Clinical Study Report

Reference P078

Reference P078

MRL Clinical Study Report: MK-0966 For The Treatment Of Mild Cognitive Impairment and Prevention Of Conversion To Alzheimer's Disease (Protocol 078)

Reference
Reports of Efficacy and Safety Studies

CLINICAL STUDY REPORT

MK-0966

MK-0966 FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT AND PREVENTION OF CONVERSION TO ALZHEIMER'S DISEASE

Generic Name: Rofecoxib	Protocol 078
Dosage Form: 25 mg	Phase III
Indication: Mild Cognitive Impairment	Study Design: Placebo-controlled, parallel-groups, double-blind (with in-house blinding). Endpoint driven: 220 endpoints achieved or maximum of 4 years.
Sponsor Name:	Merck & Co., Inc.
Clinical Monitor:	W. Hester Visser, M.D., Ph.D.
Study Initiation Date (FPI):	29-Apr-1998
Study Completion Date (LPO):	23-Apr-2003
Investigator Name/Affiliation:	Multicenter (46)
GCP Compliance:	Information regarding GCP compliance can be found in Sections 5.6 and 6.2
Clinical Study Report Date:	24-Nov-2003
Interim CSRs for the same Protocol:	none

CLINICAL STUDY REPORT

MK–0966 FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT AND PREVENTION OF CONVERSION TO ALZHEIMER'S DISEASE

TABLE OF CONTENTS

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive subset
ALT	Serum alanine aminotransferase
AN	Allocation number
APaT	All patients as treated
ApoE	Apolipoprotein E
APTC	Antiplatelet Trialists' Collaboration
AST	Serum aspartate aminotransferase
AVLT	Auditory Verbal Learning Test
BDS-ADL	Blessed Dementia Scale-Activities of Daily Living
BPH	Benign prostatic hypertrophy
BUN	Blood urea nitrogen
CBC	Complete blood count
CDR	Clinical Dementia Rating
CHF	Congestive Heart Failure
CHO	Chinese hamster ovary
CI	Confidence interval
COX	Cyclooxygenase
CSF	Cerebral spinal fluid
CSS	Comprehensive study summary
CSR	Clinical study report
CT	Computerized tomography
CV	Cardiovascular
DAP	Data analysis plan
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
GI	Gastrointestinal
HamD	Hamilton Depression
HCT	Hematocrit
HGB	Hemoglobin
HR	Heart rate
HRT	Hormone replacement therapy
IC_{50}	Inhibitory concentration 50 percent
IRB	Institutional Review Board
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
LOCF	Last observation carried forward
MAP	Mean Arterial Pressure
MCI	Mild Cognitive Impairment

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (CONT.)

MHIS	Modified Hashinski Ischemia Scale
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
MRL	Merck Research Laboratories
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NSAID	Nonsteroidal anti-inflammatory drug
PDLC	Predefined limits of change
PP	Per protocol
PUB	Perforations, ulcers, and bleeds
RBC	Red blood (cell) count
SOP	Standard operating procedure
SRT	Selective Reminding Test
SSRIs	selective serotonin reuptake inhibitors
T4	Thyroxine
TSH	Thyroid stimulating hormone
ULN	upper limit of normal
VIGOR	VIOXX Gastrointestinal Outcomes Research
WAES	Worldwide Adverse Experience System
WBC	White blood (cell) count

LIST OF TABLES

LIST OF TABLES (CONT.)

LIST OF TABLES (CONT.)

LIST OF TABLES (CONT.)

LIST OF TABLES (CONT.)

LIST OF TABLES (CONT.)

LIST OF TABLES (CONT.)

LIST OF FIGURES

LIST OF FIGURES (CONT.)

MERCK RESEARCH LABORATORIES

CLINICAL STUDY REPORT
I. SYNOPSIS

MK-0966
Rofecoxib, 25 mg
Mild Cognitive Impairment

PROTOCOL TITLE/NO.: MK-0966 For The Treatment of Mild Cognitive Impairment and Prevention of Conversion to Alzheimer's Disease #078

INVESTIGATORS/STUDY CENTERS: Multicenter (46)

PRIMARY THERAPY PERIOD: 29-Apr-1998 to 23-Apr-2003 **CLINICAL PHASE:** III

DURATION OF TREATMENT: Forty-eight months on rofecoxib 25 mg or matching placebo or until 220 endpoints of investigator-confirmed Alzheimer's disease (AD) were reached.

OBJECTIVES: (1) To evaluate the efficacy of rofecoxib 25 mg compared to placebo for the prevention of AD in patients with mild cognitive impairment (MCI). (2) To evaluate the safety and tolerability of rofecoxib 25 mg compared to placebo in patients with MCI.

STUDY DESIGN: Placebo-controlled, parallel-group, 48 months, double-blind study (with in-house blinding).

PATIENT ACCOUNTING:			
	Rofecoxib 25 mg n (%)	Placebo n (%)	Total n (%)
Screening failures			1392
Number of patients enrolled (total)	725	732	1457
Male (age range—years)	476 (63 to 94)	504 (64 to 95)	980(63 to 95)
Female (age range—years)	249 (64 to 95)	228 (64 to 93)	477(64 to 95)
Completed study:[†]	117 (16.1)	148 (20.2)	265 (18.2)
Completed study on drug	79 (10.9)	119 (16.2)	198 (13.6)
Completed study off drug[‡]	38 (5.2)	29 (4.0)	67 (4.6)
Discontinued from study (total):[§]	608 (83.8)	584 (79.8)	1192 (81.8)
Discontinued study on drug	446 (61.5)	439 (60.0)	885 (60.7)
Discontinued study off drug[¨]	162 (22.3)	145 (19.8)	307 (21.1)
Discontinued study medication (total)[¶]	646 (89.1)	613 (83.7)	1259 (86.4)
Discontinued study medication due to:			
Adverse experience (Clinical and Laboratory)	185 (25.5)	159 (21.7)	344 (23.6)
Lost to follow-up	18 (2.5)	16 (2.2)	34 (2.3)
Other (also includes Patient moved, Uncooperative, Protocol deviation)	106 (14.6)	104 (14.2)	210 (14.4)
Withdrew consent	129 (17.8)	154 (21.0)	283 (19.4)
Reached endpoint on drug and discontinued study per protocol[#]	89 (12.3)	63 (8.6)	152 (10.4)
Administrative Reasons (Site terminated by Merck & Co., Inc.; Merck & Co., Inc. terminated study ; Site closed itself)	119 (16.4)	117 (16.0)	236 (16.2)

[†] The counts of patients who completed (and subgroups) includes 4 patients who reached the study endpoint at the Month 48 study visit: n=2 and 2, for rofecoxib and placebo, respectively. One placebo patient was on drug, and 1 placebo and 2 rofecoxib patients were off study drug, at the time of study completion and reaching endpoint.
[‡] These patients discontinued study drug and remained in study follow-up for 48 months study completion.
[§] The counts of patients who discontinued the study include 191 patients who reached study endpoint.
[¨] These patients discontinued study drug and subsequently discontinued the study.
[¶] Category includes those patients who discontinued study drug and study simultaneously and those who discontinued study drug and continued in follow-up.
[#] There were an additional 21 (2.9%) patients in the rofecoxib group and 18 (2.5%) patients in the placebo group who reached endpoint off drug and discontinued study per protocol.
n = Number of patients in each category.

DOSAGE/FORMULATION NOS.: Oral administration of 25-mg tablet once per day. Rofecoxib 25 mg in 6 formulation numbers: MR-3724, MR-3726, MR-3491, MR-3489, MR-4185, MR-4325; and placebo to match rofecoxib (25 mg): MR-3530, MR-3552, MR-3361, MR-3734, MR-3736.

DIAGNOSIS/INCLUSION CRITERIA: Male and female patients, ages 65 and older, with MCI and a Mini-Mental State Examination (MMSE) score of ≥24. No more than 20% of patients enrolled at each study site could take vitamin E supplements >400 IU daily. Patients could not have used nonsteroidal anti-inflammatory drugs (NSAIDs) (including VIOXX™[†] or CELEBREX™ [celecoxib, G. D. Searle & Co.]) on a chronic basis (defined as ≥7 total days out of the last 30 days for 2 consecutive months prior to potential study entry), or have been on estrogen replacement therapy (excluding topical ointments) within 2 months of study entry.

EVALUATION CRITERIA:

Efficacy Measurements: The primary efficacy measurement was incidence of clinically diagnosed AD (possible or probable according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria confirmed by the investigator and agreed upon by consensus of the Endpoint Adjudication Committee (EAC). Other exploratory efficacy endpoints were reducing the decline of SRT, MMSE , ADAS-Cog and the CDR sum of box scores.

Safety Measurements: Prestudy measurements included physical examination, vital signs, serum chemistry, complete blood count, urinalysis, electrocardiogram (ECG), and stool hemoccult. During treatment, physical examination, vital signs, serum chemistry, complete blood count, urinalysis, and ECG were assessed. Safety was evaluated by tabulation of adverse experiences (clinical and laboratory) and laboratory abnormalities, as well as by statistical and clinical review of laboratory values and vital signs.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy:. The primary endpoint for the efficacy analysis was those patients who converted from MCI to probable or possible AD as confirmed by the investigator and the EAC. Other exploratory efficacy endpoints were investigator diagnosis of AD and investigator diagnosis of dementia. Other exploratory efficacy measures were slope estimates of the Selective Reminding Test (SRT), MMSE, Alzheimer's Disease Assessment Scale-Cognitive subset (ADAS-Cog) and the CDR sum of box scores. The primary analysis was based on the intention-to-treat (ITT) approach, which included all patients regardless of whether a patient discontinued study therapy or was a protocol violator. The per-protocol (PP) approach excluded patients who violated certain prespecified aspects of the protocol. Those who violated eligibility at baseline were excluded from the PP efficacy analysis. Those who violated concomitant therapy requirements were censored at the time the violation occurred. The PP analysis did not exclude patients who remained in the study but were not taking study drug.

Safety: A primary safety analysis evaluated all adverse experiences that occurred when patients were on treatment and up to 14 days following discontinuation of study drug. A secondary analysis, using an ITT approach, included all adverse experiences regardless of whether patients were on or off study drug. All safety analyses were based on the all-patients-as-treated (APaT) population, which consisted of all randomized patients who received one or more doses of test drug therapy (only patients who were documented to have never received study medication were excluded from analyses). Proportions of patients with adverse experiences by body systems were tabulated by treatment group. The difference of proportions between treatment groups and associated 95% confidence intervals (CIs), as calculated by Miettinen and Nurminen's method, were provided.

[†] VIOXX is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

A statistical comparison of the differences in proportions of patients with adverse experiences was conducted using the Fisher's exact test for the following clinical adverse experiences: (1) at least one adverse experience; (2) drug-related adverse experiences; (3) serious adverse experiences; (4) serious and drug-related adverse experiences; (5) deaths; (6) discontinuations from study therapy due to an adverse experience; and for tables of special interest including (7) discontinuation of study therapy due to gastrointestinal (GI) adverse experiences, (8) edema-related adverse experiences, (9) hypertension-related adverse experiences, and (10) adverse experiences associated with congestive heart failure (CHF). The corresponding risk differences and 95% CIs were provided. No formal hypotheses were prespecified for statistical testing for individual adverse experience types within a body-system category.

Adjudicated outcomes were provided for suspected upper gastrointestinal (GI) perforations, ulcers, and bleeds (PUBs), serious vascular events, and deaths. Statistical analyses were performed on adjudicated outcomes.

Formal statistical testing was conducted using Fisher's exact test for the following laboratory adverse experiences: (1) at least one laboratory adverse experience; (2) drug-related laboratory adverse experience; (3) serious laboratory adverse experience; and (4) discontinued study therapy due to a laboratory adverse experience. The difference in proportions of patients with adverse experiences between treatment groups and associated 95% CIs were provided for all laboratory adverse experiences which occurred in ≥2% of patients in any treatment group. Miettinen and Nurminen's method was used to calculate the 95% CI for the difference in proportions.

RESULTS:

Efficacy: In this 4-year study of 1457 patients with MCI, statistically significantly more patients randomized to rofecoxib converted to AD than those who were randomized to placebo; the estimated annual conversion rate to AD was 6.4% in the rofecoxib group versus 4.5% in the placebo group (hazard ratio [rofecoxib:placebo] = 1.46, 95% CI [95% CI: 1.09, 1.94] Wald Chi Square p-value = 0.011). The estimated treatment hazard ratio from the PP analysis was similar to that of the ITT analysis (hazard ratio [rofecoxib:placebo] = 1.567, Wald Chi Square p-value = 0.005). The apparent effect of rofecoxib was unexpected and was not confirmed by exploratory measures of cognition (e.g., ADAS-Cog, SRT, MMSE), which found no statistically significant or clinically meaningful differences between treatment groups.

Safety: The overall proportions of patients with clinical adverse experiences were not statistically significant between treatment groups (p=0.199, Fisher's exact test) in the on-drug population. A significantly greater proportion of patients in the rofecoxib group than the placebo group had at least one drug-related adverse experience (p=0.020, Fisher's exact test). There were no statistically significant differences between treatment groups for serious adverse experiences (p=0.365), serious adverse experiences that were considered to be drug related (p= 0.830), patients who died (p= 0.061), or those who discontinued study therapy permanently due to clinical adverse experiences: (p = 0.478). Forty-two (2.9%) patients had fatal adverse experiences while on drug or had fatal adverse experiences >14 days after the last dose of study therapy that were considered as related to precursor on-drug nonfatal adverse experiences: 27 (3.7%) in the rofecoxib group and 15 (2.1%) in the placebo group. There were 8 (1.1%) thrombotic cardiovascular deaths in the rofecoxib arm and 4 (0.5%) in the placebo arm.

Analysis of adverse experiences of special interest: Hypertension-related adverse experiences were reported for 176 (24.3%) patients in the rofecoxib treatment group and 116 (15.9%) patients in the placebo group (p<0.001, Fisher's exact test). There were no significant differences between treatment groups for edema-related adverse experiences (p=0.139, Fisher's exact test), CHF-related adverse experiences (p=0.733, Fisher's exact test), or discontinuations from study therapy due to GI and abdominal pain-related adverse experiences (p=0.132, Fisher's exact test).

Confirmed thrombotic cardiovascular events occurred in 5.3% of the rofecoxib group and in 4.9% of the placebo group. The incidence of cardiac events was slightly higher in the rofecoxib group than the placebo group (3.6 and 2.6% for rofecoxib and placebo, respectively), while the incidences of cerebrovascular (1.8 and 2.2%) and peripheral vascular events (0.0 and 0.4%) were slightly higher in the placebo group. There were 29 patients (incidence rate 4.0%) with confirmed Antiplatelet Trialists' Collaboration (APTC) events in each treatment group.

Confirmed PUB events occurred in 14 (1.9%) patients in the rofecoxib group (10 [1.4%] of the patients with confirmed events had at least one event that was adjudicated as complicated) and in 4 (0.5%) patients in the placebo group (3 [0.4%] of the patients with events had at least one event that was adjudicated as complicated).

There was a statistically significantly higher proportion of patients in the rofecoxib than the placebo group who experienced at least one laboratory adverse experience while on-drug ($p=0.031$, Fisher's exact test), who had at least one drug-related adverse experience ($p<0.001$) and who discontinued study drug due to laboratory adverse experiences ($p<0.001$). There was no statistically significant difference between treatment groups with respect to serious laboratory adverse experiences ($p=0.625$).

Adverse Experience Summary
On-Drug[†] Population

Clinical Adverse Experiences in Patients:	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	p-Value
With one or more adverse experiences	651	(90.0)	670	(92.0)	0.199
With no adverse experiences	72	(10.0)	58	(8.0)	
With drug-related adverse experiences[‡]	211	(29.2)	173	(23.8)	0.020
With serious adverse experiences	217	(30.0)	236	(32.4)	0.336
With serious drug-related adverse experiences	11	(1.5)	10	(1.4)	0.830
Who died[§]	27	(3.7)	15	(2.1)	0.061
Discontinued therapy due to adverse experiences	156	(21.6)	147	(20.2)	0.478
Laboratory Adverse Experiences in Patients:	(N=723) n	(%)[¨]	(N=728) n	(%)[¨]	
With at least one laboratory test post baseline	715	(100.0)	723	(100.0)	
With one or more adverse experiences	191	(26.7)	158	(22.9)	0.036
With no adverse experience	524	(73.3)	565	(78.1)	
With drug-related adverse experiences[‡]	55	(7.7)	21	(2.9)	<0.001
With serious adverse experiences	1	(0.1)	3	(0.4)	0.625
Discontinued therapy due to adverse experiences	23	(3.2)	5	(0.7)	<0.001

[†] On drug includes the period through 14 days after discontinuation of study drug.
[‡] Determined by the investigator to be possibly, probably, or definitely drug related.
[§] Includes 3 patients in the rofecoxib group who had fatal adverse experiences that occurred >14 days after last dose of study drug and had precursor adverse experiences on-drug that may have been related to the fatal off-drug adverse experiences.
[¨] % = Number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline x 100.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.
"With at least one laboratory test postbaseline" = number of patients for whom a laboratory test was recorded for the given treatment group.
p-Value is from Fisher's exact test.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

CONCLUSIONS: (1) Rofecoxib 25 mg daily was not superior to placebo in reducing the incidence of clinically diagnosed AD (possible or probable by NINCDS-ADRDA criteria) in patients with MCI. (2) Rofecoxib 25 mg was generally well tolerated in patients with MCI.

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II. COMPREHENSIVE STUDY SUMMARY

1. Introduction

Alzheimer's disease (AD) is the major cause of dementia and affects an estimated 3% of the general population ≥65 years of age [1.2.1][1]. Neuropathological and epidemiological data suggest that inflammatory mediators and immune mechanisms may play a role in the pathogenesis of the disorder [1.2.2, 1.2.3]. For example, the presence of acute phase reactants, chronically activated microglia, and elevated expression of cyclooxygenase-2 (COX-2) in neuritic tangles and plaques of brains of patients with AD all point to a possible role of inflammatory mechanisms [see 1.2.4, 1.2.5 for review]. These observations have led researchers to investigate whether nonsteroidal anti-inflammatory drugs (NSAIDs) might slow the progression of dementia.

NSAIDs exert their action through inhibition of prostaglandin synthesis, catalyzed by at least two isoforms of cyclooxygenase (COX): cyclooxygenase-1 (COX-1) and COX-2. COX-1 is constitutively expressed and is present in a wide variety of tissues (e.g., intestine, stomach, kidneys, platelets). In contrast, COX-2 is induced by a variety of inflammatory mediators, such as those thought to be involved in the pathogenesis of AD [1.2.6]. Based on the patterns of expression and localization, COX-2 may be primarily responsible for the synthesis of prostanoids that mediate inflammation.

As NSAIDs nonselectively inhibit both COX-1 and COX-2, a selective COX-2 inhibitor may be a potent anti-inflammatory agent without the typical NSAID adverse experience profile. In particular, gastrointestinal side effects are common with existing NSAIDs, and "NSAID gastropathy" may be attributable to COX-1 inhibition. If COX-1-mediated prostanoid synthesis does not significantly contribute to the pathogenesis of inflammation, then a COX-2 specific inhibitor, without the associated dose-limiting COX-1 inhibitor gastrointestinal adverse effects, may represent a novel and appropriate anti-inflammatory agent for the prevention of AD. An improved gastrointestinal safety profile is particularly important in the elderly population at risk for the development of AD, since the elderly have worse tolerance to nonselective NSAIDs than the younger population.

[1] Refer to 12. List of Appendices. Within a bracket, the first number refers to an Appendix Category, the second number refers to an Appendix within that Category, and the third number (optional) refers to a document within the Appendix, e.g., [1.1.3] = Appendix Category 1, Appendix 1, Document No. 3.

Several studies have been performed to investigate whether NSAIDs might slow the progression of AD. Initially, two small studies with the NSAIDs indomethacin and diclofenac provided weak evidence for efficacy over 6 months in subjects with AD [1.2.7, 1.2.8]. However, interpretation of the results from both studies was confounded by high drop-out rates, mainly due to gastrointestinal side effects. More recently, three large randomized, controlled, 12-month clinical studies with the selective COX-2 inhibitors rofecoxib or celecoxib failed to show any effects of treatment on the progression of AD [1.1.1; 1.1.2; 1.2.9]. One of these studies included the non-selective NSAID naproxen, which also failed to show any effects [1.1.2].

One possible explanation for these disappointing results is that the disease process may be too advanced to modify in patients with an established diagnosis of AD. Epidemiological evidence indicates that there may be a critical period, 2 or more years before the onset of dementia, during which exposure to NSAIDs protects against AD [1.2.10]. The clinical diagnosis of AD is conservative, requiring impairment of memory, cognition, and functional ability. Recent data have indicated that there is a group of patients, with a disorder termed mild cognitive impairment (MCI), who have memory deficits without global cognitive and functional impairment, and thus do not meet the strict criteria for AD [1.2.11; 1.2.12]. MCI may represent a transitional state between normal aging and AD. These subjects have been reported to convert to AD at an annual rate of 10 to 15% versus a rate of 1 to 2% for the general elderly population, although these estimates come from observational studies rather than randomized clinical studies [1.2.13; 1.2.14]. Given the apparent predictive value of the diagnosis of MCI as a risk factor for the development of AD in patients $\geq$65 years of age, this group may represent an appropriate population in which to evaluate the efficacy of the novel COX-2-specific inhibitor rofecoxib for the prevention of AD.

We therefore conducted a study to determine whether treatment with rofecoxib could delay the onset of AD in elderly patients with MCI [1.2.13]. The study also provided the opportunity to gather important, placebo-controlled, long-term safety data on rofecoxib in an elderly population.

2. Ethics

2.1 Ethics Review Committee/Independent Ethics Committee/Institutional Review Board

The protocol, patient consent forms, addenda, and nine amendments were each reviewed and approved by central and local Institutional Review Boards (IRB), as designated by the Primary Investigator (PI), and in accordance with ICH/GCP

guidelines. IRB approval letters were received and verified before the first shipment of study drug. Copies of each approval are on file with Merck & Co., Inc. A list by site study number of the designated IRB and names of the Committee Chairs is in the Investigator Information appendix [3.6].

2.2 Ethical Conduct of the Study

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

2.3 Patient Information and Informed Consent Form

Prior to initiation of the study, an informed consent agreement explaining the procedures of the study, including the option of having an additional blood draw for genetic testing, together with the potential risks, was read by and clearly explained to each patient. Patients provided a signature for voluntary participation in the study. Another patient signature was requested for the patient's consent to have a blood sample drawn for analysis of genotype or biochemical markers and plasma banking; they were assured of the confidentiality of this information. Nonconsent for this blood draw did not interfere with participation in the study. Before any study procedure was performed, each patient signed and received a dated copy of such an informed consent and was assured of their freedom to withdraw from the study without prejudice at any time [3.9]. Regulatory standards regarding informed consent were followed and are attached to the protocol [3.3]. Generic consent forms for the patient are in [3.9]; all original signed consent forms are on file at each study site.

3. Investigators and Study Administrative Structure

Forty-six U.S. centers participated in this study. A list of participating investigators is in [3.6] and their curricula vitae are in [3.7]. Investigators were oriented to study procedures at an Investigator Meeting held prior to study start. Investigator/rater training materials and study supplies were sent to the sites prior to first patient screened.

Blood samples for analysis of apolipoprotein E (ApoE) genotype were shipped to, processed, and archived by the Coriell Institute for future analyses by Medical Research Laboratories. Coriell did not receive any patient identifiers other than the patient allocation number. Cryopreserved samples will be stored at the Coriell Institute for 5 years in dedicated freezers with full security and monitoring.

Medical Research Laboratories received the blood samples from the Coriell Institute, analyzed the prepared ApoE genotyping samples, and sent results directly into the Merck database via electronic tape in an agreed upon format. At that time, patient identifiers were matched with the allocation numbers received from Coriell.

All routine laboratory tests (serum chemistries, complete blood counts, and urinalysis) were conducted by Quest Diagnostics (formerly SmithKline Beecham Clinical Laboratories) throughout the course of the study.

Investigational clinical supplies were received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants had access. Clinical supplies were dispensed in accordance with the protocol. The investigator was responsible for keeping accurate records of the clinical supplies received from Merck & Co., Inc., the amount dispensed to and returned by the patients, and the amount remaining at the conclusion of the study. All containers were labeled with double-blind, 3-part, tear-off labels. These labels, contained hidden disclosure information for each patient (label part 2), and were kept by the investigator in case of emergency (e.g., a serious adverse experience).

The primary endpoint of clinically diagnosed AD was adjudicated by an Endpoint Adjudication Committee (EAC), based on criteria defined in the protocol. The EAC conducted this adjudication blinded to study treatment. The details of the Endpoint Committee memberships and responsibilities are outlined in the Standard Operating Procedures for EAC in rofecoxib Protocol 078 [3.11].

The principle author's signatures for this document are in [3.1].

4. Study Hypotheses and Objectives

4.1 Hypothesis

Primary

1. Rofecoxib 25 mg daily will be superior to placebo in reducing the incidence of clinically diagnosed AD (possible or probable by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria) in patients with MCI. A reduction of one third in the risk of clinically diagnosed AD in the rofecoxib group versus the placebo group is anticipated.

2. Rofecoxib 25 mg will be safe and well tolerated in patients with MCI.

Exploratory

1. Rofecoxib 25 mg will be superior to placebo in reducing the decline on the Selective Reminding Test (SRT) Summed Recall Score.

2. Rofecoxib 25 mg will be superior to placebo in reducing the decline on the Mini-Mental State Examination (MMSE).

3. Rofecoxib 25 mg will be superior to placebo in reducing the decline on the AD Assessment Scale-Cognitive (ADAS-cog) subscale.

4.2 Objectives

Primary

1. To evaluate the efficacy of rofecoxib 25 mg compared to placebo for the prevention of AD in patients with MCI.

2. To evaluate the overall safety and tolerability of rofecoxib 25 mg compared to placebo in patients with MCI.

5. Investigational Plan

5.1 Overall Study Design and Plan: Description

This was a multicenter, placebo-controlled, double-blind study (with in-house blinding), which evaluated the safety and efficacy of rofecoxib 25 mg for the prevention of clinically diagnosed AD in male and female patients, aged 65 years and over, with MCI. The study was designed to enroll 1450 patients who were to be randomized to treatment with rofecoxib 25 mg (n=725) or placebo (n=725) in a ratio of 1:1.

Patients were to receive once-daily treatment with rofecoxib 25 mg or placebo for up to 4 years or until 220 cases of investigator-diagnosed probable or possible AD were observed.

Patients who met the entry criteria at Visit 1 (In-Clinic Screening; see Table 1: Study Flow Chart) were randomized to treatment with either rofecoxib or placebo and instructed to take 1 tablet of medication daily. No more than 20% of patients enrolled at each study site were allowed to take vitamin E supplements >400 IU daily. (Patients were considered to be users if they received vitamin E tablets/preparations as a separate supplement. Patients who received vitamin E as part of a multivitamin supplement were not considered users.) Patients were

instructed to continue once-daily dosing with study medication until either the patient reached the predefined primary endpoint, an adverse experience led to discontinuation of treatment, a patient discontinued the treatment or study for any other reason, or the study had completed.

