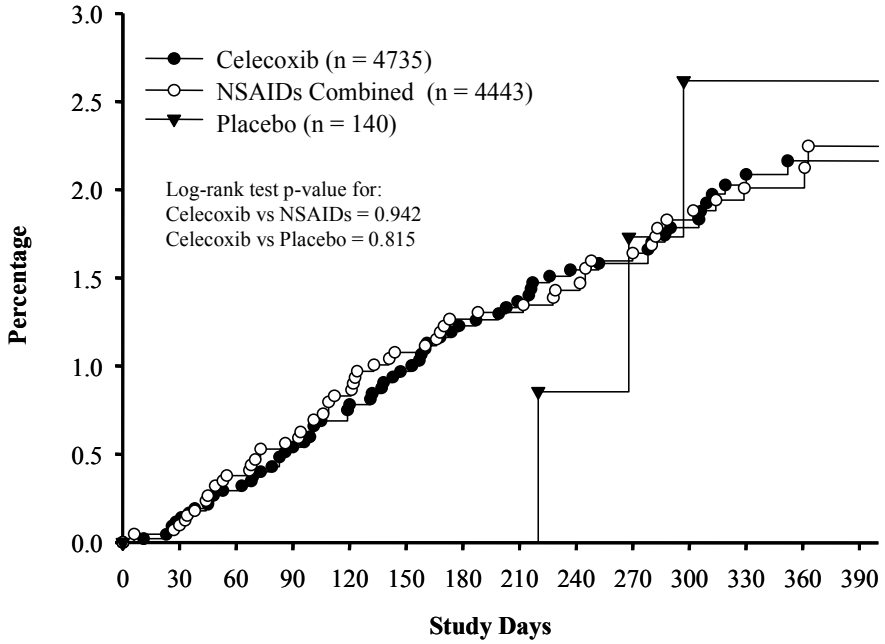
The lack of cardiovascular risk observed with celecoxib in the meta-analysis described above was driven by patients in 3 large studies: the Successive Celecoxib Efficacy and Safety Study (SUCCESS-1, Study I49-98-02-096), in which a total of 13,194 patients were treated with celecoxib, naproxen, or diclofenac for up to 12 weeks; the Celecoxib Long-Term Arthritis Safety Study (CLASS, Study N49-98-02-035/102), in which a total of 7968 patients were treated with

celecoxib, diclofenac, or ibuprofen for up to 15 months (median duration 9 months); and the CAESAR trial (Study A3191006); in which 918 patients with OA were treated with celecoxib or diclofenac for up to 1 year. These 3 studies represent 81% of the total patient exposure to celecoxib in comparison to NSAIDs for the meta-analysis described in Section 2.2.3, accounting for 82 of the 93 patients who had serious cardiovascular thromboembolic adverse events in the placebo treatment group and 70 of the 85 patients who had serious cardiovascular thromboembolic adverse events in the combined nonselective NSAIDs treatment group.

In addition to the trials with nonselective NSAID comparators described above, patients were treated with celecoxib or placebo for up to 12 months in Study IQ5-97-02-001 (425 patients with mild to moderate Alzheimer's disease). Serious cardiovascular thromboembolic adverse events in these 4 completed studies are presented below.

The 1-year studies described above also afforded sufficient time on treatment for a meaningful time-to-event analysis of serious cardiovascular adverse events (Figure 1). No statistically significant differences were observed comparing treatment with celecoxib versus treatment with nonselective NSAIDs ($p = 0.942$) or treatment with placebo ($p = 0.815$) in this analysis. It can also be observed that the hazard rate remained relatively constant throughout the year of observation, with no indication of divergence of the treatments up to one year, the extent of follow-up.

Figure 1. Kaplan-Meier Plot of Time to Serious Cardiovascular Thromboembolic Adverse Events in CLASS, CAESAR, and Alzheimer's Disease Study IQ5-97-02-001: Celecoxib (Any Dose) Versus Nonselective NSAIDs and Versus Placebo



Celecoxib doses were 400 mg BID in CLASS (Study N49-98-02-035/102), 200 mg QD in CAESAR (Study A3191006), and 200 mg BID in Alzheimer's Disease Study IQ5-97-02-001. Doses of nonselective NSAIDs were diclofenac 50 mg BID in CAESAR, diclofenac 75 mg BID and ibuprofen 800 mg TID in CLASS. Event rates are based on Kaplan-Meier estimates.

2.2.3.3.1. SUCCESS-1: Treatment With Celecoxib 100 mg or 200 mg Twice Daily for Up To 12 Weeks in Patients With Osteoarthritis or Rheumatoid Arthritis

In Study I49-98-02-096, first Successive Celecoxib Efficacy and Safety Study (SUCCESS-1), a total of 13,194 patients with OA or RA were treated with celecoxib 100 mg BID, celecoxib 200 mg BID, naproxen 500 mg BID, or diclofenac 50 mg BID for 12 weeks. The primary objective of the study was to compare the overall clinical tolerability and safety associated with treatment, and results showed that celecoxib was associated with a significantly lower incidence of adverse events in general and upper gastrointestinal events in particular compared to naproxen or diclofenac. Serious cardiovascular thromboembolic adverse events in the SUCCESS-1 trial were neither prespecified nor adjudicated at the time the study was performed, but have been adjudicated more recently as part of a published meta-analysis;[15] these adjudicated events were used for the meta-analysis described in Section 2.2.3.

The percentages of patients in the SUCCESS-1 trial with serious cardiovascular thromboembolic adverse events were similar across treatment groups (Table 7). A larger percentage of patients treated with celecoxib 100 mg BID had myocardial infarction compared to patients treated with celecoxib 200 mg BID or patients treated with naproxen or diclofenac (differences not statistically significant), although this comparison between treatment groups is of limited value for the evaluation of cardiovascular safety because the small numbers of events. Also, there was no relationship between increased celecoxib dose and increased incidence of myocardial infarction, and the observation of more myocardial infarctions with celecoxib compared to nonselective NSAIDs is inconsistent with results observed in other studies comparing celecoxib to diclofenac, including the 1-year CAESAR trial (described below), as well as to naproxen or diclofenac in the 1-year CLASS trial (described below) and in a number of 3-6 month studies submitted with the original celecoxib NDA.

Table 7. Serious Cardiovascular Thromboembolic Events: SUCCESS-1 (Study I49-98-02-096)

Number [%] of Patients

	Celecoxib 100 mg BID N = 4393 911 pt-yrs	Celecoxib 200 mg BID N = 4407 913 pt-yrs	Nonselective NSAIDs N = 4394 910 pt-yrs
Any Cardiovascular Thromboembolic	**11 (0.3)**	**14 (0.3)**	**11 (0.3)**
Any Myocardial Thromboembolic	**9 (0.2)**	**5 (0.1)**	**3 (<0.1)**
Myocardial Infarction	8 (0.2)	2 (<0.1)	1 (<0.1)
Any Cerebrovascular	**1 (<0.1)**	**7 (0.2)**	**6 (0.1)**
Stroke	1 (<0.1)	4 (0.1)	6 (0.1)
Any Peripheral Vascular	**1 (<0.1)**	**2 (<0.1)**	**2 (<0.1)**

Note: Pfizer has made 3 attempts to publish the results of SUCCESS-1: in September 2003 to the New England Journal of Medicine; in March 2004 to The Lancet; and in August 2004 to the British Journal of Medicine. The manuscript is currently being reformatted for submission to a fourth medical journal.
N = Number of patients; BID = Twice daily; TID = Three times daily.

2.2.3.3.2. CLASS: Treatment With Celecoxib 400 mg Twice Daily for Up To 15 Months in Patients With Osteoarthritis or Rheumatoid Arthritis

In the Celecoxib Long-Term Arthritis Safety Study (CLASS, Study N49-98-02-035/102),[17] 7968 patients with OA or RA were treated with celecoxib 400 mg BID (2 to 4 times the labeled dose for OA, twice the labeled dose for RA, and 4 times the 100 mg BID dose used in SUCCESS-1), diclofenac 75 mg BID, or ibuprofen 800 mg TID for up to 15 months (median duration 9 months). A total of 1783 of these 7968 patients used low-dose aspirin. Patient characteristics, including aspirin use (21% to 22% of patients), history of cardiovascular disease (40% of patients in all treatment groups), and cardiovascular risk factors, were balanced across treatment groups. The primary objective of the study was to compare the incidence of clinically significant upper gastrointestinal events across treatment groups, and results of the study showed lower incidence of such events for the celecoxib 400 mg BID treatment group compared to the nonselective NSAID treatment groups.

Serious cardiovascular thromboembolic adverse events in the CLASS trial were neither prespecified nor adjudicated at the time the study was performed, but have been adjudicated more recently as part of a published meta-analysis;[15] these adjudicated events were used for the meta-analysis described in Section 2.2.3. The percentages of patients in the CLASS trial with serious cardiovascular thromboembolic adverse events, which were neither prespecified nor adjudicated in this study, were similar across treatment groups (Table 8).

Table 8. Serious Cardiovascular Thromboembolic Adverse Events: CLASS (Study N49-98-02-035/102)

(Number [%] of Patients)

	Celecoxib 400 mg BID N = 3987 2320 pt-yrs	Nonselective NSAIDs N = 3981 2203 pt-yrs
Any Cardiovascular Thromboembolic	**48 (1.2)**	**46 (1.2)**
Any Myocardial Thromboembolic	**32 (0.8)**	**25 (0.6)**
Myocardial Infarction	19 (0.5)	13 (0.3)
Any Cerebrovascular	**4 (0.1)**	**12 (0.3)**
Stroke	4 (0.1)	11(0.3)
Any Peripheral Vascular	**13 (0.3)**	**10 (0.3)**

N = Number of patients; BID = Twice daily.

2.2.3.3.3. CAESAR: Treatment With Celecoxib 200 mg Once Daily for Up to 12 Months in Patients with Osteoarthritis

In the CAESAR trial (Study A3191006), patients ≥60 years of age with OA of the hip or knee were treated with celecoxib 200 mg QD (458 patients) or diclofenac 50 mg BID (458 patients) for up to 12 months, with the objective to compare withdrawals due to adverse events across treatment groups. Baseline patient characteristics were balanced across treatment groups, including history of hypertensive disease (40% for celecoxib and 45% for diclofenac) and of ischemic heart disease (9% for celecoxib and 10% for diclofenac). The rate of withdrawals due to adverse events during the course of the study was greater for the celecoxib 200 mg QD treatment group compared to the diclofenac 50 mg BID treatment group, but this difference was not statistically significant.

The percentages of patients in the CAESAR trial with serious cardiovascular thromboembolic adverse events, which were neither prespecified nor adjudicated, were similar across treatment groups with the exception of stroke, which occurred in a larger percentage of patients treated with diclofenac 50 mg BID compared to patients treated with celecoxib 200 mg QD (Table 9).

Table 9. Serious Cardiovascular Thromboembolic Adverse Events: CAESAR (Study A3191006)

(Number [%] of Patients)

Adverse Event Category Adverse Event	Celecoxib 200 mg QD N = 458 415 pt-yrs	Diclofenac 50 mg BID N = 458 432 pt-yrs
Any Cardiovascular Thromboembolic	**9 (2.0)**	**13 (2.8)**
Any Myocardial Thromboembolic	**5 (1.1)**	**6 (1.3)**
Myocardial Infarction	4 (0.9)	5 (1.1)
Any Cerebrovascular	**1 (0.2)**	**5 (1.1)**
Stroke	1 (0.2)	5 (1.1)
Any Peripheral Vascular	**3 (0.7)**	**2 (0.4)**

Note: Results of this study have been published or otherwise addressed as part of the Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database, available at www.clinicalstudyresults.org.
N = Number of patients; BID = Twice daily; QD = Once daily; pt-yrs = patient years.

2.2.3.3.4. Study IQ5-97-02-001: Treatment With Celecoxib for Up To 12 Months in Patients With Alzheimer's Disease

In Study IQ5-97-02-001, patients ≥50 years of age with mild to moderate Alzheimer's disease were treated with placebo (140 patients) or celecoxib 200 mg BID (285 patients) for up to 52 weeks, to assess whether treatment with celecoxib would limit or attenuate the progression of Alzheimer's disease and to evaluate the safety of celecoxib 200 mg BID in elderly patients suffering from mild to moderate Alzheimer's disease during 1 year of treatment. Results of the study showed that celecoxib did not significantly affect the symptomatic progression of Alzheimer's disease in this population.

Larger percentages of patients treated with celecoxib 200 mg BID had serious cardiovascular thromboembolic adverse events compared to patients treated with placebo in Study IQ5-97-02-001 (Table 10), although comparisons between treatment groups in this study are of limited value for the evaluation of cardiovascular safety because limited total exposure to the study medication, and small numbers of events. Moreover, interpretation of cardiovascular safety results are complicated by imbalances between treatment groups in baseline medical history (e.g., hypertension for 22% of patients treated with placebo versus 32% of patients treated with celecoxib 200 mg BID; previous aorto-coronary bypass surgery in 0.7% of patients treated with placebo versus 3.2% of patients treated with celecoxib 200 mg BID) and the complex medical condition of many of these patients. There were 17 deaths during the study, with an imbalance in deaths between treatment groups (4/140 patients treated with placebo, 2.9%; 13/285 patients treated with celecoxib, 4.6%). The deaths were attributed to causes not atypical of those expected in this patient population: for example, 5 pneumonia-related deaths out of 13 deaths total in the celecoxib treatment group. A review by an independent DSMB was conducted after all patients completed the Week 26 visit, and an interim analysis considered all adverse events in February 1999; celecoxib treatment was considered generally safe and well tolerated in the study population in both of these evaluations, the latter of which was published in

connection with the 6th International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy – 2000.

In the meta-analysis described in Section 2.2.3, Study IQ5-97-02-001 contributed 285 out of the 7444 patients from placebo-controlled studies in the celecoxib ≥200 mg TDD treatment group (250 patient-years of exposure), and accounted for 11 of the 23 patients in the celecoxib treatment group with serious cardiovascular thromboembolic adverse events. For comparison, the study contributed 140 of the 4057 patients in the placebo treatment group (120 patient-years of exposure) and accounted for 3 of the 10 patients in the celecoxib treatment group with serious cardiovascular thromboembolic adverse events.

Table 10. Serious Cardiovascular Thromboembolic Adverse Events: Alzheimer's Disease Study IQ5-97-02-001

(Number of Patients)

Adverse Event Category Adverse Event	Placebo N = 140 120 pt-yrs	Celecoxib 200 mg BID N = 285 250 pt-yrs
Any Cardiovascular Thromboembolic	**3 (2.1)**	**11 (3.8)**
Any Myocardial Thromboembolic	**0 (0.0)**	**4 (1.4)**
Myocardial Infarction	0 (0.0)	2 (0.7)
Any Cerebrovascular	**3 (2.1)**	**7 (2.5)**
Stroke	2 (1.4)	6 (2.1)
Any Peripheral Vascular	**0 (0.0)**	**1 (0.4)**

Note: Results of this study have been published or otherwise addressed as part of the Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database, available at www.clinicalstudyresults.org.
N = Number of patients; BID = Twice daily; pt-yrs = patient years.

2.3. Emerging Data From Long-Term Prevention Trials: Summary

In the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, 2600 patients were randomized to take rofecoxib 25 mg QD or placebo for 3 years with the objective to determine the cumulative incidence of recurrence of colon polyps. In an interim analysis after 18 months of treatment,[16] patients treated with rofecoxib 25 mg QD were shown to have a significant increase in the risk of serious cardiovascular thromboembolic adverse events (relative risk 1.96, 95% CI: 1.20 to 3.19 for rofecoxib over placebo for thrombotic events confirmed by adjudication, and relative risk 2.25, 95% CI: 1.24 to 4.08 for rofecoxib over placebo for the APTC composite endpoint; $p < 0.008$ for each).[19] Further, there was no significant difference in thromboembolic risk compared to the respective placebo group between patients who received rofecoxib and took aspirin for cardiovascular prophylaxis compared to patients who received rofecoxib without aspirin. This finding suggests that the increased risk observed with rofecoxib was not due to an imbalance brought about by selective inhibition of COX-2-mediated PGI_2 production without compensatory inhibition of COX-1-mediated TxA_2 production, but rather due to some other mechanism. The observation of increased cardiovascular risk with rofecoxib in the APPROVe trial prompted the DSMBs of very long-term celecoxib prevention studies (described below) to carefully re-assess cardiovascular safety in these studies, and in the case of the two colon cancer prevention trials, to commission an independent board to carefully adjudicate and analyze cardiovascular events.

In 2 spontaneous adenomatous polyposis (SAP) prevention trials and 1 Alzheimer's disease prevention trial, patients have been treated with celecoxib for up to 4 years at doses up to 400 mg BID, a dose well in excess of the celecoxib doses recommended for OA patients (100 to 200 mg TDD) and RA patients (200 to 400 mg TDD).

- For one of these SAP prevention trials, the Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC) trial, treatment with study medication was suspended before completion of the trial when a review of preliminary data by the DSMB identified a statistically significant increase in cardiovascular events for patients treated with celecoxib 200 mg BID or 400 mg BID compared to patients treated with placebo.

- No increase in cardiovascular risk for celecoxib versus placebo was observed in preliminary data for interim safety evaluations in the remaining 2 of these 3 long-term prevention trials. However, treatment with study medication was suspended in both of these remaining trials (the Prevention of Colorectal Sporadic Adenomatous Polyps trial, PreSAP, with celecoxib 400 mg QD; and the Alzheimer's Disease Anti-Inflammatory Prevention Trial, ADAPT, with celecoxib 200 mg BID) in response to the preliminary observation of increase in cardiovascular events with celecoxib observed in the APC trial.

- Efficacy analyses from both colon cancer prevention trials, the APC trial and the PreSAP trial, are forthcoming in early 2005, and, if the underlying hypothesis (35% or more reduction in recurrence of colon polyps) is validated, this could have a major impact on prevention of this fatal disease.

- In the ADAPT trial, preliminary results from an interim safety review indicate no increase in risk for gastrointestinal bleeding or for cardiovascular or cerebrovascular events in patients treated with celecoxib 200 mg BID compared to patients treated with placebo. However, significantly increased risks for gastrointestinal bleeding and for cardiovascular and cerebrovascular events were observed in patients treated with naproxen 220 mg BID compared to patients treated with placebo.

2.3.1. Sporadic Adenomatous Polyposis Prevention Trials: PreSAP and APC

In both the PreSAP trial (Protocol EQ4-00-02-018, sponsored by Pfizer) and the APC trial (Protocol IQ4-99-02-005, sponsored by the Division of Cancer Prevention at the National Cancer Institute [NCI] with the support of Pfizer [NCI Contract N01-CN-95014]), patients who had undergone colonoscopic resection of all evident polyps were randomized in double-blind fashion to receive celecoxib or placebo for 3 years. Repeat colonoscopic surveillance is performed at Year 1 and Year 3 after randomization with the intent of assessing the cumulative proportion of patients who are polyp free at 3 years. Both protocols were powered to be able to detect a 35% reduction in the recurrence of colon polyps on active treatment, and each was amended to add a 2-year extension to provide additional placebo-controlled information on the durability of adenoma prevention and the safety of celecoxib. These extensions allow patients who are adenoma-free at the completion of the initial 3-year treatment period to continue their current blinded treatment for an additional 2 years, at which time an end-of-study colonoscopy will be performed. Patients who are not eligible to continue on study drug into the 2-year extension, either because they have adenomas at Year 3 colonoscopy or because they refuse further therapy, will be offered an end-of-study colonoscopy 2 years after stopping study medication.

In the PreSAP trial as of October 2004, a total of 1561 patients had been randomized in a 2:3 ratio to either placebo or celecoxib 400 mg QD; in the APC trial, a total of 2035 patients have been randomized in a 1:1:1 ratio to celecoxib 200 mg BID, celecoxib 400 mg BID, or placebo. The initial 3-year treatment periods of both the PreSAP trial and the APC trial were due to be completed during 2005 (see Table 11 for disposition of PreSAP and APC patients as of early October 2004), after which Pfizer has proposed that 3-year efficacy and safety data should be analyzed for the purpose of publication and possible registration.

Table 11. Disposition of Patients in Celecoxib Long-Term Sporadic Adenomatous Polyposis Trials as of October 2004

	PreSAP[a]	APC[b]
First Patient Enrolled	March 2001	November 1999
Enrollment Complete	March 2002	March 2002
Number of Patients Randomized	1561	2035
Number of Patients Withdrawn During 3-Year Study	331	617
Number of Patients Completed Month 24 Visit	786	1687
Number of Patients Completed Month 36 Visit	325	1022
Number of Patients Enrolled in 2-Year Blinded Extension	242	246

[a] Prevention of Colorectal Sporadic Adenomatous Polyps trial (Study EQ4-00-02-018); enrollments were as of 1 October 2004.

[b] Prevention of Sporadic Colorectal Adenomas with Celecoxib trial (Study IQ4-99-02-005); enrollments were as of 5 October 2004.

Patient safety in both the PreSAP trial and the APC trial has been carefully monitored, and efficacy and safety data were reviewed twice yearly in both studies by independent data safety monitoring boards (DSMBs; reports of unblinded data are prepared for DSMBs by independent statisticians, in order to protect the integrity of the respective studies; only these independent statisticians and DSMB members have had access to unblinded data), paying particular attention to cardiovascular and gastrointestinal events (the DSMB for the APC trial also receives monthly reports of serious adverse events). At all interim reviews of safety and efficacy data prior to 16 December 2004, the respective DSMBs found no reason to stop either trial, and following the September 30th withdrawal of rofecoxib, each of the DSMBs restated that their safety reviews to date had identified no basis for altering the progress of these studies.

In response to the withdrawal of rofecoxib from the worldwide market, the NCI requested the formation of an expert Cardiovascular Safety Committee (CSC) to review cardiovascular safety data from the APC trial. At the request of Pfizer, this same CSC was asked to review also cardiovascular safety data from the PreSAP trial. Members of the CSC, all of whom were experienced in the evaluation of cardiovascular endpoints, reevaluated and adjudicated all potential cardiovascular events from both trials without knowledge of study treatment according to endpoint definitions established 3 December 2004. A statistician member of the CSC then analyzed these adjudicated events with respect to the frequency of occurrence in each treatment arm. On 16 December 2004, the CSC concluded the following based on preliminary evaluation of interim safety data (no data regarding patient medical history or baseline characteristics are currently available):

- At 33 months of treatment, the incidence rates for the APTC composite endpoint were 6/679 patients for placebo, 0.9%; 15/685 patients for celecoxib 200 mg BID, 2.2%; and 20/671 patients for celecoxib 400 mg BID, 3.0%. Patients in the celecoxib 200 mg BID treatment group had a relative risk of 2.5 (95% CI: 1.0 to 6.3) and patients in the celecoxib 400 mg BID treatment group had a relative risk of 3.4 (95% CI: 1.4 to 8.3) compared to placebo; both of these increases in risk were statistically significant.

- At 33 months of treatment, the incidence rates for the APTC composite endpoint in the PreSAP trial were 11/628 patients for placebo, 1.8%; and 16/933 patients for celecoxib 400 mg QD, 1.7 %. The relative risk was 1.0 (95% CI: 0.5 to 2.1) for celecoxib compared to placebo.

- In the opinion of the CSC, continued exposure to celecoxib placed patients in both trials at increased risk for serious adverse events compared to the as yet unproven benefit; as a result, the respective DMSBs recommended that treatment with study medication in both SAP prevention trials should be suspended.

Because treatment with study medication the APC trial and the PreSAP trial was suspended very recently (17 December 2004), only a preliminary DSMB report (ie, results for the interim cardiovascular safety reviews described above) is currently available; both studies remain ongoing for the purpose of collecting further efficacy and safety data. Pfizer and the NCI are currently working with the investigators and sponsors of the PreSAP and APC trials to make full study reports including comprehensive safety data available as quickly as possible after study completion, and also to make available when possible specific analyses requested by regulatory

authorities. However, Pfizer is not the sponsor of the APC trial and does not control access to either individual patient data or any reports summarizing results.

2.3.2. The Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT)

The ADAPT trial, sponsored by the National Institute of Aging (NIA) branch of the US National Institutes of Health and administered through the University of Washington and Johns Hopkins University, is a US, multicenter, double-blind, placebo-controlled trial of naproxen 220 mg BID or celecoxib 200 mg BID versus placebo to test the hypothesis that long-term use of a nonselective NSAID (naproxen) or selective COX-2 inhibitor (celecoxib) will reduce the incidence of Alzheimer's Disease (AD) in dementia-free, elderly subjects at risk for AD. As of 27 September 2004, the trial had been ongoing for 3.5 years, with a total of 2,450 subjects randomized (the enrollment target was 4500 subjects total). The majority of randomized subjects are between 70 and 74 years (56.2%), white (97%), and male (53.8%). In approximately 3900 patient-years of follow-up (including >1100 patient-years for patients treated with celecoxib), the rate of mortality in ADAPT has been low.