The primary efficacy endpoint was the incidence of clinically diagnosed AD (possible or probable AD, according to NINCDS-ADRDA criteria, by the investigator's confirmation and agreed upon by the consensus of the EAC) in patients with MCI. All investigator determined endpoints were sent to, reviewed by, and adjudicated by the EAC. The trigger for endpoint evaluation was a global clinical dementia rating (CDR) score of ≥1 (calculated by the CDR scoring algorithm and verified by a computer program); CDRs were conducted at baseline and every 4 months. For any patient who reached a CDR ≥1 at a scheduled visit, the SRT, MMSE, ADAS-cog subscale, Hamilton Depression Scale (HamD), and the Blessed Dementia Scale – Activities of Daily Living (BDS-ADL) were administered at that visit along with the regularly scheduled visit assessments. A noncontrast computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain was scheduled to rule out other possible causes of dementia, and laboratory tests including serum B12, folate, TSH, and T4 were performed. The investigator reviewed the NINCDS/ADRDA criteria to decide if the patient had clinical AD. If at a regular study visit, the investigator, in an exceptional case, judged that the patient may have developed dementia and the patient had a global CDR score <1 (e.g., 0.5), then the patient underwent all regularly scheduled assessments along with the extra exams and tests described above.

Any patient with a global CDR of ≥1 at a study visit (or in the exceptional case with a CDR score of <1) was scheduled to return in 2 months for the Endpoint Confirmation visit. The patient was instructed to remain on study medication (unless previously discontinued) until the time of this Endpoint Confirmation visit.

The Endpoint Confirmation visit consisted of efficacy measures as above (i.e., CDR, ADAS-cog, BDS-ADL, MMSE, SRT). If the global CDR score was ≥1 at the visit scheduled 2 months after the trigger visit, then the patient was considered to have reached a confirmed diagnosis of dementia and was discontinued from the study.

If, at the 2-month follow-up visit the global CDR score was <1, the investigator had to determine whether the patient was able to remain in the study. If yes, the patient continued in the study and returned to the clinic for a regular study visit. If the investigator judged that the patient could not ethically remain in the study due to dementia, the patient underwent the evaluations required for the Endpoint Confirmation visit and was discontinued from the study.

Patients in whom the diagnosis of dementia was not confirmed (i.e., those considered not to be demented at the follow-up visit) returned to the regular schedule of visits every 4 months.

Initiation of donepezil or other cholinesterase inhibitors was not permitted at any time during the study until after the Endpoint Confirmation visit. If, however, cholinesterase inhibitors were administered in violation of the protocol between the trigger visit and the Endpoint Confirmation visit, the patient was still requested to return for the Endpoint Confirmation visit. If the global CDR was ≥1, the patient was considered to have reached endpoint and was discontinued from the study. If the global CDR was <1 at the confirmation visit, the patient was also discontinued from the study. All such cases were adjudicated by the EAC. The inclusion of these endpoints in the primary data analysis depended on the determination of the EAC.

The investigator reviewed the global CDR rating and all other neuropsychological tests (i.e., ADAS-cog, BDS-ADL, MMSE, SRT) performed at the Endpoint Confirmation visit. Data packages for each patient who met the criteria for investigator diagnosed dementia were forwarded to Merck & Co., Inc., within 7 days of diagnosis. This package was then forwarded to the EAC within 7 days of Merck & Co., Inc.'s receipt. The adjudication committee indicated whether they concurred that the patient had developed dementia and whether it was consistent with possible or probable AD, or dementia of a non-Alzheimer's type (i.e., vascular dementia).

The exploratory efficacy measures were the slope estimates for the SRT, ADAS-Cog, and MMSE. The SRT was administered at the Randomization visit, every 4 months following randomization, and at the Endpoint Confirmation visit. The ADAS-cog subscale was administered at the Randomization visit, at the Months 12, 24, 36, and 48 visits, at the scheduled visit where any patient reached a CDR of ≥1, and at the Endpoint Confirmation visit. The MMSE was administered at the In-Clinic Screening visit, every 4 months following randomization, and at the Endpoint Confirmation visit.

Patients who discontinued study medication for reasons other than dementia were requested to return for their routine clinic visits for the duration of the trial to ascertain their outcome status. Patients who were unable to return for a routine visit were to have a home visit.

The primary endpoint was adjudicated by an EAC, based on criteria defined in the protocol. The EAC conducted this adjudication blinded to study treatment. The details of the Endpoint Committee memberships and responsibilities are outlined in the standard operating procedures (SOP) for EAC in rofecoxib Protocol 078 [3.11].

Table 1 shows the study visits and the examinations and procedures that were scheduled to be performed. Adverse experiences were recorded throughout the study. The protocol, amendments, and sample case report forms (CRFs) can be found in [3.3; 3.5].

The first patient was randomized (FPI) on 29-April-1998. The trial was terminated early and the final study visit was to be performed on 15-March-2003; if, however, a patient converted to AD at the final study visit, the patient was to return 2 months later for the final confirmation visit, extending the possible LPO to 15-May-2003. Last patient to complete the study (LPO) occurred on 23-April-2003. The data for this study were frozen on 30-May-2003 [3.10.1]. Critical changes were applied to the database to add prime therapy records and to modify patient status records on 11-June-2003 and 18-June-2003. Clean file was declared on 18-July-2003. Another set of critical changes was applied on 23-September-2003 to modify further patient status records.

Table 1

Study Flow Chart
Screening, Randomization, and Clinic Visits

Visit I.D.	Pre-screening	In-Clinic Screening	Random-ization	Mo 1	Mo 4	Mo 8	Mo 12	Mo 16	Mo 20	Mo 24	Mo 28	Mo 32	Mo 36	Mo 40	Mo 44	Mo 48	Endpoint Confir-mation	Home Visit (If Necessary)
Visit number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Review of entry criteria	X	X																
Physical examination		X					X			X			X			X	X	
Medical history	X	X																
Brief living arrangement history		X					X			X			X			X	X	
Telephone interview for cognitive status	X†																	
Informed consent		X																
Modified hachinski scale		X																
Auditory verbal learning test		X																
Hamilton depression scale‡		X					X			X			X			X	X	
Mini mental status examination		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blessed dementia scale (ADL) ‡		X								X			X			X	X	X
Clinical dementia rating‡		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Noncontrast MRI/CT brain scan‡																		
Selective reminding test			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
AD assessment cognitive subscale‡			X				X			X			X			X	X	

Table 1 (Cont.)

Study Flow Chart
Screening, Randomization, and Clinic Visits

Visit I.D.	Pre-screening	In-Clinic Screening	Random-ization	Mo 1	Mo 4	Mo 8	Mo 12	Mo 16	Mo 20	Mo 24	Mo 28	Mo 32	Mo 36	Mo 40	Mo 44	Mo 48	Endpoint Confir-mation	Home Visit (if necessary)
Visit number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Review of NINCDS-ADRDA Criteria§																	X	
Vital Signs		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry‖		X		X	X		X			X			X			X	X	
Blood sample for genotype archiving			X															
Complete blood count		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hemoccult for stool blood		X																
Urinalysis		X			X		X			X			X			X	X	
Electrocardiogram (ECG)		X					X			X			X			X	X	
Dispense study medication			X		X	X	X	X	X	X	X	X	X	X	X			
Count study medication tablets				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Distribute appointment reminder cards			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse experience		X----------															----------X	

† Only in potential patients identified by telephone prescreening.
‡ In any patient who had a global Clinical Dementia Rating (CDR) ≥1, the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Hamilton Depression Scale (HamD), and the Blessed Dementia activities of daily living (BDS-ADL) scale was completed in addition to the other scheduled assessments. Serum chemistries including B12, folate, TSH, and T4 and a noncontrast computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain was also performed. These assessments (excluding laboratories and CT/MRI) were repeated 2 months after the original diagnosis at an Endpoint Confirmation visit in patients who had a confirmed global CDR ≥ 1.
§ Only in patients who had a global CDR ≥1. Patients subsequently diagnosed with probable or possible clinical AD or any other type of dementia at the Endpoint Confirmation visit were discontinued from the study and referred to their physician for treatment.
‖ Vitamin B12, folate, TSH, T_4 were performed only at the In-Clinic Screening visit and at the first visit at which a patient had a global CDR≥1.
AD = Alzheimer's Disease
ADL = activities of daily living
ECG = electrocardiogram
NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

5.2 Discussion of Study Design, Including Choice of Control Groups

The study had a 48-month, placebo-controlled, parallel-group, double-blinded study (with in-house blinding) design. Patients who met the entry criteria at Visit 1 (In-Clinic Screening; see Study Flow Chart) were randomized to treatment with either rofecoxib 25 mg or placebo and instructed to take 1 tablet of medication daily. Randomization was stratified according to the patient's score on the MMSE. Patients who entered the study with scores of 24 to 26 were assigned the lowest consecutive available allocation number, and patients entering the study with scores of 27 to 30 were assigned the highest consecutive available allocation number.

5.3 Selection of Study Population

5.3.1 Inclusion Criteria

1. Patient was a male or female ≥65 years of age.
2. Patient was fluent in English.
3. Patient had completed at least 8 grades of education (beyond kindergarten).
4. Patient had a diagnosis of MCI at the In-Clinic Screening visit as defined by the following:
   a) By history, the patient had to report or be reported by the informant (see Inclusion Criteria j.), to have had a problem with memory; and the informant had to confirm that the patient's memory had declined in the past year.
   b) Global CDR score of 0.5, with a Memory score ≥0.5.
   c) A score on the Auditory Verbal Learning Test (AVLT) (Total Learning measure) ≥1 standard deviations below the mean score for normal subjects aged 65. This corresponds to a Total Learning score ≤ 37.
   d) Normal or near-normal cognition as evidenced by a MMSE score of ≥24 and supported by clinical impression.
   e) Normal activities of daily living as evidenced by a total score of ≤3.5 (no score greater than 0.5 on any individual item on Part 1) on the BDS-ADL.

5. Patient had a MHIS Score ≤4.

6. Patient had a normal serum vitamin B-12, folate, TSH, and T4 concentrations. (Patients on replacement therapy had to have been on a stable dose for ≥3 months.)

7. Patient had a HamD scale (17-question version) score <14.

8. Patient understood the study procedures, agreed to participate in the study by giving written consent, and agreed to return for follow-up visits and procedures in the event of discontinuation of study drug.

9. Patient, by investigator's clinical impression, had adequate motor and sensory capacities (when corrected if necessary) to perform neuropsychological testing.

10. Patient had a reliable informant (e.g., spouse, sibling, close friend) who was able to accompany the patient to clinic visits and able to provide information to study investigator/staff via telephone contact. (Every effort was made to ensure that information was provided by the same informant for a given patient for the duration of the study.)

5.3.2 Exclusion Criteria

1. Patient met clinical criteria for dementia.

2. Patient was anticipated to need chronic NSAID or estrogen replacement therapy during the trial. Patient was taking NSAIDs (including salicylates or other aspirin-containing compounds, CELEBREX™ (celecoxib, G. D. Searle & Co.), or VIOXX™[2] (rofecoxib) on a chronic basis (defined as ≥7 total days out of the last 30 days for 2 consecutive months prior to potential study entry), or had been on estrogen replacement therapy (excluding topical ointments) within 2 months of potential study entry. **NOTE: Patients who developed a need for cardioprotective doses of aspirin after randomization were permitted to use aspirin ≤100 mg/day.**

3. Patient had a history (within 2 years) or current evidence of major stroke, multiple lacunar infarcts, transient ischemic events, epilepsy, Parkinson's disease, progressive supranuclear palsy, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, or significant head trauma with loss of consciousness.

[2] VIOXX is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

4. Patient had a history (within 2 years) or current evidence of a major untreated depressive disorder, a psychotic disorder, or substance abuse by Diagnostic and Statistical Manual of Mental Disorders – 4th Edition (DSM-IV) criteria.

5. Patient had a history of angina or congestive heart failure with symptoms that occurred at rest. (**Note: patients with a history of myocardial infarction or coronary artery bypass grafting, angioplasty, or stent placement more than 1 year prior to study start were able to participate.**)

6. Patient had uncontrolled hypertension. (**Note: patients with medically controlled hypertension [diastolic blood pressure <95 mm Hg, systolic blood pressure <165 mm Hg] were able to participate.**)

7. Patient's estimated creatinine clearance was <30 mL/min. (Men: [140-age] x weight [kg]/[serum creatinine (mg/dL) x 72]; women: [0.85] [140-age] x weight [kg]/[serum creatinine (mg/dL) x 72]).

8. Patient had a history of active gastrointestinal bleeding within the past 3 months.

9. Patient had a history of hepatitis or hepatic disease that had been active within the past 3 months.

10. Patient had used:

    a) intravenous, intramuscular, or oral corticosteroids within 1 month of study entry.

    b) heparin or ticlopidine within 1 month of study entry.

    c) cholinesterase inhibitors (excluding ophthalmic preparations) within 1 month of study entry.

    d) estrogen replacement therapy (excluding topical ointments) within 2 months of study entry.

11. Concurrent, chronic use of psychotropic medications (e.g., antipsychotics, antidepressants, antiepileptics, or anxiolytics). **NOTE: Patients who were on stable doses of antidepressants for the preceding 2 months were eligible for entry; provided that they had a Hamilton Depression Scale score of <14 (see inclusion criteria g.). Patients taking antiepileptics for reasons other than epilepsy were approved by the Clinical Monitor on a case-by-case basis.**

12. Patient had a history or current evidence of any illness that in the opinion of the investigator or Merck & Co., Inc. monitor may have confounded the results of the study, interfered with the patient's participation for the full duration of the study, or posed an additional risk to the patient.

    NOTE: Patients with a history of basal cell carcinoma of the skin or carcinoma in situ of the cervix were eligible for entry. For patients with other kinds of cancer, the monitor was contacted regarding potential participation.

13. Patient had received an investigational drug or device within 30 days of study entry.

5.3.3 Discontinuation of Patients From Therapy or Study Observation

Every effort was made to have patients remain on blinded study therapy and continue to follow all protocol procedures. Since this was a true intention-to-treat study, patients who discontinued taking study drug for any reason other than a confirmed diagnosis of dementia (of any cause) were requested to return for all their clinic visits for the duration of the study to allow determination of endpoint status. Patients who were unable to return for a routine visit were asked to agree to have a home visit conducted by study site personnel. At the home visit, the CDR, the MMSE, and the BDS-ADL were performed.

At any time during the study, patients could withdraw consent or be dropped at the discretion of the investigator if the patient violated the study plan or if there was any administrative or safety reason. When a patient discontinued completely from the study (i.e., study medication was discontinued and there was no possibility for the patient to return for future clinic visits), a final study visit evaluation was performed at which all the procedures scheduled for Study Visit 15 (Month 48) were administered.

5.4 Treatments

5.4.1 Treatments Administered

Investigational clinical supplies were received, distributed, and handled in accordance with the protocol [3.3] and Good Pharmacy Practices. At the end of the study, opened and unopened bottles of study medication were returned and accounted for as indicated in the protocol.

Clinical supplies were packaged according to the allocation schedule. Rofecoxib tablets were supplied in dose strength of 25 mg and were to be stored at room temperature. Placebo tablets were supplied in matching image. Clinical supplies were packaged in sealed bottles for 1700 patients. Twelve bottles of study drug were prepared for each patient; each bottle contained 135 tablets, for a total of 1620 tablets per patient. Patients were allocated 1 bottle of study medication at the time of the Randomization visit, and then 1 bottle at subsequent study visits (Months 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44). The patients returned each bottle to the study site with any unused medication at each study visit before receiving a new study drug bottle. All study medication was returned to the study site at the Month 48 visit or the Discontinuation visit. In addition to the standard label text, each bottle was identified as Bottle A (Randomization), Bottle B (Month 4), Bottle C (Month 8), Bottle D (Month 12), Bottle E (Month 16), Bottle F (Month 20). Bottle G (Month 24), Bottle H (Month 28), Bottle I (Month 32), Bottle J (Month 36), Bottle K (Month 40), and Bottle L (Month 44).

Patients continued once-daily morning dosing with study medication until an adverse event led to discontinuation of treatment, a patient discontinued for any other reason, or the patient completed the study.

5.4.2 Identity of Clinical Supplies

Table 2 shows the study drug packaging and manufacturing information.

Table 2

Clinical Supplies

Drug	Formulation Number	Control Number	Strength	Package
Rofecoxib 25 mg	MR-3491	WP-E942	25-mg Tablet	Bottle
Placebo to match	MR-3530	WP-E942	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-3489	WP-D977	25-mg Tablet	Bottle
Placebo to match	MR-3552	WP-D977	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-3489	WP-D879	25-mg Tablet	Bottle
Placebo to match	MR-3361	WP-D879	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4185	WP-H138	25-mg Tablet	Bottle
Placebo to match	MR-3734	WP-H138	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-3724	WP-G307	25-mg tablet	Bottle
Placebo to match	MR-3530	WP-G307	placebo tablet	Bottle
Rofecoxib 25 mg	MR-3726	WP-H137	25-mg Tablet	Bottle
Placebo to match	MR-3734	WP-H137	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4325	WP-J196	25-mg Tablet	Bottle
Placebo to match	MR-3736	WP-J196	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4325	WP-J195	25-mg Tablet	Bottle
Placebo to match	MR-3736	WP-J195	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4325	WP-J823	25-mg Tablet	Bottle
Placebo to match	MR-3736	WP-J823	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4325	WP-J906	25-mg Tablet	Bottle
Placebo to match	MR-3736	WP-J906	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4325	WP-J907	25-mg Tablet	Bottle
Placebo to match	MR-3736	WP-J907	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4325	WP-J908	25-mg Tablet	Bottle
Placebo to match	MR-3736	WP-J908	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4325	WP-J909	25-mg Tablet	Bottle
Placebo to match	MR-3736	WP-J909	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4325	WP-J910	25-mg Tablet	Bottle
Placebo to match	MR-3736	WP-J910	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4325	WP-J911	25-mg Tablet	Bottle
Placebo to match	MR-3736	WP-J911	Placebo tablet	Bottle
Rofecoxib 25 mg	MR-4325	WP-J912	25-mg Tablet	Bottle
Placebo to match	MR-3736	WP-J912	Placebo tablet	Bottle
Placebo to match	MR-3736	WP-J520	Placebo tablet	Bottle
Placebo to match	MR-3736	WP-K227	Placebo tablet	Bottle

PRD = Pharmaceutical Research & Development.

5.4.3 Method of Assigning Patients to Treatment Groups

Patients who satisfied inclusion and exclusion criteria were randomly assigned to treatment groups of rofecoxib 25 mg or placebo according to a computer-generated allocation schedule [3.8]. Study personnel and Merck & Co., Inc., were blinded as to the assignment of treatment to allocation numbers. Randomization of patients was stratified according to their MMSE score (≤26, >26). At each investigator site, patients entering the study with MMSE scores of 24 to 26 were assigned the lowest consecutive available allocation number, and those entering the study with MMSE scores of 27 to 30 were assigned the highest consecutive available allocation number.

5.4.4 Selection of Doses in the Study and Timing of Dose For Each Patient

Selection of Dose

Studies on brain penetration following single oral dose administration with rofecoxib have been conducted in rats. Ratios of brain/plasma and cerebrospinal fluid/plasma concentrations of 0.4 and 0.07, respectively, were observed from 2 through 24 hours after dosing. These data, coupled with plasma concentration data from human volunteers, were used to simulate the expected brain and cerebrospinal fluid (CSF) rofecoxib concentrations following dosing in man to steady state with rofecoxib 25 mg daily. Following dosing with rofecoxib 25 mg daily, trough CSF levels of the free drug were estimated to be comparable to the IC_{50} for inhibition of COX-2 in the CHO cell, and brain concentrations comparable to the IC_{50} in whole blood. Thus, the dose selected for this study had to achieve adequate central concentrations of rofecoxib for inhibition of COX-2 in human brain. Additionally, data from studies in osteoarthritis, a peripheral inflammatory disorder, suggested that rofecoxib 25 mg daily offers a favorable benefit/risk profile and is safe and well tolerated in long-term use.

Timing of Dose

Patients were instructed to dose once daily in the morning. Patients continued dosing with study medication until either the study was completed, patient reached endpoint, an adverse experience led to the discontinuation of treatment, or a patient discontinued for any other reason.

5.4.5 Study Blinding

Rofecoxib was provided in individual bottles of 135 white 25-mg tablets with placebo to match. All containers were labeled with double-blind, three-part, tear-

off labels. The three-part labels were be printed with the following information: PART 1 (Affixed to container)—Patient allocation number and packaging identity number, Bottle identity (Bottles A through L), Treatment Month identity (Randomization, Months 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44), number of tablets, and dosing instructions: "Take 1 tablet every morning." PART 2—Blinded drug disclosure. PART 3—Same information as label for PART 1.

Parts 2 and 3 of the three-part labels were detached from the containers and attached to the L page of the case report form. These labels, containing hidden disclosure information for each patient on label part 2, were kept by the investigator in case of an emergency. If needed, the investigator had the ability to swab the blacked out part of the label with alcohol to reveal the treatment identity.

5.4.6 Prior and Concomitant Therapies

Prior Medications

Prior use of the following medications excluded patients from the study:

1) Chronic use of NSAIDs including VIOXX™ (rofecoxib) or CELEBREX™ (celecoxib) >7 days/month for the 2 months immediately prior to potential study entry.

2) Chronic use of estrogen replacement therapies (excluding topical ointments) within 2 months prior to potential study entry.

3) Potential need for NSAIDs or estrogen therapies during the 4 years of the study.

4) Use of intravenous, intramuscular, or oral corticosteroids within 1 month of study entry.

5) Use of heparin or ticlopidine within 1 month of study entry.

   NOTE: Patients who were on warfarin were eligible for the study, provided that there was an increased frequency of monitoring of prothrombin time following initiation of blinded study therapy.

6) Use of cholinesterase inhibitors (excluding ophthalmologic preparations) within 1 month of study entry.

Concomitant Medications

The following medications were prohibited throughout the entire study:

1) Heparin, ticlopidine.

   NOTE: Patients could be started on warfarin during the study provided that normal clinical monitoring practices were followed.

2) Estrogen replacement therapies (excluding topical cream preparations)

3) NSAIDs or oral steroids (>7 days per month).

NOTE: Patients who develop a need for cardio-protective doses of aspirin after randomization are permitted to use aspirin ≤100 mg/day.

4) Intramuscular steroids, epidural steroids.

5) Cholinesterase inhibitors, e.g., tacrine and donepezil (excluding ophthalmologic preparations).

6) Antipsychotics, antidepressants, antiepileptics, anxiolytics. NOTE: selective serotonin reuptake inhibitors (SSRIs) and nefazodone were allowed.

NOTE: Every effort was to be made to strictly adhere to the above prohibitions. However, in the event that any patient required use of NSAIDs, steroids, or estrogen replacement therapies after study start and during the study, such patients were to be continued in the trial. Patients requiring occasional use of sleep medications during the study were to be prescribed short-acting benzodiazepines or chloral hydrate. Cognitive testing was not to take place within 48 hours of using these medications.

7) CELEBREX™ (celecoxib)

8) VIOXX™ (rofecoxib)

5.4.7 Treatment Compliance

Patients were contacted by phone at scheduled times between study visits (Table 3). At each contact, patients or their informants were questioned as to compliance with study procedures. Patients were counseled as necessary to encourage continued study compliance and participation. Patients were monitored for potential adverse experiences and any changes in relevant medical history. Additionally, 3 days before scheduled visits and again the night before the visits, patients were contacted and reminded of their scheduled appointment date and time. Adherence to medication dosing instructions was monitored as follows: at each visit after randomization, the number of tablets in the medication bottle were counted, reviewed, and recorded. Any patient who missed ≥4 doses in the first month following randomization, or who missed ≥12 doses in a 4-month interval following the Month 1 visit, received weekly phone contacts made until the next scheduled visit. Appropriate re-review of the dosing regimen was conducted with the patient and informant at such phone contacts to encourage compliance with the study regimen.

Table 3

Scheduled Phone Contacts[†]

	Week 2	Mo 2	Mo 3	Mo 5	Mo 6	Mo 7	Mo 9	Mo 10	Mo 11	Mo 13	Mo 14	Mo 15	Mo 17	Mo 18	Mo 19	Mo 21	Mo 22	Mo 23	Mo 25	Mo 26
Assess patient compliance and continued study participation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review concomitant medication restrictions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor for adverse experiences	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Mo 27	Mo 29	Mo 30	Mo 31	Mo 33	Mo 34	Mo 35	Mo 37	Mo 38	Mo 39	Mo 41	Mo 42	Mo 43	Mo 45	Mo 46	Mo 47
Assess patient compliance and continued study participation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review concomitant medication restrictions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor for adverse experiences	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[†] Phone contacts were also made 3 days and again 1 night before the scheduled visits.

Data Source: [3.3]

5.5 Efficacy and Safety Parameters

5.5.1 Measurements Assessed and Timing of Assessment

For a summary of the efficacy, safety, and tolerability measures assessed, refer to Section 5.1, Overall Study Design and Plan: Description.

5.5.1.1 Efficacy Measurements

5.5.1.1.1 NINCDS/ADRDA Criteria for the Clinical Diagnosis of AD

The NINCDS/ADRDA criteria allowed determination of a diagnosis of probable or possible AD by clinical examination and documentation on neuropsychological tests, deficits in one or more areas of cognition, progressive worsening of memory, and the absence or inability of systemic disorders or other brain diseases that in themselves explained the progressive deficits in a patient.

5.5.1.1.2 CDR

The CDR is a 5-point global dementia rating which was completed by the investigator following a semistructured interview with the informant and then the patient. The interview lasted approximately 30 minutes. The CDR was the first test to be administered at visits after the Randomization visit. The CDR was administered without knowledge of psychometric test results. The trained investigator rated the patient's level of impairment in each of six areas (memory; orientation; judgment and problem solving; community affairs; home and hobbies; personal care) and then derived a single global dementia rating according to the scoring rules:

0 = No dementia

0.5 = Questionable dementia

1 = Mild dementia

2 = Moderate dementia

3 = Severe dementia

The global score on the CDR was assigned based on an algorithm. The CDR was conducted at the In-Clinic Screening visit and every 4 months thereafter up to and including the Month 48 or the Endpoint Confirmation visit. The informant had to be present at the In-Clinic Screening visit. Every effort was made to ensure that the informant attended subsequent clinic visits. In the

event that the informant was unable to attend in person for a visit after the In-Clinic Screening visit, the interview with the informant was conducted over the telephone. The interview with the informant was completed before the interview with the patient.

The primary investigator reviewed the CDR and all other neuropsychological tests (i.e., ADAS-cog, BDS-ADL, MMSE, SRT) prior to submitting the patient data package for adjudication. If the CDR was performed by a certified rater other than the primary investigator, then the primary investigator was required to initial and date the CDR worksheet in addition to the rater who performed the test.

5.5.1.1.3 SRT

The SRT is a memory test (approximate duration = 20 minutes) in which the patient was required to recall as many words as possible from a 12-word list read out by the investigator. There were 6 presentation/recall trials. After each recall attempt by the patient, the investigator reminded the patient of any words not recalled from the list. Following the final presentation/recall trial, there was a delay of 5 minutes and then a further recall trial was administered. Two measures were analyzed: Summed Recall = The total number of words correctly recalled over the 6 presentation/recall trials (range = 0 to 72; a higher score corresponded to better performance). This analysis was secondary. Delayed Recall = The number of words correctly recalled after a delay (range = 0 to 12; a higher score corresponded to better performance). This analysis was exploratory. The SRT was conducted at the Randomization visit and every 4 months thereafter up to and including the Month 48 visit or the Endpoint Confirmation visit.

5.5.1.1.4 MMSE

The MMSE is a brief (approximate duration = 10 minutes), objective, examination of cognitive function. The test yielded a single summary score of number of correct items (range = 0 to 30; a higher score corresponded to better performance). The MMSE was administered at the In-Clinic Screening, every 4 months following randomization, and at the Endpoint Confirmation visits.

5.5.1.1.5 ADAS-Cog

The cognitive subscale section of the ADAS-Cog was administered. This is a neuropsychological test battery of approximately 30 minutes' duration. The scale yielded a single score of the number of errors made by the patient (range = 0 to 70; a lower score corresponded to better performance). The ADAS-

Cog subscale was administered at the Randomization, Month 12, Month 24, Month 36, Month 48 and Endpoint Confirmation visits, and at the visit where the patient first reached a CDR of ≥1 (calculated by the algorithm and verified by the computer program).

5.5.1.1.6 BDS-ADL

The BDS-ADL is an assessment of the patient's activities of daily living. The scale was completed by the investigator, based on information provided by an informant (approximate time taken to complete scale = 10 minutes). The scale yielded a single score (range = 0 to 17; a lower score corresponded to better performance). The scale was administered at the In-Clinic Screening, Month 24, Month 36, Month 48, and Endpoint Confirmation visits, and at the visit where the patient first reached a CDR of ≥1. If the informant was not present at the clinic visit, the scale was completed by telephone contact with the informant.

5.5.1.1.7 Modified Telephone Interview for Cognitive Status

The modified Telephone Interview for Cognitive Status is a telephone-administered cognitive screening instrument based on the MMSE. The scale took approximately 15 minutes to administer and yielded a single score (range = 0 to 50; a higher score corresponded to better performance). The modified Telephone Interview for Cognitive Status was used only as a prescreening instrument for study eligibility.

5.5.1.1.8 Non-Contrast MRI/CT Brain Scan

Radiologic assessment was conducted in all patients when they first reached a CDR ≥1 at a routine visit. The purpose of this assessment was to assist the investigator in diagnosing the cause of dementia (Alzheimer versus non-Alzheimer).

5.5.1.1.9 ApoE Genotyping

Blood samples for ApoE genotyping were collected from each patient at the Randomization Visit (Visit 2). Samples were archived for future use in the event that a post hoc analysis would be undertaken based on subgroups defined by genotype. Separate informed consent was obtained for blood banking. Patients could still participate in the study if they did not give consent for blood banking.

5.5.1.1.10 HamD

The HamD is a 17-question scale (range of possible scores is 0-58) that assesses the presence of depression (higher scores indicate more depression). The HamD was administered to patients at the In-Clinic Screening, Months 12, 24, 36, 48, and Endpoint Confirmation visits, and at the visit where the patient first reached a CDR of ≥1.

5.5.1.1.11 Endpoint Adjudication Committee

The goal of the EAC was to provide blinded, external, expert adjudication of investigator-defined clinical endpoints of AD (or dementia of any cause) in patients treated with rofecoxib or placebo. The EAC determined if the results provided for a given patient were consistent or inconsistent with a clinical diagnosis of probable or possible AD or dementia of another etiology (e.g., vascular dementia) by NINCDS-ADRDA criteria. Procedures for the adjudication process are described in the SOP [3.11]

The EAC members were responsible for review of the contents of the current version of Rofecoxib Protocol 078; thorough review of all endpoint packages; and completion and return of the Endpoint Adjudication Form within 14 days of receipt of the adjudication package (or communication to MRL that review would not occur within this time frame).

The EAC was comprised of three experts external to MRL who adjudicated all investigator-defined clinical endpoints of AD (or dementia of any cause):

Steven Ferris, Ph.D.—New York University School of Medicine

Mary Sano, Ph.D.—Mount Sinai School of Medicine, Bronx Veterans Medical Research Center

Peter J. Whitehouse, M.D., Ph.D.—University Hospitals of Cleveland

5.5.1.1.12 Rater Certification

Rater re-certifications for the CDR were obtained at the start of the trial. The term "re-certification" was used to distinguish that the site CDR rater was previously certified and therefore experienced in performing CDRs. Specific testing guidelines were discussed at the Investigator's Meeting and summarized in follow-up correspondence.

All CDR raters were required to complete global CDRs for 3 subjects based on transcripts of interviews. The purpose of the exercise was to ensure that ratings were consistent across all sites participating in the study. The previously established global CDR scores for the certifications covered a range from normal (0) to differing levels of dementia.

Letters providing feedback concerning the re-certification scores obtained by raters at each site were sent upon testing completion. Investigators were asked to review the feedback with all raters at their sites, with particular emphasis on items where the raters score differed from the expert's score. Expert rater scores were indicated on the feedback letter. Only raters identified and certified by the clinical monitor were allowed to perform the respective assessments in the study. The re-certification letter was retained in the site study files.

5.5.1.2 Safety Measurements

The safety of rofecoxib was evaluated by the following:

5.5.1.2.1 Medical History, Physical, and Neurological Examinations

A medical history was taken and a physical examination was performed at the In-Clinic Screening visit. The investigator indicated whether each of the following body systems was normal or abnormal (descriptions of abnormalities were documented):

Head, eyes, ears, nose, and throat
Neck
Cardiovascular System
Respiratory System
Abdomen
Skin
Extremity
Breast
Chest (body site)
Musculoskeletal System
Rectum
Urogenital

A detailed neurological examination was conducted at the in-clinic screening visit. Height, weight, blood pressure, and pulse rate were determined during this examination at the In-Clinic Screening visit. Vital signs were repeated at the Months 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and Endpoint Confirmation visits. The physical exam and weight were repeated at the Months 12, 24, 36, 48, and Endpoint Confirmation visits.

5.5.1.2.2 Electrocardiogram

Twelve-lead electrocardiograms (ECGs) were performed at the In-Clinic Screening visit, and at the Months 12, 24, 36, 48, and Endpoint Confirmation visits. If on a second or subsequent ECG trace an abnormality was found, the trace was reviewed by a cardiologist and the investigator indicated whether or not a clinically significant change from a prior ECG had occurred, and determined if it therefore constituted an adverse experience.

5.5.1.2.3 Laboratory Tests

All routine laboratory tests were conducted by Quest Laboratories (formerly SmithKline Beecham Clinical Laboratories), who arranged for collection of blood and urine samples. Blood chemistries were performed at the In-Clinic Screening, Months 1, 4, 12, 24, 36, 48, and Endpoint Confirmation visits. Urinalyses were performed at the In-Clinic Screening, Months 4, 12, 24, 36, 48, and Endpoint Confirmation visits. Complete blood counts were performed at the In-Clinic Screening, Months 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 48, and Endpoint Confirmation visits. If a laboratory test was found to be outside the normal range, the investigator indicated whether or not it was clinically significant and if it therefore constituted an adverse experience. The tests of blood and urine samples include those shown in Table 4.

Table 4

Laboratory Tests

Hematology:	**Urinalysis:**
Hemoglobin	pH
Hematocrit	Protein
Total WBC	Glucose
Neutrophils	
Lymphocytes	**Microscopy†:**
Monocytes	WBCs
Eosinophils	RBCs
Basophils	Epithelial cells
Platelet count	Casts (specify)
Chemistry:	
BUN	
Creatinine	
Total bilirubin	
AST (SGOT)	
ALT (SGPT)	
Alkaline phosphatase	
Glucose (random)	
Albumin	
Sodium	

Table 4 (Cont.)

Laboratory Tests

Hematology:	Urinalysis:
Potassium Chloride	
Screening Visit Only:	
Vitamin B12*	
Folate‡	
T4‡	
TSH‡	
* Performed only if preceding urinalysis values were abnormal. ‡ Performed at In-Clinic Screening Visit and the first visit at which a patient had a CDR ≥1.	

Data Source: [3.3]

5.5.1.2.4 Adverse Experiences

Adverse experiences were monitored by study personnel questioning the patients throughout this study. Such events were recorded at each examination on the Adverse Experience Case Report Forms provided by Merck & Co., Inc. Adverse experience means any unfavorable and unintended change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body temporally associated with any use of a Merck product **whether or not considered related to the use of the product.** Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of a Merck product is also an adverse experience.

The investigator evaluated all adverse experiences as to:

- Maximum intensity:

— Mild (awareness of sign or symptom, but easily tolerated);

— Moderate (discomfort enough to cause interference with usual activity);

— Severe (incapacitating with inability to work or do usual activity).

- Seriousness

A serious adverse experience is any adverse experience occurring at any dose that:

† **Results in death**; or

† **Is life-threatening** (places the Patient, in the view of the investigator, at immediate risk of death from the experience as it occurred. [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]); or

† **Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or

† **Results in or prolongs an existing inpatient hospitalization** (hospitalized is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation.) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience); or

† **Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or

ALSO:

Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the Patient and may require medical or surgical intervention to prevent one of the (†) outcomes listed above.

In addition, Merck & Co., Inc. requires the collection of the following:

cancer, or

overdose (whether accidental or intentional)

5.5.1.2.5 Special Reporting Procedures for Upper Gastrointestinal PUBs

Any suspected upper gastrointestinal (GI) PUBs (gastric or duodenal perforations, peptic ulcers, or upper GI bleeds) were reported to the Merck clinical monitor within 24 hours of their occurrence, regardless of whether they were considered to be serious.

Suspected upper GI PUBs were reviewed and adjudicated by the rofecoxib Phase III GI Clinical Event Monitoring Case Review Committee according to procedures described in the SOP [3.11.1]. Investigators were required to provide documentation needed for case review, including, but not limited to, clinical notes, laboratory results, procedural test reports, x-ray reports, and hospital discharge summaries.

5.5.1.2.6 Special Reporting Procedures for Acute Thromboembolic Vascular Events and Deaths

Suspected serious cardiovascular, peripheral vascular, and cerebrovascular events were reviewed and adjudicated in a blinded manner by the rofecoxib Vascular Event Monitoring Case Review Committees, according to procedures described in the SOP [3.11.2] and according by metrics defined by the Antiplatelet Trialists' Collaboration (APTC) [3.11.3]. The purpose of the adjudication was to improve the accuracy in diagnosis across a heterogeneous group of study investigators and to standardize the evaluation of potential thrombotic cardiovascular serious adverse experiences across the ongoing clinical studies. All deaths were also adjudicated (as to cause) by the same committee prior to unblinding the database to determine if the death could have been due to a thrombotic cardiovascular serious adverse experience. The committees are composed of experts in the field of cardiology, neurology, and vascular diseases. Investigators were required to provide documentation needed for case review, including, but not limited to, clinical notes, laboratory results, procedural test reports, x-ray reports, and hospital discharge summaries.

5.5.1.2.7 Special Definitions for Events Included in On-Drug Mortality and Cardiovascular Analyses

All-Cause Mortality On-Drug

The all-cause mortality endpoint includes fatal adverse experiences that occurred while on study therapy or within 14 days after the last dose of study therapy. For fatal adverse experiences that occurred more than 14 days after the last dose of study therapy, the Worldwide Adverse Experience System (WAES) reports were reviewed by one or more MRL physicians who were blinded to treatment allocation to determine if the adverse experiences were eligible for inclusion in the all-cause mortality analysis. A fatal adverse experience which occurred more than 14 days after the last dose of study therapy could potentially have been related to a nonfatal adverse experience which started while the patient was on-drug.

Thrombotic Cardiovascular Mortality On-Drug

All deaths included in the on-drug all-cause mortality analysis were reviewed according to the SOP by the Adjudication Committee [3.11.2], which was blinded to treatment assignment, to determine if the death might have been due to a potential thrombotic event. The thrombotic cardiovascular mortality

events included thrombotic deaths such as fatal acute myocardial infarction, fatal ischemic stroke, fatal pulmonary embolism, fatal peripheral arterial thrombosis, fatal cerebrovascular thrombosis, and sudden and/or unexplained death.

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences include both arterial and venous thromboembolic events confirmed by the Adjudication Committee as acute myocardial infarction, unstable angina pectoris, transient ischemic attack, cerebrovascular accident, arterial thrombosis, deep venous thrombosis, pulmonary embolism, or sudden and/or unexplained death. Hemorrhagic strokes confirmed by the adjudication committee were considered as APTC events but not as confirmed thrombotic events.

Confirmed thrombotic cardiovascular serious adverse experiences which occurred on study therapy or within 14 days after the last dose of study therapy were included in the analyses.

Confirmed APTC Serious Adverse Experience

Confirmed APTC events include fatal and irreversible morbid cardiovascular events confirmed by the Adjudication Committee as cardiovascular, hemorrhagic, and unknown death; myocardial infarction; and cerebrovascular accident. This endpoint is the most common and widely accepted method to quantify the overall cardiovascular impact of antithrombotic compounds in cardiovascular clinical trials and represents the incidence of fatal and irreversible morbid cardiovascular events. The APTC combined endpoint is the combined incidence of cardiovascular, hemorrhagic, and unknown death, myocardial infarction, and cerebrovascular accident.

Confirmed APTC serious adverse experiences which occurred on study therapy or within 14 days after the last dose of study therapy were included in the analyses.

5.5.2 Primary Response Parameter(s)

The primary efficacy endpoint was clinically diagnosed probable or possible AD (according to NINCDS-ADRDA criteria) confirmed by the investigator. Only events of clinically diagnosed probable or possible AD in which the diagnosis of the investigator concurred with the majority diagnosis of possible or probable AD from the EAC were included as endpoints in the primary efficacy analyses.

CDR tests were conducted at baseline and at every subsequent 4-month visit. Any patient who reached a global CDR score ≥1 was required to stay on study medication (if not previously discontinued from study drug) and to return for an Endpoint Confirmation visit 2 months later. If the diagnosis of dementia was confirmed at the 2-month follow-up visit, then the type of dementia (AD or non-Alzheimer's dementia) was determined and the patient was discontinued from the trial. Otherwise the patient continued in the trial.

An intention-to-treat approach was used for the primary efficacy analysis of clinically diagnosed AD. Patients with confirmed clinically diagnosed AD were included in the primary analysis as an endpoint regardless of whether the diagnosis occurred while the patient was on test drug or had previously discontinued test drug. A diagnosis of AD was not included in the primary efficacy analysis as an endpoint for patients who had an initial diagnosis of AD but did not return for the 2-month follow-up visit.

Those who discontinued the study due to non-Alzheimer dementia or were diagnosed with AD but withdrew prior to the confirmation visit were censored at the time the diagnosis of dementia was first made (trigger visit). Patients who were otherwise withdrawn, lost to follow-up, or discontinued due to study termination were censored at the time of the last available visit.

5.6 Data Quality Assurance

Clinical studies conducted worldwide by Merck & Co., Inc., are subject to Quality Control and Quality Assurance measures as dictated by the appropriate department's SOPs. These activities include: on-site monitoring of investigator sites, on-site and in-house review of clinical study patient data and resultant databases, and review of Clinical Study Reports. Quality control activities are conducted by the individuals responsible for the day-to-day conduct of the clinical study. The Quality Assurance activities are conducted by an organization independent from those who conduct the Quality Control. Audit information is in [3.2]

As a result of routine study monitoring and study site audits, it was determined that efficacy data for 137 patients randomized at sites 019, 023, and 044 were questionable. The primary efficacy analysis was conducted with and without this data (see Section 7.2.1.4.2 and Section 11 – Table 82). Since efficacy analysis results without this data were the same as those from the analysis including these data, all patients at all sites were included in all efficacy and safety tables within this CSR.

5.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

5.7.1 Determination of Sample Size and Power Analysis to Address Study Hypotheses

Sample size and power calculations for the primary efficacy endpoint were based on the following assumptions and the published event rates in patients with MCI [1.2.11; 1.2.15], and the relative risk reduction reported with NSAIDs [1.2.16]:

- Two-tailed test with $\alpha = 0.05$.
- The cumulative incidence of probable or possible AD in the placebo group would be 30%.
- The incidence of probable or possible AD in the rofecoxib group would be reduced by 33%.
- No more than 20% of patients would discontinue from the study due to reasons other than the development of clinical AD or non-Alzheimer's dementia in each treatment group.

Under the above assumptions, the final analysis was to be performed when at least 220 clinically diagnosed AD (probable or possible) cases were observed. A total of 220 endpoints would provide about 90% power to detect the difference between treatment groups (30% versus 20%), with a significance level of 0.05 (two-sided).

5.7.2 Statistical/Analytical Methods and Issues

Methods described in this section (5.7.2) were prespecified in the Data Analysis Plan (DAP) [3.4].

5.7.2.1 Analysis Model for Primary Efficacy Parameters

The primary efficacy endpoint is clinically diagnosed AD (diagnosis of AD agreed upon by the investigator's confirmation and the EAC adjudication). An ITT approach was used for the primary analyses.

5.7.2.1.1 Analysis Model for Time-To-Event

5.7.2.1.1.1 Primary Analysis

The primary hypothesis concerning the incidence of clinically diagnosed AD was assessed based on time-to-event analysis models. The cumulative incidence of clinically diagnosed AD was estimated by the Kaplan-Meier product-limit method, both overall as well as within baseline MMSE strata (baseline MMSE ≤26 versus >26). Statistical comparison between rofecoxib and placebo were carried out by a Cox proportional hazards model [1.2.17]. The model included terms for treatment, region (see Section 5.7.2.5), and baseline MMSE stratum. The baseline MMSE stratum was included in the model as a covariate, rather than as a stratification factor, such that its effect could be estimated and tested.

To evaluate the consistency of treatment effects among regions and between MMSE strata, interactions between treatment and region and between treatment and baseline MMSE strata were evaluated. If an interaction was significant at the α=0.10 level, then the nature of the interaction was further tested (at α=0.05) using Gail and Simon's method [1.2.18]. In the event that a qualitative interaction was observed, the reason for the qualitative interaction was further explored, and results were presented by stratum level.

The assumption of proportional hazards was also assessed by testing the treatment-by-time interaction in the Cox regression model, as well as by plotting log-log survival curves. Further exploratory analyses were planned, and a stratified log-rank test (stratified by baseline MMSE stratum) was included at the request of a regulatory agency.

The primary efficacy analysis was based on the ITT approach (i.e., all patients who were randomized were included). The primary endpoint was clinically diagnosed AD (confirmed as AD by the investigators and adjudicated as AD by the EAC). Those who discontinued the trial for reasons other than clinically diagnosed AD (including, but not limited to, a diagnosis of non-Alzheimer's dementia, withdrawn consent, lost to follow-up) were censored.

5.7.2.1.1.2 Supportive Analyses

In order to evaluate the robustness of the findings from the primary efficacy analysis, the following supportive analyses were performed:

Per-Protocol Analysis

For the primary endpoint (clinically diagnosed AD), the analysis was also carried out according to the "per-protocol" (PP) approach. The PP analysis excluded data obtained after a patient violates the protocol in a way that may affect efficacy outcome measures (see Section 6.2 for a detailed list of protocol violations that were used to define the PP set). Specifically, a patient who violated the protocol at randomization was excluded. Data were censored after a patient violated the protocol during the study. The list of protocol violators was issued before data were unblinded.

Analysis of Investigator Diagnosis of AD

This analysis included all diagnoses of AD by investigators that were either (1) confirmed by the investigator, or (2) initially a diagnosis of AD by the investigator at the trigger visit without investigator confirmation due to the patient not returning for the confirmation visit. These events were included in the analysis irrespective of concurrence by the EAC. The event time was the first time the diagnosis was made.

All Dementia

This analysis included all diagnoses of dementia by investigators that were either (1) confirmed by the investigator, or (2) initially a diagnosis of dementia by the investigator at the trigger visit without investigator confirmation due to the patient not returning for the confirmation visit. These events were included in the analysis irrespective of concurrence by the EAC.

On Drug Approach

This analysis was conducted to determine if, for the subset of follow-up time that patients were actually exposed to study drug, the estimated hazard ratio varied from the ITT approach. Patient time-at-risk for this time-to-event analysis consisted of the date of randomization through 14 days after the last dose of study medication. In effect, this resulted in the

- exclusion of patients who never dosed
- censoring of patients at 14 days after their last dose if they were either:

— censored (in the ITT approach) later than 14 days after their last dose, or

— had a trigger visit that occurred more than 14 days after the last dose

All supportive analyses were performed using a Cox model with terms of treatment, region, and baseline MMSE strata.

5.7.2.1.2 Analysis Model for the Rate of Change

The supportive endpoints SRT, MMSE and global CDR scores were measured at baseline and every 4 months up to 48 months; ADAS-Cog was measured at baseline, Months 12, 24, and possibly 36 and 48 months. An ITT approach was used for these analyses. All randomized patients who had a baseline and at least one post randomization efficacy evaluation were included in the analyses.

For these continuous endpoints, a longitudinal analysis model (mixed model) was used to estimate and test the treatment difference in terms of the rate of change from baseline. The initial model included baseline MMSE strata, region, treatment, time of visit, and interactions of time by treatment, time by MMSE strata, and time by region. An unstructured covariance matrix was used to model the correlation among repeated measures.

5.7.2.2 Adjustments for Baseline Covariates

Statistical analyses were performed to investigate the consistency of the treatment effect across subgroups based on values of baseline covariates. A number of these covariates were prespecified in the DAP; several were identified post hoc (see Section 5.8 for further details).

5.7.2.3 Handling of Dropouts or Missing Data

For the primary efficacy analysis, patients who did not experience a primary endpoint of clinically diagnosed AD were censored according to the algorithm described in the DAP. For the supportive endpoints SRT, MMSE and CDR Sum of Box scores, all randomized patients who had a baseline and at least one postrandomization efficacy evaluation were included in the analyses. Data were analyzed as observed (i.e., no imputation was performed) in the prospective analyses of the rate of change from baseline (see DAP and Section 5.7.2.1.2). Additional post-hoc analyses based on last observation carried forward (LOCF) methodology are described in Section 5.8.

5.7.2.4 Interim Analysis and Data Monitoring

Per the protocol, no interim analyses of efficacy data were performed. Interim analyses of safety data by MRL personnel not involved in the conduct of the study are described below.

As part of a program-wide combined analysis of thrombotic cardiovascular (CV) events in rofecoxib Phase II to V clinical studies, several periodic interim analyses of CV safety were conducted using data from this protocol. First, data on thrombotic CV events through September 15, 2000 were incorporated into the CV analyses and were disclosed in aggregate with other placebo-controlled data in a publication [1.1.3]. Site personnel and MRL personnel monitoring the study were blinded to the individual patient data that contributed to this analysis. Since the analysis did not affect the conduct of the study, the size and power of the statistical tests remained unaffected.

Second, to support the safety analysis for rofecoxib in the VIOXX Gastrointestinal Outcomes Research (VIGOR) supplemental marketing application, data on serious adverse experiences from this study (collected though March 16, 2001) were reported to a regulatory authority in response to a request for information. For this interim report, the demographics, prior and concomitant therapy, and serious adverse experience data were unblinded to the Merck personnel who compiled the safety report. Personnel who were involved with the study conduct and monitoring remained blinded. Data in this report from this study and from Protocol 091 on thrombotic cardiovascular serious adverse experiences and on thrombotic cardiovascular mortality were combined [2.1.1] and were publically disclosed in US and Canadian product circulars approved April 2002.

Last, an update to the program-wide interim analysis of CV data and mortality events was conducted using data through 31-Jan-2002. These results were publically disclosed at scientific meetings in aggregate with other placebo-controlled data. As in the other cases, site personnel and MRL personnel monitoring the study were blinded to the individual patient data that contributed to the analysis.

5.7.2.5 Multicenter Issues

The study was conducted at 46 sites in the United States. Due to the relatively large number of the sites, a prospective analysis of regional effects was described in the DAP that was based on pooling site results for the primary endpoint of clinically diagnosed AD, based on geographic location.

The prespecified primary efficacy analysis model, as well as other models described herein, included terms for region and treatment-by-region interaction. For these statistical models, the interaction of treatment-by-region was investigated, and was dropped from the model if not statistically significant at the α=0.10 level (see DAP for details). It was recognized that the power to detect an interaction was limited.

5.7.2.6 Multiplicity

As there was only 1 primary efficacy analysis in the study (comparing risk of clinically diagnosed AD between rofecoxib and placebo), only 1 treatment contrast, and only 1 look at the efficacy data (i.e., no interim efficacy analyses), no multiplicity adjustment of critical p-values was necessary. For the exploratory analyses, no multiplicity adjustment was made due to the exploratory nature of these endpoints.

5.7.3 Analysis Model for Primary Safety Parameters

The primary safety objective for the study was to examine the safety and tolerability of rofecoxib 25 mg, compared to placebo, in patients with MCI. This was assessed by statistical and/or clinical review of all safety parameters, including adverse experiences, vital signs, and laboratory values.

All safety analyses were based on the all patients as treated (APaT) population, which consisted of all randomized patients who received one or more doses of test drug therapy (only patients who were documented to have never received study medication were excluded from analyses). Patients were counted in the treatment group for the drug they actually received, rather than the treatment group to which they were randomized (if different). Section 5.7.3.1 describes 2 methods of tabulating adverse experiences based on whether patients were on or off study therapy.

5.7.3.1 Adverse Experiences

For the APaT populations defined in Section 5.7.3, 2 methods were used for tabulation of adverse experiences. First, a primary analysis included all adverse experiences which occurred when patients were on treatment and up to 14 days following discontinuation of study drug (referred to subsequently as "on drug"). A second analysis summary based on the ITT approach included all adverse experiences regardless of whether patients were on or off study drug (referred to subsequently as "ITT"). Each safety subsection presented the on-drug results followed by the respective ITT results.

The percentage of patients with adverse experiences by body system was tabulated by treatment group. In order to further characterize the most common adverse experiences, the difference in proportions of patients with adverse experiences between treatment groups and associated 95% confidence intervals (CI) was provided for the adverse experiences which occurred in ≥2% of patients in any treatment group. Miettinen and Nurminen's method was used to calculate the 95% CI for the difference in proportions [1.2.19].

Statistical comparison of the differences in proportions of patients with adverse experiences was conducted using the Fisher's exact test for the following clinical adverse experiences: (1) at least one adverse experience; (2) drug-related adverse experiences; (3) serious adverse experiences; (4) serious and drug-related adverse experiences; (5) deaths; (6) discontinuations from study therapy due to an adverse experience; and for tables of special interest including (7) discontinuations from study therapy due to gastrointestinal (GI) adverse experiences, (8) edema-related adverse experiences, (9) hypertension-related adverse experiences, and (10) adverse experiences associated with congestive heart failure (CHF). The selections of terms used to define the adverse experiences of special interest can be found in [4.5]. The corresponding risk differences and 95% CIs were also provided. No formal hypotheses are prespecified for statistical testing for individual adverse experience types within a category.