The ADAPT trial's safety monitoring group, the Treatment Effects Monitoring Committee (TEMC), has met twice yearly since the start of the trial to scrutinize closely all safety data, assess the risk/benefit ratio for subjects, and make recommendations regarding the conduct of the trial. At its most recent meeting (10 December 2004), the TEMC analyzed safety data collected up to a cutoff date of 1 October 2004, representing approximately 750 patients with exposure to celecoxib for >1.5 years, and found no reason to stop the ADAPT trial. However, on 17 December 2004, in response to the suspension of treatment with study medication in the PreSAP and APC trials, the executive board of the ADAPT trial suspended enrollment and treatment with study medication for ADAPT patients. The TEMC for the ADAPT trial has released top-line results of the safety analysis prepared for its 10 December 2004 meeting. These preliminary results indicate significantly increased risks for gastrointestinal bleeding and for cardiovascular and cerebrovascular events in patients treated with low dose naproxen compared to patients treated with placebo at 18 months, but no increase in risk for these events in patients treated with celecoxib compared to patients treated with placebo (no data regarding patient medical history or baseline characteristics are currently available). Conclusions from this report are only preliminary, based upon only very limited information available concerning the study population, its risk factors, and any methods used to adjudicate or determine events. The sponsors of the ADAPT trial are currently working to prepare a complete report for publication.

2.4. Cardiovascular Thromboembolic Events in Prospective Clinical Studies in the Medical Literature: Summary

Reviewed below are publications concerning the cardiovascular safety of celecoxib, rofecoxib, and nonselective NSAIDs as derived from either individual randomized clinical trials or meta-analyses of randomized clinical trials.

- Published data from prospective clinical trials, including a meta-analysis of data from 15 clinical trials representing approximately 30,000 patients, show no cardiovascular safety signal for celecoxib comparable to that observed in the Vioxx Intestinal Outcomes Research Trial (VIGOR) and the APPROVe trial for rofecoxib.

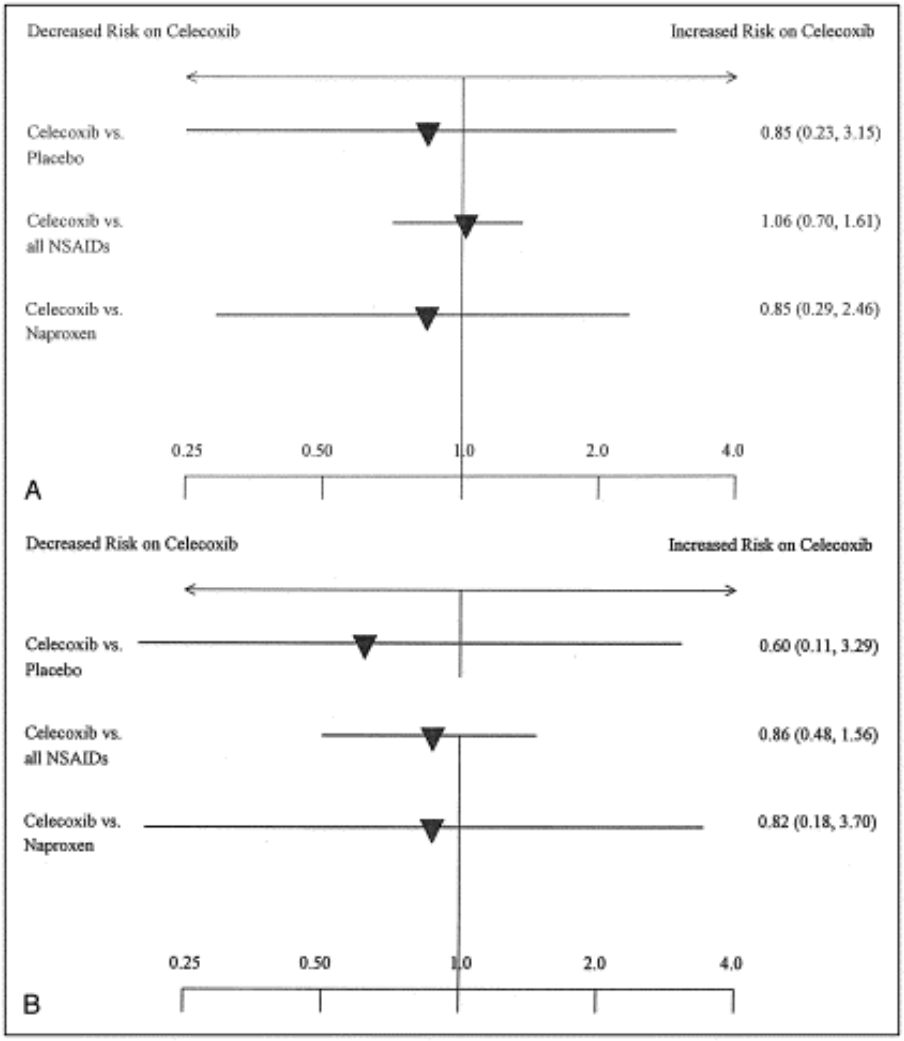
- Nonselective NSAIDs generally have not been studied in such settings, but even aspirin 325 mg QD has shown trends towards increased cardiovascular risk compared to placebo in a recent study similar in design to the APPROVe and APC trials, raising questions about the suitability of such trials for the evaluation of cardiovascular safety (Section 2.4.3).

2.4.1. Published Clinical Studies with Celecoxib

In a previous evaluation of cardiovascular safety data from arthritis clinical trials, for which independent external investigators were given complete access to the entire celecoxib clinical trials database for the purpose of adjudicating cardiovascular adverse events, data from 15 randomized clinical trials in which patients were treated with celecoxib at doses ranging from 25 mg BID up to 400 mg BID, for durations from 4 weeks up to 1 year, were integrated for analysis. Among these 15 studies, which together represent approximately 30,000 patients total and nearly 19,000 patients treated with celecoxib (for a total celecoxib exposure of 5668 patient-years), were SUCCESS-1 (Section 2.2.3.3.1) and CLASS (Section 2.2.3.3.2). The results of the analysis indicate that treatment with celecoxib did not increase the risk of thromboembolic events (APTC composite endpoint) compared to either placebo or nonselective NSAIDs (Figure 2); there also was no significant increase in risk of thromboembolic events with celecoxib when data were stratified for aspirin use versus no aspirin use or for individual NSAID comparators.[15] These results, which reflect an independent compilation, blinded adjudication, and analysis of all serious cardiovascular events in these 15 clinical trials, are similar to those observed in the more recent Pfizer meta-analysis of data from studies in chronic indications presented in Section 2.2.3.

Aside from the publication described above, no other evaluation of integrated cardiovascular safety data from multiple celecoxib clinical trials has been published. Published reports of individual clinical studies in chronic indications generally report similar efficacy for celecoxib relative to nonselective NSAID comparators and superior efficacy relative to placebo, with no cardiovascular safety signals. Cardiovascular safety results from individual celecoxib studies of particular interest, including the published CLASS trial,[17] are summarized in Section 2.2.3.3.

Figure 2. APTC Composite Endpoint for Celecoxib Versus Comparators In Arthritis Studies: Pooled Data From Completed Clinical Trials. (A) All Patients; (B) Non-Aspirin Users.



APTC = Antiplatelet Trialists Collaboration; Endpoint = deaths any cause plus cardiac events plus cerebrovascular events; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs. Triangles indicate point estimates of relative risk; bars indicate 95% confidence intervals. Data from White et al.15

2.4.2. Published Clinical Studies With Rofecoxib and Lumiracoxib

A recent meta-analysis of clinical trials data representing over 28,000 patients treated for up to one year showed no statistically significant differences in risk of cardiovascular thrombotic events when rofecoxib was compared to placebo (relative risk 0.84, 95% CI: 0.51 to 1.38), although this risk was greater for patients treated with rofecoxib compared to patients treated with naproxen (relative risk 1.69, 95% CI: 1.07 to 2.69).[18]

In the VIGOR trial, which compared rofecoxib 50 mg QD to naproxen 500 mg BID in 8076 patients with OA or RA for a mean duration of 8 months (range 6-13 months),[19] more patients treated with rofecoxib had serious cardiovascular thrombotic adverse events compared to patients treated with naproxen (65/4047 rofecoxib patients versus 33/4029 naproxen patients; relative risk 2.38, 95% CI: 1.39 to 4.00 for rofecoxib compared to naproxen, p <0.001).[20] Among the 321 VIGOR patients who entered the study with the highest cardiovascular risk (ie, medical history of stroke, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions) 8 out of 170 patients receiving rofecoxib suffered myocardial infarctions during the study, compared to none of the 151 patients receiving naproxen. Although the use of aspirin for cardiovascular prophylaxis would normally be indicated in such patients, aspirin use was not permitted in the VIGOR trial.

In contrast to the result described above for rofecoxib, a prospective clinical study of 18,325 OA patients ≥50 years of age showed that treatment for 18 months with the selective COX-2 inhibitor lumiracoxib 400 mg QD had no significant increase in risk for the APTC composite endpoint (59 events in 9117 treated patients, 0.65%) compared to patients treated with naproxen 500 mg BID (27 events in 4730 treated patients, 0.57%; hazard ratio 1.46, 95% CI: 0.89 to 2.37) or patients treated with ibuprofen 800 mg TID (23 events in 4397 treated patients, 0.52%; hazard ratio 0.76, 95% CI: 0.41 to 1.40), although incidence rates in this trial were very low.[21]

Short-term prospective clinical studies have shown that rofecoxib is associated with significantly increased blood pressure compared to nonselective NSAIDS[100,22] or to celecoxib.[98,99,100] Moreover, in the VIGOR trial, hypertension adverse events occurred in a greater percentage of patients treated with rofecoxib 50 mg QD compared to patients treated with naproxen 500 mg BID,[20] and in a recent 1 year trial in patients with mild to moderate Alzheimer's disease, patients treated with naproxen 220 mg BID or rofecoxib 25 mg QD had significantly greater risk of new onset hypertension compared to patients treated with placebo.[23]

2.4.3. Published Clinical Studies With Nonselective NSAIDs

Current understanding of the cardiovascular safety of nonselective NSAIDs is based primarily on epidemiology studies (Section 2.5); there are no publications of prospective clinical trials that report evaluation of nonselective NSAID safety in terms of cardiovascular thromboembolic adverse events comprising the APTC endpoint. Recent results from the ADAPT trial (see Section 2.3.2) indicate significantly increased risk for cardiovascular and cerebrovascular events in patients treated with naproxen compared to patients treated with placebo. Meta-analyses of interventional clinical trials have shown that nonselective NSAIDs can have lasting effects on blood pressure; these analyses suggest that indomethacin, naproxen, and piroxicam produce the largest increases in blood pressure on average, and that the effect of raising blood pressure is confined primarily to patients being treated for hypertension.[2,3] This blood pressure-destabilizing effect is most prominent in patients using (ACE inhibitors, beta-blockers, and/or diuretics (but not calcium channel blockers) to control hypertension.[4]

Finally, although generally shown to be cardioprotective in other large, long-term, placebo-controlled settings, aspirin 325 mg QD was recently associated with a trend toward increased

risk of cardiovascular events including myocardial infarction and stroke compared to placebo in a long-term SAP prevention study similar in design to the APPROVe, PreSAP, and APC trials.[24] In this 3-year study, 14 APTC-type events (5 myocardial infarctions, 5 strokes, 4 deaths) occurred amongst 372 patients treated with aspirin 325 mg QD, versus 4 events (1 myocardial infarction, no strokes, 3 deaths) amongst 372 patients treated with placebo. An aspirin 81 mg QD treatment group had an intermediate number of events (7 events: 2 myocardial infarctions, 2 strokes, 3 deaths) amongst 377 treated patients.

2.5. Epidemiology Studies of Celecoxib, Rofecoxib, and Nonselective NSAIDs: Summary

Other than randomized clinical trials and postmarketing surveillance, epidemiology studies represent the major source of cardiovascular safety data regarding nonselective NSAIDs and selective COX-2 inhibitors. Most of these studies have evaluated cardiovascular safety exclusively in terms of myocardial infarction, rather than more inclusive endpoints that represent the full spectrum of cardiovascular thromboembolic events.

- In 5 published epidemiology studies involving more than 80,000 elderly patients exposed to celecoxib, the risk of myocardial infarction among users of celecoxib was similar to the risk observed among users of nonselective NSAIDs and among non-users of NSAIDs. Moreover, the limited data available suggest that the risk of myocardial infarction is similar for low (≤200 mg/day) and high (>200 mg/day) celecoxib doses, and there is no suggestion of increased risk with increasing duration of use.

- Evidence from pooled epidemiological data suggests no overall effect on risk of myocardial infarction using combined data for nonselective NSAIDs. Depending on the specific nonselective NSAID studied and the setting, however, relative risks for MI compared to non-users of NSAIDs ranging from 0.21 to 1.7 have been reported in individual epidemiological studies.

- Rofecoxib users generally had increased risk of myocardial infarction compared to users of celecoxib or nonselective NSAIDs and to non-users of NSAIDs. Risk generally increased with increasing rofecoxib dose and duration of use.

- A possible association between use of nonselective NSAIDs and the risk of hypertension has also been observed in epidemiological studies; this association appears to be dose-dependent and higher during the first month of use. In the single study published to date, the risk of new onset hypertension associated with celecoxib is similar to that associated with nonselective NSAIDs, and lower than that associated with rofecoxib.

- A single study has assessed risk of hospital admission for congestive heart failure in new users of rofecoxib, celecoxib, or nonselective NSAIDs compared to non-users of NSAIDs; no increase in risk was observed for celecoxib. A higher risk was observed for users of rofecoxib and users of nonselective NSAIDs; no increase in risk was observed for users of celecoxib.

2.5.1. Background: Nonselective NSAIDs and Cardiovascular Risks

2.5.1.1. Nonselective NSAIDs and Cardiovascular Thromboembolic Events

In a recent systematic review[25] of 10 observational studies published from 2000 to 2004 evaluating the risk of myocardial infarction, [26-35] the pooled relative risk associated with use of NSAIDs (all nonselective NSAIDs combined) compared to non-use was 1.04 (95% CI: 1.00 to 1.07). For naproxen the relative risk was 0.88 (95% CI: 0.80 to 0.95), and for

ibuprofen the relative risk was 1.03 (95% CI: 0.96 to 1.11). Because 4 of these 10 studies evaluated the risk of myocardial infarction associated with diclofenac using a single source population, no pooled estimate for diclofenac was calculated; however, in the epidemiologic literature, relative risks have ranged in these studies from 1.2 to 1.7 for diclofenac users compared to non-users of NSAIDs.[30,32-34] Within these 10 observational studies, naproxen consistently had lower relative risk estimates for myocardial infarction compared to non-users of NSAIDs than did other individual NSAID medications.

In general, results were similar across studies for fatal and nonfatal myocardial infarction, as well as for various durations and doses of NSAID treatment. Within individual studies, results did not vary by duration of use, recent use, daily dose, or NSAID half-lives.[30,32-35] However, duration of use was evaluated in few studies,[30,31,34,35] and mainly for the overall drug class rather than for individual nonselective NSAIDs.[30,34,35] Little is known about the effects of long-term exposure to NSAIDs at high doses, although in one study, exposure to ibuprofen at high doses for longer than 60 days was associated with a statistically significant 33% increased risk of serious coronary heart disease compared to non-users of NSAIDs.[35] Results also did not vary by indication among studies that provided such an analysis; regarding a potential effect modification in arthritis patients, only one study restricted the source population to subjects with rheumatoid arthritis,[32] while another[30] found similar results in subjects with rheumatoid arthritis compared to subjects without.

Results from the systematic review of epidemiological studies described above indicate that the lower risk of myocardial infarction in users of naproxen compared to non-users of NSAIDs was more evident among subjects who did not use low-dose aspirin (relative risk 0.92 for aspirin users, 95% CI: 0.83 to 1.03; relative risk 0.79 for non-users of aspirin, 95% CI: 0.68 to 0.91) or subjects without prior history of cardiovascular disease.[25] For ibuprofen, the pooled relative risk of myocardial infarction compared to non-users of NSAIDs was 1.11 (95% CI: 1.02 to 1.21) for studies that allowed aspirin users and 0.88 (95% CI: 0.78 to 1.01) for studies that excluded aspirin users. While these results are consistent with observations from another published epidemiological study[36] and from a prospective clinical trial,[37] the same results have not been observed in other epidemiological studies.[30,38]

Little is known about the overall risk of thrombotic events other than myocardial infarction in users of NSAIDs. For cerebrovascular events, 2 case-control studies have been published, one of which evaluated the risk of intracerebral hemorrhage and found no increase in risk for nonselective NSAIDs.[39] The other study evaluated the risk of both hemorrhagic and ischemic events and found the risk of ischemic stroke to be 20% higher (a statistically significant difference) in users of nonselective NSAIDs compared to non-users.[40] In addition, a case-control study that evaluated data from patients with rheumatoid arthritis found no association between use of naproxen and the risk of thrombotic events, with cases defined as a composite of myocardial infarction, sudden death, and cerebrovascular events.[32]

Collectively, these studies indicate NSAID effects ranging from mildly favorable (naproxen and myocardial infarction) to moderately unfavorable. Individual studies vary as a result of the use of various methods, study populations, and to some degree the particular NSAID(s) chosen for study.

2.5.1.2. Nonselective NSAIDs and Cardiorenal Events

Several observational studies of various designs in various populations suggest that treatment with NSAIDs in susceptible patients might trigger the occurrence of heart failure.[9-12] The risk of heart failure overall was moderate in these studies, and was greater during the first month of therapy and independent of treatment indication.[9,11] No dose relationship was observed in two of these studies;[9,12] in a third study, a dose effect was observed, but only among patients with prior heart disease.[10] In all 3 of these studies, the risk was greater in patients with history of hypertension, diabetes, renal failure, or heart disease. Based on a single study, the risk of recurrent heart failure was estimated to be 10 times higher for current NSAID users compared to non-users.[11] Only one study presented data for individual NSAIDs;[12] the relative risk of incident heart failure in this study ranged from 1.1 for diclofenac to 3.4 for indomethacin use as compared to non-use. The attributable risk of heart failure in this study was calculated to be 2-3 cases per 1,000 NSAID users per year for all subjects and 6-7 cases per 1,000 NSAID users in the elderly.

Two epidemiology studies have found an association between use of NSAIDs and the risk of hypertension:

- One study evaluated 9411 cases of initiation of antihypertensive medications and 9629 control cases among elderly Medicaid beneficiaries; the adjusted odds ratio associated with current or recent use of NSAIDs in this study was 1.66 (95% CI: 1.54 to 1.80) compared with non-use.[7] The odds for initiation of antihypertensive medication increasing with increased average daily NSAID dose (low dose: odds ratio 1.55; 95% CI: 1.38 to 1.74; high dose: odds ratio 1.82; 95% CI: 1.62 to 2.05). The increase in risk of hypertension was greater for patients with duration of NSAID use between 30 and 90 days (odds ration 1.90; 95% CI: 1.65 to 2.18) than for patients with either shorter or longer durations of use.

- The Nurses Health Cohort Study evaluated the incidence of hypertension among 51,630 women aged 44 to 69 years, with analgesic use assessed using a mailed questionnaire.[8] During 381,078 person-years of follow-up in this study, 10,579 incident cases of hypertension were identified. Compared with non-users, women who used NSAIDs 5 or more days per month had a relative risk of 1.35 (95% CI: 1.25 to 1.46). There was a significant trend toward an increased risk of hypertension with increasing frequency of NSAID use that reached a plateau after 21 days of use.

Most epidemiological studies evaluating the association between NSAIDs and acute renal failure have found an increased risk of developing acute renal failure in patients taking NSAIDs.[41-47] Generally, risk was greater in the first month of NSAID use in these studies; a strong dose-effect relationship was reported in two studies,[45,47] and a weak dose effect was found in a third.[46] More recently, a case-control analysis nested in a cohort of 386,916 United Kingdom patients aged 50-84 years has shown the relative risk of hospitalization for acute renal failure with NSAID use to be 3.2 (95% CI: 1.8 to 5.8) compared to non-use; this risk declined once treatment was discontinued.[48] The increased risk was present with both short- and long-term therapy and was slightly greater among users of NSAIDs at high doses. History of heart failure, hypertension, diabetes, hospitalizations and consultant visits in the previous year all were associated with a greater risk of acute renal failure, and there was a suggestion of a modification of the effect of

NSAIDs in patients with preexisting hypertension or heart failure. Use of selected cardiovascular drugs was associated with a 5-fold increase in the risk for acute renal failure.

2.5.2. Celecoxib and Cardiovascular Risk

2.5.2.1. Cardiovascular Thromboembolic Events in Epidemiology Studies

A total of 5 formal epidemiology studies have been published as of 15 December 2004 that evaluate the risk of coronary heart disease in users of selective COX-2 inhibitors, including rofecoxib and celecoxib. Together, these 5 epidemiological studies represent >64,000 rofecoxib users and >80,000 celecoxib users, compared with almost 2 million users of nonselective NSAIDs including >1 million ibuprofen users and >500,000 naproxen users. These studies also represent many hundreds of events, compared to the small numbers of events (tens) that have accrued in even the largest, longest-term randomized clinical trials or in meta-analyses of multiple randomized clinical trials. Two of the studies were conducted specifically in elderly populations (≥65 years of age), and in the other 3 studies the mean age of participants was over 65 years. All of the studies included a high proportion of subjects with prior cardiovascular disease, diabetes, hypertension and use of cardiovascular drugs; only one study was conducted in people without prior history of myocardial infarction. In all of these studies, users of selective COX-2 inhibitors had a higher cardiovascular risk profile at baseline than users or non-users of nonselective NSAIDs, suggesting high-risk subjects are preferentially prescribed selective COX-2 inhibitors relative to nonselective NSAIDs. Descriptions of individual studies are as follows:

- In a US FDA-funded, nested case-control study of 1.4 million Kaiser Permanente beneficiaries (US, mean age 67 years) who were treated with celecoxib (40,405 subjects), rofecoxib (26,748 subjects), or nonselective NSAIDs, there was **no increase in the risk of acute myocardial infarction or sudden cardiac death in subjects treated with celecoxib** (relative risk 0.86, 95% CI: 0.62 to 1.07) compared to control subjects who had not used anti-inflammatory medications for the previous 60 days. In contrast, **rofecoxib >25 mg/day was associated with a 3-fold increase in risk compared to controls** (relative risk 3.15, 95% CI: 1.14 to 8.75), and the relative risk of rofecoxib ≤25 mg/day compared to controls was 1.29 (95% CI: 0.93 to 1.79). Comparison of relative risks in this study showed that treatment with rofecoxib ≤25 mg/day increased the risk of acute myocardial infarction or sudden cardiac death significantly compared to celecoxib (relative risk 1.50, 95% CI: 1.02 to 2.21). Risk was also increased relative to control subjects (remote use of anti-inflammatory medications) for users of naproxen (relative risk 1.18, 95% CI: 1.04 to 1.35), diclofenac (relative risk 1.69, 95 CI: 0.97 to 2.93), and indomethacin (relative risk 1.33, 95% CI 1.09 to 1.63). A survey of subjects in this study showed use of aspirin was similar regardless of selective COX-2 inhibitor or nonselective NSAID use.[26]

- In a matched case-control study of 54,475 subjects ≥65 years of age who were Medicare beneficiaries in 2 US states, current use of **celecoxib (odds ratio 0.93, 95% CI: 0.84 to 1.02) was not associated with an increased relative risk** of hospitalization for acute myocardial infarction compared to control subjects not treated with nonselective NSAIDs, and **rofecoxib was associated with an elevated relative risk of myocardial**

infarction compared to celecoxib (odds ratio 1.24, 95% CI: 1.05 to 1.46) or to controls (odds ratio 1.14, 95% CI: 1.00 to 1.31). The relative risk of acute myocardial infarction was also significantly elevated for rofecoxib subjects compared to celecoxib subjects at low rofecoxib doses (≤25 mg/day) versus low celecoxib doses (≤200 mg/day), at high rofecoxib doses (>25 mg/day) versus high celecoxib doses (>200 mg/day), and when evaluated for subgroups of subjects who took the respective medications for 1 to 30 days, 31 to 90 days, or >90 days. The baseline cardiovascular risk profiles for rofecoxib and celecoxib users in this study were similar, but both showed greater risk compared to users of nonselective NSAIDs; a survey of subjects showed use of aspirin was similar regardless of selective COX-2 inhibitor or nonselective NSAID use.[49]

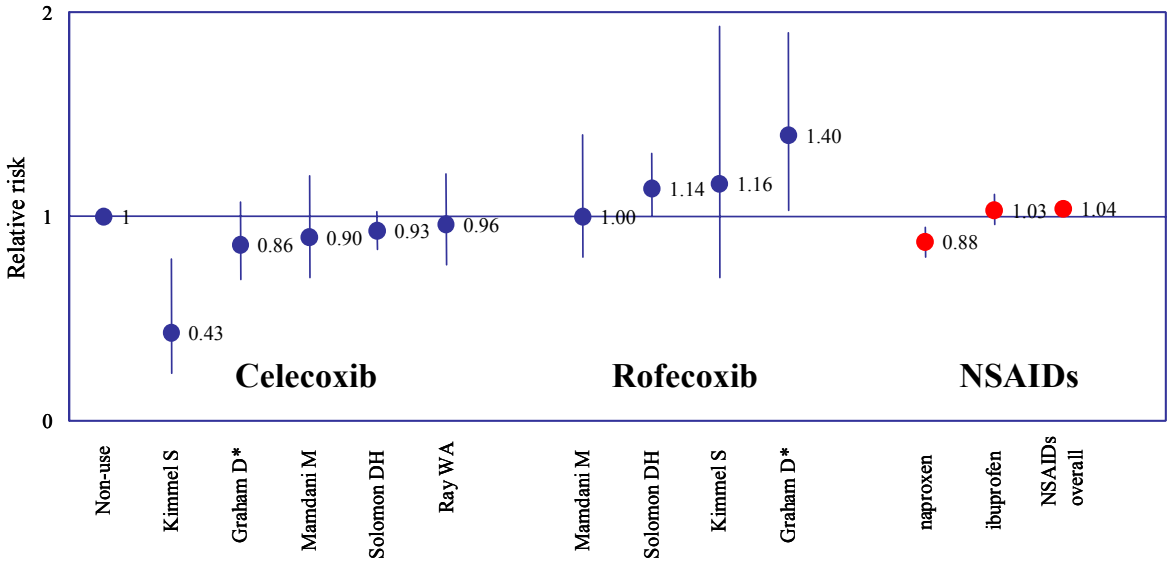
- A field case-control study (1718 cases and 6800 controls) that evaluated the association between use of selective COX-2 inhibitors and risk of nonfatal myocardial infarction, compared to non-users of NSAIDs, found no significant increase in risk overall in patients treated with selective COX-2 inhibitors; however, although possible bias, confounding, and non-participation my limit interpretation of results for this study, **celecoxib (odds ratio 0.43; 95% CI: 0.23 to 0.79) and rofecoxib (odds ratio 1.16; 95% CI 0.70 to 1.93) had different effects** compared to non-users of NSAIDs.[50]

- In a retrospective cohort study using data from the expanded Tennessee Medicaid program, subjects 50-84 years of age who were either new or current users of NSAIDs including naproxen (70,384 subjects), rofecoxib at doses ≤25 mg/day (20,245 subjects) and **celecoxib at any dose (22,337 subjects) showed similar risk of hospitalization acute myocardial infarction or death from coronary heart disease, with no significant increases in risk** (202,916 subjects; relative risks compared to non-users ranging from 0.88 to 1.03; p >0.19 for all comparisons) relative to non-users of NSAIDs. However, users of rofecoxib at doses >25 mg/day (3887 subjects) had an increased risk (not statistically significant) compared to non-users of NSAIDs (relative risk 1.70, 95% CI: 0.98 to 2.95). **New users of rofecoxib at doses >25 mg/day were at significantly greater risk of myocardial infarction compared to non-users of NSAIDs (relative risk 1.93, 95% CI: 1.09-3.42) and to users of celecoxib (relative risk 2.20, 95% CI: 1.17 to 4.10)**.[51]

- In a population-based, retrospective cohort study using administrative health care data from Ontario, Canada, an NSAID-naïve cohort was used to assess the risk of hospitalization for myocardial infarction in subjects >65 years of age treated with celecoxib (15,271 subjects), rofecoxib (12,156 subjects), naproxen (5669 subjects), or nonselective NSAIDs other than naproxen (33,868 subjects) compared to a cohort of non-users of NSAIDs (100,000 subjects). While the study did not show significant increases in risk of myocardial infarction in subjects treated with celecoxib, rofecoxib, or nonselective NSAIDs compared to non-NSAID users, potential differences were not investigated according to selective COX-2 inhibitor or nonselective NSAID dose.[52]

In all of these studies, the relative risk associated with celecoxib was <1.0 and the relative risk associated with rofecoxib was ≥1.0 (Figure 3.). However, information from epidemiology studies on chronic use of celecoxib and rofecoxib at high doses is limited.

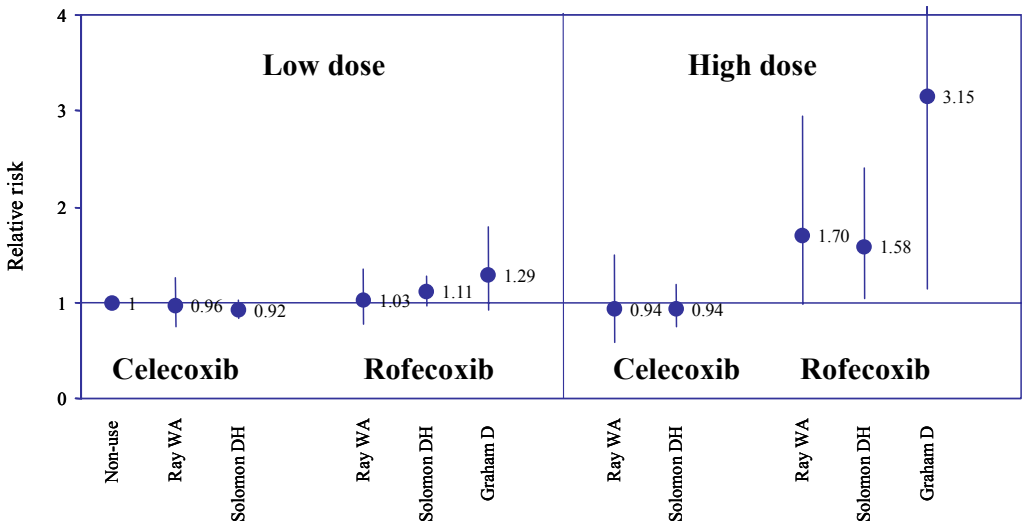
Figure 3. Risk of Myocardial Infarction and Use of Selective COX-2 Inhibitors and Nonselective NSAIDs in Epidemiological Studies



Points indicate relative risk estimates compared to non-use, and bars indicate 95% confidence intervals, from data published by Graham D et al,[26] Solomon DH et al,[49] Kimmel S et al,[50] Ray WA et al,[51] and Mamdani M et al;[52] for estimates of relative risks presented by Graham et al (indicated by asterisks), the reference group was remote NSAID use. Relative risks for nonselective non-steroidal anti-inflammatory drugs (NSAIDs) are from pooled estimates presented by Hernandez-Diaz et al (confidential; submitted for publication).[25]

Three of these 5 epidemiology studies evaluated the dose effect of celecoxib and rofecoxib. As shown in Figure 4., a dose-response relationship is suggested for rofecoxib with respect to the risk of myocardial infarction, with the highest risk at doses above 25 mg/day (relative risks ranged from 1.7 to 3.2 in various studies for high-dose rofecoxib compared to nonuse of NSAIDs). However, no dose-response relationship was suggested for celecoxib.

Figure 4. Risk of Myocardial Infarction and Use of COX-2 Inhibitors in Epidemiological Studies by Dose



Points indicate relative risk estimates compared to non-use, and bars indicate 95% confidence intervals, from data published by Graham D et al [26] Solomon DH et al,[49] and Ray WA et al;[51] for estimates of relative risks presented by Graham et al (indicated by asterisks), the reference group was remote NSAID use. Low doses were defined as ≤200 mg/day for celecoxib and ≤25 mg/day for rofecoxib; high doses were defined as >200 mg/day for celecoxib and >25 mg/day for rofecoxib.

Altogether, the results of these 5 epidemiological studies provide evidence that an increased risk of myocardial infarction is associated with use of rofecoxib, but not with use of celecoxib, compared to use of nonselective NSAIDs or non-use of NSAIDs. In all of these studies, the effects observed place celecoxib at the favorable end of the range of effects demonstrated for NSAIDs in general in epidemiology studies. No formal epidemiology studies have published that evaluated the risk of thrombotic events other than myocardial infarction associated with use of selective COX-2 inhibitors.

2.5.2.2. Cardiorenal Events in Epidemiology Studies

To date, only a single published observational study has evaluated the risk of hospital admission for heart failure among new users of celecoxib and rofecoxib, compared with nonselective NSAIDs or non-NSAID users, using administrative health care data from Ontario, Canada.[53] In this population-based, retrospective cohort study, both rofecoxib (relative risk 1.8; 95% CI: 1.5 to 2.2) and nonselective NSAIDs (relative risk 1.4; 95% CI: 1.0 to 1.9) significantly increased the risk of hospital admission for congestive heart failure relative to non-NSAID subjects, but celecoxib (relative risk 1.0, 95% CI: 0.8 to 1.3) did not. Compared with celecoxib users, admission was significantly more likely in users of nonselective NSAIDs (relative risk 1.4; 95% CI: 1.0 to 1.9) and rofecoxib (relative risk 1.8; 95% CI: 1.4 to 2.4). Risk of admission for rofecoxib users was higher than that for users of nonselective NSAIDs (relative risk 1.5; 95% CI: 1.1 to 2.1). Among patients with no admission in the past 3 years, only rofecoxib users were at increased risk of subsequent admission relative to controls (relative risk 1.8; 95% CI: 1.4 to 2.3).

No information on dose was provided in this study; durations of use ranged, on average, up to 3 months for users of nonselective NSAIDs and up to 6 months for users of celecoxib.

The risk of hypertension associated with use of selective COX-2 inhibitors has been evaluated in only a single formal epidemiological study published to date: the risk of new onset hypertension requiring treatment was examined in a retrospective case-control study involving 17,844 patients aged ≥65 years who were Medicare beneficiaries in 1999-2000.[49] Patients who used celecoxib (878 patients) or rofecoxib (386 patients) were compared with patients using a nonselective NSAID (869 patients) or no NSAID (15,711 patients). The risk of new onset hypertension was similar among celecoxib users compared to either users of nonselective NSAIDs or non-users. Rofecoxib users were at a significantly increased risk of new onset hypertension compared to patients treated with celecoxib (odds ratio 1.6; 95% CI: 1.2 to 2.1), patients treated with a non-selective NSAID (odds ratio 1.4; 95% CI: 1.1 to 1.9), or non-users of NSAIDs (odds ratio 1.6; 95% CI: 1.3 to 2.0). In patients with a history of chronic renal disease, liver disease, or congestive heart failure, the risk of new onset hypertension was twice as high in those taking rofecoxib compared with those taking celecoxib (odds ratio 2.1; 95% CI 1.0-4.3). There were no clear dosage or duration effects.

2.6. Spontaneous Reports of Adverse Events With Celecoxib

Although it historically represents the least precise of methods for evaluation of cardiovascular risk, analysis of spontaneous reports shows results consistent with both randomized clinical trial data and epidemiology data indicating no increase in cardiovascular risk with celecoxib.

2.6.1. Methods for Analysis

Pfizer's early alert safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported from health authorities, cases published in the medical literature, and cases of serious adverse events reported from clinical studies and Pfizer-sponsored marketing programs (solicited cases) regardless of causality. For this review the database was searched for all celecoxib non-clinical study cases reported from 1 December 1998 through 31 October 2004.

The database was further searched to identify celecoxib cases reporting thrombotic events (including events suggestive of coronary artery disease or thromboembolism or occlusion, cardiac ischemia, myocardial infarction, or arrhythmia events likely to be associated with coronary thromboembolism or ischemia; cerebrovascular thromboembolism or occlusion or ischemia or infarction, cerebrovascular hemorrhage, or neurologic events likely to be associated with cerebrovascular ischemia or hemorrhage; non-coronary or non-cerebrovascular thromboembolism, occlusion, ischemia, or infarction) and cardiorenal events (events suggestive of hypertension, abnormal or fluctuating or inadequately controlled or increased blood pressure, cardiac failure, or edema events possible related to hypertension or cardiac failure). Cases identified by these searches were then further reviewed to characterize the nature of any cardiovascular risk factors present.

In addition, in an effort to compare information on the reporting of these types of adverse events for COX-2 inhibitors and the conventional non-selective NSAIDs, the FDA's Adverse Event Reporting System (AERS) database, available under the Freedom of Information Act, was reviewed using Drug Logic's QScan (version 3.0) for information on adverse events reported to FDA for the COX-2 inhibitors celecoxib and rofecoxib, and for the conventional NSAIDs diclofenac, ibuprofen, naproxen, and piroxicam using the same search strategy that was employed to search for celecoxib cases in Pfizer's database.

2.6.2. Results: Spontaneous Reports of Adverse Events for Celecoxib

Review of Pfizer's early alert safety database identified a total of 47,279 celecoxib non-clinical study cases reported through 31 October 2004 following treatment of approximately 70.6 million patients worldwide. Of these, there were 1072 cases reporting thrombotic events (of which 537 reported cardiac events, 353 reported cerebrovascular events, and 195 reported peripheral vascular events; 980 of these 1072 cases met the reporting criteria for a serious case, and deaths were reported in 198 of these 980 serious cases) and 3603 cases reported cardiorenal events (984 of these 3603 cases met the reporting criteria for a serious case, and deaths were reported in 67 of these 984 serious cases). When the reporting of these events for celecoxib to the FDA's AERS system was compared to the reporting of these events for rofecoxib, diclofenac, ibuprofen,

naproxen, and piroxicam, the proportion of cases reporting these events was generally greatest for rofecoxib, and the proportion of celecoxib cases reporting these events was generally similar to the proportion of diclofenac cases reporting these events.

For celecoxib cases reported to Pfizer, the cases reporting cardiac events, cerebrovascular events, and all thrombotic events had a greater proportion of elderly and male patients, suggesting a patient population generally already at elevated cardiovascular risk. Cases reporting these events were also more likely to have reported co-suspect drugs, concomitant medications, and medical history than were all celecoxib cases, also suggesting that these cases involved patients at greater risk of adverse events. Review of the data for daily dose of celecoxib identified no suggestion of increased risk for any of the event categories reviewed with increased dose. For cardiac, cerebrovascular, and all thrombotic events, the most commonly reported durations of therapy at event onset were ≤ 1 day and 1-6 months. For peripheral vascular events, the most commonly reported duration of therapy was 1-6 months. For cardiorenal events the most commonly reported durations of therapy at event onset were ≤ 1 day and 1-6 months. Interpretation of these data is made difficult by the fact that duration of use was unknown or not reported in more than half of the cases for all event categories reviewed. There was no apparent association between any of the event categories reviewed and concurrent aspirin therapy.

For all event categories reviewed, cases where the patient was reported to have died had a greater proportion of elderly and male patients than did all celecoxib non-clinical study cases and all cases for the corresponding event categories. Cases reporting hypertension were no more likely to have reported concurrent cardiac or cerebrovascular events than were all celecoxib non-clinical study cases, and it is unclear if such events are independent of hypertension in celecoxib-treated patients or if hypertension-related events are underreported in celecoxib cases reporting cardiac and/or cerebrovascular events.

Overall, this review of celecoxib non-clinical study cases did not identify any signal that celecoxib therapy increases risk of cardiac, cerebrovascular, peripheral vascular, all thrombotic, or cardiorenal adverse events independent of risk inherent in the patient population likely to be treated with celecoxib.

2.7. Conclusions, Celecoxib Cardiovascular Safety

Data presented and reviewed in this evaluation of celecoxib cardiovascular safety support the following conclusions:

- Preliminary data from long-term prevention trials (non-arthritis indications, treatment durations up to 4 years) with chronic celecoxib use have shown inconsistent results, with only 1 out of 3 trials showing increased incidence of cardiovascular events for celecoxib compared to placebo (Section 2.3). In another of these trials, naproxen (but not celecoxib) was associated with increased cardiovascular risk compared to placebo. Nonselective NSAIDs generally have not been studied in such settings, but even aspirin 325 mg QD has shown trends towards increased cardiovascular risk in this type of study (Section 2.4.3).

- Published epidemiology studies have consistently shown a similar risk of myocardial infarction and cardiorenal adverse events with celecoxib compared to nonselective NSAIDs and to non-use of NSAIDs, although information on chronic use at high doses is limited. Again, this observation of no increase in risk with celecoxib is in contrast to observations with rofecoxib (Section2.5).

- A meta-analysis of cardiovascular safety data from randomized clinical trials in over 44,000 patients with treatment durations up to 1 year shows no increased cardiovascular thromboembolic risk for celecoxib compared to placebo or nonselective NSAIDs (Section 2.2). Several large 1-year studies contributed to this meta-analysis, and all support these overall conclusions when evaluated individually. The meta-analysis also included an assessment of cardiorenal risk, which demonstrated that celecoxib, while showing more effects than placebo, has a favorable cardiorenal safety profile compared to nonselective NSAIDs.

- Published clinical studies have consistently shown a similar risk of thrombotic and cardiorenal adverse events with celecoxib compared to nonselective NSAIDs, in contrast to observations with rofecoxib, which showed a higher risk (Section 2.4).

- Postmarketing safety surveillance representing a total of 47,279 celecoxib non-clinical study cases reported through 31 October 2004 following treatment of approximately 70.6 million patients worldwide does not show a cardiovascular safety signal for celecoxib (Section 2.6).

These results consistently demonstrate that celecoxib is safe and well tolerated when used as directed, presenting a cardiovascular safety profile comparable to that of nonselective NSAIDs and different from that of rofecoxib, which is associated with increased cardiovascular risk. The most prominent alternatives to treatment for arthritis with celecoxib are nonselective NSAIDs. Although widely used for decades, the long-term cardiovascular safety of nonselective NSAIDs has not been demonstrated.

3. VALDECOXIB CARDIOVASCULAR SAFETY

Data presented and reviewed in this evaluation of valdecoxib cardiovascular safety include a new Pfizer meta-analysis of data from chronic dosing clinical trials of up to 1 year duration compared to both placebo and nonselective NSAIDs (Section 3.2), and an integrated analysis of cardiovascular safety in short-term post-surgical and other acute pain settings (Section 3.3). These shorter-term studies are analyzed primarily in comparison to placebo with all patients receiving underlying standard of care analgesia. Also in this setting, the results of 3 individual clinical trials are discussed (Section 3.4.1): 2 placebo-controlled trials in CABG surgery patients using sequential treatment with parecoxib sodium/valdecoxib, and trial in general surgery patients of similar design; results from these 3 studies are also generalized to the larger set of post-surgical studies (Section 3.4.2.4). Post-marketing experience is presented in Section 3.5. For valdecoxib, there are no clinical trials longer than 1 year in duration, nor are there any published epidemiological studies.

3.1. Valdecoxib Clinical Development Program

In November 2001, valdecoxib (BEXTRA®) was approved in the US for treatment of the signs and symptoms of OA and RA at a dose of 10 mg QD, and for the treatment of primary dysmenorrhea at a dose of 20 mg BID/as needed (PRN). In November 2002, the valdecoxib US Package Insert was revised to include a Contraindication for use in patients demonstrating allergic reactions to sulfonamides and a Warning for serious skin reactions. In November 2004, the valdecoxib US Package Insert was again revised to reflect a Boxed Warning for serious skin reactions and to include a Contraindication for the treatment of post-operative pain immediately following CABG surgery. At that time, clinical safety data from investigational post-surgical studies of valdecoxib was also included in the Clinical Studies section, to describe results from trials in the CABG and general surgery populations.

On 27 March 2003, valdecoxib (trade names BEXTRA & VALDYN®) was approved for marketing in the European Union (EU) via the centralized procedure. Valdecoxib is currently approved in more than 60 countries worldwide (trade names BEXTRA, VALDYNE®, and VALDURE®) for indications that include OA, RA, primary dysmenorrhea, and the management of acute pain, including preoperative dosing for the prevention or reduction of postoperative pain and concomitant administration with opioid analgesics to reduce opioid requirements. On 10 December 2004, Pfizer submitted to FDA an amended NDA for parecoxib sodium, a water-soluble prodrug of valdecoxib for parenteral administration, seeking an indication for treatment of acute post-surgical pain.

Parecoxib sodium, a water-soluble prodrug converted metabolically to valdecoxib, was approved for marketing in the European Union (trade names DYNASTAT® and RAYZON®) via the centralized procedure on 22 March 2002 with an indication for the short-term treatment of post-operative pain in adult patients, at an initial dose of 40 mg administered intramuscularly (IM) or intravenously (IV), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day total daily dose (TDD); for elderly patients or patients with hepatic impairment, the TDD should not exceed 40 mg. Parecoxib sodium is approved for marketing in over 50 countries worldwide for treatment of acute pain or post-operative pain. Because of its COX-2

selectivity, valdecoxib does not affect platelet aggregation, making the soluble prodrug parecoxib sodium suitable for use in perioperative settings without the risk of increased bleeding. During the fourth quarter of 2004, Pfizer submitted to FDA an amended NDA in support of a parecoxib sodium indication for acute pain. Discussion of parecoxib sodium in this document is limited to its use in the 2 CABG surgery studies and the general surgery study described in Section 3.4.1.

The valdecoxib clinical development program has comprised clinical studies in patients with chronic pain conditions including OA, RA, chronic low back pain (CLBP), and cancer pain; in patients with acute pain conditions including general surgery, ankle sprain, CABG surgery, and oral surgery; in patients with dysmenorrhea, and in patients with migraine. Patients in OA, RA, CLBP, and cancer pain (ie, chronic pain) studies were treated with valdecoxib for treatment periods from 2 weeks up to 1 year in duration. These patients constitute the clinical study population with the greatest valdecoxib exposure; a meta-analysis of data from 19 chronic pain studies is presented in Section 3.2. For the remaining indications, clinical studies were shorter in duration: the acute pain clinical program included both single-dose studies (post oral-surgery) and multiple-dose studies (general surgery, CABG surgery, and ankle sprain) in which patients were treated with valdecoxib or parecoxib sodium/valdecoxib for durations ranging from 1 to 14 days. Single-dose studies are not evaluated for cardiovascular safety in this Briefing Document; an integrated analysis of data from 18 multiple-dose acute pain studies is presented in Section 3.3.

In addition to the studies mentioned above, other valdecoxib clinical studies (post-oral surgery, migraine, dysmenorrhea) were conducted in healthier populations or using single-dose, intermittent, or very short-term treatment regimens, and do not provide meaningful data regarding cardiovascular risk. To date, there has been no valdecoxib clinical trial longer than 1 year in duration, and no such study is currently ongoing as of 1 January 2005. No clinical epidemiology study evaluating the cardiovascular safety of treatment with valdecoxib has been published as of 1 January 2005.

In a separate formal ECG study in patients treated with valdecoxib (Study N91-01-02-109), no drug-related or dose-related changes were apparent for any ECG parameter, including QTc and heart rate. A second study (Study N91-00-08-056), which evaluated ECG data for potential prolongation of QT intervals and for potential correlation with plasma concentrations of valdecoxib, also found no apparent effect on ECG parameters.

3.2. Meta-Analysis of Data From Chronic Pain Studies: Summary

To evaluate valdecoxib cardiovascular safety, 19 clinical studies, representing a total of 12,254 patients with chronic pain conditions, were identified for meta-analysis. Patients in these 19 studies were treated with valdecoxib at doses ranging from 1 to 80 mg TDD for durations ranging from 2 weeks to 12 months; all studies had randomized, parallel-group designs with placebo and/or active (naproxen, diclofenac, ibuprofen, or rofecoxib) comparators. Results for all 19 studies that met criteria for meta-analysis either have been published in the medical literature or have been published or otherwise addressed as part of the Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database, available at www.clinicalstudyresults.org.

Endpoints selected for meta-analysis were composites of serious cardiovascular thromboembolic adverse events, myocardial thrombolic events, cerebrovascular events, peripheral vascular events, and the individual adverse events myocardial infarction and stroke; the Cochran-Mantel-Haenszel test, stratified by study, was used to analyze differences in numbers of events per patient-year of treatment. Data were integrated across studies for summarization and comparison of cardiorenal adverse events categorized as follows: hypertension/hypertension aggravated; edema/edema generalized/edema peripheral; and cardiac failure/cardiac failure left/cardiac failure right; differences between treatment groups in percentages of patients with these events were analyzed using Fisher's exact test

The results of this meta-analysis of cardiovascular thromboembolic adverse events and cardiorenal adverse events support the following conclusions:

- The risk of serious cardiovascular thromboembolic events in patients treated with valdecoxib is similar to that observed in patients treated with placebo or nonselective NSAIDs.

- As expected, percentages of patients with hypertension and edema were greater among patients treated with valdecoxib compared to patients treated with placebo. Percentages of patients with these events were similar when patients treated with valdecoxib were compared to patients treated with nonselective NSAIDs. Cardiac failure adverse events were similarly rare regardless of treatment.