5.8 Changes in the Conduct of the Study or Planned Analyses

Protocol 078 was amended with the following changes in Amendment 01 [3.3] on 08-May-1998:

The original protocol title, "The Safety and Efficacy of MK-0966 for the Prevention of Alzheimer's Disease in Patients at Risk", was changed to "MK-0966 for the Treatment of MCI and Prevention of Conversion to Alzheimer's Disease".

The note "(global Clinical Dementia Rating of ≥1)" was added for clarification to define patients with a confirmed diagnosis of dementia.

The following criteria were changed in the Study Design and Duration section: Mini-Mental State Examination score was changed from >25 to ≥24; the Blessed Dementia Scale (ADL) score was changed from ≤2 to ≤3.5.

The measure referred to as "Total" Clinical Dementia Rating in the Design and Duration section was changed to "Global" Clinical Dementia Rating throughout the Protocol.

The following statement was added to the Study Design and Duration section: "Randomization will be stratified according to the patient's score on the Mini-Mental Sate Examination."

The statement "and sum of box scores >1.0" was deleted after "Memory scores of ≥0.5" in the Inclusion Criteria d.2.

The following examples were deleted from Inclusion Criteria "f": "(>150 pg/mL)" after "vitamin B-12", and "(>3 ng/mL)" after "folate".

The word "untreated" was added to "depressive disorder" for clarification in Exclusion Criteria d.4.

The note: "Patients who are on stable doses of SSRIs or nefazodone for the preceding 2 months are eligible for entry, provided that they have a Hamilton Depression Scale score <14 (see Inclusion Criteria g.)" was added for clarification after Exclusion Criteria "k."

The following paragraph was removed from the Summary of Study Design section on page 12: "The study will be conducted under the direction of the Steering Committee (Appendix 13). The study will also be conducted under the auspices of an independent Data Monitoring Committee (DMC, Appendix 13), which is responsible for identifying safety issues and interpreting emerging study data at the interim analysis (see Data Analysis, Section I.I) and making any recommendations regarding modification or termination of the study confidentiality to the Steering Committee, DMC, and Endpoint Committee memberships and responsibilities will be outlined in the Standard Operating Procedures of the respective committees (see Appendix 13)."

The following paragraph under Summary of Study Design (second paragraph on page 12) was modified to delete references to the Steering Committee and DMC: "The primary endpoint will be adjudicated by an Endpoint Adjudication Committee, based on criteria defined in the protocol. The Endpoint Adjudication Committee will conduct this adjudication blinded to study treatment. The details of the Endpoint Committee membership and responsibilities will be outlined in the Standard Operating Procedure (see Appendix 13).

The following paragraph (first paragraph) in the Treatment Plan section was modified to include randomization stratification procedures: "Patients who meet the entry criteria at Visit 1 (In-Clinic Screening; see Study Flow Chart) will be randomized to treatment with either MK-0966 or placebo and instructed to take 1 tablet of medication daily. Randomization of patients will be stratified according

to their Mini Mental State Examination score. Patients entering the study with scores of 24 to 26 will be assigned the lowest consecutive available allocation number, and patients entering the study with scores of 27 to 30 will be assigned the highest consecutive available allocation number. No more than 10% of the patients at any study site should be using vitamin E at the time of enrollment. (Patients will be considered users if they receive vitamin E tablets/preparations as a separate supplement. Patients receiving vitamin E as part of a multivitamin supplement will not be considered users.) Patients will continue once-daily dosing with study medication until the endpoint for a patient has been reached, an adverse experience leads to discontinuation of treatment, a patient discontinues for any other reason, or the study is completed."

The requirement that the same person who administers the CDR should administer the Blessed Dementia Scale in item 5 on page 13 under the Order and Administration of Clinical Dementia Rating, Selective Reminding Test, Mini Mental State Examination, Alzheimer's Disease Assessment Scale, and Blessed Dementia Scale section was removed.

The time listed in the Note under the Order and Administration of Clinical Dementia Rating, Selective Reminding Test, Mini Mental State Examination, Alzheimer's Disease Assessment Scale, and Blessed Dementia Scale section was changed from five minutes to ten minutes for the separation interval between tests.

The definition of the chronic use of NSAIDs in the Prior Medications section was modified from greater than 7 days/month to greater than or equal to 7 days/month.

The definition of the chronic use of NSAIDs in the Concomitant Medications section was modified from greater than 7 days per month to greater than or equal to 7 days per month.

The note "Note: SSRIs and nefazodone are allowed" was added to item number six under Concomitant Medications

The statements, "Patients requiring occasional use of sleep medications during the study should be prescribed short-acting benzodiazepines or chloral hydrate. Cognitive testing should not take place within 48 hours of using these medications." were added to the note under Item 6 in the section under Concomitant Medications.

The paragraph describing telephone prescreening procedures under Study Procedures was modified with a change in scoring instructions. The statement "Potential patients with scores of 26 to 40 will be referred to the local study site for an in-clinic screening evaluation" was changed to "Potential patients with scores of 19-37 will be referred to the local study site for an in-clinic screening evaluation."

The first paragraph on page 16 under the Prescreening/Identification of Potential Patients section was modified to indicate that the informant must attend the In-clinic Screening visit as follows: "Potential patients must attend the In-Clinic Screening visit with an informant (spouse, close friend, or relative)."

The following criteria were changed in the Inclusion Criteria section: Mini-Mental State Examination score was changed from >25 to ≥24; the Blessed Dementia Scale (ADL) score was changed from ≤2 to ≤3.5.

The following scores were changed in the Visit 1 – In-Clinic Screening section: Mini-Mental State Examination score was changed from >25 to ≥24; the Blessed Dementia Scale (ADL) score was changed from ≤2 to ≤3.5.

Table 1 under Visit 1 – In-Clinic Screening section on page 17 was modified to change the sequence of test administration at the in-clinic screening visit. The order was changed in numbers 3 to 8 in Table 2.

The following statements were added to the first paragraph under the Visit 2-Randomization section: "Randomization will be stratified according to the patient's score on the Mini Mental State Examination at the In-Clinic Screening visit. Patients entering the study with scores of 24 to 26 will be assigned the lowest consecutive available allocation number, and patients entering the study with scores of 27 to 30 will be assigned the highest consecutive available allocation number."

The following sentence was added to the first paragraph under the Determination of Endpoint and the Role of the Endpoint Adjudication Committee section: "(If a CTT or MRI scan has been performed as part of the study within the previous 6 months, then it need not be repeated, unless any clinically relevant abnormalities were noted on the initial scan.)."

The following paragraph under the Endpoint Confirmation section on page 22 was modified (modifications shown as bolded text): "This visit will be conducted 2 months after the usual study visit only if a patient has a **global** Clinical Dementia Rating ≥1. At this visit, **t**he Clinical Dementia Rating will be performed **and if the global Clinical Dementia Rating is still ≥1,** then the Selective Reminding Test, the Mini Mental State Examination, the Alzheimer's Disease Assessment Scale-Cognitive subscale, the Blessed Dementia Scale (ADL), and Hamilton Depression Scale will be administered, along with a physical exam, laboratory tests, ECG, and vital signs. The investigator will then determine whether the patient still meets NINCDS-ADRDA criteria for probable or possible Alzheimer's disease (Appendix 11), or has a non-Alzheimer dementia. Patients with a diagnosis of

dementia will be discontinued from the study and referred to their physicians for appropriate follow-up. Patients in whom the diagnosis of dementia is not confirmed at this visit **(global Clinical Dementia Rating <1)** will return to the normal schedule of clinic visits."

The first paragraph under the Early Discontinuation From Study Medication section was modified to remove the requirement for a Steering Committee.

The following modifications were made to the paragraphs under the Clinical Dementia Rating section on page 24: The first paragraph was modified to clarify that the semistructured interview takes place with the informant first, then with the patient. The first paragraph was also modified to clarify that the CDR is the first test to be administered at visits after the Randomization visit. In the second paragraph under the Clinical Dementia Rating section, the following clarification was added: "The informant must be present at the In-Clinic Screening visit. Every effort should be made to ensure that the informant attends subsequent clinic visits. In the event that the informant is unable to attend in person for a visit after the In-Clinic Screening visit, then the interview with the informant must be completed before the interview with the patient."

The second paragraph, "The Blessed Dementia Scale will only be used to assist the investigator in the diagnosis of dementia." was deleted from the Blessed Dementia Activities of Daily Living Scale section.

The second paragraph under the Medical History, Physical, and Neurological Examinations section was modified to remove the requirement for the height examination to be performed at Months 12 and 24 as follows: "The physical exam and weight will be repeated at the Months 12, 24, and Endpoint Confirmation visits."

The term, "stratification factor" was added to the first paragraph under the Primary Efficacy Analysis section as follows: "The effects of treatment, stratification factor, and study site will be assessed." The sentence, "The effects of stratification by Mini Mental State Examination score and study site will also be considered as factors in the log rank test." in the second paragraph, same section was modified for clarification.

The entire section, "Interim Analysis" under the Exploratory Analysis section (page 38), was deleted.

The paragraph under the Multiplicity Adjustment section was modified and the last two sentences which mention the interim analysis were deleted, as follows: "Since there is only one primary efficacy analysis in the study, no multiplicity adjustment of critical p-values will be made."

The first three paragraphs under the Power and Sample Size section (pages 39 and 40) were modified, removing all mention of the interim analysis.

The following paragraph was inserted before section 6.a, under the Exploratory Analysis section: "The analyses of the secondary efficacy variables are considered to be exploratory. The analyses will be more descriptive and estimating rather than hypotheses testing."

The third paragraph under the Selective Reminding Test, Mini Mental State Examination, and the Alzheimer's Disease Assessment Scale-Cognitive Subscale section was deleted, to remove the reference to the interim analysis.

The first paragraph under the Labeling and shipment of Specimens for Genotyping section (page 45) was modified to change the number of collection tubes from "3" to "2."

Protocol 078 was amended with the following changes in Amendment 02 [3.3] on 01-Sep-1998:

The performance measure on the Auditory Verbal Learning Test (AVLT) scoring under Study Design and Duration in the Protocol Synopsis section was changed to more specifically address the appropriate score for inclusion. Text was changed from "... performance on the Auditory Verbal Learning Test of >1.5 standard deviations below the age-appropriate mean." to "...performance on the Auditory Verbal Learning Test of ≥1 standard deviation below the mean score for normal subjects aged 65 (i.e., Total Learning score <37)." The performance measure on the AVLT score was also changed in the Inclusion Criteria section under d.3) to indicate a patient would be included in the study if they met the criteria of "A score on the Auditory Verbal Learning Test of ≥1 standard deviations below the mean score for normal subjects aged 65. This corresponds to a Total Learning score <37."

The percentage of patients allowed to take vitamin E was changed from 10% of patients enrolled at each site (except as part of a multivitamin supplement) to "No more than 20% of patients enrolled at each study site may be taking vitamin E supplements >400 IU daily." Under the Patient Sample section in the Protocol Synopsis.

Warfarin was deleted as an exclusion criteria under j.2.

The percentage of patients allowed to take vitamin E was updated to 20% in the Treatment Plan section under Treatment on page 12.

The following note was added to number five of the Prior Medications section on page 14: "Patients who are on warfarin are eligible for the study, provided that there is an increased frequency of monitoring of prothrombin time following initiation of blinded study therapy."

The following note was added to number one of the Concomitant Medications section on page 14: "Patient may be started on warfarin during the study provided that normal clinical monitoring practices are followed."

The performance measure on the AVLT score (Total Learning measure) was also changed in the Visit 1-In-Clinic Screening section under Study Procedures on page 16 to: "... performance on the Auditory Verbal Learning Test (Total Learning measure) >1 standard deviations below the mean score for normal subjects aged 65 (i.e., Total Learning score <37."

The following question was added to number four under AVLT on the Visit 1—In-Clinic Screening flow chart on page 17: "Is score ≥1 standard deviation below the mean score for normal subjects aged 65 (i.e., Total Learning score <37? If yes:"

Amendment 03 (29-Apr-1999) [3.3] contained the following revisions:

The drug CELEBREX™ (celecoxib) was added to the list of chronic NSAIDs prohibited at any time during the study to the Patient Sample section under Study Design and Duration, In addition to the Exclusion criteria on pages 10 and 11, and both the Prior and Concomitant Medications sections on page 14.

The sentence, "Patients are prohibited from taking CELEBREX™ (celecoxib) at any time during the study." was added to statements regarding the use of NSAIDs.

The paragraph, "For any patient who reaches a CDR of 1 or greater, the primary investigator must review the CDR and all other neuropsychological test (i.e., ADAS-cog, Blessed Dementia Scale, MMSE, SRT) prior to submitting the patient data package for adjudication. If the CDR is performed by a certified rater other than the primary investigator, then the primary investigator must initial and date the CDR worksheet in addition to the rater who performed the test. Data on all patients with a CDR of 1 or greater will be forwarded to the Endpoint Adjudication Committee within 7 days of receipt of data at Merck." was added to the Efficacy Measurements section under Study Design and Duration. This information was also added to the Visit 3—Month 1 section under Study Procedures on page 18, the Determination of Endpoint and the Role of the Endpoint Adjudication Committee section on page 19, and to the Clinical Dementia Rating section on page 24.

The distinction that the Endpoint Adjudication Committee would indicate whether they concur that said patient had developed dementia and whether it was consistent with possible or probable AD or dementia of a non-Alzheimer's type (i.e., vascular dementia) was made clear under the Efficacy Measurements section under the Protocol Synopsis as well as the Determination of Endpoint and the Role of the Endpoint Adjudication Committee section on page 19.

Table 3 on page 21: The CDR Trigger for Endpoint Determination and Confirmation of Probable or Possible Alzheimer's Disease was modified to add the following step in the second box down on the left: "e) Prior to submitting adjudication package, the primary investigator must: 1. Review the CDR ratings and other test. 2. Initial and date CDR worksheets in addition to the rater who performed the test."

The statement, "Only endpoints of clinical Alzheimer's disease where the Endpoint Adjudication Committee and the investigator concur will be the subject of the primary analysis." was added to the Primary Efficacy Analysis section under Data Analysis on page 37.

Amendment 04 (20-Aug-1999) [3.3] contained the following revisions:

The drug VIOXX™ (rofecoxib) was added to the list of chronic NSAIDs prohibited at any time during the study to the Patient Sample section under Study Design and Duration, in addition to the Exclusion criteria, and both the Prior and Concomitant Medications sections.

The sentence, "Patients are prohibited from taking VIOXX™ (rofecoxib) at any time during the study." was added to statements regarding the use of NSAIDs.

The specification that the primary investigator must review the CDR and all other neurological tests prior to submitting the patient data package for adjudication following the Endpoint Confirmation visit was added to the Efficacy Measurements section and the Study Procedures section d, Visit 3—Month 1 on page 18.

The requirement, "Within 7 days of the completion of the Endpoint Confirmation visit, a patient data package on all patients with a CDR of 1 or greater will be forwarded to the endpoint Adjudication Committee within 7 days of receipt of data at Merck." was added to the Efficacy Measurements section in the Protocol Synopsis.

The note for Exclusion Criteria k. was revised as follows: **"NOTE: Patients who were on stable doses of SSRIs or nefazodone for the preceding 2 months were eligible for entry, provided that they had a Hamilton Depression Scale score of <14 (see inclusion criteria g.). Patients taking antiepileptics for reasons other than epilepsy were approved by the Clinical Monitor on a case-by-case basis."**

The provision that patients who were scheduled for their Endpoint Confirmation visit (in 2 months) were to remain on study medication until the time of the Endpoint Confirmation visit was made in the Determination of Endpoint and the Role of the Endpoint Adjudication Committee on page 19.

The sentence, "For any patient who reaches a CDR of 1 or greater at a study visit, all patient data from that visit, all prior patient data, and the Endpoint Confirmation visit data, will be sent to Merck by the study site within 7 days of the completion of the Endpoint Confirmation visit." was modified to specify the inclusion of the Endpoint Confirmation visit data in that data package. This sentence is found in the Determination of Endpoint and the Role of the Endpoint Adjudication Committee section of Page 19.

The sentence, "If a clinical diagnosis of dementia is not confirmed at the Endpoint Confirmation visit, the patient will remain in the study and continue on study medication." was added to the Determination of Endpoint and the Role of the Endpoint Adjudication Committee section of Page 19.

The following statements were added to the Endpoint Confirmation section on page 22: "All data, including the endpoint Confirmation visit data for these patients, will be forwarded to the endpoint Adjudication Committee. The patient data package is to be forwarded to Merck within 1 week after the completion of the endpoint Confirmation visit. Also in the last sentence of this same section; the clarification that patient in whom the diagnosis of dementia was not confirmed at the Endpoint Confirmation visit, were required to return to the normal schedule of clinic visits and remain on study medication.

Amendment 05 (14-Feb-2000) [3.3] contained the following revisions:

The study treatment period was extended to include reaching 220 endpoints (where patients had a global CDR ≥ 1.0 calculated by the algorithm and verified by the computer program at the Endpoint Confirmation visit) or up to a maximum of 4 years. Statements to this effect were placed in the Study Design and Duration section of the Protocol Synopsis, and anywhere study duration was discussed. (The original protocol was written for a 2 year treatment period.)

The original sample size (approximately 1300) was increased by 150 to approximately 1450 patients to compensate for patient discontinuations. In addition, the approximate number of patients randomized to receive either rofecoxib 25 mg or placebo to match was modified to include 725 patients for each treatment group.

The clinical phase of the protocol, indicated as Phase V in the original version of the protocol, was changed to Phase III in the Protocol Synopsis.

The specification that the investigator was not to override the algorithm when determining the CDR global score (global CDR of 1 or greater as calculated by the algorithm and verified by the computer program) was made in the Efficacy Measurements section of the protocol.

The explanation and discussion of an "exceptional case" was inserted into the Efficacy Measurements section as follows: "The trigger for endpoint evaluation is a global CDR of 1 or greater (calculated by the algorithm and verified by the computer program). The investigator may not override the algorithm when determining the global CDR, as the scale does not allow this practice. If in an exceptional case, the trigger of a global CDR of 1 or greater has not been reached, but the principal investigator judges that the patient may have developed dementia, the patient will return to the clinic for additional evaluation in 2 months. At that time, if the global CDR has increased and is greater than or equal to 1 (calculated by the algorithm and verified by the computer program), the patient will be considered to have reached endpoint, and this visit will serve as the Endpoint Confirmation Visit. All procedures required for an Endpoint Confirmation Visit will be performed for this patient. In addition to those procedures required at the Endpoint Confirmation Visit, a noncontrast CT or MRI of the brain, and laboratory tests including serum B12, folate, TSH, and T4 will be performed.

If the global CDR is still <1 (calculated by the algorithm and verified by the computer program) at this 2-month follow-up visit, the investigator will determine whether the patient is able to remain in the study. If so, the patient will continue in the trial and return to the clinic for a regular study visit in 2 months. However, if the investigator judges that the patient cannot ethically remain in the study due to dementia, the patient will undergo the Endpoint Confirmation Visit at this time. In addition to those procedures required at the Endpoint Confirmation Visit, a noncontrast CT or MRI of the brain, and laboratory tests including serum B12, folate, TSH, and T4 will be performed."

The word "dementia" was added to the following statement in the Efficacy Measurements section: "Within 7 days of the completion of the Endpoint Confirmation Visit, a patient data package on all patients with dementia will be forwarded to the Endpoint Adjudication Committee within 7 days of receipt of data at Merck."

Due to the extended treatment period to a maximum of 4 years, all references to "Month" time frames for required procedures at visits were revised throughout the document to include Months 28 to 48 as appropriate. The addition of specific Months (clinic visits) was made in the Efficacy measurements section, specifically the Study Flow Chart (including Scheduled Phone Contacts section of the chart),

Study Procedures, Clinical Dementia Rating, SRT, ADAS-cog, BDS-ADL, and Hamilton Depression Scale sections; in the Safely Measurements section revisions were made specifically to the Medical History, Physical, and Neurological Examinations, ECG, and Laboratory Tests sections; as well as the Study Duration and Submission of Data section; and the Data Analysis sections, specifically the Variables of Interest and, Power and Sample Size sections; and finally in the Labeling, Packaging, storage, and return of Clinical Supplies section under Part II, Administrative and Regulatory.

The sentence, "The raw incidence rate of clinical AD will also be compared between treatment groups." was added to 6b., the Impact of Discontinuation on Primary Efficacy Analyses section under Data analysis.

Revisions to the Labeling, Packaging, Storage, and Return of Clinical Supplies section was necessary due to the study length adjustment and patient sample size increase. The second paragraph in this section (page 43) was modified to allow for these changes.

Amendment 06 (11-Apr-2000) included the change below which was added to statements regarding the use of NSAIDS:

The sentence, "Patients who develop a need for cardio-protective doses of aspirin after randomization are permitted to use aspirin ≤100 mg/day."

The study conduct was altered by Amendment 07 on 14-Jul-2000 [3.3]:

The following paragraph was added to the following sections: Protocol Synopsis, Prior and Concomitant Medication(s)/Treatment(s), Determination of Endpoint and the Role of the Endpoint Adjudication Committee, and Endpoint Confirmation. "Initiation of Aricept or other cholinesterase inhibitors is not permitted at any time during the study until after the Endpoint Confirmation Visit. If cholinesterase inhibitors are administered in contradistinction to the protocol, after the initial endpoint has been determined but prior to the Endpoint Confirmation Visit, the patient should nevertheless return for the Endpoint Confirmation Visit 2 months after the initial determination of dementia. The investigator will attempt to confirm the diagnosis of dementia at the Endpoint Confirmation Visit. If the global CDR is ≥1 (calculated by the algorithm and verified by the computer program) the patient will be considered to have reached endpoint and discontinued from the study. If the global CDR is <1, the patient will also be discontinued from the study. In either case, the patient will undergo all procedures for the Endpoint Confirmation Visit. All such cases will be adjudicated by the EAC. The inclusion of these endpoints in the primary data analysis will depend on the determination of the Endpoint Adjudication Committee."

Since follow-up of upper GI PUBs for patients who discontinued from the trial was no longer a program requirement, the following sentence was added to Section G.6., Special Reporting Procedures for Upper Gastrointestinal PUBs: "DPF (Discontinued Patient Follow-up) data will no longer be collected, therefore the DPF data form and data collection procedures (located in Appendix 12 to Protocol 078-00) will no longer be utilized" has been added to the Special Reporting Procedures for Upper Gastrointestinal PUBs section of the protocol.

The following sentences were added to the Primary Efficacy Analysis section: "The primary endpoints for the efficacy analysis are those confirmed by the investigator and the Endpoint Adjudication Committee." and "Patients who are placed on treatment with cholinesterase inhibitors and are not confirmed at the Endpoint Confirmation Visit will be discontinued from the study. Such patients will be censored at the time of the initial endpoint visit."

Amendment 08 (21-Nov-2000) [3.3] contained the following revisions:

The addition of an interim analysis of cardiovascular safety to the Data analysis section of the Synopsis (Page iii) and Section I.I.7., Interim Analysis of Cardiovascular Safety (Page 42).00-**Amendment 09 (23-Apr-2001, final revision) [3.3] contained the following revisions:**

The addition of an interim analysis of mortality events to the Data Analysis section of the Synopsis (Page 4), and to Section I.I.8., Interim Analysis of Mortality Events (Page 42).

Trial Termination:

This trial was terminated based on blinded projections of the following: higher than expected discontinuation rate during the study and slowing rate of endpoint accrual, near achievement of targeted number of endpoints, and because allowing the study to continue would not have significantly augmented the large safety database that already had been accrued.

5.8.1 Additional Analyses Not Included in Data Analysis Plan

5.8.1.1 Estimates of Conversion Rates for Clinically Diagnosed AD

A post-hoc analysis of annual conversion rates were estimated by calculating the number of events per 100 patient-years in order to determine if these rates were comparable to those reported in the literature for similar patient populations. 95% CIs were also included.

5.8.1.2 Identification of Risk Factors

In order to assess which risk factors may have played a prognostic role in the progression of patients to AD, as well as a means of investigating whether these risk factors had a consistent effect as described in the literature, post-hoc identification of risk factors over and above that which was specified in the DAP was performed via univariate analyses for progression to AD. Hazard ratios, 95% CIs, and p-values were determined for each factor as the only covariate in a Cox proportional hazards model of time to clinically diagnosed AD.

5.8.1.3 Subgroup Analyses

By-treatment tabulations of clinically diagnosed AD by subgroup were performed post-hoc for the set of risk factors identified via the analyses described in Section 5.8.1.2, as well as postrandomization factors that were likely to be related to progression to AD (i.e., concomitant medication use).

5.8.1.4 Blood Pressure Changes Relative to Progression to AD

Post-hoc analyses of blood pressure changes relative to conversion to clinically diagnosed AD were performed in an attempt to determine whether increases in blood pressure were associated with an increased risk of progression to AD. The crude proportions of patients with clinically diagnosed AD were summarized based on changes from baseline in the mean arterial pressure.

In addition, an analysis was conducted to determine if the occurrence of a postrandomization predefined limit of change (PDLC) in systolic blood pressure (increase) was related to conversion to AD. This criterion was not prespecified in the DAP [3.4] and was defined as a postrandomization value that was ≥180 mmHg and ≥20 mmHg increase from baseline.

5.8.1.5 Additional Statistical Models

Additional post-hoc statistical models were fit to the primary endpoint data to investigate the effect of known prognostic covariates, as well as to assess whether increased exposure to study drug influenced risk of conversion to clinically diagnosed AD.

5.8.1.5.1 Stratified Log-Rank

The stratified log-rank test was utilized for post-hoc analysis of the primary endpoint with the baseline MMSE strata (MMSE ≤26 versus MMSE>26) as

the stratification factor. This analysis was included based on a regulatory request that was agreed to by the sponsor prior to unblinding of the database. The DAP, however, was not modified to include this analysis. The regulatory request resulted from concerns about the validity of assumptions associated with the Cox proportional hazards model. This analysis was included as a check for the sensitivity of the results to the assumption that the treatment-specific hazards were proportional over the duration of the study.

5.8.1.5.2 Stepwise Model Selection

A post-hoc stepwise procedure was used to build the Cox PH regression model using a significance level of 0.10 as the criterion for inclusion of a covariate. The comprehensive candidate list of covariates included: treatment, baseline MMSE stratum, gender, prior NSAID use (yes/no), number of days treated with concomitant NSAID therapy, number of days exposed to concomitant NSAID therapy (first date to last date), age category (<75 yrs/>75 yrs), prior ginkgo biloba use (yes/no), concomitant statin use (yes/no), prior statin use (yes/no). Note that ApoE genotype was not included as this information was missing for a substantial proportion of patients.

5.8.1.5.3 Per Protocol and 80% Compliant Analysis

An additional PP analysis was performed post-hoc that was based on the subset of patients who were 80% compliant during the study participation period, regardless of the length of study participation.

5.8.1.6 Last Observation Carried Forward Approach To Exploratory Efficacy Measure Changes Over Time

A post-hoc LOCF approach was used to investigate the effect of treatment over time on the mean changes from baseline in ADAS-Cog, MMSE, and CDR Sum of Box scores for the following populations:

- All patients
- By baseline MMSE stratum

5.8.1.7 Investigation of Study Discontinuation Rates and Patient Disposition

5.8.1.7.1 Analysis of Study Discontinuation Rates

Due to a substantial, though not unexpected, dropout rate over the four-year study period, a post-hoc investigation was performed to determine if rates of study discontinuation due to reasons that could be related to the progression of

the disease were differential between treatment groups. A Kaplan-Meier curve was constructed for the set of all patients randomized for time to study discontinuation due to the following reasons: withdrawn consent, patient uncooperative, and lost to follow-up. All other outcomes were considered to be a censoring event for this analysis (e.g., completed the study, experienced an endpoint, discontinued due to a clinical adverse experience, etc.).

5.8.1.7.2 Efficacy Measures: Change from Baseline to Study Discontinuation or Completion

In order to determine if, for either treatment group, there was a fundamental difference between the patients who discontinued the study and the patients who completed the study, a post-hoc analysis of change from baseline to the last measured time point for ADAS-Cog, MMSE, and CDR Sum of Box scores by treatment group and patient status was performed.

5.8.1.8 Special Safety Analyses

Analyses, summaries, and statistical analyses of safety data not specified in the DAP are described in the following sections.

This section describes analysis approaches that

1) were designed to directly address regulatory requests regarding rofecoxib safety data, or

2) were included to be consistent with safety analyses performed in other rofecoxib studies based on program-wide study interests.

5.8.1.8.1 Analysis of Mortality

For each mortality endpoint on-drug (including All-Cause Mortality and Thrombotic Cardiovascular Mortality), the crude proportions (i.e., crude rates) and patient-year adjusted incidence rates (95% CI) were provided. These analyses are in addition to the prespecified tabulation of on-drug deaths described in Section 5.7.3.1.

5.8.1.8.2 Analysis of Cardiovascular Serious Adverse Experiences

Crude proportions and patient-year adjusted incidence rates were provided for each class and term for on-drug events.

5.8.1.8.3 Perforations, Ulcers, or Upper Gastrointestinal Bleeding (PUBs)

In addition to the tabulation of upper GI PUBs (gastric or duodenal perforations, peptic ulcers, or upper GI bleeds) which occurred on drug, the crude proportions (i.e., crude rates), patient-year adjusted incidence rates, and 95% CIs were provided for on drug confirmed events and confirmed complicated events.

5.8.1.8.4 Discontinuation of Study Drug Due to Adverse Experiences of the GI System

The type of adverse experience of special interest prespecified in the DAP [3.4] for NSAID-Type GI adverse experiences was changed to be consistent within the rofecoxib program. A summary of adverse experiences in the GI Disorders system that led to discontinuation of study drug was performed.

5.8.1.8.5 Fractures

A posthoc analysis of fractures was performed including crude proportions and patient-year adjusted incidence rates for fractures by treatment group based on specific types of fractures (terms for fractures listed in [4.5]). In addition, a 95% CI was calculated for the difference in proportions of patients with a fracture.

5.8.1.9 Time to Clinically Diagnosed AD Excluding Data from Sites Identified Through Audit Procedures

As a result of routine study monitoring and study site audits, the 137 patients who took study medication at Sites 019, 023, and 044 were excluded from the primary efficacy analyses of time to clinically diagnosed AD. The summary of these analyses is in 7.2.1.4.2 and Section 11 – Table 82. Since the conclusions from the analysis excluding these patients were the same as those from the analysis including all patients from all sites, all study sites were included in all efficacy and safety analyses and conclusions for the remainder of this report.

6. Study Patients and Data Sets Analyzed

6.1 Accounting for Patients in the Study

Patients were entered at 46 sites. Enrollment at each site ranged from 6 to 108 patients. The number of patients enrolled by investigator and treatment group is shown in Table 5. Investigator information is in [3.6].

Table 5

Number of Patients Entered by Investigator and Treatment

Study Number	Investigator Name	Rofecoxib 25 mg (N=725)	Placebo (N=732)	Total (N=1457)
001	Baumel, Barry	19	21	40
002	Charles, Lorna	17	17	34
003	Zolnouni, Parvaneh	36	36	72
004	Derbenwick, Mary	15	16	31
005	Edwards, Keith	5	5	10
006	Eisner, Larry	24	24	48
007	Ellis, Jay	27	27	54
008	England, Donald	27	28	55
009	Nunez, MD, Margarita	16	16	32
010	Gorman, David	12	14	26
011	Holub, Richard	15	15	30
012	Jenkyn, Lawrence	8	9	17
013	Kirby, MD, Louis	54	54	108
014	Margolin, David	8	8	16
015	Relkin, Norman	13	12	25
016	Reyes, Patricio	12	12	24
017	Ripley, Peter	19	19	38
018	Rymer, Marilyn	13	13	26
019	Stoukides, John	13	12	25
021	Thein, Stephen	27	27	54
022	Tindel, Jerry	5	6	11
023	Wendt, Jeanette	20	20	40
024	Loreck, David	3	3	6
025	Goldstein, Jerome	40	39	79
026	Antuono, Piero	13	13	26
027	Londborg, Peter	15	15	30
029	DuBoff, Eugene	9	8	17
030	Ferguson, James	9	10	19
031	Green, Robert	8	8	16
032	Hartford, James	7	6	13
033	Kinney, Cleveland	6	6	12
034	Kumar, Vinod	16	16	32
035	McEntee, William	13	12	25
036	Pahl, Jorg	16	16	32
037	Heiser, Jonathan	21	21	42
038	Tilker, Harvey	8	7	15
039	Tomlinson, Jack	17	16	33
040	Weisler, Richard	11	11	22
041	Rovner, Barry	3	3	6
042	Bell, Karen	5	6	11
043	Porsteinsson, Anton	20	21	41
044	Cummins, Howard	33	34	67
045	Smith, Ward	16	16	32
046	Doraiswamy, Murali	19	20	39
047	Ross, Joel	9	10	19
048	Pfeiffer, Eric	3	4	7
The study was not initiated at sites assigned to site numbers 20 and 28.				

Data Source: [4.1]

6.1.1 Overall Patient Disposition

The discussion of patient accounting is divided into 2 parts: 1) patients who discontinued the study, and 2) those who discontinued study drug (a combination of those who discontinued the study drug and continued in the study for follow-up and those who discontinued the study and study drug simultaneously).

This trial was terminated early based on blinded projections of the high discontinuation rate during the study (65% of the patients had discontinued the study prior to termination by Merck & Co., Inc.), the slowing rate of endpoint accrual, the near achievement of targeted number of endpoints, and because allowing the study to continue would not have significantly augmented the large safety database that already had been accrued. The final study visit was to be performed on 15-March-2003; if, however, a patient converted to AD at the final study visit, the patient was to return 2 months later for the final confirmation visit, extending the LPO to 15-May-2003. The 4 patients who converted to AD at their 48 month visit (completed study) had their confirmation visits prior to 15-May-2003; actual LPO was met on 23-April-2003.

6.1.1.1 Discontinuation of Study

A total of 1457 patients were enrolled in the study: 725 in the rofecoxib group and 732 in the placebo group. Table 6 summarizes the number of patients who entered, completed, and discontinued the study and includes a summary of the reasons patients discontinued the study. The reasons for study discontinuation include those for patients who discontinued the study either while dosing with drug or after they had previously discontinued study drug use.

More than twice as many male patients were enrolled in this study than females. A total of 980 male patients were enrolled (age range of 63 to 95 years): 476 (65.7%) in the rofecoxib group and 504 (68.9%) in the placebo group whereas 477 female patients were enrolled in the study (age range 64 to 95): 249 (34.3%) in the rofecoxib group and 228 (31.1%) in the placebo group.

At the time the study was terminated by Merck & Co., Inc., 244 patients were still participating in the study. Of these, 78 patients in each treatment group were still taking study medication at the time of discontinuation. The full 48-months of study participation was completed by 265 (18.2%) of enrolled patients (117 [16.1%] and 148 [20.2%] in the rofecoxib and placebo groups, respectively). Of these, 198 patients remained on study drug for the entire 48 months, 79 (10.9%) in the rofecoxib group and 119 (16.2%) in the placebo group. There were 67 patients who completed 48 months of study participation after discontinuation of study therapy: 38 (5.2%) patients in the rofecoxib group and 29 (4.0%) patients in the placebo group.

The study endpoint of a diagnosis of investigator-confirmed AD was reached by 4 patients at the final study visit: 2 in the rofecoxib group and 2 in the placebo group; 1 patient in the placebo group reached study endpoint while on drug, the other 3 (2 and 1, in the rofecoxib and placebo groups, respectively) were off drug when study endpoint was reached.

A total of 1192 patients discontinued the trial: 608 (83.8%) in the rofecoxib group and 584 (79.8%) in the placebo group. A total of 885 (60.7%) patients discontinued the study while on drug (61.5 and 60.0% of patients on rofecoxib and placebo, respectively). A total of 307 (21.1%) patients discontinued drug, continued in the study for follow-up, and then discontinued the study: 162 (22.3%) in the rofecoxib group and 145 (19.8%) in the placebo group.

The most common reason for discontinuation of the study was due to withdrawal of consent for 366 (25.1%) patients: 172 (23.7%) in the rofecoxib and 194 (26.5%) in the placebo group. There were 51 (3.5%) patients lost to follow-up: 28 (3.9%) and 23 (3.1%) in the rofecoxib and placebo groups, respectively.

A total of 152 patients (10.4%) discontinued the trial due to clinical adverse experiences: 82 (11.3%) in the rofecoxib group and 70 (9.6%) in the placebo group. Two patients (placebo group) discontinued the trial due to a laboratory adverse experience.

A total of 345 patients were discontinued from the study due to administrative reasons. Twenty-five patients (1.7%) were discontinued from the study when sites closed due to reasons independent from the study. Merck & Co., Inc., terminated study participation at 2 sites, thereby discontinuing 76 (5.2%) patients from the study. When Merck & Co., Inc., terminated the study, a total of 244 patients (16.7%) were discontinued (121 and 123 patients in the rofecoxib and placebo groups, respectively).

There were 191 patients who reached study endpoint prior to completing the study and were discontinued from the study per the protocol; when including the patients who reached endpoint upon completion of 48 months of study participation, the total number of patients who reached endpoint was 195.

Table 6

Overall Disposition of Patients
Intention-to-Treat Population

	Rofecoxib 25 mg n (%)	Placebo n (%)	Total n (%)
Screening failures			1392
Number of patients enrolled (total)	725	732	1457
Male (age range - years)	476 (63 - 94)	504 (64 - 95)	980 (63-95)
Female (age range - years)	249 (64 - 95)	228 (64 - 93)	477 (64-95)
Completed study†	117 (16.1)	148 (20.2)	265 (18.2)
Completed study on drug	79 (10.9)	119 (16.2)	198 (13.6)
Completed study off drug ‡	38 (5.2)	29 (4.0)	67 (4.6)
Discontinued from study (total)	608 (83.8)	584 (79.8)	1192 (81.8)
Discontinued study on drug	446 (61.5)	439 (60.0)	885 (60.7)
Discontinued study off drug§	162 (22.3)	145 (19.8)	307 (21.1)
Discontinued study due to: ‖			
Clinical adverse experience	82 (11.3)	70 (9.6)	152 (10.4)
Laboratory adverse experience	0 (0.0)	2 (0.3)	2 (0.1)
Lost to follow-up	28 (3.9)	23 (3.1)	51 (3.5)
Other (e.g. loss of caregiver; prohibited med use)	14 (1.9)	20 (2.7)	34 (2.3)
Patient moved	13 (1.8)	17 (0.2)	30 (2.1)
Uncooperative	15 (2.1)	3 (0.4)	18 (1.2)
Withdrew consent	172 (23.7)	194 (26.5)	366 (25.1)
Protocol deviation	1 (0.1)	2 (0.3)	3 (0.2)
Reached study endpoint	110 (15.2)	81 (11.0)	191 (13.1)
Site terminated by Merck & Co., Inc.	38 (5.2)	38 (5.2)	76 (5.2)
Merck & Co., Inc., terminated study	121 (16.7)	123 (16.8)	244 (16.7)
Site closed itself	14 (2.0)	11 (1.5)	25 (1.7)

† This count includes 4 patients who reached study endpoint after completing 48 months of study participation; n=2 and 2, for rofecoxib and placebo, respectively. One placebo patient was on drug, and 1 placebo and 2 rofecoxib patients were off study drug, at the time of study completion and reaching endpoint.
‡ These patients discontinued study drug and continued in the study to completion.
§ These patients discontinued study drug and subsequently discontinued the study.
‖ Category includes those patients who discontinued the study either while dosing with drug or after they had previously discontinued study drug use.
n= Number of patients in each category.

Data Source: [4.1]

6.1.1.2 Discontinuation of Study Drug

Since in this study patients who permanently discontinued all blinded study therapy were encouraged to remain in the trial for follow-up purposes, it was relevant to assess the reasons why study drug was stopped. Table 7 summarizes the number of patients who permanently discontinued all double-blind study therapy and the reasons for discontinuation of the therapy. Patients who discontinued study medication may have remained in the study for follow-up or completely discontinued the study.

A total of 1259 patients discontinued study medication: 646 (89.1%) in the rofecoxib group and 613 (83.7%) in the placebo group. The most common reason for discontinuing study therapy was for clinical adverse experiences: 160 (22.1%) patients in the rofecoxib group and 152 (20.8%) in the placebo group. Thirty-two patients (2.2%) discontinued therapy due to laboratory adverse experiences: 25 (3.4 %) patients in the rofecoxib group and 7 (1.0%) patients in the placebo group.

A total of 152 patients reached study endpoint of confirmed AD and discontinued the study per protocol while dosing with study medication: 89 (12.3%) in the rofecoxib group, and 63 (8.6%) in the placebo group; 39 additional patients (21 [2.9%] in the rofecoxib group, and 18 [2.5%] in the placebo group) reached study endpoint after discontinuing study medication.

When Merck & Co., Inc., decided to terminate the study, there were 156 ongoing patients still dosing with study drug; 78 patients in each treatment group (10.8% in rofecoxib group and 10.7% in placebo group); 88 (6.0%) patients had previously discontinued study medication and were remaining in follow-up when the study was terminated (43 and 45 patients in the rofecoxib and placebo groups, respectively).

Table 7

Reasons for Discontinuing Study Drug
Intention-to-Treat Population

	Rofecoxib 25 mg		Placebo		Total	
	n (%)		n (%)		n (%)	
Number of patients enrolled (total)	725		732		1457	
Discontinued study drug (total):	646	(89.1)	613	(83.7)	1259	(86.4)
Discontinued study drug and continued in study*	200	(27.6)	174	(23.8)	374	(25.7)
Discontinued study drug and study	446	(61.5)	439	(60.0)	885	(60.7)
Discontinued study drug due to:						
Clinical adverse experience	160	(22.1)	152	(20.8)	312	(21.4)
Laboratory adverse experience	25	(3.4)	7	(1.0)	32	(2.2)
Other (e.g., loss of caregiver; prohibited med use)	77	(10.6)	79	(10.8)	156	(10.7)
Lost to follow-up	18	(2.5)	16	(2.2)	34	(2.3)
Patient moved	7	(1.0)	13	(1.8)	20	(1.4)
Uncooperative	22	(3.0)	10	(1.4)	32	(2.2)
Withdrew consent	129	(17.8)	154	(21.0)	283	(19.4)
Protocol deviation	0	(0.0)	2	(0.3)	2	(0.1)
Reached study endpoint	89	(12.3)	63	(8.6)	152	(10.4)
Site terminated by Merck & Co., Inc.	30	(4.1)	30	(4.1)	60	(4.1)
Merck & Co., Inc., terminated trial	78	(10.8)	78	(10.7)	156	(10.7)
Site closed itself	11	(1.5)	9	(1.2)	20	(1.4)

* These patients discontinued study drug and continued to participate in the study for follow-up. Patients could subsequently complete or discontinue the study.
n=Number of patients in each category

Data Source: [4.1]

6.1.2 Nonrandomized Patients

Table 8 shows the reasons why patients were excluded from trial participation. A total of 1392 patients were not randomized into the study.

There were 110 patients (7.9%) who were not randomized because they met the exclusion criteria of a history or current evidence of any illness that, in the opinion of the investigator or Merck monitor, might have confounded the results of the study, interfered with the patient's participation for the full duration of the study, or posed an additional risk to the patient. There were 92 (6.6%) patients who met the exclusion criteria because of anticipation of the need for chronic NSAID or estrogen replacement therapy during the study or because they had been taking NSAIDs on a chronic basis prior to study entry, or had been on estrogen replacement therapy (excluding topical ointments) within 2 months of potential study entry.

A total of 705 patients (50.6%) did not meet the inclusion criteria of a score on the AVLT (Total Learning measure) >1.5 standard deviations below the age-appropriate mean. The inclusion criteria of normal or near-normal cognition, as evidenced by a MMSE score of ≥24 and supported by clinical impression, were not met by 127 patients (9.1%).

Table 8

Summary of Patients Not Randomized into the Study

Exclusion Criteria	Non-Randomized Patients N=1392 Yes	
	n	(%)
Concurrent, chronic use of psychotropic medications, e.g., antipsychotics, antidepressants, antiepileptics, or anxiolytics. NOTE: Patients who are on stable doses of SSRIs or nefazodone for the preceding 2 months are eligible for entry, provided that they have a Hamilton Depression Scale score <14 (see Inclusion criteria g.).	23	(1.7)
Patient has a history (within 2 years) or current evidence of a major untreated depressive disorder, a psychotic disorder, or substance abuse by DSM-IV criteria.	11	(0.8)
Patient has a history (within 2 years) or current evidence of major stroke, multiple lacunar infarcts, transient ischemic events, epilepsy, Parkinson's disease, progressive supranuclear palsy, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, or significant head trauma with loss of consciousness.	20	(1.4)
Patient has a history of active gastrointestinal bleeding within the past 3 months.	9	(0.6)
Patient has a history of angina or congestive heart failure with symptoms that occur at rest. (Note: patients with a history of myocardial infarction or coronary artery bypass grafting, angioplasty, or stent placement more than 1 year prior to study start may participate.)	6	(0.4)
Patient has a history of hepatitis or hepatic disease that has been active within the past 3 months.	2	(0.1)
Patient has a history or current evidence of any illness that in the opinion of the investigator or MRL monitor might confound the results of the study, interfere with the patient's participation for the full duration of the study, or pose an additional risk to the patient.	110	(7.9)
Patient has received an investigational drug or device within 30 days of study entry.	8	(0.6)
Patient has uncontrolled hypertension. (Note: patients with medically controlled hypertension [diastolic blood pressure less than 95 mm Hg, systolic blood pressure less than 165 mm Hg] may participate.)	10	(0.7)
Patient has used cholinesterase inhibitors (excluding ophthalmic preparations) within 1 month of study entry.	2	(0.1)
Patient has used estrogen replacement therapy (excluding topical ointments) within 2 months of study entry.	8	(0.6)
Patient has used intravenous, intramuscular, or oral corticosteroids within 1 month of study entry.	8	(0.6)
Patient has used warfarin, heparin, or ticlopidine within 1 month of study entry.	8	(0.6)

Table 8 (Cont.)

Summary of Patients Not Randomized into the Study

Exclusion Criteria	Non-Randomized Patients N=1392 Yes n	(%)
Patient is anticipated to need chronic NSAID or estrogen replacement therapy during the trial. Patient is taking NSAIDs (including salicylates or other aspirin-containing compounds) on a chronic basis (defined as greater than or equal to 7 total days out of the last 30 days for 2 consecutive months prior to potential study entry), or has been on estrogen replacement therapy (excluding topical ointments) within 2 months of potential study entry.	92	(6.6)
Patient meets clinical criteria for dementia.	31	(2.2)
Patient's estimated creatinine clearance is <30 mL/min. (Men: [140-age] x weight [kg]/[serum creatinine (mg/dL) x 72]; women: [0.85] [140-age] x weight [kg]/[serum creatine (mg/dL) x 72])	5	(0.4)
Inclusion Criteria	**No n**	**(%)**
A score on the Auditory Verbal Learning Test (Total Learning measure) >1.5 standard deviations below the age-appropriate mean.	705	(50.6)
By history, the patient must report or be reported, by the informant, to have a problem with memory.	28	(2.0)
Total Global Clinical Dementia Rating score of 0.5, with a Memory box score ≥0.5 and the sum of box scores ≥1.	82	(5.9)
Informant must confirm that the patient's memory has declined in the past year.	42	(3.0)
Normal activities of daily living as evidenced by a total score of ≤3.5 (no score >0.5 on any individual item on Part 1) on the Blessed Dementia Scale (ADL).	12	(0.9)
Normal or near-normal cognition as evidenced by a Mini Mental State Examination score of ≥24 and supported by clinical impression.	127	(9.1)
Patient has a Hamilton Depression scale (17-question version) score <14.	5	(0.4)
Patient has a Modified Hachinski Ischemia Scale Score ≤4.	14	(1.0)
Patient has a normal serum vitamin B-12, folate, TSH and T4 concentrations. (Patients on replacement therapy must have been on a stable dose for ≥3 months.)	51	(3.7)
Patient has a reliable informant (e.g., spouse, sibling, close friend) who is able to accompany the patient to clinic visits and is able to provide information to study investigator/staff via telephone contact. (Every effort should be made to ensure that any information is provided by the same informant for a given patient for the duration of the study.)	23	(1.7)

Table 8 (Cont.)

Summary of Patients Not Randomized into the Study

Inclusion Criteria (Cont.)	Non-Randomized Patients N=1392 Yes	
	n	(%)
Patient has completed at least 8 grades of education (beyond kindergarten).	7	(0.5)
Patient is a male or female ≥65 years of age.	16	(1.1)
Patient understands the study procedures, agrees to participate in the study by giving written consent, and agrees to return for follow-up visits and procedures in the event of discontinuation of study drug.	72	(5.2)
Patient, by investigator's clinical impression, has adequate motor and sensory capacities (when corrected if necessary) to perform neuropsychological testing.	5	(0.4)

N=number of patients not randomized.
n=number of patients in each category.

Data Source: [4.1]

6.2 Protocol Violators

For the PP efficacy analyses, patients who violated the protocol in ways that may have affected the efficacy outcomes (e.g., not satisfying certain inclusion and exclusion criteria, taking prohibited concomitant medication) were identified according to the following criteria prespecified in the DAP [3.4]:

- Patient was considered a violator upon study entry if:
  - — MMSE <24.
  - — HamD ≥14.
  - — MHIS >4.
  - — Global CDR ≥1 or memory box score = 0.
  - — BDS-ADL >3.5.
  - — AVLT >37.
  - — Patient did not have an appropriate informant.
  - — Patient had an insufficient washout period of prior therapy (see Table 9) that could have affected efficacy outcome(s).

Table 9

Definition of Protocol Violation for Prior Therapy

Prior Therapy	Protocol Violation if
Estrogen replacement therapy	Washout <8 weeks prior to screening after chronic use
NSAIDs (except aspirin ≤100 mg daily), CELEBREX™, VIOXX™	Washout <4 weeks after chronic use (≥7 days/month)
Cholinesterase inhibitors (excluding ophthalmic preparations)	Any use within 4 weeks prior to screening
Intravenous, intramuscular, or oral corticosteroids	Any use within 4 weeks prior to screening

Data Source: [3.4]

- Patient used a concomitant therapy that could have had an effect on efficacy outcome (see Table 10).

Table 10

Definition of Protocol Violation for Concomitant Therapy

Concomitant Therapy	Protocol Violation if
NSAIDs (except aspirin ≤100 mg/day), VIOXX™, CELEBREX™	Used continuously (i.e., daily) for ≥12 weeks (PRN use is not a violation)
COGNEX™ (tacrine HCl)	Any use initiated postrandomization
ARICEPT™ (donepezil HCl), EXELON™ (ravistigmine)	Any use initiated postrandomization
Estrogen replacement therapy (excluding topical cream preparations)	Continuous use (i.e., daily) for ≥12 weeks initiated postrandomization
Vitamin E >400 IU daily	Continuous use (i.e., daily) for ≥12 weeks initiated postrandomization
Oral steroids	Period of daily use ≥12 weeks (PRN use is not a violation) Less than 2 week washout prior to any assessment following a period of daily use ≥12 weeks (PRN use is not a violation).

Data Source: [3.4]

- Patients whose treatment was prematurely unblinded.
- Patients who took >1 tablet of study medication daily for ≥4 weeks.
- Patients who took incorrect study medication (i.e., patient dosed with study medication from a different allocation; see Section 8.0).

- Those who violated the eligibility at baseline were excluded from the PP efficacy analyses. Efficacy measures for those who violated concomitant therapy during the course of the study were censored at the time the violation occurred. All patients who met the protocol violation criteria are listed in [3.10.3].

6.2.1 Protocol Deviations

Several patients were granted a waiver by Merck & Co., Inc., which permitted entry into the study even though they did not meet entry criteria. The listing of these patients is in [4.4].

Sixty-two patients with uncontrolled hypertension received waivers to enter the study (i.e., diastolic blood pressure >95 mm Hg and systolic blood pressure >165 mm Hg); patients were also allowed to enter the study if hypertension were considered by the investigator to be a nonclinically significant condition for the patient.

Fifteen (1.0%) patients were allowed to enter the study who used prohibited medications within specified time frames (e.g., NSAIDs, estrogen, psychotropic medications).

Five (0.3%) patients were allowed to enter the study who had recent histories of prohibited medical conditions (e.g., strokes, angina, CHF).

Four (0.3%) patients were granted waivers to participate based on recalculation of estimated creatinine clearance due to age. Sixteen patients did not meet the criteria for normal serum vitamin B-12, folate, TSH or T4 concentrations; most of these patients were put on replacement therapy after the screening test and met criteria upon re-test.

Eight (0.5%) patients who did not meet the entry criteria for neuropsychological test scores were granted waivers based on investigators' judgment of patient behavior.

Thirteen (0.9%) patients did not have appropriate informants to participate in the study; 10 of these informants were professional caregivers paid by Site 013 to accompany the patients to all study visits.

Seven (0.5%) patients were allowed to enter the study with fewer than 8 grades of education.

Twenty-four (1.6%) patients were allowed to enter the study who did not meet the age cut-off of 65 years; 23 patients were 64 years of age and 1 patient was 63 years of age.

6.3 Patients Whose Treatment Was Prematurely Unblinded

Table 11 lists patients who were prematurely unblinded during the course of the study. The unblinding of patients occurred based on regulatory agency requirements for specific reported serious adverse experiences (i.e., "prompt indicated that the agency will unblind the patient based on the reported term and specific criteria related to that term, e.g., "life-threatening"). Thirteen serious adverse experiences were reported which led to selected unblinding of the clinical team responsible for the administration of this protocol via unblinded MedWatch reports sent to the Investigators.