The results of this meta-analysis of 19 chronic pain studies are consistent with the results observed in a meta-analysis of cardiovascular safety data from 10 arthritis studies studies recently published:[54] No cardiovascular safety signal was observed for valdecoxib, at any dose, in either case.

3.2.1. Chronic Pain Studies Included in Meta-Analysis

The criteria for selection of chronic pain studies to be included in this meta-analysis were as follows:

- Randomized, parallel-group study design;

- At least one treatment group with valdecoxib TDD ≥10 mg;
- At least one placebo, nonselective NSAID, or rofecoxib comparator group;
- Planned duration ≥2 weeks; and
- Study completed and study report finalized by a cutoff date of 31 October 2004.

A search of the Pfizer Corporate Clinical Trials Registry using these criteria identified 19 chronic pain studies for meta-analysis (Table 12) in which a total of 12,254 patients were treated with valdecoxib, placebo, or active comparators. In these 19 chronic pain studies, valdecoxib doses ranged from 1 to 80 mg TDD, and doses of active comparator medications were consistent with the current standard of care for OA and RA (naproxen 1000 mg TDD, diclofenac 150 mg TDD, ibuprofen 2400 mg TDD, and rofecoxib 25 mg TDD); all patients treated with valdecoxib 80 mg TDD were enrolled in cancer pain studies. The predominant exposure to valdecoxib was in the range of 10 to 40 mg TDD, including and exceeding doses recommended for OA and RA patients (10 to 20 mg TDD); the predominant NSAID exposure was to naproxen. Eleven of the 20 studies included in the meta-analysis were 3 months or longer in duration.

Table 12. Valdecoxib Chronic Pain Studies Included in Meta-Analysis

Indication Protocol ID	Duration of Treatment	Treatment groups (all medications oral)
Osteoarthritis or Rheumatoid Arthritis		
N91-97-02-015	6 weeks	Placebo, Valdecoxib 0.5 mg BID, 1.25 mg BID, 2.5 mg BID, 5 mg BID, 10 mg QD, 10 mg BID, Naproxen 500 mg BID
N91-97-02-016	6 weeks	Placebo, Valdecoxib 0.5 mg BID, 1.25 mg BID, 2.5 mg BID, 5 mg BID, 10 mg QD, 10 mg BID, Naproxen 500 mg BID
N91-99-02-047	26 weeks	Valdecoxib 20 mg QD, 40 mg QD, Naproxen 500 mg BID
N91-98-02-048	12 weeks	Placebo, Valdecoxib 10 mg QD, 20 mg QD, Ibuprofen 800 mg BID, Diclofenac 75 mg BID
N91-99-02-049	12 weeks	Placebo, Valdecoxib 5 mg QD, 10 mg QD, Naproxen 500 mg BID
N91-99-02-053	12 weeks	Placebo, Valdecoxib 5 mg QD, 10 mg QD, 20 mg QD, Naproxen 500 mg BID
N91-99-02-060	12 weeks	Placebo, Valdecoxib 10 mg QD, 20 mg QD, 40 mg QD, Naproxen 500 mg BID
N91-99-02-061	12 weeks	Placebo, Valdecoxib 10 mg QD, 20 mg QD, 40 mg QD, Naproxen 500 mg BID
I91-99-02-062	26 weeks	Valdecoxib 20 mg QD, 40 mg QD, Diclofenac 75 mg BID
I91-99-02-063	12 months	Valdecoxib 10 mg QD, 20 mg QD, Diclofenac 75 mg BID
872-IFL-0513-004	6 weeks	Placebo, Valdecoxib 20 mg QD, Rofecoxib 25 mg QD
VALA-0513-142	2 weeks	Placebo, Valdecoxib 10 mg QD, Rofecoxib 25 mg QD
VALA-0513-143	2 weeks	Placebo, Valdecoxib 10 mg QD, Rofecoxib 25 mg QD
Chronic Low Back Pain		
N91-01-02-097	4 weeks	Placebo, Valdecoxib 40 mg QD
N91-01-02-108	4 weeks	Placebo, Valdecoxib 40 mg QD
N91-01-02-132	12 weeks	Placebo, Valdecoxib 20 mg QD, 40 mg QD
N91-01-12-133	12 weeks	Placebo, Valdecoxib 10 mg QD, 20 mg QD
Cancer Pain		
N91-01-32-040	12 weeks	Opioid + Placebo BID, Opioid + Valdecoxib 40 mg BID
N91-00-02-079	6 weeks	Opioid + Placebo BID, Opioid + Valdecoxib 20 mg BID, Opioid + Diclofenac 75 mg BID

BID = Twice daily; QD = Once daily

3.2.2. Methodology for Meta-Analysis

For this meta-analysis of safety data from valdecoxib chronic pain studies, cardiovascular thromboembolic and cardiorenal adverse events were categorized and statistical methods were employed as described in Section 2.2.2.1 for the meta-analysis of safety data from celecoxib studies in chronic indications.

3.2.3. Results: Meta-Analysis of Data From Chronic Pain Studies

Baseline characteristics for patients in chronic pain studies were generally balanced across integrated treatment groups (Table 13). Mean patient age ranged from 57 to 63 years across treatment groups, and women in each treatment group outnumber men by approximately 2:1. Use of aspirin was also balanced across treatment groups (13 to 14% of patients).

Table 13. Baseline Patient Characteristics, Chronic Pain Studies

	Treatment Group		
Category Characteristic	Placebo N = 2235	Valdecoxib ≥10 mg TDD N = 7061	Combined NSAIDs N = 2323
Age (years)			
Mean	56.6	57.5	58.6
≥ 65 years	678 (30.3)	2191 (31.0)	792 (34.1)
≥ 75 years	161 (7.2)	572 (8.1)	203 (8.7)
Gender, n (%)			
Male	772 (34.5)	2179 (30.9)	657 (28.3)
Female	1463 (65.5)	4882 (69.1)	1666 (71.7)
Indication			
OA/RA	1464 (65.5)	5986 (84.8)	2261 (97.3)
Chronic Low Back Pain	593 (26.5)	897 (12.7)	0 (0.0)
Cancer Pain	178 (8.0)	178 (2.5)	62 (2.7)
Aspirin Use, n (%)	286 (12.8)	949 (13.4)	320 (13.8)

NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, and ibuprofen (combined totals); TDD = Total daily dose; OA = osteoarthritis; RA = rheumatoid arthritis.

3.2.3.1. Serious Cardiovascular Thromboembolic Adverse Events

The relative risk for serious cardiovascular thromboembolic adverse events, comparing the valdecoxib ≥10 mg TDD treatment group and the placebo treatment group, was not statistically significant for the all patients cohort, for non-users of aspirin, or for aspirin users (Table 14). However, because of the small numbers of events (12 events total) and limited exposure to treatment in placebo-controlled studies, comparisons between valdecoxib treatment and placebo treatment for cardiovascular risk, as well as comparisons stratified for non-users of aspirin versus aspirin users, should be interpreted with caution.

When normalized for patient exposure to study medication in placebo-controlled studies, more serious cardiovascular thromboembolic adverse events occurred among aspirin users (7.2 events per 100 patient-years in the valdecoxib ≥10 mg TDD treatment group and 5.8 events per

100 patient-years in the placebo treatment group) compared to non-users of aspirin (0.69 events per 100 patient-years in the valdecoxib ≥10 mg TDD treatment group and zero events in the placebo treatment group). This difference likely reflects differences in baseline cardiovascular risk for aspirin users versus non-users of aspirin.

Table 14. Serious Cardiovascular Thromboembolic Events, Chronic Pain Studies: Valdecoxib ≥10 mg Total Daily Dose Versus Placebo

Event Category or Adverse Event Population	Valdecoxib n/N	Valdecoxib Exposure (pt-years)	Placebo n/N	Placebo Exposure (pt-years)	Relative Risk (95%CI)	p-Value[a]
Any Cardiovascular Thromboembolic						
All Patients	10/4438	655.4	2/2235	280.3	1.80 (0.47, 6.97)	0.394
Non-Users of Aspirin	4/3849	572.8	0/1949	246.5	--	0.087
Aspirin Users	6/589	82.5	2/286	33.8	0.54 (0.11, 2.75)	0.457
Any Myocardial Thromboembolic						
All Patients	5/4438	655.4	1/2235	280.3	1.38 (0.17, 11.30)	0.765
Non-Users of Aspirin	1/3849	572.8	0/1949	246.5	--	0.598
Aspirin Users	4/589	82.5	1/286	33.8	0.60 (0.06, 6.45)	0.677
Myocardial Infarction						
All Patients	5/4438	655.4	1/2235	280.3	1.38 (0.17, 11.30)	0.765
Non-Users of Aspirin	1/3849	572.8	0/1949	246.5	--	0.598
Aspirin Users	4/589	82.5	1/286	33.8	0.60 (0.06, 6.45)	0.677
Any Cerebrovascular						
All Patients	4/4438	655.4	1/2235	280.3	1.57 (0.23, 10.71)	0.646
Non-Users of Aspirin	2/3849	572.8	0/1949	246.5	--	0.213
Aspirin Users	2/589	82.5	1/286	33.8	0.47 (0.05, 4.45)	0.514
Stroke						
All Patients	3/4438	655.4	1/2235	280.3	1.31 (0.19, 8.99)	0.782
Non-Users of Aspirin	2/3849	572.8	0/1949	246.5	--	0.213
Aspirin Users	1/589	82.5	1/286	33.8	0.24 (0.02, 2.61)	0.240
Any Peripheral Vascular						
All Patients	1/4438	655.4	0/2235	280.3	--	0.297
Non-Users of Aspirin	1/3849	572.8	0/1949	246.5	--	0.275
Aspirin Users	0/589	82.5	0/286	33.8	--	--

N = Number of patients treated with study medication; n = number of patients with events; CI = Confidence interval; TDD = Total daily dose.

[a] Relative risks and p-values based on Cochran-Mantel-Haenszel test stratified by study; p-values ≤0.05 are indicated in **bold font**; -- indicates value cannot be calculated.

The relative risk of serious cardiovascular thromboembolic adverse events, comparing the valdecoxib ≥10 mg TDD treatment group and the combined nonselective NSAIDs treatment group, was not statistically significant for the all patients cohort, for non-users of aspirin, or for aspirin users (Table 15). For adverse events in the myocardial thromboembolic subcategory and for the individual adverse event myocardial infarction, relative risk in the all patients cohort was significantly lower in the valdecoxib ≥10 mg TDD treatment group compared to the combined NSAIDs treatment group; differences for other event subcategories or individual adverse events analyzed were not statistically significant.

When normalized for patient exposure to study medication in nonselective NSAID-controlled studies, more serious cardiovascular thromboembolic adverse events occurred among aspirin users (4.9 events per 100 patient-years in the valdecoxib ≥10 mg TDD treatment group and 6.3 events per 100 patient-years in the combined nonselective NSAIDs treatment group) compared to non-users of aspirin (0.68 events per 100 patient-years in the valdecoxib ≥10 mg TDD treatment group and 1.41 events per 100 patient-years in the combined nonselective NSAIDs treatment group). This difference likely reflects differences in baseline cardiovascular risk for aspirin users versus non-users of aspirin.

Table 15. Serious Cardiovascular Thromboembolic Events, Chronic Pain Studies: Valdecoxib ≥10 mg Total Daily Dose Versus Nonselective NSAIDs

	Valdecoxib		Nonselective NSAIDs			
Event Category or Adverse Event Population	n/N	Exposure (pt-years)	n/N	Exposure (pt-years)	Relative Risk (95%CI)	p-Value[a]
Any Cardiovascular Thromboembolic						
All Patients	17/4591	1345.1	14/2323	662.1	0.55 (0.27, 1.14)	0.106
Non-Users of Aspirin	8/3981	1163.9	8/2003	567.3	0.45 (0.18, 1.28)	0.142
Aspirin Users	9/610	182.1	6/320	95.2	0.61 (0.20, 1.82)	0.374
Any Myocardial Thromboembolic						
All Patients	7/4591	1345.1	9/2323	662.1	0.32 (0.12, 0.87)	**0.025**
Non-Users of Aspirin	3/3981	1163.9	5/2003	567.3	0.26 (0.07, 0.99)	**0.049**
Aspirin Users	4/610	182.1	4/320	95.2	0.37 (0.09, 1.62)	0.187
Myocardial Infarction						
All Patients	6/4591	1345.1	7/2323	662.1	0.33 (0.11, 098)	**0.047**
Non-Users of Aspirin	2/3981	1163.9	4/2003	567.3	0.20 (0.04, 0.99)	**0.049**
Aspirin Users	4/610	182.1	3/320	95.2	0.45 (0.10, 2.00)	0.294
Any Cerebrovascular						
All Patients	8/4591	1345.1	5/2323	662.1	0.72 (0.24, 2.18)	0.557
Non-Users of Aspirin	3/3981	1163.9	3/2003	567.3	0.47 (0.10, 2.17)	0.335
Aspirin Users	5/610	182.1	2/320	95.2	1.09 (0.19, 6.11)	0.926
Stroke						
All Patients	5/4591	1345.1	3/2323	662.1	0.75 (0.18, 3.06)	0.687
Non-Users of Aspirin	2/3981	1163.9	3/2003	567.3	0.32 (0.05, 1.65)	0.174
Aspirin Users	3/610	182.1	0/320	95.2	--	0.252
Any Peripheral Vascular						
All Patients	2/4591	1345.1	1/2323	662.1	1.37 (0.07, 26.31)	0.837
Non-Users of Aspirin	2/3981	1163.9	1/2003	567.3	1.40 (0.07, 27.70)	0.826
Aspirin Users	0/610	182.1	0/320	95.2	--	--

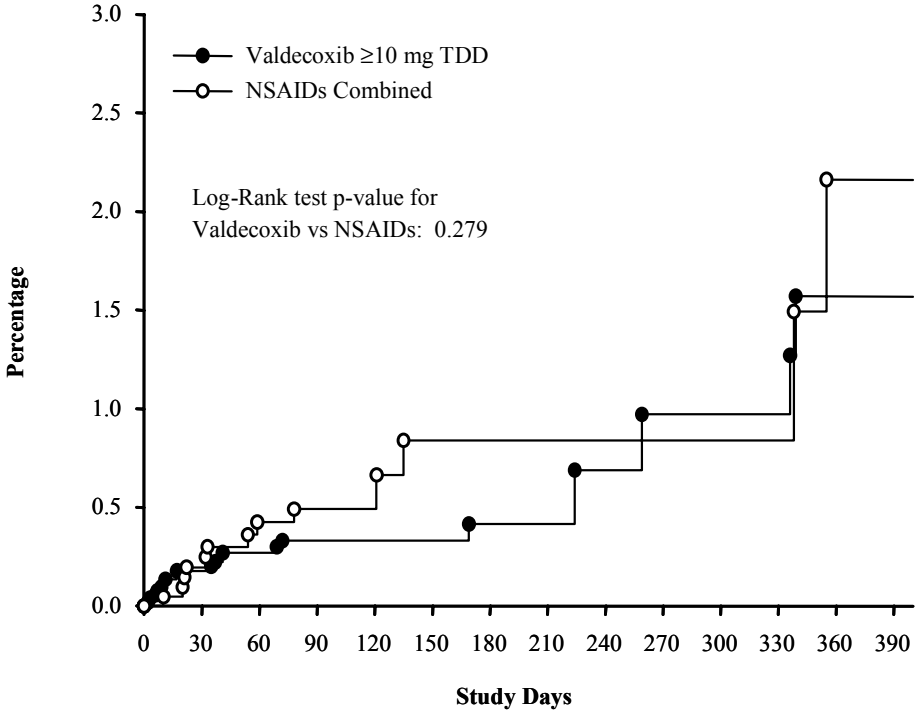
N = Number of patients treated with study medication; n = number of patients with events; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs naproxen, diclofenac, ibuprofen (combined totals); CI = Confidence interval; TDD = Total daily dose.

[a] Relative risks and p-values based on Cochran-Mantel-Haenszel test stratified by study; p-values ≤0.05 are indicated in **bold font**.

Additional analyses of cardiovascular thromboembolic events stratified according to valdecoxib dose, comparison versus individual nonselective NSAIDs, age, and gender were not useful for the statistical evaluation of cardiovascular risk due to small numbers of events.

A time-to-event analysis comparing treatment with valdecoxib (any dose) versus treatment with nonselective NSAIDs (combined) in OA and RA studies with treatment periods >2 weeks and nonselective NSAID comparators (Figure 5) shows no statistically significant difference for serious cardiovascular thromboembolic adverse events (p = 0.279); however, data are very sparse after 6 months.

Figure 5. Kaplan-Meier Plot of Time to Serious Cardiovascular Thromboembolic Adverse Event in Osteoarthritis and Rheumatoid Arthritis Studies With >2 Weeks Duration: Valdecoxib (Any Dose) Versus Combined NSAIDs



3.2.3.2. Cardiorenal Adverse Events

Percentages of patients with cardiorenal adverse events in the hypertension/hypertension aggravated subcategory and the edema/edema generalized/edema peripheral subcategory were significantly greater in the integrated valdecoxib (any dose) treatment group compared to the integrated placebo group. This is to be expected, since NSAIDs, including selective COX-2 inhibitors, are known to have cardiorenal effects.[2-12] Differences in percentages of patients with cardiorenal adverse events in all subcategories were not statistically significant when the integrated valdecoxib (any dose) treatment group was compared to the combined nonselective NSAIDs treatment group.

Table 16. Cardiorenal Adverse Events: Chronic Pain Studies

(Number [%] of Patients)

Comparison Adverse Event Subcategory	Valdecoxib	Comparator	p-Value[a]
Valdecoxib (any dose) Versus Placebo, N[b]	**5256**	**2235**	
Hypertension/Hypertension Aggravated	98 (1.9)	18 (0.8)	**<0.001**
Edema/Edema Generalized/Edema Peripheral	156 (3.0)	46 (2.1)	**0.029**
Cardiac Failure/Cardiac Failure Left/Cardiac Failure Right	6 (0.1)	2 (<0.1)	--
Valdecoxib (any dose) Versus NSAIDs, N[c]	**5409**	**2323**	
Hypertension/Hypertension Aggravated	189 (3.5)	74 (3.2)	--
Edema/Edema Generalized/Edema Peripheral	177 (3.3)	82 (3.5)	--
Cardiac Failure/Cardiac Failure Left/Cardiac Failure Right	8 (0.1)	6 (0.3)	--

N = Number of patients treated with study medication; n = number of patients with events;
NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, and ibuprofen (combined totals).

[a] P-values based on Fisher's exact test; p-values ≤0.05 are indicated in **bold font**; -- indicates p-value >0.20 or cannot be calculated.

[b] Includes only data from studies with placebo comparators.

[c] Includes only data from studies with NSAID comparators.

3.3. Analysis of Integrated Data From Acute Pain Studies: Summary

Cardiovascular and cardiorenal safety data from 18 clinical studies that were conducted to treat acute pain in a variety of surgical settings and ankle sprain were integrated for evaluation; these integrated data represent 4087 patients treated with valdecoxib 20-60 mg TDD and 2468 patients treated with placebo. Based on World Health Organization Adverse Reaction Terminology (WHOART) preferred terms, cardiovascular adverse events were categorized either as cardiovascular-thromboembolic events or as other-cardiovascular-related events; cardiorenal events were defined as edema, cardiac failure, and hypertension.

- Similar percentages of patients had cardiovascular-thromboembolic adverse events in the valdecoxib 20-60 mg TDD (15/4087 patients, 0.4%) and placebo (12/2666 patients, 0.5%) treatment groups, and differences for the myocardial, cerebrovascular, and peripheral vascular subcategories, and for individual adverse events in these categories, were not statistically significant.

- Percentages of patients with other-cardiovascular-related adverse events were also similar across treatment groups, with the exception that atrial fibrillation and palpitation occurred significantly less frequently ($p \leq 0.05$) in the valdecoxib 20-60 mg TDD treatment group versus the placebo group.

- Serious cardiovascular thromboembolic and cardiorenal adverse events were rare (<1%), as would be expected in this short-term setting, and no individual serous adverse event occurred for a significantly different percentage of patients in the valdecoxib 20-60 mg TDD treatment group versus the placebo group.

- Results were similar when stratified for use of aspirin or other concomitant medications, age, sex, and medical history.

The results of this integrated analysis demonstrate that in general surgery/ankle sprain patients, short-term treatment with valdecoxib for acute pain (up to 10 days) is safe and well tolerated.

3.3.1. Acute Pain Studies Included in Integrated Analysis

Cardiovascular safety data collected from 18 clinical studies in various acute pain settings including surgery and ankle sprain were integrated for analysis (Table 17), comprising 8 orthopedic surgery studies, 3 gynecologic surgery studies, 2 laparoscopic cholecystectomy study, 2 general surgery study, 1 hernia repair, 1 CABG surgery study, and 1 ankle sprain study, in which patients were treated for up to 10 days with valdecoxib (parecoxib sodium/valdecoxib sequential treatment in Studies 93-044, 93-069, and 93-071; throughout this document, valdecoxib studies will be identified using only the last 3-digits of the respective protocol identifiers, except that study numbers preceded by the number "93" represent studies in which patients were treated with both valdecoxib and parecoxib sodium, the prodrug parenteral product with active moiety valdecoxib) or comparators. Although the acute pain clinical program also included a number of post-oral surgery studies, the oral surgery patient population is excluded

from the integrated analysis due to its younger, healthier patient population and limited drug exposure (single doses).

Only data from the PO treatment periods (valdecoxib or placebo) of studies that included valdecoxib follow-on treatment following an initial parecoxib sodium IV treatment period (Studies 93-044, 93-069, and 93-071) were integrated with those from the other general surgery studies. After 3 days of postsurgical exposure to parecoxib sodium (or placebo) in these studies, patients were scheduled to transition to PO medication (valdecoxib or placebo). However, some patients were unable to make this transition to PO medication at that time and so remained on IV medication for a more extended period; data for this extended period on IV medication (ie, beyond Day 3) were nonetheless considered to be part of the IV treatment period of the respective study, and only adverse events data collected after patients took the first dose of valdecoxib PO were integrated for this analysis.

Table 17. Valdecoxib Surgery and Ankle Sprain Studies Integrated for Analysis

Study Type	Study ID	Short Description (dose, duration, population)
Orthopedic Surgery	032	Valdecoxib 20 mg PO or valdecoxib 40 mg PO on Day 1 followed by valdecoxib 20 mg PO or valdecoxib 40 mg PO q4-6h PRN on Days 2-4, adult males and females for orthopedic total hip arthroplasty
	037	Single PO dose of valdecoxib 20, 40, or 80 mg, adult males and females for bunionectomy surgery
	038	Valdecoxib 20 mg BID or valdecoxib 40 mg BID (single postoperative dose followed by dose q12h for up to 48 hours), adult males and females for unilateral knee arthroplasty surgery
	051	Valdecoxib 20 mg BID or valdecoxib 40 mg BID (single preoperative dose followed by dose q12h for up to 48 hours), adult males and females for primary hip arthroplasty
	081	Single PO dose of valdecoxib 40 mg, adult males and females for bunionectomy surgery
	110	Valdecoxib 40 mg PO QD with optional single redose of valdecoxib 40 mg PO on Day 1 followed by valdecoxib 40 mg PO QD on Days 2-7, adult males and females for anterior cruciate ligament reconstruction surgery
	144	Valdecoxib 40 mg PO followed by valdecoxib 20 mg PO within 1-12 hours on Day 1 and Days 2-5 valdecoxib 20 mg BID PO or valdecoxib 20 mg QD PO, adult males and females for bunionectomy surgery
	149	Valdecoxib 40 mg PO followed by valdecoxib 20 mg PO or valdecoxib 40 mg PO followed by placebo, 24 hours, adult males and females for bunionectomy surgery
Gynecologic Surgery	011	Single PO dose of valdecoxib 20 mg or 40 mg on Day 1 followed by Days 2-4 dosing of valdecoxib 20 mg PO Q4-6h PRN or valdecoxib 10 mg PO Q4-6h PRN, adult females for elective hysterectomy or a myomectomy
	033	Single PO dose of valdecoxib 10 mg or 20 mg or 40 mg, adult females for elective hysterectomy or a myomectomy
	084	Single PO dose of valdecoxib 20 mg or valdecoxib 40 mg, adult females for elective lower abdominal gynecologic surgery
General Surgery	010	Single PO dose of valdecoxib 10 mg or 20 mg on Day 1 followed by Days 2-7 dosing Q4-6h PRN of valdecoxib 10 mg PO or valdecoxib 20 mg PO, adult males and females following major surgery
	052	Valdecoxib 20 mg BID PO or valdecoxib 40 mg BID PO for 36 hours, adult males and females for inguinal hernia repair surgery
	93-044	Single preoperative dose of parecoxib sodium 40 mg IV on Day 1, followed by valdecoxib 40 mg PO 6-12 hours after parecoxib, then valdecoxib 40 mg PO every AM on Days 1-4 and valdecoxib 40 mg PO daily PRN for Days 5-7, males or females for elective laparoscopic cholecystectomy surgery
	93-069	Parecoxib sodium 40 mg IV followed by 20 mg IV every 12 hours up to 72 hours through at least Day 3 followed by valdecoxib 20 mg q12h through Day 10, adult males and females for major orthopedic or general surgery
	145	Valdecoxib 40 mg PO followed by valdecoxib 20 mg PO on Day 1, then valdecoxib 20 mg PO BID or valdecoxib 20 mg PO QD on Days 2-5, adult males and females for laparoscopic cholecystectomy surgery
CABG	93-071	Parecoxib sodium 40 mg IV at time of extubation and 20 mg IV q12h up to 72 hours followed by 14 doses of valdecoxib 20 mg PO q12h, adult males or females requiring primary coronary artery bypass graft surgery
Ankle Sprain	IFL-0513-008	Valdecoxib 40 mg PO loading dose followed by valdecoxib 20 mg PO QD or 20 mg PO BID for 7 days, adult male and females with lateral ankle sprain

3.3.2. Methodology for Analysis of Integrated Data

3.3.2.1. Categorization of Adverse Events

Adverse events were coded and categorized using the World Health Organization Adverse Reaction Terminology (WHOART) dictionary. Cardiovascular adverse events were selected adverse events grouped into 1 of 2 categories: "any cardiovascular thromboembolic event" (see Table 18) and "any other cardiovascular-related adverse event." For the purposes of this analysis, cardiorenal events were defined as adverse events that coded to the WHOART terms 'hypertension', 'edema', and 'cardiac failure.'