Several interim analysis were performed using data from this study; however, results which were publically disclosed were combined with other placebo-controlled data (see Section 5.7.2.4 for discussion of analyses). Study and monitoring personnel were blinded to the data and results of these analyses.

Table 11

List of Patients Whose Treatment Allocations were Prematurely Unblinded

Investigator	Site Number	Alloc	Reason for Unblind	Knowledge of Unblind	Protocol Violator
Charles	078002	0059	MCA (U.K.) prompt	WPSE MCA only	No
Ellis	078007	0128	FDA prompt	WPSE 078 Clinical Team Investigator	Yes
Nunez	078009	0277	FDA prompt	WPSE 078 Clinical Team Investigator	Yes
Nunez	078009	0297	MCA (U.K.) prompt	WPSE MCA only	No
Nunez	078009	0359	FDA prompt	WPSE 078 Clinical Team Investigator	No
Nunez	078009	0360	MCA (U.K.) prompt	WPSE MCA only	No
Nunez	078009	0411	MCA (U.K.) prompt	WPSE MCA only	No
Nunez	078009	0425	MCA (U.K.) prompt	WPSE MCA only	No
Relkin	078015	0451	FDA prompt	WPSE 078 Clinical Team Investigator	Yes

Table 11 (Cont.)

List of Patients Whose Treatment Allocations were Prematurely Unblinded

Investigator	Site Number	Alloc	Reason for Unblind	Knowledge of Unblind	Protocol Violator
Ripley	078017	0538	FDA prompt	WPSE 078 Clinical Team Investigator	Yes
Ripley	078017	0600	AEM (Sp.) and URPL(Pol.)	WPSE AEM URPL	No
Ripley	078017	0628	MCA (U.K.) prompt	WPSE MCA only	No
Ripley	078017	0690	MCA (U.K.) prompt	WPSE MCA only	No
England	078008	0800	WPSE unblind per Clinical's request. Patient's family requested information due to patient's nonserious AEs of increased creatinine and BUN, and acute renal failure.	WPSE Investigator	Yes
Londborg	078027	0839	FDA prompt	WPSE 078 Clinical Team Investigator	Yes
Smith	078045	0874	FDA prompt	WPSE 078 Clinical Team Investigator	Yes
Smith	078045	0882	FDA prompt	WPSE 078 Clinical Team Investigator	Yes
Hartford	078032	1003	Patient possibly prematurely unblinded because at time of drug supply return, 3 market image VIOXX 25-mg tablets discovered in used Bottle H.	PRD	Yes
Hartford	078032	1017	AEM (Sp.) and URPL(Pol.)	WPSE AEM URPL	No
Hartford	078032	1221	MCA (U.K.) prompt	WPSE MCA only	No

Table 11 (Cont.)

List of Patients Whose Treatment Allocations were Prematurely Unblinded

Hartford	078032	1240	FDA prompt	WPSE 078 Clinical Team Investigator	No
Hartford	078032	1338	MCA (U.K.) prompt	WPSE MCA only	No
Hartford	078032	1365	FDA prompt	WPSE 078 Clinical Team Investigator	No
Hartford	078032	1453	WPSE unblind per Clinical's request. Patient's family requested information due to patient's fatal SAE of acute myelogenous leukemia.	WPSE Investigator	No
Doraiswamy	078046	1461	FDA prompt	WPSE 078 Clinical Team Investigator	Yes
Doraiswamy	078046	1475	MCA (U.K.) prompt	WPSE MCA only	No
Doraiswamy	078046	1478	FDA prompt	WPSE 078 Clinical Team Investigator	No
Porsteinsson	078043	1525	FDA prompt	WPSE 078 Clinical Team Investigator	Yes

WPSE= Worldwide Product Safety & Epidemiology.
SAE = Serious adverse experience.
AEM (Sp.)=The European Agency for the Evaluation of Medicinal Products (Spain).
URPL (Pol.) =Urad Rejestracji Produktow Leczniczych (Poland).
MCA (U.K.)=Medicines Control Agency (United Kingdom).

Data Source: [3.10]

6.4 Efficacy Populations Analyzed

The primary efficacy endpoint was clinically diagnosed AD (confirmed by the investigators and adjudicated as AD by the EAC). Statistical comparisons on change from baseline were performed on the exploratory endpoints SRT, MMSE, ADAS-Cog, and the CDR sum of box scores.

6.4.1 Intention-to-Treat Analysis

The primary analysis was based on the ITT approach, which included all randomized patients regardless of whether they discontinued study therapy or were protocol violators.

Table 12 summarizes the number of evaluable patients included in the analysis of continuously distributed exploratory efficacy endpoints, which was determined by the number of patients in the ITT population who had at least one post-randomization efficacy evaluation recorded. The percentage of nonevaluable patients was twice as high for the ADAS-Cog as for the other measures, primarily due to the collection frequency (only assessed annually for ADAS-Cog, other efficacy measures assessed at every visit).

Table 12

Number of Evaluable Patients in the Analyses

	Number of Patients Evaluable† (Not-Evaluable)	
Efficacy Measure	Rofecoxib (N=725)	Placebo (N=732)
SRT Summed Recall	679 (46)	699 (33)
SRT Delayed Recall	679 (46)	699 (33)
MMSE	683 (42)	704 (28)
ADAS-Cog	624 (101)	656 (76)

†Patients who had a baseline measure and at least one postrandomization measure.
N = Number of patients randomized.
SRT = Selective Reminding Test.
MMSE = Mini-Mental State Examination.
ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognition subset.

Data Source: [4.3]

6.4.2 PP Analysis

The PP approach for the primary efficacy analysis excluded patients who violated aspects of the protocol that were pre-specified in [3.4]. A description of these criteria is listed in Section 6.2. Those who violated study eligibility at baseline were excluded from the PP efficacy analysis. Those who violated concomitant therapy requirements were censored at the time the violation occurred. The PP analysis did not exclude patients who remained in the study but were not taking test drug. Table 13 provides a summary of the number of patients included in the ITT and PP approaches to the primary analysis.

Table 13

Number of Patients in Approaches to the Primary Efficacy Analysis

Analysis Approach	Number of Patients	
	Rofecoxib 25 mg (N=725)	Placebo (N=732)
Intention-to-treat	725	732
Per-protocol	698	696
Excluded due to Protocol Violation	27	36
Censored due to Protocol Violation	119	123
N=Number of patients randomized.		

Data Source: [3.10]

6.5 Demographic and Other Baseline Characteristics

6.5.1 Patient Characteristics

Table 14 shows the baseline patient characteristics for patients entered in the study. There were markedly fewer females (447) than males (980) in the patient population. There were more females in the rofecoxib (34.3%) than the placebo (31.1%). The mean age in the patient population was 75.1 years in the rofecoxib group and 74.8 years in the placebo group, with an age range across both groups of 63 to 95 years. There were slightly more patients in the rofecoxib (53.1%) than the placebo (50.6%) group with age >75 years.

Table 14

Baseline Patient Characteristics by Treatment Group

	Rofecoxib 25 mg (N=725)		Placebo (N=732)		Total (N=1457)	
	n	(%)	n	(%)	n	(%)
Gender						
Female	249	(34.3)	228	(31.1)	477	(32.7)
Male	476	(65.7)	504	(68.9)	980	(67.3)
Age						
64 and Under	12	(1.7)	12	(1.6)	24	(1.6)
65 to 74	328	(45.2)	349	(47.7)	677	(46.5)
75 to 84	341	(47.0)	329	(44.9)	670	(46.0)
Over 84	44	(6.1)	42	(5.7)	86	(5.9)
Mean	75.1		74.8		75.0	
SD	5.99		6.00		5.99	
Median	75.0		75.0		75.0	
Range	63 to 95		64 to 95		63 to 95	
Race						
African	1	(0.1)	0	(0.0)	1	(0.1)
Asian	7	(1.0)	7	(1.0)	14	(1.0)
Black	15	(2.1)	18	(2.5)	33	(2.3)
Hispanic American	13	(1.8)	14	(1.9)	27	(1.9)
Native American	3	(0.4)	1	(0.1)	4	(0.3)
Polynesian	0	(0.0)	1	(0.1)	1	(0.1)
White	686	(94.6)	691	(94.4)	1377	(94.5)

N= Number of patients randomized in each treatment group.
n = Number of patients in each category.
SD = Standard deviation.

Data Source: [4.1]

6.5.2 Baseline Demographics

Baseline demographics are shown on Table 15. Overall, the two treatment groups were similar for all categories of demographics. There were slightly more patients in the rofecoxib (31.2%) than the placebo (29.5%) group with a family history of AD. Most of the patients in each group had 12 or more years of education and were married. Scores on the baseline efficacy measures for the CDR, MMSE, ADAS-Cog, HamD, MHIS, SRT, BDS-ADL, and AVLT were similar in each group and are shown on Table 15. There were slightly more patients in the rofecoxib (14.9%) than the placebo (13.0%) group who used statins upon study entry.

Genotyping samples were not taken from every patient; a separate consent was issued for this procedure to be performed and participation was declined by 136 patients. The genotyping category of Table 15 indicates the number of patients who had specific ApoE genotypes and those who did not have the test performed (indicated as 'no result').

Table 15

Baseline Demographic Counts

	Rofecoxib 25 mg (N=725)		Placebo (N=732)		Total (N=1457)	
	n	(%)	n	(%)	n	(%)
Family History of Alzheimer's						
Family history	226	(31.2)	216	(29.5)	442	(30.3)
No family history	497	(68.6)	516	(70.5)	1013	(69.5)
No response	2	(0.3)	0	(0.0)	2	(0.1)
Marital Status						
Never married	17	(2.3)	13	(1.8)	30	(2.1)
Married	517	(71.3)	525	(71.7)	1042	(71.5)
Widowed	134	(18.5)	130	(17.8)	264	(18.1)
Separated, divorced	57	(7.9)	64	(8.7)	121	(8.3)
Years of Education						
<8	3	(0.4)	4	(0.5)	7	(0.5)
8 to 11	78	(10.8)	68	(9.3)	146	(10.0)
12	190	(26.2)	205	(28.0)	395	(27.1)
13 to 15	199	(27.4)	221	(30.2)	420	(28.8)
16 to 17	158	(21.8)	143	(19.5)	301	(20.7)
≥18	97	(13.4)	91	(12.4)	188	(12.9)
Major Lifetime Occupation						
Not in labor force	53	(7.3)	47	(6.4)	100	(6.9)
Official or administrator	92	(12.7)	98	(13.4)	190	(13.0)
Professional	224	(30.9)	202	(27.6)	426	(29.2)
Technician	40	(5.5)	41	(5.6)	81	(5.6)
Protective service worker	12	(1.7)	14	(1.9)	26	(1.8)

Table 15 (Cont.)

Baseline Demographic Counts

	Rofecoxib 25 mg (N=725)		Placebo (N=732)		Total (N=1457)	
	n	(%)	n	(%)	n	(%)
Paraprofessional	39	(5.4)	43	(5.9)	82	(5.6)
Administrative support	123	(17.0)	138	(18.9)	261	(17.9)
Skilled craft worker	105	(14.5)	108	(14.8)	213	(14.6)
Service-maintenance	37	(5.1)	41	(5.6)	78	(5.4)
Alcohol						
No consumption of alcohol	355	(49.0)	354	(48.4)	709	(48.7)
One or more drinks per week	370	(51.0)	378	(51.6)	748	(51.3)
Tobacco						
Used tobacco	444	(61.2)	445	(60.8)	889	(61.0)
Never used tobacco	281	(38.8)	287	(39.2)	568	(39.0)
ApoE Genotyping						
2/2	2	(0.3)	3	(0.4)	5	(0.3)
2/3	60	(8.3)	71	(9.7)	131	(9.0)
2/4	11	(1.5)	14	(1.9)	25	(1.7)
3/3	339	(46.8)	333	(45.5)	672	(46.1)
¾	201	(27.7)	213	(29.1)	414	(28.4)
4/4	39	(5.4)	35	(4.8)	74	(5.1)
No result	73	(10.1)	63	(8.6)	136	(9.3)
BLAH						
Private home or apartment	707	(97.5)	716	(97.8)	1423	(97.7)
Independent Living Facility	8	(1.1)	8	(1.1)	16	(1.1)
Assisted Living Facility (board and care)	0	(0.0)	1	(0.1)	1	(0.1)
Continuing Care Retirement Community - Independent living arrangement	5	(0.7)	6	(0.8)	11	(0.8)
Continuing Care Retirement Community - Assisted living (board and care)	1	(0.1)	1	(0.1)	2	(0.1)
No response	2	(0.3)	0	(0.0)	2	(0.1)
Nursing home - Intermediate Care Facility	1	(0.1)	0	(0.0)	1	(0.1)
Daughter's home	1	(0.1)	0	(0.0)	1	(0.1)
CDR Global Scores						
0.5	725	(100.0)	731	(99.9)	1456	(99.9)
>0.5	0	(0.0)	1	(0.1)	1	(0.1)
CDR Sum of Box Scores						
Mean	1.4		1.4		1.4	
SD	0.8		0.8		0.8	
Median	1.5		1.0		1.0	
Range	0.5 to 4.5		0.5 to 7		0.5 to 7	
MMSE						
Mean	27.4		27.3		27.4	
SD	1.7		1.7		1.7	
Median	27.0		27.0		27.0	
Range	24 to 30		23 to 30		23 to 30	

Table 15 (Cont.)

Baseline Demographic Counts

	Rofecoxib 25 mg (N=725)		Placebo (N=732)		Total (N=1457)	
	n	(%)	n	(%)	n	(%)
Stratum						
MMSE >26	496	(68.4)	490	(66.9)	986	(67.7)
MMSE ≤26	229	(31.6)	242	(33.1)	471	(32.3)
ADAS Cog						
Mean	9.2		9.4		9.3	
SD	4.0		3.8		3.9	
Median	9.0		9.0		9.0	
Range	0 to 24		0 to 31		0 to 31	
HAMD						
Mean	3.2		3.2		3.2	
SD	2.7		2.9		2.8	
Median	3.0		3.0		3.0	
Range	0 to 13		0 to 14		0 to 14	
Modified Hachinski						
Mean	0.5		0.5		0.5	
SD	0.8		0.8		0.8	
Median	0.0		0.0		0.0	
Range	0 to 4		0 to 4		0 to 4	
Selective Reminding Summary Scores						
Mean	33.4		33.6		33.5	
SD	9.0		9.1		9.1	
Median	33.0		33.0		33.0	
Range	6 to 60		11 to 65		6 to 65	
Selective Reminding Delayed Scores						
Mean	4.4		4.5		4.5	
SD	2.5		2.4		2.4	
Median	4.0		4.0		4.0	
Range	0 to 11		0 to 12		0 to 12	
Blessed Dementia (ADL)						
Mean	1.1		1.1		1.1	
SD	0.8		0.7		0.7	
Median	1.0		1.0		1.0	
Range	0 to 3.5		0 to 4		0 to 4	
Auditory Verbal Learning						
Mean	28.6		28.6		28.6	
SD	5.7		5.8		5.8	
Median	29.0		29.0		29.0	
Range	11 to 40		7 to 39		7 to 40	
Estrogen Use at Baseline						
Patients on Estrogen at baseline	3	(0.4)	10	(1.4)	13	(0.9)
Patients not on Estrogen at baseline	722	(99.6)	722	(98.6)	1444	(99.1)

Table 15 (Cont.)

Baseline Demographic Counts

	Rofecoxib 25 mg (N=725)		Placebo (N=732)		Total (N=1457)	
	n	(%)	n	(%)	n	(%)
Statin Use at Baseline						
Patients on Statin at baseline	108	(14.9)	95	(13.0)	203	(13.9)
Patients not on Statin at baseline	617	(85.1)	637	(87.0)	1254	(86.1)

N=total number of randomized patients in the treatment group.
n=number of patients in each category.
SD=Standard deviation.
MMSE=Mini-Mental State Examination.
HamD=Hamilton Depression test.
ApoE=Apolipoprotein E.
ADL=Activities of Daily Living.
ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subset.
CDR=Clinical Dementia Rating.
BLAH=Brief Living Arrangement History.

Data Source: [4.1]

6.5.3 Secondary Diagnosis

The number and percent of patients with specific secondary diagnoses that occurred in ≥3% of either treatment group are shown in Table 16. The rofecoxib and placebo treatment groups were comparable in nearly every body system category. Records for all specific secondary diagnoses are provided in [4.1].

Table 16

Number (%) of Patients With Specific Secondary Diagnoses by Body System
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Patients with one or more secondary diagnoses	720	(99.3)	729	(99.6)
Patients with no secondary diagnosis	5	(0.7)	3	(0.4)
Blood and Lymphatic System Disorders	**35**	**(4.8)**	**30**	**(4.1)**
Cardiac Disorders	**187**	**(25.8)**	**184**	**(25.1)**
Angina pectoris	26	(3.6)	27	(3.7)
Arrhythmia nos	18	(2.5)	22	(3.0)
Atrial fibrillation	25	(3.4)	31	(4.2)
Coronary artery disease nos	35	(4.8)	46	(6.3)
Myocardial infarction	21	(2.9)	32	(4.4)
Congenital, Familial and Genetic Disorders	**20**	**(2.8)**	**23**	**(3.1)**
Ear and Labyrinth Disorders	**214**	**(29.5)**	**231**	**(31.6)**
Deafness nos	143	(19.7)	138	(18.9)
Hypoacusis	36	(5.0)	44	(6.0)
Tinnitus	26	(3.6)	30	(4.1)
Vertigo	22	(3.0)	21	(2.9)
Endocrine Disorders	**82**	**(11.3)**	**91**	**(12.4)**
Hypothyroidism	63	(8.7)	78	(10.7)
Eye Disorders	**322**	**(44.4)**	**326**	**(44.5)**
Cataract	140	(19.3)	132	(18.0)
Glaucoma nos	44	(6.1)	44	(6.0)
Hypermetropia	20	(2.8)	23	(3.1)
Macular degeneration	28	(3.9)	31	(4.2)
Myopia	54	(7.4)	48	(6.6)
Presbyopia	38	(5.2)	35	(4.8)
Gastrointestinal Disorders	**378**	**(52.1)**	**381**	**(52.0)**
Colonic polyp	21	(2.9)	29	(4.0)
Constipation	57	(7.9)	47	(6.4)
Diarrhea nos	23	(3.2)	21	(2.9)
Diverticulitis nos	27	(3.7)	9	(1.2)
Diverticulum nos	15	(2.1)	31	(4.2)
Dyspepsia	73	(10.1)	67	(9.2)
Gastroesophageal reflux disease	62	(8.6)	64	(8.7)
Hemorrhoids	60	(8.3)	63	(8.6)
Hiatus hernia	40	(5.5)	48	(6.6)
Inguinal hernia nos	44	(6.1)	57	(7.8)
Peptic ulcer	24	(3.3)	15	(2.0)
General Disorders and Administration Site Conditions	**110**	**(15.2)**	**108**	**(14.8)**
Edema peripheral	40	(5.5)	38	(5.2)

Table 16 (Cont.)

Number (%) of Patients With Specific Secondary Diagnoses by Body System
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Hepatobiliary Disorders	**52**	**(7.2)**	**54**	**(7.4)**
Cholelithiasis	24	(3.3)	22	(3.0)
Immune System Disorders	**251**	**(34.6)**	**227**	**(31.0)**
Drug hypersensitivity	177	(24.4)	159	(21.7)
Seasonal allergy	86	(11.9)	75	(10.2)
Infections and Infestations	**242**	**(33.4)**	**225**	**(30.7)**
Appendicitis	35	(4.8)	30	(4.1)
Measles	29	(4.0)	27	(3.7)
Mumps	22	(3.0)	21	(2.9)
Nail fungal infection nos	22	(3.0)	20	(2.7)
Pneumonia nos	31	(4.3)	34	(4.6)
Tonsillitis	22	(3.0)	25	(3.4)
Urinary tract infection nos	20	(2.8)	22	(3.0)
Varicella	26	(3.6)	23	(3.1)
Injury, Poisoning and Procedural Complications	**179**	**(24.7)**	**204**	**(27.9)**
Head injury	12	(1.7)	22	(3.0)
Upper limb fracture nos	24	(3.3)	20	(2.7)
Investigations	**193**	**(26.6)**	**183**	**(25.0)**
Cardiac murmur nos	47	(6.5)	44	(6.0)
Colonoscopy	21	(2.9)	28	(3.8)
Metabolism and Nutrition Disorders	**257**	**(35.4)**	**262**	**(35.8)**
Diabetes mellitus non-insulin-dependent	26	(3.6)	23	(3.1)
Diabetes mellitus nos	47	(6.5)	50	(6.8)
Gout	24	(3.3)	20	(2.7)
Hypercholesterolemia	131	(18.1)	142	(19.4)
Hyperlipidemia nos	37	(5.1)	28	(3.8)
Musculoskeletal and Connective Tissue Disorders	**443**	**(61.1)**	**470**	**(64.2)**
Arthralgia	49	(6.8)	38	(5.2)
Arthritis nos	140	(19.3)	142	(19.4)
Back pain	66	(9.1)	72	(9.8)
Intervertebral disc herniation	9	(1.2)	24	(3.3)
Muscle cramp	23	(3.2)	17	(2.3)
Osteoarthritis nos	161	(22.2)	178	(24.3)
Osteoporosis nos	43	(5.9)	47	(6.4)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**212**	**(29.2)**	**210**	**(28.7)**
Basal cell carcinoma	59	(8.1)	61	(8.3)
Breast cancer nos	25	(3.4)	22	(3.0)
Prostate cancer nos	49	(6.8)	32	(4.4)
Seborrheic keratosis	17	(2.3)	27	(3.7)

Table 16 (Cont.)

Number (%) of Patients With Specific Secondary Diagnoses by Body System
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Nervous System Disorders	**276**	**(38.1)**	**273**	**(37.3)**
Carpal tunnel syndrome	19	(2.6)	24	(3.3)
Dizziness	32	(4.4)	31	(4.2)
Headache	92	(12.7)	83	(11.3)
Psychiatric Disorders	**181**	**(25.0)**	**163**	**(22.3)**
Depression	83	(11.4)	72	(9.8)
Insomnia	84	(11.6)	72	(9.8)
Renal and Urinary Disorders	**148**	**(20.4)**	**157**	**(21.4)**
Nephrolithiasis	29	(4.0)	44	(6.0)
Nocturia	26	(3.6)	19	(2.6)
Pollakiuria	20	(2.8)	24	(3.3)
Urinary incontinence	29	(4.0)	27	(3.7)
Reproductive System and Breast Disorders	**253**	**(34.9)**	**267**	**(36.5)**
Benign prostatic hyperplasia	136	(18.8)	138	(18.9)
Erectile dysfunction nos	48	(6.6)	50	(6.8)
Prostatic hypertrophy	41	(5.7)	38	(5.2)
Prostatitis	19	(2.6)	22	(3.0)
Respiratory, Thoracic and Mediastinal Disorders	**179**	**(24.7)**	**192**	**(26.2)**
Asthma nos	28	(3.9)	32	(4.4)
Bronchitis nos	29	(4.0)	24	(3.3)
Chronic obstructive airways disease	18	(2.5)	24	(3.3)
Rhinitis allergic nos	36	(5.0)	34	(4.6)
Skin and Subcutaneous Tissue Disorders	**187**	**(25.8)**	**179**	**(24.5)**
Actinic keratosis	45	(6.2)	44	(6.0)
Social Circumstances	**37**	**(5.1)**	**40**	**(5.5)**
Surgical and Medical Procedures	**636**	**(87.7)**	**648**	**(88.5)**
Adenoidectomy	27	(3.7)	16	(2.2)
Appendicectomy	135	(18.6)	128	(17.5)
Cataract extraction	145	(20.0)	119	(16.3)
Cholecystectomy	75	(10.3)	87	(11.9)
Coronary artery surgery	28	(3.9)	25	(3.4)
Hemorrhoid operation	34	(4.7)	42	(5.7)
Hernia repair nos	77	(10.6)	87	(11.9)
Hip arthroplasty	22	(3.0)	21	(2.9)
Hysterectomy	74	(10.2)	78	(10.7)
Inguinal hernia repair	46	(6.3)	51	(7.0)
Knee arthroplasty	34	(4.7)	27	(3.7)
Knee operation	22	(3.0)	26	(3.6)
Polypectomy	35	(4.8)	31	(4.2)
Prostatectomy nos	33	(4.6)	19	(2.6)
Skin neoplasm excision	39	(5.4)	47	(6.4)
Spinal laminectomy	19	(2.6)	28	(3.8)
Tonsillectomy	119	(16.4)	116	(15.8)
Transurethral prostatectomy	59	(8.1)	59	(8.1)

Table 16 (Cont.)

Number (%) of Patients With Specific Secondary Diagnoses by Body System
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Vascular Disorders	**317**	**(43.7)**	**302**	**(41.3)**
Hypertension nos	273	(37.7)	251	(34.3)
Varicose veins nos	32	(4.4)	29	(4.0)
Although a patient may have had 2 or more secondary diagnoses, the patient is counted only once within a category. The same patient may appear in different categories.				

Data Source: [4.1]

6.5.4 Prior Drug Therapies

Specific therapies taken prior to study start by at least 3% of patients in either treatment group are shown in Table 17. Prior therapies were taken by 93.9% of patients in the rofecoxib group and by 94.5% of patients in the placebo group. Common prior therapies were vitamins (61 and 61.5% in the rofecoxib and placebo group, respectively), analgesics (26.5% in the rofecoxib group and 22.5% in the placebo group), drugs for acid related disorders (19.2 and 17.6%, respectively), and serum lipid reducing agents (17.1 and 14.9%, respectively). Ginkgo biloba extract was used by more patients in the rofecoxib group than those in the placebo group (12.6 and 11.2%, respectively). Records of all specific prior therapies are provided in [4.1].

Table 17

Number (%) of Patients With Specific Prior Therapies
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Patients with one or more prior therapies	681	(93.9)	692	(94.5)
Patients with no prior therapy	44	(6.1)	40	(5.5)
Alimentary Tract and Metabolism				
Drugs for Acid Related Disorders	***139***	***(19.2)***	***129***	***(17.6)***
Calcium carbonate	42	(5.8)	36	(4.9)
Omeprazole	40	(5.5)	33	(4.5)
Laxative	***42***	***(5.8)***	***41***	***(5.6)***
Drug Used in Diabetes	***58***	***(8.0)***	***59***	***(8.1)***
Glyburide	23	(3.2)	26	(3.6)
Vitamin	***442***	***(61.0)***	***450***	***(61.5)***
Ascorbic acid	166	(22.9)	150	(20.5)
Minerals (unspecified) (+) vitamins (unspecified)	38	(5.2)	41	(5.6)
Vitamin B complex	39	(5.4)	31	(4.2)
Vitamin E	245	(33.8)	260	(35.5)
Vitamins (unspecified)	285	(39.3)	289	(39.5)
Mineral Supplement	***150***	***(20.7)***	***151***	***(20.6)***
Calcium (unspecified)	72	(9.9)	88	(12.0)
Potassium chloride	26	(3.6)	21	(2.9)
Zinc (unspecified)	24	(3.3)	21	(2.9)
Blood and Blood Forming Organs				
Antithrombotic Agent	***43***	***(5.9)***	***38***	***(5.2)***
Antianemic Preparation	***67***	***(9.2)***	***63***	***(8.6)***
Cyanocobalamin	40	(5.5)	47	(6.4)
Folic acid	22	(3.0)	12	(1.6)
Cardiovascular System				
Cardiac Therapy	***56***	***(7.7)***	***50***	***(6.8)***
Digoxin	29	(4.0)	27	(3.7)
Antihypertensive	***61***	***(8.4)***	***86***	***(11.7)***
Doxazosin mesylate	19	(2.6)	30	(4.1)
Terazosin hydrochloride	32	(4.4)	45	(6.1)
Diuretic	***82***	***(11.3)***	***86***	***(11.7)***
Furosemide	24	(3.3)	27	(3.7)
Hydrochlorothiazide	34	(4.7)	31	(4.2)
Beta Blocking Agent	***84***	***(11.6)***	***88***	***(12.0)***
Atenolol	30	(4.1)	26	(3.6)
Calcium Channel Blocker	***93***	***(12.8)***	***91***	***(12.4)***
Amlodipine besylate	26	(3.6)	15	(2.0)
Diltiazem hydrochloride	24	(3.3)	19	(2.6)
Nifedipine	12	(1.7)	23	(3.1)

Table 17 (Cont.)

Number (%) of Patients With Specific Prior Therapies
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Agent Acting on the Renin-Angiotensin System	***114***	***(15.7)***	***106***	***(14.5)***
Lisinopril	33	(4.6)	41	(5.6)
Serum Lipid Reducing Agent	***124***	***(17.1)***	***109***	***(14.9)***
Atorvastatin calcium	31	(4.3)	22	(3.0)
Pravastatin sodium	25	(3.4)	20	(2.7)
Simvastatin	28	(3.9)	32	(4.4)
Genitourinary System and Sex Hormones				
Urological	***60***	***(8.3)***	***53***	***(7.2)***
Systemic Hormonal Preparations, Excluding Sex Hormones				
Corticosteroid for Systemic Use	***14***	***(1.9)***	***29***	***(4.0)***
Thyroid Therapy	***66***	***(9.1)***	***78***	***(10.7)***
Levothyroxine sodium	64	(8.8)	73	(10.0)
Anti-Infectives for Systemic Use				
Antibacterial for Systemic Use	***32***	***(4.4)***	***30***	***(4.1)***
Musculoskeletal System				
Anti-Inflammatory and Antirheumatic Product	***61***	***(8.4)***	***75***	***(10.2)***
Ibuprofen	31	(4.3)	46	(6.3)
Drug for Treatment of Bone Diseases	***24***	***(3.3)***	***28***	***(3.8)***
Alendronate sodium	23	(3.2)	27	(3.7)
Nervous System				
Analgesic	***192***	***(26.5)***	***165***	***(22.5)***
Acetaminophen	106	(14.6)	79	(10.8)
Aspirin	73	(10.1)	66	(9.0)
Psycholeptic	***25***	***(3.4)***	***28***	***(3.8)***
Psychoanaleptic	***64***	***(8.8)***	***55***	***(7.5)***
Respiratory System				
Drugs for Obstructive Airway Diseases	***46***	***(6.3)***	***47***	***(6.4)***
Antihistamine for Systemic Use	***23***	***(3.2)***	***24***	***(3.3)***
Antihistamine, Route Unspecified	***24***	***(3.3)***	***22***	***(3.0)***
Sensory Organs				
Ophthalmological	***33***	***(4.6)***	***28***	***(3.8)***
Various				
All Other Therapeutic Products, Including Homeopathic and Herbal Preparations and Composition Unspecified	***191***	***(26.3)***	***169***	***(23.1)***
Garlic extract	25	(3.4)	25	(3.4)
Ginkgo biloba extract	91	(12.6)	82	(11.2)
Glucosamine	29	(4.0)	23	(3.1)
Saw palmetto	31	(4.3)	24	(3.3)
General Nutrient	***26***	***(3.6)***	***18***	***(2.5)***

This table was run using a "percent incidence." This means that a row will appear on this report only if one of the columns is greater than or equal to that percentage, after rounding. The category row will contain all the patients in that category, regardless of the percent incidence.

Data Source: [4.1]

6.5.5 Concomitant Therapies

Specific concomitant therapies taken during the study by at least 3% of patients in either treatment group are shown in Table 18. Six specific concomitant therapies are discussed in Section 6.5.5.1 because of their possible influence on cognitive performance. Concomitant therapies were taken by 98.6% of patients in the rofecoxib group and by 98.4% of patients in the placebo group. The most common concomitant therapies were analgesics (61.0 and 60.8 % in the rofecoxib and placebo groups, respectively), antibacterials for systemic use (45.7 and 47.5%, respectively), and drugs for acid related disorders (35.9 and 31.3%, respectively). In general, more patients in the rofecoxib treatment group were using concomitant medications for treatment of hypertension, e.g., there were 168 (23.2%) patients in the rofecoxib group and 131 (17.9%) patients in the placebo group using calcium channel blockers, and 232 (32%) and 186 (25.4%) of patients in the rofecoxib and placebo groups, respectively, using agents acting on the renin-angiotensin system. Records of all specific concomitant therapies are provided in [4.1].

Table 18

Number (%) of Patients With Specific Concomitant Therapies
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Patients with one or more concomitant therapies	715	(98.6)	720	(98.4)
Patients with no concomitant therapy	10	(1.4)	12	(1.6)
Alimentary Tract and Metabolism				
Drugs for Acid Related Disorders	***260***	***(35.9)***	***229***	***(31.3)***
Calcium carbonate	72	(9.9)	53	(7.2)
Cimetidine	22	(3.0)	18	(2.5)
Famotidine	45	(6.2)	41	(5.6)
Lansoprazole	43	(5.9)	39	(5.3)
Omeprazole	67	(9.2)	60	(8.2)
Ranitidine	49	(6.8)	35	(4.8)
Ranitidine hydrochloride	22	(3.0)	16	(2.2)
Drugs for Functional Gastrointestinal Disorders	***65***	***(9.0)***	***48***	***(6.6)***
Laxative	***149***	***(20.6)***	***110***	***(15.0)***
Docusate sodium	41	(5.7)	42	(5.7)
Psyllium husk	46	(6.3)	34	(4.6)
Antidiarrheal, Intestinal Anti-Inflammatory/Anti-Infective Agent	***38***	***(5.2)***	***44***	***(6.0)***
Loperamide hydrochloride	18	(2.5)	29	(4.0)
Drug Used In Diabetes	***72***	***(9.9)***	***82***	***(11.2)***
Glipizide	19	(2.6)	24	(3.3)
Glyburide	28	(3.9)	35	(4.8)
Metformin hydrochloride	24	(3.3)	30	(4.1)

Table 18 (Cont.)

Number (%) of Patients With Specific Concomitant Therapies
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Vitamin	***511***	***(70.5)***	***517***	***(70.6)***
Ascorbic acid	206	(28.4)	204	(27.9)
Minerals (unspecified) (+) vitamins (unspecified)	52	(7.2)	56	(7.7)
Vitamin B complex	54	(7.4)	50	(6.8)
Vitamin E	292	(40.3)	318	(43.4)
Vitamins (unspecified)	349	(48.1)	327	(44.7)
Mineral Supplement	***229***	***(31.6)***	***247***	***(33.7)***
Calcium (unspecified)	112	(15.4)	124	(16.9)
Potassium (unspecified)	18	(2.5)	28	(3.8)
Potassium chloride	50	(6.9)	55	(7.5)
Selenium (unspecified)	26	(3.6)	23	(3.1)
Zinc (unspecified)	33	(4.6)	31	(4.2)
Other Alimentary Tract and Metabolism Product	***23***	***(3.2)***	***21***	***(2.9)***
Blood and Blood Forming Organs				
Antithrombotic Agent	***123***	***(17.0)***	***115***	***(15.7)***
Clopidogrel bisulfate	55	(7.6)	48	(6.6)
Warfarin	34	(4.7)	36	(4.9)
Warfarin sodium	24	(3.3)	27	(3.7)
Antianemic Preparation	***134***	***(18.5)***	***122***	***(16.7)***
Cyanocobalamin	62	(8.6)	67	(9.2)
Ferrous sulfate	23	(3.2)	18	(2.5)
Folic acid	41	(5.7)	32	(4.4)
Cardiovascular System				
Cardiac Therapy	***116***	***(16.0)***	***101***	***(13.8)***
Digoxin	46	(6.3)	46	(6.3)
Nitroglycerin	57	(7.9)	36	(4.9)
Antihypertensive	***119***	***(16.4)***	***130***	***(17.8)***
Doxazosin mesylate	45	(6.2)	47	(6.4)
Terazosin hydrochloride	65	(9.0)	68	(9.3)
Diuretic	***185***	***(25.5)***	***167***	***(22.8)***
Furosemide	67	(9.2)	74	(10.1)
Hydrochlorothiazide	82	(11.3)	58	(7.9)
Hydrochlorothiazide (+) triamterene	36	(5.0)	35	(4.8)
Beta Blocking Agent	***160***	***(22.1)***	***163***	***(22.3)***
Atenolol	61	(8.4)	52	(7.1)
Metoprolol	28	(3.9)	36	(4.9)
Calcium Channel Blocker	***168***	***(23.2)***	***131***	***(17.9)***
Amlodipine besylate	70	(9.7)	37	(5.1)
Diltiazem hydrochloride	44	(6.1)	42	(5.7)
Nifedipine	29	(4.0)	27	(3.7)
Verapamil	27	(3.7)	28	(3.8)

Table 18 (Cont.)

Number (%) of Patients With Specific Concomitant Therapies
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Agent Acting on the Renin-Angiotensin System	***232***	***(32.0)***	***186***	***(25.4)***
Benazepril hydrochloride	28	(3.9)	13	(1.8)
Enalapril maleate	27	(3.7)	17	(2.3)
Lisinopril	90	(12.4)	82	(11.2)
Quinapril hydrochloride	23	(3.2)	16	(2.2)
Serum Lipid Reducing Agent	***201***	***(27.7)***	***201***	***(27.5)***
Atorvastatin calcium	73	(10.1)	70	(9.6)
Fluvastatin sodium	22	(3.0)	20	(2.7)
Pravastatin sodium	48	(6.6)	42	(5.7)
Simvastatin	61	(8.4)	73	(10.0)
Dermatologicals				
Corticosteroid, Dermatological Preparation	***32***	***(4.4)***	***34***	***(4.6)***
Genitourinary System and Sex Hormones				
Sex Hormone and Modulator of the Genital System	***26***	***(3.6)***	***43***	***(5.9)***
Urological	***123***	***(17.0)***	***126***	***(17.2)***
Finasteride	27	(3.7)	23	(3.1)
Oxybutynin chloride	27	(3.7)	31	(4.2)
Sildenafil citrate	33	(4.6)	31	(4.2)
Tamsulosin hydrochloride	37	(5.1)	38	(5.2)
Tolterodine tartrate	25	(3.4)	27	(3.7)
Systemic Hormonal Preparations, Excluding Sex Hormones				
Corticosteroid for Systemic Use	***156***	***(21.5)***	***158***	***(21.6)***
Cortisone	26	(3.6)	29	(4.0)
Prednisone	50	(6.9)	45	(6.1)
Triamcinolone acetonide	17	(2.3)	26	(3.6)
Thyroid Therapy	***88***	***(12.1)***	***95***	***(13.0)***
Levothyroxine sodium	84	(11.6)	91	(12.4)
Anti-Infectives for Systemic Use				
Antibacterial for Systemic Use	***331***	***(45.7)***	***348***	***(47.5)***
Amoxicillin	61	(8.4)	59	(8.1)
Amoxicillin (+) clavulanate potassium	24	(3.3)	19	(2.6)
Antimicrobial (unspecified)	25	(3.4)	33	(4.5)
Azithromycin	46	(6.3)	38	(5.2)
Cephalexin	57	(7.9)	46	(6.3)
Ciprofloxacin	55	(7.6)	52	(7.1)
Ciprofloxacin hydrochloride	29	(4.0)	32	(4.4)
Clarithromycin	30	(4.1)	28	(3.8)
Levofloxacin	41	(5.7)	47	(6.4)
Sulfamethoxazole (+) trimethoprim	33	(4.6)	47	(6.4)
Vaccine	***114***	***(15.7)***	***123***	***(16.8)***
Influenza virus vaccine	103	(14.2)	110	(15.0)

Table 18 (Cont.)

Number (%) of Patients With Specific Concomitant Therapies
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Antineoplastic and Immunomodulating Agents				
Antineoplastic Agent	***17***	***(2.3)***	***22***	***(3.0)***
Endocrine Therapy	***24***	***(3.3)***	***23***	***(3.1)***
Musculoskeletal System				
Anti-Inflammatory and Antirheumatic Product	***224***	***(30.9)***	***254***	***(34.7)***
Celecoxib	41	(5.7)	40	(5.5)
Ibuprofen	100	(13.8)	118	(16.1)
Ketorolac tromethamine	18	(2.5)	28	(3.8)
Naproxen	42	(5.8)	33	(4.5)
Naproxen sodium	25	(3.4)	21	(2.9)
Rofecoxib	36	(5.0)	36	(4.9)
Muscle Relaxant	***31***	***(4.3)***	***35***	***(4.8)***
Drug for Treatment of Bone Diseases	***51***	***(7.0)***	***47***	***(6.4)***
Alendronate sodium	49	(6.8)	42	(5.7)
Nervous System				
Anesthetic	***69***	***(9.5)***	***72***	***(9.8)***
Lidocaine	33	(4.6)	32	(4.4)
Analgesic	***442***	***(61.0)***	***445***	***(60.8)***
Acetaminophen	209	(28.8)	218	(29.8)
Acetaminophen (+) codeine phosphate	27	(3.7)	26	(3.6)
Acetaminophen (+) diphenhydramine hydrochloride	24	(3.3)	27	(3.7)
Acetaminophen (+) hydrocodone bitartrate	64	(8.8)	63	(8.6)
Acetaminophen (+) oxycodone hydrochloride	26	(3.6)	23	(3.1)
Acetaminophen (+) propoxyphene napsylate	36	(5.0)	45	(6.1)
Aspirin	230	(31.7)	219	(29.9)
Meperidine hydrochloride	35	(4.8)	35	(4.8)
Antiepileptic	***36***	***(5.0)***	***28***	***(3.8)***
Psycholeptic	***131***	***(18.1)***	***134***	***(18.3)***
Lorazepam	19	(2.6)	35	(4.8)
Midazolam hydrochloride	33	(4.6)	24	(3.3)
Zolpidem tartrate	24	(3.3)	21	(2.9)
Psychoanaleptic	***212***	***(29.2)***	***186***	***(25.4)***
Donepezil hydrochloride	69	(9.5)	56	(7.7)
Paroxetine hydrochloride	27	(3.7)	23	(3.1)
Sertraline hydrochloride	51	(7.0)	35	(4.8)
Respiratory System				
Nasal Preparation	***52***	***(7.2)***	***53***	***(7.2)***
Drugs for Obstructive Airway Diseases	***113***	***(15.6)***	***107***	***(14.6)***
Albuterol	40	(5.5)	35	(4.8)
Beclomethasone dipropionate	26	(3.6)	18	(2.5)
Fluticasone propionate	41	(5.7)	29	(4.0)
Ipratropium bromide	24	(3.3)	17	(2.3)

Table 18 (Cont.)

Number (%) of Patients With Specific Concomitant Therapies
(≥3% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Cough and Cold Preparation	***95***	***(13.1)***	***124***	***(16.9)***
Guaifenesin	32	(4.4)	45	(6.1)
Antihistamine for Systemic Use	***104***	***(14.3)***	***90***	***(12.3)***
Diphenhydramine hydrochloride	39	(5.4)	40	(5.5)
Meclizine	22	(3.0)	18	(2.5)
Antihistamine, Route Unspecified	***69***	***(9.5)***	***64***	***(8.7)***
Fexofenadine hydrochloride	33	(4.6)	31	(4.2)
Loratadine	37	(5.1)	39	(5.3)
Sensory Organs				
Ophthalmological	***73***	***(10.1)***	***62***	***(8.5)***
Latanoprost	21	(2.9)	25	(3.4)
Various				
All Other Therapeutic Products, Including Homeopathic and Herbal Preparations and Composition Unspecified	***269***	***(37.1)***	***240***	***(32.8)***
Chondroitin sulfate sodium (+) glucosamine hydrochloride	39	(5.4)	36	(4.9)
Garlic extract	33	(4.6)	34	(4.6)
Ginkgo biloba extract	99	(13.7)	92	(12.6)
Glucosamine	49	(6.8)	42	(5.7)
Herbs (unspecified)	24	(3.3)	31	(4.2)
Saw palmetto	55	(7.6)	41	(5.6)
General Nutrient	***50***	***(6.9)***	***43***	***(5.9)***
Dietary supplement (unspecified)	28	(3.9)	18	(2.5)
Although a patient may have had 2 or more concomitant therapies, the patient is counted only once within a category. The same patient may appear in different categories.				

Data Source: [4.1]

6.5.5.1 Specific Concomitant Therapies

Six specific concomitant therapies were explicitly reviewed for patient use during the study: NSAIDs, estrogen therapy, cholinesterase inhibitors, vitamin E >400 IU, ginkgo biloba, and statins. These results are displayed in Tables 19 through 24. These particular therapies were examined for extent of use because they were prohibited during the study or because they are presumed to enhance cognitive abilities. The tables below show counts of patients who used these medications at any dose and frequency (whether or not the dosing was exceeded and thus prohibited).

NSAIDs were used as a concomitant medication by 30.9% of patients in the rofecoxib group and by 34.7% of patients in the placebo group, as shown in Table 19. The most commonly used NSAID was ibuprofen, which was taken by 13.8 and 16.1%, respectively. The median duration of concomitant NSAIDs use was 5.6 weeks and 7.4 weeks, respectively. Overall, the median duration of concomitant use when calculated from start date to last date of use (whether or not there were intervening days without NSAIDs use) was 11 weeks and 25.4 weeks, respectively (Table 81 - Section 11).

Table 19

Number (%) of Patients on NSAID Therapy
(>0% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Patients with one or more concomitant therapies	224	(30.9)	254	(34.7)
Patients with no concomitant therapy	501	(69.1)	478	(65.3)
Musculoskeletal System				
Anti-Inflammatory and Antirheumatic Product	***224***	***(30.9)***	***254***	***(34.7)***
Celecoxib	41	(5.7)	40	(5.5)
Diclofenac	3	(0.4)	7	(1.0)
Diclofenac potassium (+) diclofenac sodium	1	(0.1)	1	(0.1)
Diclofenac sodium	8	(1.1)	10	(1.4)
Diclofenac sodium (+) misoprostol	1	(0.1)	6	(0.8)
Etodolac	3	(0.4)	9	(1.2)
Flurbiprofen	1	(0.1)	3	(0.4)
Flurbiprofen sodium	1	(0.1)	0	(0.0)
Hydrocodone bitartrate (+) ibuprofen	1	(0.1)	1	(0.1)
Ibuprofen	100	(13.8)	118	(16.1)
Ibuprofen (+) pseudoephedrine hydrochloride	2	(0.3)	1	(0.1)
Indomethacin	7	(1.0)	6	(0.8)
Ketoprofen	2	(0.3)	1	(0.1)
Ketorolac	1	(0.1)	1	(0.1)
Ketorolac tromethamine	18	(2.5)	28	(3.8)
Meclofenamate sodium	2	(0.3)	0	(0.0)
Meloxicam	4	(0.6)	5	(0.7)
Morniflumate	1	(0.1)	0	(0.0)
Nabumetone	10	(1.4)	14	(1.9)
Naproxen	42	(5.8)	33	(4.5)
Naproxen sodium	25	(3.4)	21	(2.9)
Naproxen sodium (+) pseudoephedrine Hydrochloride	0	(0.0)	1	(0.1)
Nimesulide	1	(0.1)	0	(0.0)

Table 19 (Cont.)

Number (%) of Patients on Estrogen Replacement Therapy
(>0% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Nonsteroidal anti-inflammatory drug (unspecified)	0	(0.0)	1	(0.1)
Oxaprozin	3	(0.4)	8	(1.1)
Piroxicam	2	(0.3)	0	(0.0)
Rofecoxib	36	(5.0)	36	(4.9)
Sulindac	4	(0.6)	4	(0.5)
Valdecoxib	2	(0.3)	4	(0.5)
Although a patient may have had 2 or more concomitant therapies, the patient is counted only once within a category. The same patient may appear in different categories.				

Data Source: [4.1]

Estrogen replacement therapy (other than topical cream preparations) was prohibited during the study. Concomitant estrogen therapy was taken by 2.6% of patients in the rofecoxib group and by 4.8% of patients the placebo group, as shown in Table 20.

Table 20

Number (%) of Patients on Estrogen Replacement Therapy
(>0% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Patients with one or more concomitant therapies	19	(2.6)	35	(4.8)
Patients with no concomitant therapy	706	(97.4)	697	(95.2)
Genitourinary System and Sex Hormones				
Sex Hormone and Modulator of the Genital System	***19***	***(2.6)***	***35***	***(4.8)***
Dienestrol	0	(0.0)	2	(0.3)
Estradiol	5	(0.7)	4	(0.5)
Estradiol (+) norethindrone acetate	0	(0.0)	1	(0.1)
Estrogens (unspecified)	0	(0.0)	1	(0.1)
Estrogens, conjugated	6	(0.8)	17	(2.3)
Estrogens, conjugated (+) medroxyprogesterone acetate	4	(0.6)	1	(0.1)
Estrogens, esterified	1	(0.1)	1	(0.1)
Estropipate	0	(0.0)	2	(0.3)
Ethinyl estradiol (+) norethindrone	0	(0.0)	1	(0.1)
Raloxifene hydrochloride	7	(1.0)	10	(1.4)
Although a patient may have had 2 or more concomitant therapies, the patient is counted only once within a category. The same patient may appear in different categories.				

Data Source: [4.1]

Cholinesterase inhibitors were taken by 11.2% of patients in the rofecoxib group and by 8.6% of patients in the placebo group, as shown in Table 21. The most commonly used cholinesterase inhibitor was donepezil hydrochloride, which was taken by 9.5 and 7.7% of patients, respectively.

Table 21

Number (%) of Patients on Cholinesterase Inhibitor Therapy
(>0% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Patients with one or more concomitant therapies	81	(11.2)	63	(8.6)
Patients with no concomitant therapy	644	(88.8)	669	(91.4)
Nervous System				
Psychoanaleptic	***80***	***(11.0)***	***63***	***(8.6)***
Donepezil hydrochloride	69	(9.5)	56	(7.7)
Galantamine hydrobromide	6	(0.8)	4	(0.5)
Rivastigmine	8	(1.1)	11	(1.5)
Other Nervous System Drug	***1***	***(0.1)***	***0***	***(0.0)***
Pyridostigmine bromide	1	(0.1)	0	(0.0)
Although a patient may have had 2 or more concomitant therapies, the patient is counted only once within a category. The same patient may appear in different categories.				

Data Source: [4.1]

Use of vitamin E >400 IU daily was limited per the protocol to 20% of the patients at each site. Vitamin E >400 IU daily was taken by 7.3% of the patients in the rofecoxib group and by 7.5% of patients in the placebo group, as shown in Table 22.

Table 22

Number (%) of Patients on Vitamin E >400 IU Therapy
(>0% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Patients with one or more concomitant therapies	53	(7.3)	55	(7.5)
Patients with no concomitant therapy	672	(92.7)	677	(92.5)
Alimentary Tract and Metabolism				
Vitamin	***53***	***(7.3)***	***55***	***(7.5)***
Vitamin E	53	(7.3)	55	(7.5)
Although a patient may have had 2 or more concomitant therapies, the patient is counted only once within a category. The same patient may appear in different categories.				

Data Source: [4.1]

Ginkgo biloba extract was taken by 13.7% of patients in the rofecoxib group and by 12.8% of patients in the placebo group, as shown in Table 23.

Table 23

Number (%) of Patients on Ginkgo Biloba Extract Therapy
(>0% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Patients with one or more concomitant therapies	99	(13.7)	94	(12.8)
Patients with no concomitant therapy	626	(86.3)	638	(87.2)
Cardiovascular System				
Vasoprotective	***0***	***(0.0)***	***1***	***(0.1)***
Ginkgo biloba extract (+) heptaminol hydrochloride (+) troxerutin	0	(0.0)	1	(0.1)
Various				
All Other Therapeutic Products, Including Homeopathic and Herbal Preparations and Composition Unspecified	***99***	***(13.7)***	***93***	***(12.7)***
Amino acids (unspecified) (+) antioxidants (unspecified) (+) beta carotene (+) delphinidin 3-glucoside (+) eyebright (+) ginkgo biloba extract (+) quercetin (+) schisandra (+) taurine (+) thioctic acid (+) vitamins (unspecified)	0	(0.0)	1	(0.1)
Ginkgo biloba extract	99	(13.7)	92	(12.6)
Although a patient may have had 2 or more concomitant therapies, the patient is counted only once within a category. The same patient may appear in different categories.				

Data Source: [4.1]

Statins were taken by 24.8% of patients in the rofecoxib group and by 24.9% of patients in the placebo group, as shown in Table 24. The most commonly used statin was atorvastatin calcium, which was taken by 10.1 and 9.6% of patients, respectively.

Table 24

Number (%) of Patients on Statin Therapy
(>0% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=725)		Placebo (N=732)	
	n	(%)	n	(%)
Patients with one or more concomitant therapies	180	(24.8)	182	(24.9)
Patients with no concomitant therapy	545	(75.2)	550	(75.1)
Cardiovascular System				
Serum Lipid Reducing Agent	***180***	***(24.8)***	***182***	***(24.9)***
Atorvastatin calcium	73	(10.1)	70	(9.6)
Cerivastatin sodium	13	(1.8)	15	(2.0)
Fluvastatin sodium	22	(3.0)	20	(2.7)
Lovastatin	20	(2.8)	16	(2.2)
Pravastatin sodium	48	(6.6)	42	(5.7)
Simvastatin	61	(8.4)	73	(10.0)
Although a patient may have had 2 or more concomitant therapies, the patient is counted only once within a category. The same patient may appear in different categories.				

Data Source: [4.1]

6.6 Measurements of Treatment Compliance

In this study, regular phone contact with the informant/caregiver was used to ensure that patients took study medication per protocol. The number of tablets in the medication bottle was counted, reviewed, and recorded. This number was used to calculate patient compliance.

Patients were considered compliant if they took one tablet orally per day. For each patient, the percent of compliance was calculated using the following formula:

$$\text{Percent of Compliance} = \frac{\text{Number of days on Therapy}}{\text{Number of days should be on therapy}} \times 100.$$

For a patient who was followed for the entire study period, the "number of days should be on therapy" is the total number of days from randomization to the last study follow-up visit for that patient. For a patient who discontinued from the study permanently, the "number of days should be on therapy" represented the total number of days from randomization to the date of discontinuation, regardless of whether the patient was on or off study drug.