Table 18. Categorization of Cardiovascular Adverse Events: Integrated Acute Pain Studies

Cardiovascular Thromboembolic Adverse Events		
Myocardial	**Cerebrovascular**	**Peripheral Vascular**
Cardiac arrest	Cerebrovascular disorder	Pulmonary embolism
Circulatory failure		Peripheral ischemia
Myocardial infarction		Deep thrombophlebitis
Myocardial ischemia		
Tachycardia ventricular		

Adverse events summarized in the "any other cardiovascular-related adverse events" category include (but are not limited to) the following: angina pectoris, aortic stenosis, arrhythmia, atrial arrhythmia, nodal arrhythmia, ventricular arrhythmia, atrioventricular block, bradycardia, bundle branch block, cardiac failure, left cardiac failure, central venous pressure decreased, intermittent claudication, abnormal ECG, extrasystoles, atrial fibrillation, flushing, heart block, heart disorder, hematoma not otherwise specified, hepatic hemorrhage, hypertension, hypertension aggravated, hypotension, postural hypotension, mitral insufficiency, palpitation, pericardial effusion, pericarditis, peripheral vascular disease, phlebitis, superficial phlebitis, tachycardia, supraventricular tachycardia, thrombophlebitis, superficial thrombophlebitis, vasculitis, and vein disorder.

3.3.2.2. Statistical Methods

Adverse events are summarized in this integrated analysis using the numbers of patients who reported a particular adverse event rather than numbers of times the respective adverse events occurred. Because a particular patient may experience more than one adverse event in a particular cardiovascular adverse event category or WHOART body system, the total number of patients with adverse events cannot be calculated by summing individual counts within the adverse events category. Adverse events were summarized across individual and combined dose groups using integrated data from the 18 studies listed in Table 17. For studies that included a valdecoxib oral (PO) follow-on treatment period (Studies 93-044, 93-069, and 93-071), only data from the PO treatment period (valdecoxib or placebo) were integrated. All pairwise comparisons between the 20-60 mg TDD treatment group and the placebo treatment group were performed using Fisher's exact test without adjustment for multiple comparisons.

Evaluations of differences in percentages of patients with adverse events according to patient subgroups defined by use of aspirin or other concomitant medications, age, gender, and medical

history are discussed in terms of risk differences (RDs) between treatment groups, which are defined as the difference between the percentage of patients with a particular adverse event in the valdecoxib 20-60 mg TDD treatment group and the percentage of patients with the respective adverse event in the placebo treatment group. The difference in RD for a particular event that is associated with a particular stratification condition is defined as the excess risk associated with the presence of the condition incremental to the risk associated with the absence of the condition. For example, if in patients with condition X, event Y occurs in 25% of patients treated with active study medication compared to 8% of the patient treated with placebo (RD = 17%), and in patients without condition X, event Y occurs in 10% of patients treated with active study medication compared to 5% of the patient treated with placebo (RD = 5%), then the difference in RDs between strata is 12%. Comparisons between treatment groups were made using Breslow-Day analyses of asymptotic distribution. Because small numbers of patients within a subgroup or small numbers of adverse events that occurred within treatment groups sometimes limit interpretation of the data from analyses by subgroup, discussion in this section will focus on adverse events for which there was a statistically significant difference in the RD. A statistically significant difference in RD was defined as follows: $p < 0.05$; a total of at least 20 adverse events combined across the treatment groups; and at least 6 adverse events for both treatment groups (combined) within each intrinsic or extrinsic factor subgroup. These criteria were applied to avoid situations where a small sample size would carry a disproportionate weight in the analyses.

3.3.3. Results: Integrated Data From Acute Pain Studies

Integrated safety data were analyzed from 4087 patients who received at least 1 dose of valdecoxib 20-60 mg TDD and 2468 patients who received placebo; demographic characteristics of patients were comparable in these 2 treatment groups. The percentages of patients with adverse events in the cardiovascular thromboembolic category and the cardiorenal category were not significantly different for the valdecoxib 20-60 mg TDD treatment group compared to the placebo treatment group (Table 19). Percentages of patients with adverse events in the myocardial, cerebrovascular, and peripheral vascular subcategories were also not significantly different when these two groups were compared. Among individual adverse events, significantly greater percentages of patients had atrial arrhythmia and palpitation in the placebo treatment group compared to the valdecoxib 20-60 mg TDD treatment group.

In an inferential analysis comparing treatment groups for a composite of cardiorenal adverse events (namely, generalized edema, peripheral edema, hypertension, or aggravated hypertension with diastolic blood pressure >95 mm Hg, increased ≥5 mm Hg from post-surgery baseline), the percentage of patients with this composite cardiorenal adverse event was smaller for the valdecoxib 20-60 mg TDD treatment group (8/3380 patients for whom blood pressure data were available, 0.2%) than for the placebo treatment group (8/2376 patients, 0.3%; treatment difference not statistically significant.

Table 19. Analysis of Cardiovascular and Cardiorenal Adverse Events: Valdecoxib Acute Pain Studies

(Number [%] of Patients)

Adverse Event Category Adverse Event	Placebo N = 2468	Valdecoxib 20-60 mg[a] N = 4087	p-value[b]
Any Thromboembolic	**10 (0.4)**	**15 (0.4)**	**--**
Myocardial	**2 (<0.1)**	**7 (0.2)**	**--**
Cardiac arrest	0 (0.0)	1 (<0.1)	--
Myocardial infarction	0 (0.0)	3 (<0.1)	--
Tachycardia ventricular	2 (<0.1)	3 (<0.1)	--
Cerebrovascular	**3 (0.1)**	**3 (<0.1)**	**--**
Cerebrovascular disorder	3 (0.1)	3 (<0.1)	--
Peripheral vascular	**5 (0.2)**	**5 (0.1)**	
Embolism pulmonary	2 (<0.1)	3 (<0.1)	--
Peripheral ischemia	0 (0.0)	1 (<0.1)	--
Thrombophlebitis deep	4 (0.2)	2 (<0.1)	--
Cardiorenal			
Edema generalized	1 (<0.1)	2 (<0.1)	--
Edema peripheral	19 (0.8)	39 (1.0)	--
Hypertension	17 (0.7)	19 (0.5)	--
Hypertension aggravated	2 (<0.1)	2 (<0.1)	--
Other Cardiovascular-Related[c]			
Arrhythmia atrial	7 (0.3)	3 (<0.1)	**0.048**
Bradycardia	3 (0.1)	9 (0.2)	--
Fibrillation atrial	22 (0.9)	40 (1.0)	--
Hypertension	17 (0.7)	19 (0.5)	--
Hypotension	16 (0.6)	21 (0.5)	--
Palpitation	0 (0.0)	8 (0.2)	**0.029**
Pericardial effusion	1 (<0.1)	8 (0.2)	0.167
Tachycardia	15 (0.6)	12 (0.3)	0.072

[a] Indicates valdecoxib total daily dose.

[b] P-values based on Fisher's exact test; p-values ≤0.05 are indicated in **bold font**; -- indicates p-value >0.20 or cannot be calculated.

[c] Only events that occurred in ≥0.2% of patients treated with valdecoxib or had p <0.10 are presented in this table for this category.

3.3.3.1. Serious Adverse Events, Integrated Data From Acute Pain Studies

When integrated data for the valdecoxib 20-60 mg TDD treatment group and placebo treatment group were compared, no statistically significant differences were observed for any serious cardiovascular or cardiorenal adverse events (Table 20). All serious cardiovascular or cardiorenal adverse events were rare in both treatment groups (≤0.3% of patients).

Table 20. Serious Cardiovascular Adverse Events: Valdecoxib Acute Pain Studies With a Valdecoxib 20-60 mg Total Daily Dose Group

(Number [%] of Patients)

Adverse Event Category Adverse Event	Placebo N = 2468	Valdecoxib 20-60 mg[a] N = 4087
Myocardial		
Cardiac arrest	0 (0.0)	2 (<0.1)
Myocardial infarction	1 (< 0.1)	3 (<0.1)
Cerebrovascular		
Cerebrovascular disorder	3 (0.1)	3 (<0.1)
Peripheral vascular		
Pulmonary embolism	3 (0.1)	5 (0.1)
Deep thrombophlebitis	5 (0.2)	2 (<0.1)
Cardiorenal		
Cardiac failure	1 (<0.1)	6 (0.1)
Edema legs	0 (0.0)	1 (<0.1)
Edema peripheral	0 (0.0)	1 (<0.1)
Pulmonary edema	1 (<0.1)	1 (<0.1)
Other Cardiovascular-Related		
Arrhythmia	0 (0.0)	1 (<0.1)
Arrhythmia atrial	2 (<0.1)	2 (<0.1)
Bradycardia	0 (0.0)	1 (<0.1)
Cardiac failure	1 (<0.1)	6 (0.1)
Cardiac tamponade	0 (0.0)	1 (<0.1)
Circulatory failure	0 (0.0)	1 (<0.1)
Fibrillation atrial	6 (0.2)	14 (0.3)
Fibrillation ventricular	0 (0.0)	2 (<0.1)
Heart block	1 (<0.1)	0 (0.0)
Heart valve disorder	1 (<0.1)	0 (0.0)
Hematoma NOS	2 (<0.1)	3 (<0.1)
Pericardial effusion	2 (<0.1)	4 (<0.1)
Post myocardial infarction syndrome	1 (<0.1)	0 (0.0)
Tachycardia	1 (<0.1)	1 (<0.1)
Tachycardia supraventricular	0 (0.0)	2 (<0.1)
Thrombophlebitis	1 (<0.1)	0 (0.0)
Thrombophlebitis superficial	0 (0.0)	1 (<0.1)

* Indicates $p \leq 0.05$; p-values were calculated using Fisher's exact test.
[a] Indicates valdecoxib total daily dose.

3.3.3.2. Patient Subgroups: Integrated Data From Acute Pain Studies

When stratified according to use of aspirin, use of other concomitant medications (angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, cardiac glycosides, furosemide, diuretics, nitrates, and statins, loop diuretics, NSAIDs, and opioids), age (≥65 years versus <65 years of age), gender, and medical history (angina, hypertension, congestive heart failure, coronary artery atherosclerosis, coronary artery disease, myocardial infarction, peripheral edema, cerebrovascular ischemia, stroke, transient ischemic attack, hyperlipemia, hyperlipidemia, peripheral vascular disease, deep venous thrombosis, pulmonary

embolism, and embolism pulmonary), statistically significant results (as defined in Section 3.3.2.2) comparing risk differences (RD = incidence with valdecoxib minus incidence with placebo) with and without the factor of interest, as were detected only for the patient subgroups and cardiovascular or cardiorenal adverse events summarized in Table 21.

Table 21. Statistically Significant Differences in RD for Patient Subgroups: Valdecoxib Acute Pain Studies

(Number [%] of Patients)

Stratification / Adverse Event	Valdecoxib	Placebo	RD	Valdecoxib	Placebo	RD	RD Comparison* Difference	RD Comparison* p-Value
Aspirin	**With Concomitant Use**			**Without Concomitant Use**				
N	1090	577		2997	1891			
Hypertension	5 (0.5)	0 (0.0)	0.5	14 (0.5)	17 (0.9)	-0.4	0.9	0.034
Gender	**Males**			**Females**				
N	1861	1095		2226	1373			
Hypertension	12 (0.6)	4 (0.4)	0.3	7 (0.3)	13 (0.9)	-0.6	0.9	0.020
Fibrillation atrial	36 (1.9)	15 (1.4)	0.6	4 (0.2)	7 (0.5)	-0.3	0.9	0.037

* Differences in RD = RD with concomitant use minus RD without concomitant use; p-values were calculated using the Breslow-Day test stratified by medication group, and a statistically significant difference in RD was defined as follows: $p < 0.05$; a total of at least 20 of the respective adverse event across treatment groups, and at least 6 of the respective adverse event for both treatment groups (combined) within each subgroup (eg, with versus without concomitant use).

RD = Risk difference; N = Number of patients.

3.4. Cardiovascular Thromboembolic Adverse Events in CABG Surgery Studies 93-035 and 93-071 and General Surgery Study 93-069: Summary

- Studies 93-035 and 93-071 indicate that CABG surgery patients treated with parecoxib sodium/valdecoxib are at higher risk for cardiovascular thromboembolic adverse events (and for deep surgical infections and sternal wound complications; data not shown) compared to patients treated with placebo/placebo upon a background of standard of care. Therefore, treatment of acute post-surgical pain with parecoxib sodium/valdecoxib is contraindicated following CABG surgery.

- Currently there are no published data regarding the effect of nonselective NSAIDs or selective COX-2 inhibitors on cardiovascular risk in post-CABG surgery patients, and hence no way to put the above information into clinical context.

- No cardiovascular safety signal was observed in general surgery patients in Study 93-069 with a parecoxib sodium/valdecoxib treatment regimen similar to that used in CABG Surgery Study 93-071, compared to a placebo/placebo treatment regimen, suggesting that cardiovascular adverse effects are limited to high-risk high risk patients undergoing coronary bypass procedures. A post-hoc analysis looking at analogous serious adverse events across the entire general surgery trial database similarly failed to find an increase in these events with valdecoxib, consistent with the analysis described in Section 3.3.

3.4.1. Background: Parecoxib Sodium/Valdecoxib Sequential Treatment

To evaluate the extended safety of parecoxib sodium and valdecoxib treatment for acute pain, Pfizer sponsored 3 large clinical studies (Studies 93-035, 93-069, and 93-071) in which patients were treated immediately post-surgery for 3 days with parecoxib sodium or placebo, followed by valdecoxib or placebo for up to 14 days. Two of these studies (Studies 93-035 and 93-071) were in patients who had undergone CABG surgery, and the remaining study (Study 93-069) was in a general surgery population. Safety in these 3 studies was evaluated primarily according to a set of clinically relevant adverse events (CRAEs) that were prespecified and adjudicated by a panel of independent experts.

Cardiovascular CRAEs prespecified for Study 93-035 were:

- Myocardial infarction or severe myocardial ischemia (myocardial events);

- Cerebrovascular accident, transient ischemic attack, or hemorrhage (cerebrovascular events);

- Peripheral arterial occlusion, deep vein thrombosis, or pulmonary embolism (peripheral vascular events); and

- Congestive heart failure or renal failure (cardiorenal events).

Subsequent to the observation of a potential cardiovascular safety signal in Study 93-035, Studies 93-069 and 93-071 were initiated to determine whether the observed cardiovascular risk was specific to CABG surgery patients. For Studies 93-069 (general surgery patients) and 93-071 (CABG surgery patients), cardiovascular thromboembolic CRAEs were defined as follows: cardiac events (myocardial infarction, severe myocardial ischemia, cardiac arrest, or sudden cardiac death); cerebrovascular events (acute ischemic or hemorrhagic stroke, hemorrhagic infarction, or transient ischemic attack); and peripheral vascular events (vascular thrombosis [lower limb deep vein thrombosis], or pulmonary embolism). In addition, renal CRAEs were prespecified as renal failure or severe renal dysfunction.

3.4.2. Coronary Artery Bypass Graft (CABG) Surgery Studies

Patients who have undergone CABG surgery are normally considered to be at high risk for postoperative adverse events due to risks inherent in anesthesia, cardiac surgery, cardiopulmonary bypass procedures, and underlying cardiovascular disease. In particular, cardiopulmonary bypass procedures, used in the large majority of patients in Study 93-035 and all patients in Study 93-071, are often associated with a systemic inflammatory response syndrome that can be induced by at least 3 mechanisms:[55] exposure of blood to the plastic tubing and oxygenation systems used to maintain extracorporeal circulation; ischemic reperfusion injury to brain, heart, lungs, kidney, and liver caused by periods of aortic cross-clamping; and splanchnic ischemia that may result in the systemic release of endotoxin. In this setting, COX-2 is up-regulated, and TxA_2 appears to be elevated by multiple mechanisms including heparin-protamine interaction;[56] this increase in TxA_2 may be severe enough to cause pulmonary hypertension. Also, cardiopulmonary bypass procedures activate and partially deplete circulating platelets, and platelet regeneration following surgery is markedly increased, resulting in an apparent "aspirin resistance" if aspirin is administered QD only (ie, because the plasma half-life of aspirin is very short, QD administration is insufficient to produce circadian platelet inhibition when new platelets are generated at a rate higher than normal). Interactions between the various pro- and anti-thrombotic and -inflammatory mediators that contribute to these effects and their clinical consequences are not well understood.[55]

In summary, the first few days after cardiopulmonary bypass procedures represent a unique and highly dynamic pro-thrombotic and inflammatory syndrome, with effects on cardiovascular morbidity that are orders of magnitude greater than those seen in other types of surgery,[57] giving rise to complication rates of 15% or higher that affect the heart, brain, kidneys, or intestinal function.[58] Nearly 13% of CABG surgery patients discharged following the procedure are readmitted to the hospital within 30 days due to complications of the surgery, including infection, congestive heart failure, myocardial infarction/ischemia, and arrhythmias.[59]

Demographic characteristics of patients in Studies 93-035 and 93-071 were similar across treatment groups in each study, as well as between studies. The mean patient age by treatment group was approximately 61 years in both studies, more than 90% of the patients in each study were white, and most patients (between 85% and 90% per treatment group) were male. Concomitant aspirin use was required in both studies. Patients in both studies had primary isolated CABG surgery (ie, without associated valvular replacement, aortic reconstruction, or ventriculoplasty) via median sternotomy; for a majority of patients in Study 93-035 (90% in the parecoxib sodium/valdecoxib treatment group and 86% in the placebo/placebo treatment group),

and for all of the patients in Study 93-071, CABG surgery procedures included cardiopulmonary bypass.

3.4.2.1. Coronary Artery Bypass Graft Surgery Study 93-035

In Study 93-035, treatment with parecoxib sodium/valdecoxib was evaluated at a dose of 80 mg TDD using a double-blind, parallel-group study design with IV treatment (parecoxib sodium or placebo) for at least 3 days followed by PO treatment (valdecoxib or placebo) for a total treatment duration (IV plus PO) of 14 days. Patients with inadequate pain relief at any time during the study were allowed to receive supplemental opioid analgesia consistent with standard of care, and all patients were required to use concomitant low-dose aspirin. Of the 462 patients randomized in Study 93-035, 311 patients were treated with parecoxib sodium/valdecoxib and 151 were treated with placebo/placebo. Approximately 90% of the patients in each treatment group completed study Day 3 (287/311 patients, 92%, in the parecoxib sodium/valdecoxib treatment group and 135/151 patients, 89%, in the placebo treatment group), which was the day of the protocol-scheduled switch from IV to PO medication for those patients who were able to tolerate oral medication.

When cardiovascular CRAEs were evaluated in Study 93-035 for the entire period of treatment (ie, the IV administration period and the PO administration period considered together), results indicated a potential cardiovascular safety signal associated with parecoxib sodium/valdecoxib treatment in CABG surgery patients compared to placebo/placebo treatment (Table 22).

Table 22. Cardiovascular and Renal Adverse Events Prespecified as Clinically Relevant in Coronary Artery Bypass Graft Surgery Study 93-035: IV and Oral Dosing Periods Together

(Number [%] of Patients)

Adverse Event or Event Category	Placebo/ Placebo N = 151	Parecoxib Sodium/Valdecoxib N = 311	p-value
Myocardial infarction or severe ischemia	1 (0.7)	1 (0.3)	-
Cerebrovascular accident	1 (0.7)	9 (2.9)	0.177
Deep vein thrombosis	0 (0.0)	3 (1.0)	-
Pulmonary embolism	0 (0.0)	2 (0.6)	-
Congestive heart failure	1 (0.7)	4 (1.3)	-
Renal failure/dysfunction	7 (4.6)	29 (9.3)	0.096

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.
- Indicates p >0.20; p-values were calculated using Fisher's exact test.

When major CRAEs were evaluated separately for the IV dosing period in Study 93-035, a potential cardiovascular safety signal was observed with parecoxib sodium/valdecoxib treatment in CABG surgery patients compared to placebo/placebo treatment, but differences between treatment groups were not statistically significant (Table 23). When evaluated for the entire study (IV and PO dosing periods together), the composite major CRAE endpoint (defined in footnote to Table 23) was significantly more likely in the parecoxib sodium/valdecoxib treatment group compared to the placebo/placebo treatment group; no significant differences were observed for any major CRAE subcategories or individual adverse events that comprise the composite endpoint.

Table 23. Major Clinically Relevant Adverse Events in IV Dosing Period: Coronary Artery Bypass Graft Surgery Study 93-035

(Number [%] of Patients)

Adverse Event or Event Category	Placebo/ Placebo N = 151	Parecoxib Sodium/Valdecoxib N = 311	p-value
Major Clinically Relevant Adverse Event[a]			-
Intravenous dosing period only	4 (2.6)	17 (5.5)	-
Entire study	7 (4.6)	35 (11.3)	0.024
Death			-
Intravenous dosing period only	0 (0.0)	2 (0.6)	-
Entire study	0 (0.0)	4 (1.3)	-
Myocardial infarction or severe myocardial ischemia			-
Intravenous dosing period only	0 (0.0)	1 (0.3)	-
Entire study	1 (0.7)	1 (0.3)	-
Cerebrovascular accident			-
Intravenous dosing period only	0 (0.0)	5 (1.6)	0.178
Entire study	1 (1.7)	9 (2.9)	0.177
Deep vein thrombosis			-
Intravenous dosing period only	0 (0.0)	0 (0.0)	-
Entire study	0 (0.0)	3 (1.0)	-
Pulmonary embolism			-
Intravenous dosing period only	0 (0.0)	1 (0.3)	-
Entire study	0 (0.0)	2 (0.6)	-
Renal failure/dysfunction			-
Intravenous dosing period only	3 (2.0)	8 (2.6)	-
Entire study	4 (2.6)	8 (2.6)	-
Gastrointestinal event			-
Intravenous dosing period only	0 (0.0)	0 (0.0)	-
Entire study	0 (0.0)	4 (1.3)	-
Infection			-
Intravenous dosing period only	1 (0.7)	3 (1.0)	-
Entire study	1 (0.7)	12 (3.9)	0.069

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.

[a] Major clinically relevant adverse events were defined as death, all cardiovascular events; all gastrointestinal events; infections that required re-operation or parenteral antibiotics, plus all cases of sepsis; renal events associated with serum creatinine >2.0 mg/dL and increased >0.7 mg/dL from baseline.

- Indicates p >0.20 or could not be calculated; p-values were calculated using Fisher's exact test.

3.4.2.2. Coronary Artery Bypass Graft Surgery Study 93-071

In Study 93-071, treatment with parecoxib sodium/valdecoxib was evaluated at a dose of 40 mg TDD using a double-blind, parallel-group study design with IV treatment (parecoxib sodium or placebo) for 3 days followed by PO treatment (valdecoxib or placebo) for 7 days; patients with inadequate pain relief at any time during the study were allowed to receive supplemental opioid analgesia consistent with standard of care, and all patients were required to

use concomitant low-dose aspirin. To ensure equal distribution across treatment groups, patients were stratified by baseline cardiovascular risk (eg, aspirin use, cerebrovascular accident, history of myocardial infarction) into either a high or low risk group. Of the 1671 patients randomized in Study 93-071, 544 patients received parecoxib sodium/valdecoxib, 544 patients received placebo/valdecoxib, and 548 patients received placebo/placebo treatment. The remainder of the patients were randomized but did not receive study medication. Between 85% and 88% of the patients in each treatment group completed the study, and the duration and extent of exposure to study medication were comparable across treatment groups.

When cardiovascular-thromboembolic CRAEs were evaluated over the entire period of treatment (ie, the IV administration period and the PO administration period considered together), results from Study 93-071 confirmed the cardiovascular safety signal observed in Study 93-035 (Section 3.4.2.1): a significantly larger percentage of patients ($p = 0.033$) had cardiovascular-thromboembolic CRAEs in the parecoxib sodium/valdecoxib treatment group (11/544 patients, 2.0%) versus the placebo/placebo group (3/548 patients, 0.5%). Differences in percentages of patients with cardiovascular-thromboembolic CRAEs were not statistically significant when the placebo/valdecoxib treatment group (6/544 patients, 1.1%) was compared to the placebo/placebo treatment group.

Table 24. Cardiovascular and Renal Adverse Events Prespecified as Clinically Relevant in Coronary Artery Bypass Graft Surgery Study 93-071: IV and Oral Dosing Periods Together

(Number [%] of Patients)

Adverse Event Category Adverse Event or Subcategory	Pbo/Pbo N = 548	Pbo/Valde N = 544	Pare/Valde N = 544	p-value, Pbo/Valde vs Pbo/Pbo	p-value, Pare/Valde vs Pbo/Pbo
Cardiovascular Thromboembolic	**3 (0.5)**	**6 (1.1)**	**11 (2.0)**	**--**	**0.033**
Myocardial infarction, severe myocardial ischemia, cardiac arrest, or sudden cardiac death	0 (0.0)	2 (0.4)	4 (0.7)	--	0.061
Myocardial infarction	0 (0.0)	1 (0.2)	1 (0.2)	--	--
Cardiac arrest, non-resuscitated	0 (0.0)	0 (0.0)	1 (0.2)	--	--
Cardiac arrest, resuscitated	0 (0.0)	1 (0.2)	1 (0.2)	--	--
Sudden cardiac death	0 (0.0)	1 (0.2)	1 (0.2)	--	--
Stroke or transient ischemic attack	2 (0.4)	2 (0.4)	5 (0.9)	--	--
Cardioembolic, probable	1 (0.2)	1 (0.2)	2 (0.4)	--	--
Cardioembolic, possible	1 (0.2)	0 (0.0)	0 (0.0)	--	--
Acute ischemic stroke of unknown cause	0 (0.0)	1 (0.2)	0 (0.0)	--	--
Transient ischemic attack	0 (0.0)	0 (0.0)	3 (0.6)	--	0.123
Vascular thrombosis	1 (0.2)	0 (0.0)	0 (0.0)	--	--
Pulmonary embolism	1 (0.2)	2 (0.4)	2 (0.4)	--	--
Renal Dysfunction/Failure	3 (0.5)	4 (0.7)	7 (1.3)	--	--
Due to need for peritoneal or hemodialysis post-surgery	0 (0.0)	2 (0.4)	2 (0.4)	--	--
Due to persistently elevated serum creatinine	3 (0.5)	2 (0.4)	5 (0.9)	--	--

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.
-- Indicates p >0.20; p-values were calculated using Fisher's exact test.
Pbo = Placebo; Pare = 60 mg TDD on Day 1 and 40 mg total daily dose thereafter for 72 hours;
Valde = Valdecoxib 40 mg total daily dose for a total treatment duration (Pare = Valde) of 10 days.

When cardiovascular thromboembolic and renal dysfunction/failure CRAEs were evaluated separately for the IV and oral dosing periods in Study 93-071, no statistically significant differences were observed for either the placebo/valdecoxib treatment group or the parecoxib sodium/valdecoxib treatment group compared to the placebo/placebo treatment group (Table 25). When evaluated for the oral dosing period only, the composite CRAE endpoint, which includes gastrointestinal events and surgical wound complications in addition to cardiovascular thromboembolic events and renal dysfunction/failure events, was significantly more likely in the placebo/valdecoxib treatment group compared to the placebo/placebo treatment group. This result was driven largely by patients with surgical wound complications.

Table 25. Clinically Relevant Adverse Events in IV Versus Oral Dosing Period: Coronary Artery Bypass Graft Surgery Study 93-071

(Number [%] of Patients)

Adverse Event or Event Category	Pbo/Pbo N = 548	Pbo/Valde N = 544	Pare/Valde N = 544	p-value, Pbo/Valde vs Pbo/Pbo	p-value, Pare/Valde vs Pbo/Pbo
Any Clinically Relevant Adverse Event					
Intravenous dosing period only	5 (0.9)	10 (1.8)	13 (2.4)	-	0.061
Oral dosing period only	17 (3.4)	31 (6.2)	27 (5.3)	0.039	0.165
Any Cardiovascular Thromboembolic					
Intravenous dosing period only	1 (0.2)	3 (0.6)	4 (0.7)	-	-
Oral dosing period only	2 (0.4)	3 (0.6)	7 (1.4)	-	0.178
Myocardial[a]					
Intravenous dosing period only	0 (0.0)	2 (0.4)	1 (0.2)	-	-
Oral dosing period only	0 (0.0)	0 (0.0)	3 (0.6)	-	-
Stroke or Transient Ischemic Attack[b]					
Intravenous dosing period only	1 (0.2)	1 (0.2)	3 (0.6)	-	-
Oral dosing period only	1 (0.2)	1 (0.2)	2 (0.4)	-	-
Vascular Thrombosis					
Intravenous dosing period only	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Oral dosing period only	1 (0.2)	0 (0.0)	0 (0.0)	-	-
Pulmonary Embolism					
Intravenous dosing period only	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Oral dosing period only	1 (0.2)	2 (0.4)	2 (0.4)	-	-
Renal failure/dysfunction					
Intravenous dosing period only	3 (0.5)	4 (0.7)	6 (1.1)	-	-
Oral dosing period only	0 (0.0)	0 (0.0)	1 (0.2)	-	-

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.
- Indicates p >0.20 or could not be calculated; p-values were calculated using Fisher's exact test.
Pbo = Placebo; Pare = Parecoxib; Valde = Valdecoxib
[a] Includes cardiac arrest, non-resuscitated; cardiac arrest, resuscitated; myocardial infarction; sudden cardiac death.
[a] Includes cardioembolic, possible; cardioembolic, probable; acute ischemic stroke of unknown cause; transient ischemic attack.

3.4.2.3. General Surgery Study 93-069

In Study 93-069, treatment with parecoxib sodium/valdecoxib was evaluated at a dose of 40 mg TDD using a double-blind, parallel-group study design with IV treatment (parecoxib sodium or placebo) for 3 days followed by PO treatment (valdecoxib or placebo) for 7 days; patients with inadequate pain relief at any time during the study were allowed to receive supplemental opioid analgesia consistent with standard of care. Of the 1050 patients who received study medication, 525 patients were treated with placebo/placebo and 525 patients were treated with parecoxib sodium/valdecoxib. Approximately 88% of patients in both treatment groups completed the study. The duration and extent of exposure to study medication were comparable across treatment groups, and no significant differences were observed between

treatment groups in baseline demographics, vital signs, or medical histories and risk factors. Also, no significant differences between treatment groups were observed for the categories of general surgery performed (orthopedic, 27% of patients in both treatment groups; gastrointestinal, 38% for placebo and 36% for parecoxib sodium/valdecoxib; gynecologic, 20% for placebo and 19% for parecoxib sodium/valdecoxib; thoracic, 2% for both treatment groups; and other, 18% for placebo and 20 % for parecoxib sodium/valdecoxib) or for the details of surgical procedures.

The mean patient ages in Study 93-069 were 53-54 years across treatment groups, approximately 40% of patients were males, and more than 90% of the patients in each treatment group were white (demographics are summarized in Table 7 of the clinical study report for Study 93-069).

When cardiovascular thromboembolic CRAEs were evaluated in Study 93-069 for the entire period of treatment (ie, the IV administration period and the PO administration period considered together), no differences were observed between the parecoxib sodium/valdecoxib 40 mg TDD treatment group and the placebo/placebo treatment group (Table 26). Additionally, no statistically significant differences were observed between treatment groups when cardiovascular thromboembolic CRAEs were evaluated separately for the IV and PO administration periods.

Table 26. Cardiovascular and Renal Adverse Events Prespecified as Clinically Relevant in General Surgery Study 93-069: IV and Oral Dosing Periods Together

(Number [%] of Patients)

Adverse Event Category Adverse Event	Placebo/ Placebo N = 525	Parecoxib Sodium/Valdecoxib N = 525	p-value
Cardiovascular Thromboembolic	**5 (1.0)**	**5 (1.0)**	-
Myocardial infarction	0 (0.0)	2 (0.4)	-
Cardiac arrest or sudden cardiac death	1 (0.2)	1 (0.2)	-
Acute ischemic stroke	1 (0.2)	0 (0.0)	-
Deep vein thrombosis	2 (0.4)	1 (0.2)	-
Pulmonary embolism	1 (0.2)	1 (0.2)	-
Renal	**0 (0.0)**	**1 (0.2)**	**-**
Renal failure/dysfunction	0 (0.0)	1 (0.2)	-

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.
- Indicates p >0.20; p-values were calculated using Fisher's exact test.

When cardiovascular thromboembolic and renal failure/dysfunction CRAEs were evaluated separately for the IV and oral dosing periods in Study 93-069, no differences were observed for the parecoxib sodium/valdecoxib treatment group compared to the placebo/placebo treatment group (Table 27).

Table 27. Clinically Relevant Adverse Events in IV Versus Oral Dosing Period: General Surgery Study 93-069

(Number [%] of Patients)

Adverse Event or Event Category	Placebo/ Placebo N = 525	Parecoxib Sodium/ Valdecoxib N = 525	p-value
Any Clinically Relevant Adverse Event			
Intravenous dosing period only	6 (1.1)	3 (0.6)	-
Oral dosing period only	11 (2.1)	11 (2.1)	-
Any Cardiovascular Thromboembolic			
Intravenous dosing period only	1 (0.2)	2 (0.4)	-
Oral dosing period only	4 (0.8)	3 (0.6)	-
Myocardial infarction			-
Intravenous dosing period only	0 (0.0)	1 (0.2)	-
Oral dosing period only	0 (0.0)	1 (0.2)	-
Cardiac arrest or sudden cardiac death			-
Intravenous dosing period only	1 (0.2)	0 (0.0)	-
Oral dosing period only	0 (0.0)	1 (0.2)	-
Acute Ischemic Stroke of Unknown Cause			
Intravenous dosing period only	0 (0.0)	0 (0.0)	-
Oral dosing period only	1 (0.2)	0 (0.0)	-
Deep vein thrombosis			
Intravenous dosing period only	0 (0.0)	0 (0.0)	-
Oral dosing period only	2 (0.4)	1 (0.2)	-
Pulmonary embolism			-
Intravenous dosing period only	0 (0.0)	1 (0.2)	-
Oral dosing period only	1 (0.2)	0 (0.0)	-
Renal failure/dysfunction			-
Intravenous dosing period only	0 (0.0)	1 (0.2)	-
Oral dosing period only	0 (0.0)	0 (0.0)	-

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.
- Indicates p >0.20 or could not be calculated; p-values were calculated using Fisher's exact test.

These results, which show no cardiovascular safety signal in general surgery patients, suggest the hypothesis that the increased cardiovascular risk observed for patients treated with parecoxib sodium/valdecoxib in Studies 93-035 and 93-071 is limited to the setting of post-CABG surgery, ie, procedures involving coronary bypass in high risk cardiovascular patients, but not general surgery patients undergoing major abdominal and orthopedic procedures. This hypothesis is further confirmed by the post hoc analysis described below.

3.4.2.4. Post Hoc Analysis of Clinically Relevant Adverse Events (CRAEs): Integrated Data From General Surgery Studies

The CRAE analyses from Studies 93-069 and 93-071 provided data on specially designated categories of adjudicated adverse events. In these studies, analysis of composite CRAEs (including cardiovascular thromboembolic CRAEs, together with other CRAEs relevant to surgery patients) constituted the primary evaluation of parecoxib sodium and valdecoxib safety. In a post-hoc evaluation of integrated data from 17 general surgery and ankle sprain studies using valdecoxib 20-60 mg TDD (ie, the 18 general surgery and ankle sprain studies listed in Table 17, excluding CABG Surgery Study 93-071), adverse events were summarized for categorization as follows:

- First, WHOART preferred adverse event terms were matched as closely as possible, using best clinical judgment, to the definitions of CRAEs prespecified for Studies 93-069, and 93-071.

- Second, analyses of the specific groupings of adverse event terms identified above were compared with corresponding analyses of CRAEs from Studies 93-069, and 93-071 to confirm that both analyses yielded similar safety conclusions.

- Confirmation that the CRAE and matching WHOART preferred term analyses described above yielded similar safety conclusions validated the hypothesis that matching WHOART preferred terms could be used post hoc to evaluate the integrated dataset from 17 general surgery studies in a manner analogous to the CRAE analyses in Studies 93-069 and 93-071.

Integrated data from 17 valdecoxib general surgery studies, evaluated for CRAE-matching WHOART preferred adverse event terms as described above, indicated no significant differences between the valdecoxib 20-60 mg TDD treatment group and the placebo treatment group (Table 28). Therefore, safety concerns identified in the CABG surgery patient population are not characteristic of the broader surgery patient population.

Table 28. Analysis of Selected Cardiovascular and Renal Adverse Events Based on Matching CRAE Definitions: General Acute Pain Studies With a Valdecoxib 20-60 mg Total Daily Dose Group

(Number [%] of Patients)

	Adverse Events			Serious Adverse Events		
Adverse Event Category / Adverse Event[a]	Placebo N = 1965	Valde N = 3076	p-value	Placebo N = 1965	Valde N = 3076	p-value
Any Event	**34 (1.7)**	**41 (1.3)**	**--**	**15 (0.8)**	**15 (0.5)**	**--**
Any Cardiovascular Event	**9 (0.5)**	**6 (0.2)**	**0.114**	**8 (0.4)**	**5 (0.2)**	**0.151**
Myocardial	1 (<0.1)	1 (<0.1)	--	1 (<0.1)	1 (<0.1)	--
Cerebrovascular	2 (0.1)	1 (<0.1)	--	2 (0.1)	1 (<0.1)	--
Deep vein thrombosis	5 (0.3)	3 (<0.1)	--	4 (0.2)	2 (<0.1)	--
Pulmonary embolism	2 (0.1)	2 (<0.1)	--	2 (0.1)	2 (<0.1)	--
Any Renal Event	**1 (<0.1)**	**3 (<0.1)**	**--**	**0 (0.0)**	**2 (<0.1)**	**--**

-- Indicates p >0.20; p-values were calculated using Fisher's exact test.
Valde = Valdecoxib 20-60 mg total daily dose.
[a] Adverse events summarized in this table were identified post hoc using WHOART preferred terms that matched as closely as possible, using best clinical judgment, the clinically relevant adverse events (CRAEs) prespecified for Studies 93-069, and 93-071.

3.5. Spontaneous Reports of Adverse Events With Valdecoxib

Although it historically represents the least precise of methods for evaluation of cardiovascular risk, analysis of spontaneous reports shows results consistent with both randomized clinical trial data and epidemiology data indicating no increase in cardiovascular risk with valdecoxib.

3.5.1. Methods for Analysis

Pfizer's early alert safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported from health authorities, cases published in the medical literature, and cases of serious adverse events reported from clinical studies and Pfizer-sponsored marketing programs (solicited cases) regardless of causality. For this review the database was searched for all valdcoxib non-clinical study cases reported from 1 November 2001 through 31 October 2004.

The database was further searched to identify valdecoxib cases reporting thrombotic events (including events suggestive of coronary artery disease or thromboembolism or occlusion, cardiac ischemia, myocardial infarction, or arrhythmia events likely to be associated with coronary thromboembolism or ischemia; cerebrovascular thromboembolism or occlusion or ischemia or infarction, cerebrovascular hemorrhage, or neurologic events likely to be associated with cerebrovascular ischemia or hemorrhage; non-coronary or non-cerebrovascular thromboemolism, occlusion, ischemia, or infarction) and cardiorenal events (events suggestive of hypertension, abnormal or fluctuating or inadequately controlled or increased blood pressure, cardiac failure, or edema events possible related to hypertension or cardiac failure). Cases identified by these searches were then further reviewed to characterize the nature of any cardiovascular risk factors present.

In addition, in an effort to compare information on the reporting of these types of adverse events for COX-2 inhibitors and the conventional non-selective NSAIDs, the FDA's Adverse Event Reporting System (AERS) database available under the Freedom of Information Act was reviewed using Drug Logic's QScan (version 3.0) for information on adverse events reported to FDA for the COX-2 inhibitors valdecoxib and rofecoxib, and for the conventional NSAIDs diclofenac, ibuprofen, naproxen, and piroxicam using the same search strategy that was employed to search for valdcoxib cases in Pfizer's database.

3.5.2. Results: Spontaneous Reports of Adverse Events for Valdecoxib

Review of Pfizer's early alert safety database identified a total of 13,924 valdecoxib non-clinical study cases reported through 31 October 2004 following treatment of approximately 13.5 million patients worldwide. Of these, there were 138 cases reporting thrombotic events (of which 72 reported cardiac events, 49 reported cerebrovascular events, and 20 reported peripheral vascular events; 111 of these 138 cases met the reporting criteria for a serious case, and deaths were reported in 16 of these 111 serious cases) and 1,142 cases reporting cardiorenal events (198 of these 1142 cases met the reporting criteria for a serious case, and deaths were reported in 3 of these 193 serious cases). When the reporting of these events for valdecoxib to the FDA's AERS system was compared to the reporting of these events for rofecoxib, diclofenac, ibuprofen,

naproxen, and piroxicam, the proportion of cases reporting these events was generally greatest for rofecoxib, and the proportion of valdecoxib cases reporting these events was generally similar to the proportion of diclofenac cases reporting these events.

For valdecoxib cases reported to Pfizer, the cases reporting cardiac events, cerebrovascular events, and all thrombotic events had a greater proportion of elderly and male patients, suggesting a patient population generally already at elevated cardiovascular risk. Cases reporting these events were also more likely to have reported concomitant medications and information concerning medical history than were all valdecoxib cases, also suggesting that these cases involved patients at greater risk of adverse events. Review of the data for daily dose of valdecoxib identified no suggestion of increased risk for any of the event categories reviewed with increased dose. For cardiac, cerebrovascular, peripheral vascular, and all thrombotic events, the most commonly reported durations of therapy at event onset were ≤ 1 day and 8 days-6 months. For cases reporting cardiorenal events, the distribution of cases reporting duration of therapy at onset of the first events was similar to that of all valdecoxib non-clinical study cases. Interpretation of these data is made difficult by the fact that duration of use was unknown or not reported in more than half of the cases for all event categories reviewed. There was no apparent association between any of the event categories reviewed and concurrent aspirin therapy.

Cases where the patient was reported to have died for all event categories reviewed had a greater proportion of elderly patients than did all valdecoxib non-clinical study cases and all cases for the corresponding event categories. Cases reporting hypertension were no more likely to have reported concurrent cardiac or cerebrovascular events than were all valdecoxib non-clinical study cases, and it is unclear if such events are independent of hypertension in valdecoxib-treated patients or if hypertension-related events are underreported in valdecoxib cases reporting cardiac and/or cerebrovascular events.

Overall, this review of valdecoxib non-clinical study cases did not identify any signal indicating that valdecoxib therapy increases risk of cardiac, cerebrovascular, peripheral vascular, all thrombotic, or cardiorenal adverse events independent of the risk inherent in the patient population likely to be treated with valdecoxib.

3.6. Conclusions, Valdecoxib Cardiovascular Safety

Data presented and reviewed in this evaluation of valdecoxib cardiovascular safety support the following conclusions:

- A meta-analysis of cardiovascular safety data from randomized clinical trials in over 12,254 patients with treatment durations up to 1 year shows no increased cardiovascular thromboembolic risk for valdecoxib compared to placebo or nonselective NSAIDs (Section 3.2).

- Analysis of integrated safety data from 20 completed clinical studies, representing 4689 patients treated with valdecoxib ≥20 mg TDD, shows no cardiovascular safety risk associated with valdecoxib treatment when used for up to 14 days in acute post-surgical settings (Section 3.3).

- An increase in cardiovascular adverse events was observed with sequential parecoxib sodium/valdecoxib treatment compared to placebo treatment with exposure for up to 14 days in CABG Surgery Studies 035 and 071 (Section 3.4). CABG surgery patients represent a high-risk population due to cardiopulmonary bypass procedures and the resulting potential for a unique and highly dynamic pro-thrombotic and inflammatory syndrome. As a result, the use of parecoxib sodium or valdecoxib in the post-CABG surgery setting is contraindicated. No increases in cardiovascular adverse events were observed in any other post-surgical setting (Sections 3.4.2.3 and 3.4.2.4). However, valdecoxib safety has not been evaluated in other revascularization procedures.

- Postmarketing safety surveillance representing a total of 13,924 valdecoxib non-clinical study cases reported through 31 October 2004 following treatment of approximately 13.5 million patients worldwide does not show a cardiovascular safety signal for valdecoxib (Section 3.5).

The cumulative data presented and reviewed in this Briefing Document suggest that valdecoxib is safe and well tolerated when used as directed, presenting a cardiovascular risk profile comparable to that of nonselective NSAIDs, the most prominent alternatives for treatment of arthritis. Longer-term data and epidemiologic studies are required, however, to enhance the valdecoxib cardiovascular safety database, which is currently more limited than for celecoxib; Pfizer's initial plans to address this limitation are as described in Section 5. Cutaneous reactions need to be factored into the risk/benefit calculation for individual patients taking valdecoxib as communicated in recent additions to the Bextra US Package Insert.

4. IS INCREASED CARDIOVASCULAR RISK A CLASS EFFECT OF SELECTIVE COX-2 INHIBITORS?

Executive Summary and Conclusions: To date no specific mechanism for the increased cardiovascular risk consistently observed in patients taking rofecoxib long-term has been positively identified. In particular, there is no direct evidence that this increase in risk results from a class effect common to all selective COX-2 inhibitors, and no evidence that all selective COX-2 inhibitors have less favorable cardiovascular safety profiles than nonselective NSAIDs

- At doses well above those observed to be effectively anti-inflammatory doses, rofecoxib, celecoxib, and valdecoxib spare COX-1 activity; therefore, differences in molecular structure between rofecoxib and celecoxib or rofecoxib must account for any differences in cardiovascular risk. Differences in selectivity only become relevant at much higher doses than are used in any clinical trials or approved indications.

- In contrast to celecoxib and valdecoxib, rofecoxib promotes oxidative damage to low-density lipoprotein (LDL) and phospholipids. This may occur either via a unique interaction between rofecoxib and membrane phospholipids or via the formation of potentially toxic rofecoxib metabolites. These processes may increase cardiovascular risk via damage to endothelial cells and effects on blood pressure, and clinical studies show that treatment with celecoxib can have beneficial effects on endothelial function that are not observed with rofecoxib.

- Published data from clinical studies indicate that treatment with rofecoxib has greater effects on blood pressure than celecoxib, whereas the blood pressure effects of celecoxib and valdecoxib are comparable to those observed with nonselective NSAIDs. The incremental increase in blood pressure with rofecoxib may account for some of the increased risk observed with rofecoxib treatment.

Taken together, the observations described above suggest alternative hypotheses to explain the increased cardiovascular risk observed in patients taking rofecoxib without postulating a class effect common to all selective COX-2 inhibitors. These hypotheses are consistent with the body of clinical trial and epidemiology data presented in this Briefing Document showing that celecoxib and valdecoxib both fit into the spectrum of cardiovascular safety encompassed by nonselective NSAIDs, while rofecoxib lies outside that spectrum.

4.1. Clinical Evidence Does Not Support The Hypothesis That Prostacyclin-Thromboxane Imbalance Accounts for Increased Cardiovascular Risk

Cyclooxygenases help to regulate thrombotic homeostasis and vascular tone through conversion of arachidonic acid to intermediates necessary for the synthesis, respectively, of thromboxane A_2 (TxA_2), a promoter of platelet aggregation and vasoconstriction, and prostacyclin (PGI_2), an inhibitor of platelet aggregation and promoter of vasodilatation.[60] As a result, it has been hypothesized by FitzGerald et al. that selectively blocking COX-2 may predispose patients to increased cardiovascular risk,[61-64] including elevated blood pressure, accelerated atherogenesis, and a possibly exaggerated thrombotic response to the rupture of atherosclerotic plaques.[65] However, to date no specific mechanism for the increased cardiovascular risk observed in patients taking rofecoxib has been positively identified; in particular, there is no direct evidence that this increase in risk results from an imbalance in levels of TxA_2 versus PGI_2 like that postulated by FitzGerald et al. Moreover, there is evidence suggesting alternative hypotheses to explain the increased cardiovascular risk observed in patients taking rofecoxib, without postulating a class effect common to all selective COX-2 inhibitors.

In a pair of clinical trials with similar designs in similar numbers of OA and RA patients (>8000 patients in each trial), treatment with rofecoxib 50 mg QD (6 to 13 months in the VIGOR trial) significantly increased the risk of cardiovascular adverse events compared to treatment with naproxen 500 mg BID (relative risk 2.38, $p < 0.001$),[19] but treatment with celecoxib 800 mg QD (up to 15 months in the CLASS trial; median duration 9 months) did not significantly increase the risk of cardiovascular adverse events compared to treatment with diclofenac 75 mg BID or ibuprofen 800 mg TID ($p = 0.973$ for celecoxib versus diclofenac and ibuprofen combined).[17] FitzGerald and colleagues have suggested that one explanation for this difference in cardiovascular risk may be that celecoxib is less selective than rofecoxib for COX-2 versus COX-1 inhibition; thus, it is inferred that celecoxib is more likely to have antiplatelet effects.[66] However, treatment with celecoxib does not significantly reduce platelet aggregation ex vivo compared to either pre-treatment levels or treatment with placebo, even at a dose (1200 mg BID) greater than the 400 mg BID supratherapeutic celecoxib dose used in the CLASS trial.[67] Therefore, differences in selectivity are probably inadequate to explain the differences in cardiovascular risk observed for rofecoxib versus other selective COX-2 inhibitors in a manner consistent with the FitzGerald hypothesis, since at clinically relevant doses all of these agents remain highly selective.

Additionally, in the APPROVe trial, the subset of patients taking aspirin showed the same increase in risk for cardiovascular events as the subset of patients not taking aspirin (Section 2.4.2 and Section 2.3, respectively). This is inconsistent with the FitzGerald hypothesis, which would have predicted a reduction of relative risk with aspirin because of the putative inhibition by rofecoxib of endothelial cell-generated PGI_2 production would, in patients taking aspirin, be balanced by aspirin inhibition of platelet-generated TxA_2 production.

Alternative hypotheses to explain the adverse cardiovascular effects of rofecoxib, without postulating a class effect and probably involving mechanisms other than COX-2 inhibition, should be considered.

4.2. Alternative Hypotheses May Explain the Unique Effect of Rofecoxib on Cardiovascular Risk

4.2.1. In contrast to Celecoxib and Valdecoxib, Rofecoxib Promotes Oxidative Damage to Low-Density Lipoprotein and Phospholipids

Recently, it was demonstrated that rofecoxib, a methyl sulfone, promotes oxidative damage to LDL and phospholipids in vitro, but that the sulfonamide-type selective COX-2 inhibitors celecoxib and valdecoxib, like nonselective NSAIDs (meloxicam, diclofenac, naproxen, ibuprofen), do not.[68] This pro-oxidant activity of rofecoxib occurs in the absence of COX-2, increases with increasing rofecoxib concentration, and is attenuated in the presence of an antioxidant. Analysis using small-angle x-ray diffraction has shown that rofecoxib interacts with membrane phospholipids in a manner likely to increase permeability to free radical ions and/or free radical diffusion, whereas celecoxib does not, suggesting that such interactions tend to disrupt membrane structure and expose LDL and phospholipids to oxidative damage.[68] This finding supports the hypothesis that methyl sulfone-containing compounds like rofecoxib are unique among selective COX-2 inhibitors (and NSAIDs generally) in their ability to promote oxidative damage to both LDL and cell membrane phospholipids, using a mechanism that does not involve COX-2 inhibition. Clinically, the presence of oxidized LDL is a marker for plaque instability[69] and acute coronary syndromes.[70]

According to the oxidative-modification hypothesis of atherosclerosis, the activation of macrophages in response to uptake of oxidized LDL via the scavenger receptor[71,72] results in inflammation of the endothelium and underlying intimal tissue,[73-75] with consequences that include foam cell formation and endothelial dysfunction.[76,77] Additionally, non-enzymatic free-radical attack on arachidonic acid during lipid peroxidation can result in the formation of isoprostanes capable of acting as prostaglandin analogs. One major isoprostane product of such a reaction, 8-epi $PGF_{2\alpha}$, has biological activity similar to that of TxA_2,[78] including activation of platelets,[79] promotion of vasoconstriction,[80] and increased neutrophil adhesion.[81] The formation of both oxidized LDL and isoprostanes is significantly increased in vitro in the presence of rofecoxib but not in the presence of celecoxib.[68] These observations together suggest the hypothesis that chemical differences between selective COX-2 inhibitors of the sulfone type and the sulfonamide type, rather than the effect of selective COX-2 inhibition on PGI_2 versus TxA_2 balance, may account for at least some of the increased cardiovascular risk observed in patients taking rofecoxib, using a mechanism that promotes atherogenesis via oxidative stress.

Figure 6. Rofecoxib Increases Formation of Isoprostanes and Oxidized Low Density Lipoprotein In Vitro Through a Non-Enzymatic Process

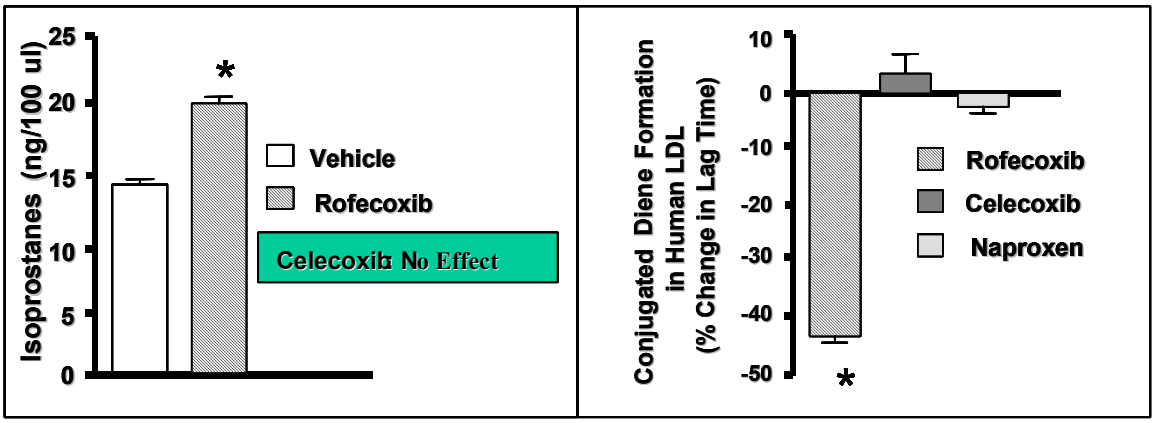


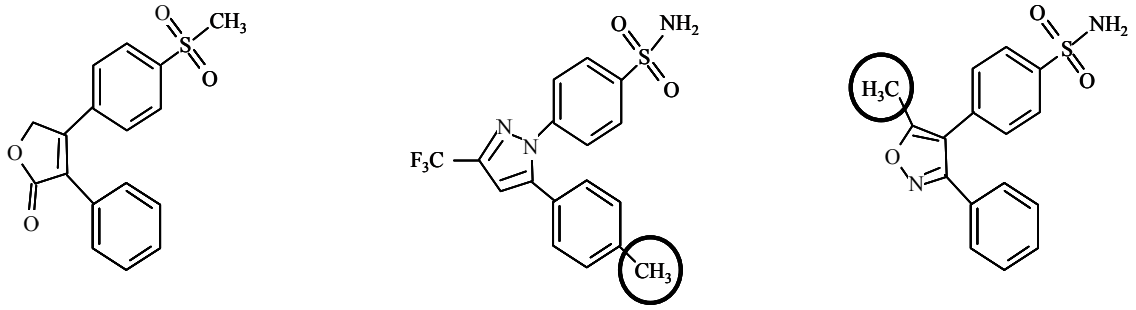
Figure adapted from Walter et al.[68]

In addition to PGI_2, a number of other factors contribute to the regulation of vasodilatation in opposition to the vasoconstrictive effect of TxA_2. Perhaps the most important of these factors is nitric oxide (NO), which is produced by the endothelium and platelets in response to a variety of stimuli including increased blood flow. In atherosclerosis, inflammation of the endothelium results in diminished capacity to produce NO, and one result is diminished ability to induce vasodilatation in response to increased blood flow, which increases blood pressure.[82] In animal models, NO has also been shown to modulate the activity of COX-2,[83] and in a head-to-head study of endothelial function in an animal model of hypertension, treatment with celecoxib significantly improved endothelial function, but treatment with rofecoxib or diclofenac did not.[84] Moreover, clinical studies have shown that celecoxib improves endothelial function in patients with hypertension or atherosclerosis, but rofecoxib does not (Section 4.2.3.2), and that rofecoxib has unique effects on blood pressure that are not shared with celecoxib or nonselective NSAIDs (Section 4.2.3.1).

4.2.2. Formation of Potentially Toxic Rofecoxib Metabolites

Structurally, rofecoxib lacks a methyl group that is present on both celecoxib and valdecoxib (circled in Figure 7). During the design of celecoxib and valdecoxib, this methyl group was added intentionally in order to ensure that each could be inactivated via a predictable, high-capacity enzyme system, namely hepatic cytochrome P450.[85,86] As a result, celecoxib and valdecoxib have more predictable metabolism than rofecoxib,[87] which is inactivated via cytosolic reductases (5-beta-reductase) to produce a variety of metabolites.[88,89]

Figure 7. Chemical Structures of Selective COX-2 Inhibitors

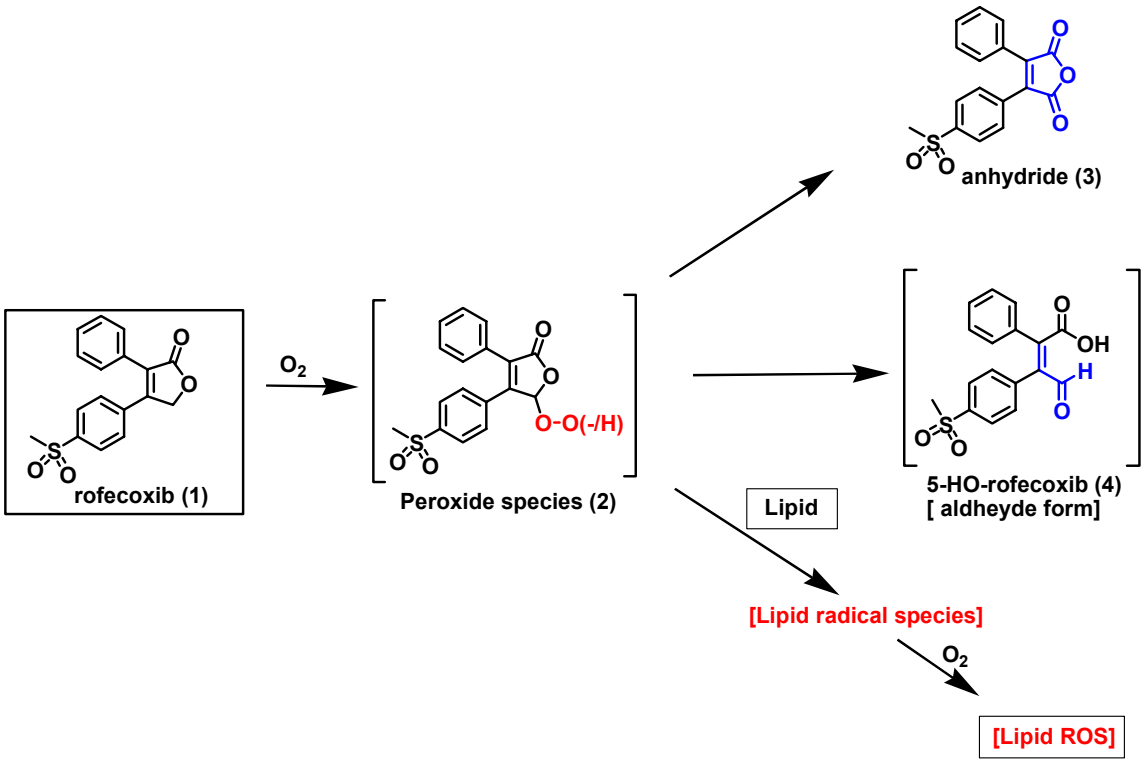


Rofecoxib Celecoxib Valdecoxib

Additionally, rofecoxib has been shown to react with oxygen to form 5-hydroxyrofecoxib (Structure 4 in Figure 8).[90] As there is a precedent for the reaction of organic compounds with oxygen to proceed through a peroxide intermediate, it is possible that a peroxide species (Structure 2 in Figure 8) is produced as an intermediate in the formation of 5-hydroxyrofecoxib. Peroxides are among reactive oxygen species known to oxidize lipids and to diminish the bioavailability of nitric oxide, an important mediator of vasodilation. Notably, following administration of a single dose of radiolabelled rofecoxib to normal human volunteers, only 86% of the original dose could be recovered, suggesting that up to 14% of the dose administered is retained in humans as metabolites.[88]

Furthermore, Reddy and Corey have reported that rofecoxib is capable of undergoing spontaneous oxidation as it circulates to oxygenated tissues in vivo, and that the resulting rofecoxib metabolites include anhydrides (Structure 3 in Figure 8) that have the potential to react with nucleophilic groups in biomolecules, especially amino acids.[91] One potential result of this reactivity may be a toxicity associated with rofecoxib that is not associated with celecoxib or valdecoxib; Reddy and Corey have hypothesized that this toxicity may have cardiovascular effects in humans that become apparent only with long-term rofecoxib treatment.

Figure 8. Chemically Active Rofecoxib Metabolites



4.2.3. Clinical Evidence Suggests Unique Effects for Rofecoxib on Blood Pressure and Endothelial Function

4.2.3.1. Blood Pressure Effects: Comparative Data for Rofecoxib and Celecoxib

Renal effects including retention of sodium and water are observed in some patients taking any drug that inhibits COX-2, including both nonselective NSAIDs and selective COX-2 inhibitors. This retention of sodium and water is thought to contribute at least in part to transient increases in mean blood pressure among patients who take NSAIDs.[92] However, meta-analyses of interventional clinical trials have shown that nonselective NSAIDs can have lasting effects on blood pressure beyond this transient effect; these analyses suggest that indomethacin, naproxen, and piroxicam produce the largest increases in blood pressure on average, and that the effect of raising blood pressure is confined primarily to patients being treated for hypertension.[2,3] This blood pressure-destabilizing effect is most prominent in patients using angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and/or diuretics (but not calcium channel blockers) to control hypertension.[4] It is believed that modulation of renal hemodynamics and tubular function by prostaglandins may contribute to blood pressure destabilization in patients taking these kinds of medications,[5] although the role of COX-2 and its inhibition in this effect is unclear.[6] Experimental studies have shown that administration of NSAIDs to susceptible individuals can increase systemic vascular resistance and reduce renal blood flow, glomerular filtration, and sodium excretion.[93] In these individuals, the combination of these mechanisms can be expected to increase the risk of developing clinical heart failure,[94] and even small increases in blood pressure similar to those associated with NSAIDs in these studies can contribute significantly to cardiovascular morbidity and mortality.[95]

In healthy volunteers treated with rofecoxib[96] or celecoxib,[97] sodium and water excretion usually returns to baseline levels within 5-7 days of continuous dosing. However, review of the clinical study database supporting the rofecoxib New Drug Application (NDA; published by the US FDA as indicated in footnotes to Table 29) showed that the percentages of patients who experienced hypertension adverse events increased in a dose-related manner across the approved rofecoxib dose range (12.5 to 50 mg per day), and that hypertension adverse events occurred in a greater percentage of patients treated with rofecoxib 25 mg QD or rofecoxib 50 mg TDD compared to patients treated with ibuprofen 2400 mg TDD or diclofenac 150 mg TDD (Table 29). Similarly, hypertension adverse events in the VIGOR trial occurred in a greater percentage of patients treated with rofecoxib 50 mg QD (8.5%, comparable to the 8.2% observed for rofecoxib 50 mg QD in the NDA database) compared to patients treated with naproxen 500 mg BID (5%).

Table 29. Hypertension Adverse Events in Rofecoxib Clinical Trials

	NDA Database[a]					VIGOR[b]	
	Rofecoxib (mg/day)			Ibuprofen	Diclofenac	Rofecoxib	Naproxen
	12.5	25	50	2400 mg/day	150 mg/day	50 mg/day	1000 mg/day
Number of Patients	1215	1614	476	847	498	4047	4029
Patients with Hypertension[c]	2.8%	4.0%	8.2%	2.9%	1.6%	8.5%	5.0%

NDA = New Drug Application; VIGOR = Vioxx Gastrointestinal Outcomes Research.
[a] Data from US Food and Drug Administration cardiovascular-renal safety review: Rofecoxib NDA 21-042. Available at: http://www.fda.gov/cder/foi/nda/99/021042_52_vioxx_medr_P34.pdf
[b] Data from US Food and Drug Administration review of cardiovascular safety database, Consultation NDA 21-042, S-007. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.doc.
[c] Indicates percentages of patients for whom hypertension was reported as an adverse event.

In contrast, review of the clinical study database supporting the celecoxib NDA (published by the FDA as indicated in footnotes to Table 30) showed no increase in percentages of patients taking celecoxib who experienced hypertension adverse events compared to patients taking NSAIDs; furthermore, in the CLASS trial, a significantly smaller percentage of patients treated with celecoxib at the supratherapeutic dose of 400 mg BID had hypertension adverse events compared to patients treated with ibuprofen 2400 mg QD (Table 30).

Table 30. Hypertension Adverse Events in Celecoxib Clinical Trials

	NDA Database[a]				CLASS[b]		
	Celecoxib (mg/day)			NSAIDs	Celecoxib	Diclofenac	Ibuprofen
	200	400	800	Any Dose	800 mg/day	150 mg/day	2400 mg/day
Number of Patients	1764	1208	99	1388	3987	1996	1985
Patients with Hypertension[c]	0.7%	1.2%	0.0%	0.9%	2.0%	2.0%	3.1%*

*P < 0.05 versus celecoxib 800 mg/day
NDA = New Drug Application; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs used as comparators, namely naproxen or diclofenac; CLASS = Celebrex Long-Term Arthritis Safety Study
[a] Data from US Food and Drug Administration review of cardiovascular safety Celecoxib NDA 20 998. Available at: http://www.fda.gov/cder/foi/nda/98/20998AP_medr_P10.pdf
[b] Data from US Food and Drug Administration Arthritis Advisory Committee meeting, February 2001. Available at: http://www.fda.gov/ohrms/dockets/as/01/briefing/3677b2_01_merck.pdf
[c] Indicates percentages of patients for whom hypertension was reported as an adverse event.

When the effects of rofecoxib 25 mg QD and celecoxib 200 mg QD were compared directly in two randomized, double-blind clinical trials involving approximately 2400 patients with controlled hypertension and osteoarthritis, significantly more patients treated with rofecoxib developed clinically significant elevations in systolic blood pressure (defined as an increase >20 mmHg together with a value >140 mmHg) compared to patients treated with celecoxib (17% for rofecoxib versus 11% for celecoxib, p = 0.0032, in one study; 14.9% for rofecoxib versus 6.9% for celecoxib, p <0.01, in the other).[98,99] Also in these 2 trials, the percentages of patients treated with rofecoxib who had clinically meaningful elevations in systolic blood pressure increased from Week 1 to Week 2 to Week 6 of treatment; such increases were not observed in patients treated with celecoxib, and mean systolic blood pressure, while increased by approximately 3 mmHg in patients treated with rofecoxib, did not increase in patients treated with celecoxib over the same period.

In a randomized, double-blind clinical trial using ambulatory blood pressure monitoring (ABPM) to evaluate the effects of rofecoxib, celecoxib, and naproxen on 24-hour mean systolic blood pressure in 404 patients with type 2 diabetes, hypertension, and osteoarthritis, rofecoxib 25 mg QD induced significant increases in blood pressure compared to baseline when measured after both 6 and 12 weeks of treatment. In contrast, celecoxib 200 mg BID and naproxen 500 mg BID were not associated with significant changes in blood pressure from baseline. The treatment difference comparing rofecoxib to celecoxib was 3.78 mmHg (95% CI: 1.18 to 6.38 mmHg, p = 0.05), while the treatment difference comparing rofecoxib to naproxen was 3.85 mmHg (95% CI: 1.15 to 6.55 mmHg).[100] Moreover, in a further study using ABPM in patients with hypertension controlled by the angiotensin-converting enzyme (ACE) inhibitor benazepril, rofecoxib 25 mg QD increased 24-hour mean systolic blood pressure by 4.5 mmHg (95% CI: 2.2 to 6.8 mmHg); in comparison, indomethacin 75 mg/day increased 24-hour mean systolic blood pressure by 2.0 mmHg (95% CI: -0.3 to 4.4 mmHg) in the same study.[22] In contrast, an ABPM study in patients with hypertension controlled by the ACE inhibitor lisinopril has shown that celecoxib 200 mg BID causes no statistically significant increase in mean blood pressure relative to placebo.[101]

In summary, these cardiorenal data show that treatment with rofecoxib results in sustained increases in systolic blood pressure of approximately 3-4 mmHg relative to treatment with celecoxib, which has a negligible effect compared to baseline. In clinical trials and epidemiologic studies, differences in systolic blood pressure of this magnitude have been associated with significantly increased incidence of myocardial infarction and stroke.[102-106]

4.2.3.2. Effects on Endothelial Function: Comparative Data for Rofecoxib and Celecoxib

In atherosclerosis, inflammation of the endothelium results in diminished capacity to produce nitric oxide (NO), which is normally produced in response to a variety of stimuli including increased blood flow. As a result, the ability to induce vasodilatation in response to increased blood flow is also diminished; thus, flow-mediated vasodilation (ie, arterial diameter after arterial occlusion with a blood pressure cuff versus arterial diameter before, usually measured using brachial artery ultrasound) can be used to evaluate endothelial function, and diminished flow-mediated vasodilation is characteristic of patients with cardiovascular disease.[82] Clinical studies to evaluate effects of rofecoxib and celecoxib on endothelial function are described below:

- In 3 randomized clinical studies designed to evaluate the impact of prolonged COX-2 inhibition on inflammation and endothelial function in patients with ischemic heart disease, rofecoxib 25 mg QD was compared versus placebo over treatment periods of 3 months,[107] 6 months,[108] and 9 months.[109] In all 3 of these studies, despite evidence of anti-inflammatory effects as expected, no significant differences were observed when patients treated with rofecoxib were compared to patients treated with placebo for endothelium-dependent vasodilation, measured as flow-mediated dilation of the brachial artery.

- In a double-blind, crossover study in which 14 male patients with severe coronary artery disease received celecoxib 200 mg BID or placebo for 2 weeks, endothelium-dependent

vasodilation was significantly improved when patients were treated with celecoxib compared to the same patients treated with placebo (3.3 ± 0.4% for celecoxib versus 2.0 ± 0.5% for placebo; p = 0.026), whereas endothelium-independent vasodilation (ie, brachial artery diameter after administration of nitroglycerin versus brachial artery diameter before) remained unchanged.[110] Also in this study, plasma levels of CRP and oxidized LDL were significantly reduced after celecoxib treatment compared to placebo, but plasma levels of PGI_2 were unchanged. These results indicate that anti-inflammatory and anti-atherogenic effects that may not have been mediated by PGI_2 accompanied the observed improvement in endothelial function.

- In a double-blind study in which 29 hypertensive patients were randomized to receive celecoxib 200 mg BID or placebo, endothelium-dependent vasodilation in patients treated with celecoxib improved significantly during the 3 hours following the first dose of study medication (from 7.9 ± 4.5% at baseline to 9.9 ± 5.1% at 3 hours; p = 0.005), and this improvement was maintained over 1 week of treatment (10.1 ± 6.1% after 1 week; p = 0.006 compared to baseline); treatment with placebo had no significant effect.[111] Also in this study, urinary metabolites of PGI_2 but not TxA_2 were significantly reduced in patients treated with celecoxib but not in patients treated with placebo, indicating that PGI_2 activity, measured as a function of urinary metabolites, does not contribute substantially to flow-mediated dilation in these patients. These findings provide insight into the causes of endothelial dysfunction in hypertension and raise the possibility that celecoxib could be beneficial for hypertensive patients.

Together with mechanistic data described above, these results indicate that although both have significant anti-inflammatory effects, rofecoxib and celecoxib may differ in their effects on endothelial function, probably through a mechanism that does not involve COX-2 inhibition. This can contribute directly to cardiovascular effects with rofecoxib and also, in turn, may inform the incremental effects of rofecoxib on blood pressure, which would also increase cardiovascular effects. This hypothesis would explain why rofecoxib is evidently an outlier with respect to cardiovascular risk, and why celecoxib and valdecoxib have cardiovascular safety profiles that fall within the range of those observed for nonselective NSAIDs in all setting in which they have been compared.

5. PLANS FOR FURTHER EVALUATION OF CARDIOVASCULAR SAFETY, CELECOXIB AND VALDECOXIB

5.1. Prospective Clinical Trials

5.1.1. The Celecoxib 4C Trial (Study A3191172)

Pfizer currently has tentative plans for a prospective clinical trial, designated Study A3191172, to explore the cardiovascular safety of celecoxib in comparison with placebo and a nonselective NSAID, diclofenac, in patients with atherosclerotic coronary artery disease and signs of inflammation (Protocol title: A Double-Blind, Double-Dummy, Randomized, Parallel-Group, Active- and Placebo-Controlled Study of the Effects of Celecoxib on Cardiovascular Events and C-Reactive Protein in Osteoarthritis Patients with Coronary Artery Disease [4C]). This study is intended to address the following concerns:

- No randomized clinical trial with chronic celecoxib dosing of any duration has been designed specifically to evaluate cardiovascular adverse events. Current long-term trials have been hampered by too few events and limited data collection to support firm conclusions or to be able to identify subsets of patients at cardiovascular risk.

- No long-term randomized clinical trial capable of assessing cardiovascular events with treatment durations longer than one year has been conducted with celecoxib in an arthritis population; such a population would represent the large majority of users of nonselective NSAIDs and selective COX-2 inhibitors in clinical practice. The fact that increased cardiovascular risk was observed in a study of aspirin used longer than 1 year in a colon cancer prevention setting[24] provides possible evidence of confounding effects in the colon cancer prevention population.

- There are scant comparative data regarding the cardiovascular safety of nonselective NSAIDs in a randomized clinical trial of more than 1 year. The preliminary results of the ADAPT study suggest the need to evaluate carefully the comparative cardiovascular safety of celecoxib versus a nonselective NSAID in addition to placebo in arthritis patients.

For this purpose, patients clinically stable after an acute coronary syndrome (ACS) with concomitant mild to moderate osteoarthritis and who have persistent evidence of inflammation (elevated CRP) will receive placebo or celecoxib 200 mg twice daily or diclofenac (sustained release) 75 mg twice daily. The primary endpoint of the study will be the time to the first occurrence of major adverse cardiovascular events (MACE) after an ACS, with MACE defined as a composite of death any cause, myocardial infarction, stroke, revascularization (percutaneous angioplasty or coronary artery bypass graft), and rehospitalization for ACS. Secondary endpoints will include the incidence of clinically significant upper and/or lower gastrointestinal events, and changes in serum levels of CRP from baseline to the end of treatment. Rigorous monitoring of cardiovascular safety will be performed by a DSMB, including blinded adjudication of all cardiovascular events. All adverse events and serious adverse events will be

processed in accordance with normal regulatory timelines, including those that are study endpoints.

As currently planned, approximately 9,480 patients with OA who have been hospitalized for an episode of ACS at least 3 months and no more than 9 months prior to enrollment and are currently clinically stable will be included in Study A3191172. After treatment initiation, study visits will occur at 2 weeks, 1, 2, 4, 8 and 12 months, and thereafter every 6 months; subjects will receive treatment and will be followed for a minimum of 18 months. During the trial period, subjects will be allowed rescue medication for breakthrough pain of their OA. Additionally, all subjects must be on low-dose aspirin (75-100 mg) with or without clopidogrel, and will receive the optimal care for their cardiac conditions, according to local norms or/and guidelines including but not limited to: statins, ACE-inhibitors, beta-blockers, and other antihypertensive medications. All subjects randomized will be provided with omeprazole 20 mg to be taken once daily as a background medication.

Protocol details for Study A3191172 will be discussed with the FDA and other regulatory agencies in the near future, so that suggestions can be incorporated into future design refinements.

5.1.2. Valdecoxib Cardiovascular Safety Trial

For similar reasons, Pfizer intends to conduct a valdecoxib cardiovascular safety study analogous to the celecoxib cardiovascular safety trial described above for celecoxib (the 4C trial, Study A3191172). The study is expected to be similar to Celecoxib Study A3191172 in design, patient population, treatment duration, and endpoints, and protocol details will be discussed with the FDA and other regulatory agencies so that suggestions can be incorporated into the study design.

D.1.2 Epidemiological Studies

Epidemiology studies either fully sponsored by Pfizer or partially funded by Pfizer IRGs that are currently ongoing or planned, in which celecoxib is among prespecified investigational study drugs, are as follows. Pfizer is supporting these studies in order to obtain additional data from actual clinical practice with celecoxib and to generate similar data for valdecoxib, for which there are currently no completed epidemiology studies:

Risk of acute myocardial infarction in users of COX-2 specific inhibitors in Saskatchewan, Canada.
Principal investigator - Varas-Lorenzo C, Pfzer Global Epidemiology
Study ongoing. Final report/manuscript 3Q05
Retrospective cohort study with a nested case-control analysis conducted in the Saskatchewan Health Services database to estimate the risk of acute myocardial infarction and coronary death in subjects aged 40-84 users of celecoxib, rofecoxib, and nonselective NSAIDs between November 15, 1999 and December 31, 2001. Effects of dose, duration and concomitant medications will be studied. Cases were identified using ICD-9 codes from Hospital Discharge Services and Vital Statistics. Case validation is conducted for a random sample of 200 identified cases of acute myocardial infarction (ICD-9 code 410) and all patients with an ICD-9 code 411.

Risk of acute myocardial infarction in users of valdecoxib and other COX-2 specific inhibitors in Medicare, US (IRG).
Principal investigator - Solomon DH, Harvard Medical School
Study ongoing. Final report/manuscript 2Q05
Retrospective cohort study conducted using the Pennsylvania and New Jersey Medicare databases to estimate the risk of cardiovascular (acute myocardial infarction and coronary death) and cerebrovascular events (ischemic stroke) associated with the use of COX-2 specific inhibitors, including valdecoxib, celecoxib and rofecoxib, and nonselective NSAIDS during the years 2002 and 2003. Cases are identified using ICD-9 codes from Hospital Discharge Services and Vital Statistics. Case validation will be not conducted. Confounders such as over-the-counter NSAIDs and ASA use, body mass index, smoking and socio-economic status will be estimated through a survey. The exposure assessment will be studied for low and high doses and for current and past users.

Risk of acute myocardial infarction in patients with osteoarthritis and rheumatoid arthirits in MediCal, US (IRG).
Principal investigator - Singh G, Institute for Clinical Outcomes Research and Education (ICORE)/Stanford University
Study ongoing. Final report/manuscript 2Q05
ICORE is involved in conducting cardiovascular outcomes research in a number of therapeutic areas, supported in part by unrestricted research grants from multiple organizations and companies. One of the many studies conducted by ICORE scientists is a nested case-control study conducted in the MediCal Healthcare System database to estimate the risk of acute myocardial infarction associated with the use of COX-2 specific inhibitors, valdecoxib, celecoxib and rofecoxib, and nonselective NSAIDS in patients aged over 18 years with arthritis (OA/RA) and/or musculoskeletal disorders. Cases are identified using ICD-9 and CPT codes from reimbursement records. There is no medical record case validation conducted. The effect of dose, recent use, over-the-counter NSAIDs and aspirin use and other risk factors is also assessed.

Risk of acute myocardial infarction in a high risk population (Medicaid Tennessee/ Saskatchewan, Canada/GPRD UK).
Principal investigator - Ray W, Vanderbilt University
Study ongoing. Final report/manuscript 4Q05
Retrospective cohort study conducted in the Medicaid Tennessee, the Saskatchewan Health Services and the United Kingdom General Practice Research (GPRD) databases to estimate the risk of recurrent cardiovascular heart disease (myocardial infarction, unstable angina, and revascularization procedures) associated with the use of COX-2 specific inhibitors, celecoxib and rofecoxib, and nonselective NSAIDs in patients older than 40 years from January 1, 1999 to December 31, 2003. Cases will be identified using ICD-9 codes from Hospital Discharge Services and Vital Statistics. Case validation will be partially conducted. The effect of low and high dose, risk factors and concomitant medications will also be studied.

Risk of acute myocardial infarction in France – CADERIS, France.
Principal investigator - Moore N, Victor Segalen University, Bordeaux, France
Pilot study ongoing. Final report October 2005
Phase IV commitment cohort study conducted in France among users of COX-2 specific inhibitors and nonselective NSAIDs with the objective of estimating the risk of cardiovascular events, including myocardial infarction, associated with the use of these drugs. The study includes a total of 44,746 users identified in the ERASME database. Assessment of events is conducted through a questionnaire sent by mail to users and physicians.

Risk of cerebrovascular events associated with the use of COX-2 inhibitors in Medicaid Tennessee, US. Principal investigator - Griffin M, Vanderbilt University
Study ongoing. Final report/manuscript 4Q05
Retrospective cohort study conducted in the Medicaid Tennessee database to assess the risk of cerebrovascular diseases (ischemic and hemorrhagic stroke) in patients aged 50 to 84 years associated with the use of COX-2 specific inhibitors, including valdecoxib, celecoxib, and rofecoxib, and nonselective NSAIDS, between January 1, 1999 and June 30, 2003. Cases will be identified using ICD-9 codes from Hospital Discharge Services and Vital Statistics. A random sample of 100 study cases will be validated.

6. BENEFIT/RISK ASSESSMENT, CELECOXIB AND VALDECOXIB

6.1. Arthritis and Pain Are Prevalent and Require Treatment

An estimated 17 million patient in the US use NSAIDs on a daily basis,[112] and each year health care providers write approximately 60 million prescriptions for various NSAIDs. These agents have been widely used for decades despite their risks because they serve a significant medical need and allow mobility and relief from chronic pain. Due to this widespread use, concern regarding the risk of gastrointestinal adverse effects with nonselective NSAIDs, together with new concerns regarding possible cardiovascular safety signals recently observed in preliminary data from the APPROVe, APC, and ADAPT trials, will complicate benefit/risk considerations for both nonselective NSAIDs and selective COX-2 inhibitors. Approximately 3.6 times as many NSAID prescriptions are written for elderly patients compared to younger patients.[113] Eighty percent of the US population >65 years of age have x-ray evidence of OA and virtually all have OA by the age of 80,[114] and half of all NSAID prescriptions in the elderly are for this indication.[115] This will affect large numbers of patients in the US and worldwide, and the problem will increase in scope as populations increase in average age: Increased use of nonselective NSAIDs in an aging population will increase the numbers of gastrointestinal, cardiorenal, and possibly cardiovascular adverse events related to NSAID use. It has been estimated that 5% to 7% of US hospital admissions are related to adverse effects associated with medication use, and hospitalizations for gastrointestinal, nervous system, renal, or allergic effects associated with use of aspirin or non-aspirin nonselective NSAIDs are responsible for approximately 30 percent of this total.[116]

The various NSAIDs have proven effective in the treatment of a variety of acute and chronic painful and inflammatory musculoskeletal conditions including OA, which affects 16-20 million US patients, most of them elderly.[117] In OA patients the balance of positive effects measured against the potential adverse effects is particularly critical given the increased potential for NSAID-induced toxic effects mediated partially by age.

6.2. Nonselective NSAIDs and Selective COX-2 Inhibitors Treat Pain and Inflammation Effectively

FDA approval of celecoxib with indications for OA and RA was based on demonstration of equivalent efficacy versus nonselective NSAIDs in 5 clinical trials involving >5200 patients; all 5 of these trials had similar parallel-group designs comparing celecoxib at various doses to placebo and naproxen. Statistically significant improvement on multiple co-primary endpoints was observed for celecoxib ≥100 mg BID compared to placebo, and similar improvement compared to naproxen, was observed in all 5 of these studies, including replicate studies in OA patients and in RA patients. Evidence of efficacy comparable to both naproxen and diclofenac in both OA and RA patients has been observed in published clinical trials also.[118-121] Similar evidence of equivalent efficacy in OA for rofecoxib versus diclofenac[122] and ibuprofen[123,124] and in RA for valdecoxib versus naproxen[125] has also been published.

A controversial question in the management of OA is whether NSAIDs are superior to simple analgesics with respect to pain relief. Unfortunately, NSAIDs do not seem to affect the pathophysiology of joint destruction in OA, whether by reducing osteophyte formation, protecting cartilage or preventing mechanical mal-alignment. However, NSAIDs have been shown to provide benefits including reduced pain, decreased gel phenomena, and improved function in OA patients;[126] it is not clear whether any of these benefits are due specifically to anti-inflammatory effects. Recently, two important trials have revisited the question of the importance of NSAIDs in the treatment of patients >40 years of age with OA of the hip or knee. These double-blinded, randomized, controlled trials used a crossover design to compare the effects of NSAIDs for analgesia with acetaminophen; hence, each patient provided data for both NSAID treatment and the acetaminophen control. Patients were treated for six weeks in each of 2 treatment periods, with a washout period separating the 2 treatment periods; treatments were diclofenac/misoprostol, (a nonselective NSAID and gastroprotectant in fixed combination) 75 mg/200 mcg BID versus acetaminophen 1000 mg QID in one trial,[127] and celecoxib 200 mg/day versus acetaminophen 4000 mg/day in the other.[128] In the respective trials, both diclofenac/misoprostol and celecoxib were superior to acetaminophen in all FDA-required outcome measures, ie, patient assessment of pain using visual analog scale (VAS); the Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC), an assessment of functional outcome; and a patient global measure. Adverse events were significantly more common with diclofenac/misoprostol treatment but not with celecoxib treatment compared to acetaminophen, and patient preferences significantly favored both diclofenac/misoprostol and celecoxib over acetaminophen. A third trial of somewhat different design has shown similar results comparing diclofenac versus acetaminophen in a similar patient population. Together, these data suggest that in patients whose pain is associated with a low-grade inflammatory process, medications with both anti-inflammatory and analgesic activities provide superior efficacy compared to a simple analgesic.

6.3. Selective COX-2 Inhibitors Offer a Gastrointestinal Benefit

The incidence rate for serious gastrointestinal complications among non-users of NSAIDs is 0.9 events per 1000 person-years (95% CI: 0.66 to 1.27) for bleeding or perforated lesions, and 1.0 events per 1000 person-years (95% CI: 0.83 to 1.15) for serious gastrointestinal ulcer; rates increase with age, and are approximately twice as high in men compared to women.[129] In a systematic review of epidemiology studies conducted from 1990 to 1999, the risk of upper gastrointestinal bleeding was four times greater in nonselective NSAID users relative to non-users of NSAIDs (pooled relative risk 3.8; 95% CI, 3.6 to 4.1).[130]

Because COX-1 acts constitutively in the gastric mucosa to produce prostaglandins that promote generation of a protective mucous barrier lining the gastric lumen,[131-133] the most clinically significant and well-characterized adverse effects with nonselective NSAIDs are related to the degradation of this protective barrier. As a result, such agents may precipitate a variety of pathologies including esophagitis, esophageal stricture, gastritis, mucosal erosions, hemorrhage, the development of peptic ulcer or its complications including perforation and obstruction.[134-138] Additionally, there is increasing evidence of small and large bowel mucosal effects including induction of both gut permeability dysfunction and strictures with resulting obstruction.[139-141]

It has been demonstrated by endoscopic studies that nonselective NSAIDs classically produce shallow erosions or submucosal hemorrhages which can occur at any site in the alimentary tract but more commonly are observed in the stomach near the prepyloric area and the antrum. Typically, many of these gastrointestinal lesions are asymptomatic, making prevalence data very difficult to determine. Unfortunately, we also do not know what proportion of these lesions typically progress to develop ulceration and then extend to frank perforation, obstruction of the viscous, or serious gastrointestinal hemorrhage and subsequent death. Although many patients develop important gastrointestinal damage with no warning, there are known risk factors for the development of gastrointestinal effects with nonselective NSAIDs. These risk factors include increased age; history of peptic ulcer disease or gastrointestinal bleeding; prior use of antiulcer therapy for any reason; concomitant use of glucocorticoids, particularly in patients with rheumatoid arthritis; comorbid illness such as significant cardiovascular disease; and extensive or severe rheumatoid arthritis.[142-145] Additionally, combinations of NSAIDs can increase the risk for significant gastrointestinal adverse effects, and all of the presently available nonselective NSAIDs when used at high enough anti-inflammatory doses may induce significant GI mucosal damage.

Thus, the nonselective NSAIDs are clearly associated with increased risk for clinically important gastrointestinal events that may lead to increased risk of death directly related to therapy. The COX-1 sparing effects of celecoxib and valdecoxib are associated with evidence of less mucosal damage as demonstrated in several trials. Representative of these results from surveillance endoscopy is a trial in which 688 patients with rheumatoid arthritis were randomly assigned to various doses of celecoxib or to naproxen or placebo for 12 weeks.[118] All doses of celecoxib and naproxen improved signs and symptoms of arthritis compared to placebo. The incidence of endoscopically determined gastroduodenal ulcers among patients taking celecoxib was similar to that observed with placebo (approximately 4%) and was significantly lower than observed with naproxen (26%). Both valdecoxib and rofecoxib provide similar benefits.

Recent epidemiology studies estimate the relative risk of upper gastrointestinal bleeding in celecoxib users to be 1.0 to 1.7.[146-148] Pooled data from randomized, controlled trials in the celecoxib NDA (14 trials in OA and RA patients) show significantly reduced incidence of complicated ulcers with celecoxib compared to naproxen, and data from the SUCCESS-1 and CLASS trials show significantly reduced incidences of a composite of symptomatic ulcers and complicated ulcers with celecoxib compared to naproxen and ibuprofen, respectively. Significant benefits were also observed for celecoxib versus naproxen, ibuprofen, and diclofenac in most comparisons for endoscopic ulcers, blood loss, and gastrointestinal tolerability.

In summary, randomized controlled trials show that celecoxib has a favorable gastrointestinal safety profile compared to naproxen and ibuprofen, and that valdecoxib is associated with a lower risk of ulcer complications compared to combined nonselective NSAIDs. Also, epidemiology studies indicate that unlike nonselective NSAIDs, celecoxib is not associated with increased risk of gastrointestinal bleeding. Together, these observations suggest that the medical need for improved gastrointestinal safety is fulfilled with selective COX-2 inhibitors.

6.4. Cardiovascular Safety Signals With COX-2 Inhibitors are Inconsistent and Uncertain

The possibility of increased cardiovascular risk with rofecoxib was first evident in clinical trials data with the results of the VIGOR trial, in which 8076 patients with OA or RA were treated for a median duration of 8 months with rofecoxib or naproxen (Section 2.4.2). The recent preliminary observation of increased cardiovascular risk with rofecoxib compared to placebo in the APPROVe trial is consistent with the VIGOR result, and shows increased risk with increasing rofecoxib dose (Section 2.3). Also consistent with these observations are the results of 4 out of 5 published epidemiology studies in which myocardial infarction has been compared in users of selective COX-2 inhibitors, users of nonselective NSAIDS, and non-users of NSAIDs (Section 2.5.2.1); these 4 studies all show significantly increased risk of myocardial infarction in rofecoxib users compared to users of nonselective NSAIDs or non-NSAID users.

In contrast, no cardiovascular safety risk was observed for celecoxib relative to naproxen and diclofenac in the CLASS trial, in which 7968 patients were treated for a median duration of 9 months at a dose that was supratherapeutic relative to the approved doses in OA and RA patients (Section 2.2.3.3.2). Neither is any increase in cardiovascular safety risk observed for celecoxib compared to placebo or nonselective NSAIDs in the new Pfizer meta-analysis presented in Section 2.2, which represents >44,000 treated patients in 41 clinical studies. Also, in 5 out of the 5 published epidemiology trials described above, no increase in risk of myocardial infarction was observed for celecoxib at any dose compared to users of nonselective NSAIDs or to non-NSAID users; in 4 out of these 5 studies, the risk of myocardial infarction was significantly increased in rofecoxib users compared to celecoxib users.

All of the above, which was known prior to the release of preliminary cardiovascular safety results from the APC, PreSAP and ADAPT trials in December 2004, suggests quite strongly that not all selective COX-2 inhibitors are alike with respect to cardiovascular risk. Additional evidence in support of this hypothesis comes from a recently published trial in which 18,325 patients with OA were treated with lumiracoxib, naproxen, or ibuprofen for 18 months, with no increase in cardiovascular risk for patients treated with lumiracoxib compared to patients treated with naproxen or diclofenac (Section 2.3).

Preliminary results from the APC, PreSAP, and ADAPT trials, in which patients have been treated with high-dose celecoxib for 33, 33, and 18 months, respectively (Section 2.3), show increased incidence of serious cardiovascular thromboembolic adverse events for celecoxib compared to placebo in one trial (APC) but no increase compared to placebo in 2 others (PreSAP and ADAPT). This observation of increased events in a single trial runs counter to all other evaluations of celecoxib cardiovascular safety outcomes to date, as described above. Moreover, increased cardiovascular safety risk was evident for naproxen in one of these trials (ADAPT), and a cardiovascular safety signal has been associated with aspirin in a similar trial (Section 2.4.3), calling into question the suitability of cancer prevention trials like APC, PreSAP, and ADAPT (and APPROVe) for the evaluation of cardiovascular risk.

Given the unclear picture provided by outcome trials to date, as described above, it is impossible to make a definitive statement regarding the cardiovascular safety of selective COX-2 inhibitors as a class. Moreover, clinical studies of effects on blood pressure and endothelial function

distinguish between rofecoxib on the one hand and celecoxib, together with nonselective NSAIDs, on the other: Over and above the increased risk of fluid retention, hypertension, and other renal effects common to nonselective NSAIDs and COX-2 inhibitors due to inhibition of prostaglandin-dependent renal compensatory mechanisms, treatment with rofecoxib has been shown to result in sustained, incremental blood pressure effects that may contribute to increased risk of cardiovascular events. There is evidence that structural features of the rofecoxib molecule not shared with other selective COX-2 inhibitors can promote damage to LDL and membrane phospholipids in vitro in a manner that suggests a mechanism for these effects that is unique to rofecoxib.

If the effects of nonselective NSAIDs and selective COX-2 inhibitors on fluid retention and hypertension risk lie along a spectrum, evidence to date places celecoxib at the end of the spectrum that represents mild effects. Other nonselective NSAIDs likely fall in the middle of such a spectrum, as does valdecoxib, while rofecoxib has consistently shown itself to be at the higher end of the spectrum. Although these effects are usually manageable, they may be a major contributor to the overall risk of cardiovascular events among chronic users of these agents.[149]

Although data from the current prospective outcomes trials are too limited to draw any conclusion, epidemiology data suggest that with respect to cardiovascular outcomes, nonselective NSAIDs may again represent a spectrum of risk, since relative risks for myocardial infarction range from <1 to 1.7 for various nonselective NSAIDS across several studies. Clinical trial and epidemiology data to date again place celecoxib at the mild end of such a spectrum, together with naproxen, and rofecoxib appears to be an outlier at the upper end, beyond the range defined by NSAIDs in most epidemiology studies (current data may not be sufficient to indicate a place on this spectrum for valdecoxib). An important caveat, however, is that clinical setting can be an important variable in the evaluation of cardiovascular risk.

As demonstrated in this document, in the short-term clinical trial setting (up to one year), both celecoxib and valdecoxib have shown a similar cardiovascular safety profile compared to nonspecific NSAIDs, while rofecoxib in this setting showed increased cardiovascular risk. No trials longer than 1 year have been performed with arthritis patients, but in the setting of long-term prevention trials the selective COX-2 inhibitors, like the less well-studied nonselective NSAIDs, have shown mixed results. It remains likely that as more definitive long-term studies are performed specifically to evaluate cardiovascular events, an overlap in the safety profiles of selective COX-2 inhibitors and nonselective NSAIDs will be observed, with individual drugs in both classes defining a spectrum of effects in this setting as well.

6.5. Benefit/Risk Conclusions

For patients with chronic inflammatory pain, there are few therapeutic alternatives. Opioids are not effective against inflammatory conditions and are addictive, and acetaminophen efficacy is inadequate for many of these patients. The only remaining options are NSAIDs, whether nonselective or selective COX-2 inhibitors. As a result, patients requiring this type of relief who discontinue treatment with selective COX-2 inhibitors will turn to nonselective NSAIDs.

Weighing the available total evidence, it appears that, as with the nonselective NSAIDs, all selective COX-2 agents are not alike. Furthermore, there is clear evidence that there are some

patients who derive significant benefits from the use of the selective COX-2 inhibitors. These medications are equally efficacious compared to nonselective NSAIDs in multiple chronic and acute situations. In addition, for certain patients the selective COX-2 inhibitors provide a better gastrointestinal safety profile than do the nonselective NSAIDs. These patients are typically older and require chronic pain relief, but are at higher risk for gastrointestinal adverse events and associated complications. However, it is also clear that these patients may have an increased risk for cardiovascular thromboembolic events. Only further study will allow an understanding of those risks weighed against the known risks for gastrointestinal complications and whether all of the selective COX-2 inhibitors carry the same risk. Given the available data showing comparability of cardiovascular safety for celecoxib versus nonselective NSAIDs and the emerging data regarding cardiovascular safety for valdecoxib in similar settings, it is highly important to continue to allow access to these drugs.

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