Patient compliance with study therapy is summarized in Table 25. Compliance was high overall and similar between the treatment groups. A compliance rate of 80% or higher was achieved by 61.0% of the rofecoxib and 70.8% of the placebo patients.

Table 25

Summary of Patient's Compliance on Taking Study Therapy
Intention-to-Treat Population

Percent of Compliance	Rofecoxib 25 mg (N=725)		Placebo (N=732)		Total (N=1457)	
	n	%†	n	%	n	%
100%	3	(0.4)	2	(0.3)	5	(0.3)
90 to <100%	365	(50.3)	433	(59.2)	798	(54.8)
80 to <90%	75	(10.3)	83	(11.3)	158	(10.8)
70 to <80%	57	(7.9)	45	(6.1)	102	(7.0)
60 to <70%	38	(5.2)	29	(4.0)	67	(4.6)
<60%	187	(25.8)	140	(19.1)	327	(22.4)

N = total number of patients in the treatment group.
n = number of patients in the category.
† % = n/N.

Data Source: [4.2]

7. Efficacy Evaluation and Results

The primary efficacy analysis was based on the ITT population (discussed in Section 6.4.1) which included all randomized patients regardless of whether a patient discontinued study therapy or was a protocol violator.

One patient in the rofecoxib group (AN 0237) inadvertently did not have all of the data from the final study visit (Visit 15.1) entered into the database. When the missing data error was discovered, the decision was made not to enter the data based on criteria in the Clinical Trial System SOP 3.401 Frozen File and Unblinding Procedures [3.11.5]. The patient stopped study drug on Day 1065 after randomization due to a clinical adverse experience of transient ischemic attack. The investigator diagnosed the patient with Alzheimer's disease at Visit 15 (1456 days after randomization), thus the patient had completed the study after having discontinued study medication and reached the study endpoint trigger visit. The protocol specified 2-month follow-up visit for confirmation of Alzheimer's disease was performed at Visit 15.1 (1523 days after randomization). A portion of data from Visit 15.1 that was not entered in the database included efficacy results from the BLAH, CDR, SRT, MMSE, ADAS, BDS-ADL, and HamD. These were all secondary efficacy measures. Per the Data Analysis Plan, analyses of secondary efficacy measures included data obtained through the trigger visit (Visit 15), and not data from the confirmation visit; therefore, the missing Visit 15.1 data did not have an effect on the efficacy analyses.

7.1 Endpoint Confirmation and Adjudication

The primary efficacy endpoint is clinically diagnosed AD (diagnosis of AD agreed upon by the investigator's confirmation and the EAC adjudication).

7.2 Efficacy Endpoints

Section 7.2.1 describes the results of the primary analysis in detail, and Section 7.2.2 describes subgroup analyses and an investigation of risk factors, which were performed to explore the finding on the primary endpoint. In Section 7.2.1.4.1, additional covariates were included in the primary statistical model (based on identified risk factors). Additional analyses included in this section based on compliance and exposure were performed to determine if increased exposure to rofecoxib resulted in an increased risk of progression to disease.

7.2.1 Time to Event Analyses

7.2.1.1 Primary Analysis—Clinically Diagnosed AD

The primary endpoint of this study, clinically diagnosed AD, only included patients confirmed to have developed AD and did not include patients who developed dementia of any other cause. In the rofecoxib group, 107 of 725 (14.8%) patients had an event of clinically diagnosed AD over the 4-year study period versus 82 of 732 (11.2%) placebo patients over 4 years (Table 26). The treatment-by-Log (time) interaction was not statistically significant, indicating that the proportional hazards assumption was reasonably met. The estimated hazard ratio (Rofecoxib:Placebo), adjusting for the effects of baseline MMSE stratum and region, was 1.46 (95% confidence interval 1.09-1.94), which was statistically significant (p=0.011, Wald Chi Square test) in favor of placebo. Baseline MMSE stratum had a statistically significant effect on outcome ($p<0.0001$), as the estimated hazard ratio (MMSE $\leq$26: MMSE >26) was 3.23 (95% CI 2.42-4.32). Treatment effects were determined to be relatively consistent across MMSE stratum levels and geographic regions.

Table 26

Test Results for Time to Clinically Diagnosed AD
Intention-to-Treat Population

Test	Event Counts: Rofecoxib 25 mg n/N(%)	Event Counts: Placebo n/N(%)	Hazard Ratio	95% CI.	p-Value
Treatment (rofecoxib: placebo)	107/725 (14.8)	82/732 (11.2)	1.456	(1.091, 1.942)	0.011
Stratum (MMSE ≤26: MMSE >26)			3.234	(2.424, 4.315)	<0.0001
Region					0.604
Treatment*region					0.250
Treatment*stratum					0.451
Treatment*log (Time) †					0.260

† Interaction of treatment-by-natural logarithm of time.
Note: The final model used to test for treatment effect contained terms for treatment, stratum, and region.

Data Source: [4.3; 4.1]

The crude proportions, as well as the Kaplan-Meier (KM) estimated proportions, of patients with clinically diagnosed AD as determined by 4-month increments are displayed in Table 27. A separation in event rates between treatment groups existed at the earliest time point (4 months) and was evident within the first 16 months, a gap which was maintained through the last follow-up time point of 48 months (Figure 1 and Figure 2). Figure 2 is a rescaled presentation of the KM curves, which better illustrates the differences at all time points.

Table 27

Cumulative Proportions of Clinically Diagnosed AD
Intention-to-Treat Population

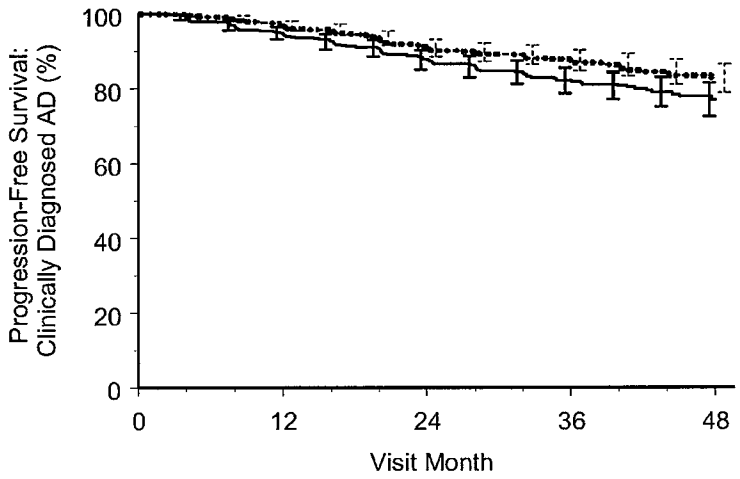
Month After Treatment	Crude Proportions				Kaplan-Meier Estimated Proportions	
	Rofecoxib 25 mg (N=725)		Placebo (N=732)		Rofecoxib 25 mg (N=725)	Placebo (N=732)
	No. Cens†	n (%)	No. Cens†	n (%)	%	%
0	--	0 (0.0)	--	0 (0.0)	0.0	0.0
4	37	6 (0.8)	23	2 (0.3)	0.9	0.3
8	62	21 (2.9)	56	10 (1.4)	3.1	1.4
12	109	34 (4.7)	86	21 (2.9)	5.1	3.1
16	142	48 (6.6)	123	28 (3.8)	7.4	4.2
20	181	58 (8.0)	163	41 (5.6)	9.2	6.4
24	236	74 (10.2)	218	56 (7.7)	12.3	9.2
28	299	82 (11.3)	281	61 (8.3)	14.2	10.3
32	326	88 (12.1)	309	64 (8.7)	15.7	11.0
36	371	96 (13.2)	352	70 (9.6)	17.9	12.5
40	411	100 (13.8)	418	74 (10.1)	19.3	13.7
44	462	104 (14.3)	476	79 (10.8)	21.0	15.6
48	550	107 (14.8)	564	82 (11.2)	23.0	17.4

AD=Alzheimer's disease
N = Total number of patients randomized to each treatment group.
n= number of confirmed cases of clinically diagnosed AD by investigator and EAC (cumulative).
† No. Cens = Cumulative number of patients censored prior to time point.
%= n/N.

Data Source: [4.3]

Figure 1

Kaplan-Meier Estimates (95% CIs)
Progression-Free Survival—Clinically Diagnosed AD



Number of Patients													
—— Rofecoxib 25 mg	725	682	642	582	535	486	415	344	311	258	214	159	68
------ Placebo	732	707	666	625	581	528	458	390	359	310	240	177	86

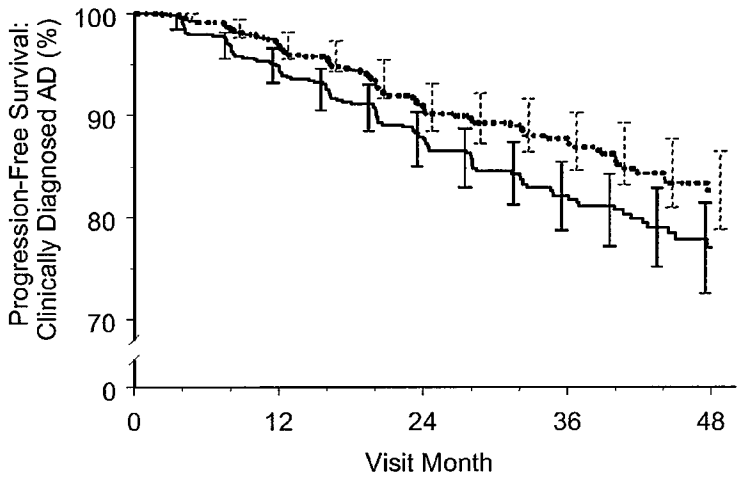
Number of Patients=Number at Risk (number who have not been censored nor had an event up to, but not including, that time point)

Note: Confidence intervals are for each time point and do not represent the overall statistical test of treatment effects

Data Source: [4.3]

Figure 2

Kaplan-Meier Estimates (95% CI's) (Re-Scaled)
Progression-Free Survival—Clinically Diagnosed AD



Number of Patients													
—— Rofecoxib 25 mg	725	682	642	582	535	486	415	344	311	258	214	159	68
------ Placebo	732	707	666	625	581	528	458	390	359	310	240	177	86

3 axis break

Number of Patients=Number at Risk (number who have not been censored nor had an event up to, but not including, that time point)

Note: Confidence intervals are for each time point and do not represent the overall statistical test of treatment effects
Note: Vertical axis is re-scaled which results in an apparent magnification of the treatment effect

Data Source: [4.3]

Table 28 summarizes the crude cumulative proportions of patients converted to AD, as well as the estimated annual conversion rates and KM estimated cumulative conversion rates. The estimates of the annual conversion rate were reasonable statistics to calculate as the estimated hazard rates over time were relatively constant (results shown in Section 11, Figure 25). The annual conversion rates for this study were estimated post-hoc in order to determine how results compared with the 10-15% rates typically reported for MCI patients in the literature [1.2.13; 1.2.20; 1.2.21; 1.2.22].

Table 28

Conversion Rates for Clinically Diagnosed AD
Intention-to-Treat Population

	Proportions/Rates	
	Rofecoxib 25 mg ($N^{\dagger}$=725)	Placebo ($N^{\dagger}$=732)
Crude cumulative proportion ($n/N^{\dagger}$) (95% $CI^{\ddagger}$) (prespecified analysis)	14.8% (107/725) (12.2,17.3)	11.2% (82/732) (8.9, 13.5)
KM estimated cumulative (48 month) proportions (95% CI) (prespecified analysis)	23.1% (18.6, 27.6)	17.4% (13.5, 21.3)
Annual conversion rate (events/100 pt-years [95% CI]) (post-hoc analysis)	6.4% (5.3, 7.7)	4.5% (3.6, 5.6)

† N = Total number of patients randomized to each treatment group.
‡ Confidence interval based on the normal approximation to the binomial distribution.
CI= Confidence interval
KM= Kaplan Meier

Data Source: [4.3]

Table 29 contains results of a stratified log-rank analysis, adjusting for baseline MMSE stratum. There was a statistically significant result (p=0.0143) in favor of placebo in the lower (worse prognosis) stratum (MMSE ≤26), and an estimated treatment effect that favored placebo but did not reach statistical significance in the upper stratum. Additional explorations of stratum-by-treatment interactions determined that the treatment differences were consistent across stratum level. The pooled analysis that adjusted for baseline MMSE stratum resulted in p=0.0094 in favor of placebo, similar to the results from the Cox model.

Table 29

Log-Rank Analysis of Clinically Diagnosed AD Stratified by Baseline MMSE Stratum
Intention-to-Treat Population

Treatment Comparison	Stratified Log Rank Two-Tailed p-Value†	Event Counts		Cox Proportional Hazards Model‡			
		Rofecoxib n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	Two-Tailed p-Value	% Risk Reduction
Rofecoxib:placebo	0.0094§	107/725 (14.8)	82/732 (11.2)	1.456	(1.091, 1.942)	0.011	-45.6%
MMSE≤26	0.0143	61/229 (26.6)	44/242 (18.2)	1.628	(1.103, 2.402)	0.014	-62.8%
MMSE>26	0.2461	46/496 (9.3)	38/490 (7.8)	1.294	(0.841, 1.989)	0.241	-29.4%

† Test stratified by MMSE stratum.
‡ Model with terms for treatment, stratum, and region.
§ Results of pooled analysis.

Data Source: [4.3]

7.2.1.2 Exploratory Endpoints

Nearly all cases of dementia reported by investigators (197/204, 97%) were due to AD, rather than other causes, and the EAC concurred with the investigator's diagnosis in nearly all instances (189/197, 96%). Table 30 defines and summarizes results for endpoints of investigator reported AD and investigator reported dementia, along with the primary endpoint. Estimates of treatment effect for these endpoints were similar to the Cox proportional hazard (Table 26) and log-rank (Table 29) analyses presented above.

Table 30

Cox Model Estimates of Treatment Effect for Prespecified Endpoint Definitions

Test	Event Counts: Rofecoxib 25 mg n/N(%)	Event Counts: Placebo n/N(%)	Hazard Ratio[†]	95% CI.	p-Value
Clinically diagnosed AD[‡]/ITT approach	107/725 (14.8)	82/732 (11.2)	1.456	(1.091, 1.942)	0.011
Clinically diagnosed AD /Per-Protocol approach	93/698 (13.3%)	66/696 (9.5%)	1.567	(1.143, 2.149)	0.005
Investigator diagnosis of AD[§]/ITT approach	111/725 (15.3)	86/732 (11.7)	1.439	(1.085, 1.908)	0.011
All diagnoses of dementia by investigators[¶]	115/725 (15.9)	89/732 (12.2)	1.437	(1.089, 1.896)	0.010

All models include treatment, MMSE stratum and geographic region as main effects.
[†]Hazard ratio of rofecoxib: placebo
AD=Alzheimer's disease
ITT=Intention to Treat
[‡]Defined as patients who had an investigator-confirmed diagnosis of AD which was adjudicated as AD.
[§]Includes patients with investigator-confirmed AD and those who had an initial investigator diagnosis of AD, but were lost to follow-up prior to confirmation.
[¶]Includes patients with investigator-confirmed dementia of any cause and those patients who had an initial investigator diagnosis of dementia of any cause, but were lost to follow-up prior to confirmation.
MMSE=Mini Mental State Examination.

Data Source: [4.1; 4.3]

7.2.1.3 Risk Factors and Subgroup Analyses

Risk factors were identified (post-hoc) based on a review of the scientific literature as well as investigation of any association between covariates collected and the rates of conversion to AD in this study [2.1.3]. Adjustments were made for covariates determined to be statistically significantly associated with AD conversion (see Section 7.2.1.3.1).

7.2.1.3.1 Identification of Risk Factors

In order to assess the factors that may have played a prognostic role in the progression of patients to AD, as well as a means of investigating whether these risk factors had a consistent effect as described in the literature, univariate analyses were performed of prerandomization risk factors for progression to AD (Table 31). Hazard ratios, 95% CIs, and p-values are presented for each factor as the only covariate in a Cox proportional hazards model of time to clinically diagnosed AD. Those patients in the following subgroups were at highest risk of conversion to AD: MMSE <26, age ≥75, female gender, prior ginkgo biloba use, lack of prior statin use, and presence of ApoE ε4, regardless of treatment group. All of these, except for ginkgo biloba use, have been identified in the literature as potential risk factors [1.2.23]. The increased risk associated here with prior ginkgo biloba use contravenes reports in the literature [1.2.24].

Attributes that have been documented as risk factors in the literature but were not correlated with progression in the present study included family history of AD, prior tobacco use, and prior estrogen use.

Table 31

Hazard Ratios and 95% Confidence Intervals for Pre-Randomization Risk Factors of Clinically Diagnosed AD Without Respect to Treatment
Intention-to-Treat Population

Risk Factor	Hazard Ratio[†]	95% CI	p-Value
MMSE stratum (≤26/>26)	3.18	(2.39, 4.24)	<0.001
Age (75+ years/<75 years)	1.77	(1.32, 2.38)	<0.001
Gender (Female/Male)	1.95	(1.46, 2.60)	<0.001
Prior alcohol use (Yes/No)	0.94	(0.70, 1.25)	0.655
Prior tobacco use (Yes/No)	0.86	(0.65, 1.15	0.316
Prior estrogen use (Yes/No)	0.60	(0.08, 4.30)	0.614
Prior ginkgo biloba use (Yes/No)	1.70	(1.17, 2.47)	0.006
Prior statin use (Yes/No)	0.56	(0.33, 0.93)	0.025
Family history of AD (Yes/No)	1.03	(0.76, 1.40)	0.845
Prior NSAID use (Yes/No)	0.49	(0.26, 0.93)	0.028
ApoE genotype (2/4, 3/4, 4/4)/(2/2, 2/3, 3/3)	1.92	(1.42, 2.60)	<0.001

[†] Hazard Ratio Estimates were based on univariate models (i.e., a separate model was utilized for each estimate of a main effect)

Data Source: [4.1; 4.2; 4.3]

7.2.1.3.2 Subgroup Analyses

By-treatment tabulations of clinically diagnosed AD by subgroup for the set of risk factors identified in the previous section, as well as post-randomization factors that were likely to be related to progression to AD (i.e., concomitant medication use), are presented in Table 32. Figure 3 contains a plot of the hazard ratios (Rofecoxib:Placebo) and 95% CIs for the subgroups with more than a minimal number of patients in each treatment group within each subgroup. The direction of the treatment effect in favor of placebo is relatively consistent across levels of these risk factors.

Although the number of patients who used NSAIDs were similar in the rofecoxib and placebo groups (224 and 254 patients respectively), the median duration of concomitant NSAIDs use was 5.6 weeks in the rofecoxib group and 7.4 weeks in the placebo group. Overall, the median duration of concomitant use, when calculated from start date to last date of use (whether or not there were intervening days without NSAIDs use), was 11 weeks in the rofecoxib group and 25.4 weeks in the placebo group (Table 82, Section 11). The concomitant use of estrogen was low (2/19 [10.5 %; ANs 0267 and 0673] of patients with concomitant estrogen use in the rofecoxib group and 3/35 [8.6%; ANs 0686, 1414, and 1586] of patients with concomitant estrogen use in the placebo group had clinically diagnosed AD) and is therefore not reported in the table.

Table 32

Subgroup Tabulations of Clinically Diagnosed AD
Intention-to-Treat Population

Subgroup	Category	Event Counts Rofecoxib n/N(%)	Placebo n/N(%)
Pre-Randomization Factors			
Age category	<75 Years	38/340 (11.2%)	32/361 (8.9%)
	≥75 Years	69/385 (17.9%)	50/371 (13.5%)
Prior alcohol	No	55/355 (15.5%)	38/354 (10.7%)
	Yes	52/370 (14.1%)	44/378 (11.6%)
ApoE	2/2,2/3,3/3	48/401 (12.0%)	30/407 (7.4%)
	2/4,3/4,4/4	46/251 (18.3%)	41/262 (15.6%)
Years of education	11 or less	13/ 81 (16.0%)	10/ 72 (13.9%)
	12	35/190 (18.4%)	23/205 (11.2%)
	13-15	24/199 (12.1%)	25/221 (11.3%)
	16-17	22/158 (13.9%)	14/143 (9.8%)
	18 or more	13/ 97 (13.4%)	10/ 91 (11.0%)
Prior estrogen	No	107/722 (14.8%)	81/722 (11.2%)
	Yes	0/ 3 (0%)	1/ 10 (10.0%)
Family history of AD	No	74/497 (14.9%)	55/516 (10.7%)
	Yes	32/226 (14.2%)	27/216 (12.5%)
Prior ginkgo biloba	No	87/634 (13.7%)	69/650 (10.6%)
	Yes	20/91 (22.0%)	13/82 (15.9%)
Race category	White	100/686 (14.6%)	76/691 (11.0%)
	non-White	7/ 39 (17.9%)	6/ 41 (14.6%)
Region	East and Midwest	13/113 (11.5%)	18/115 (15.7%)
	North East	24/124 (19.4%)	14/127 (11.0%)
	South East	22/130 (16.9%)	14/131 (10.7%)
	South and Middle	12/ 95 (12.6%)	11/ 95 (11.6%)
	West	36/263 (13.7%)	25/264 (9.5%)
Gender	Female	53/249 (21.3%)	30/228 (13.2%)
	Male	54/476 (11.3%)	52/504 (10.3%)
Prior statin	No	95/617 (15.4%)	78/637 (12.2%)
	Yes	12/108 (11.1%)	4/95 (4.2%)
MMSE stratum	MMSE ≤26	61/229 (26.6%)	44/242 (18.2%)
	MMSE >26	46/496 (9.3%)	38/490 (7.8%)
Females*stratum	Female -MMSE ≤26	34/ 85 (40.0%)	20/ 68 (29.4%)
	Female -MMSE >26	19/164 (11.6%)	10/160 (6.3%)
Males*stratum	Male -MMSE ≤26	27/144 (18.8%)	24/174 (13.8%)
	Male -MMSE >26	27/332 (8.1%)	28/330 (8.5%)
Prior NSAID Use	No	102/664 (15.4%)	77/657 (11.7%)
	Yes	5/61 (8.2%)	5/75 (6.7%)
Prior tobacco	No	46/281 (16.4%)	35/287 (12.2%)
	Yes	61/444 (13.7%)	47/445 (10.6%)

Table 32 (Cont.)

Subgroup Tabulations of Clinically Diagnosed AD
Intention-to-Treat Population

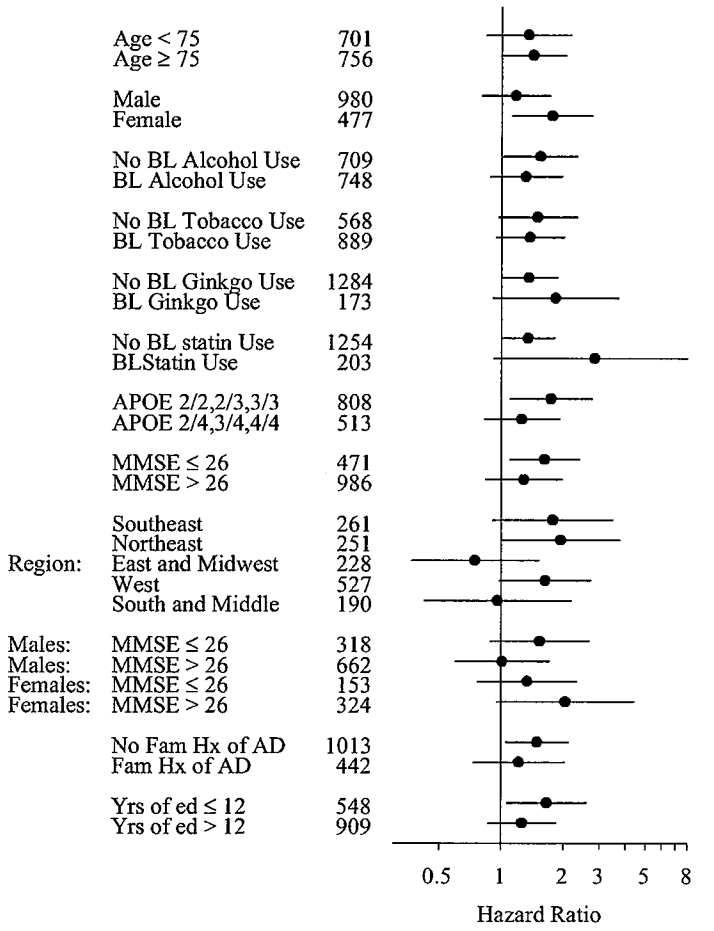
		Event Counts	
Subgroup	Category	Rofecoxib n/N(%)	Placebo n/N(%)
Post-Randomization Factors			
Conc statin use	No	86/545 (15.8%)	76/550 (13.8%)
	Yes	21/180 (11.7%)	6/182 (3.3%)
Conc AChEI use	No	74/644 (11.5%)	58/669 (8.7%)
	Yes	33/81 (40.7%)	24/63 (38.1%)
Conc NSAID use	No	89/501 (17.8%)	60/418 (12.6%)
	Yes	18/224 (8.0%)	22/254 (8.7%)

n = Number of patients with clinically diagnosed AD in each category.
N=Number of randomized patients within each subgroup.
ApoE = Apolipoprotein E.
MMSE = Mini Mental State Examination.
Conc = Concomitant.
NSAID = Nonsteroidal anti-inflammatory drug.
AChEI = Acetylcholinesterase inhibitor.

Data Source: [4.1; 4.2; 4.3]

Figure 3

Hazard Ratios (95% CI's)
Time to Clinically Diagnosed AD by Subgroup—Pre-Randomization Factors
Intention-to-Treat Population



Data Source: [4.1; 4.2; 4.3]

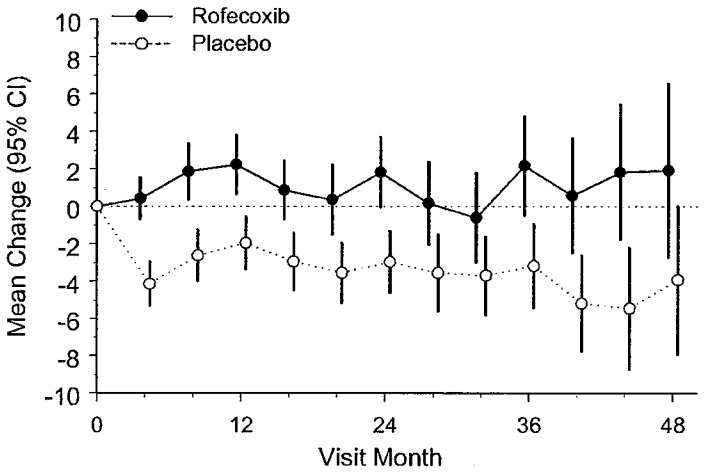
7.2.1.3.3 Blood Pressure Changes Relative to Progression to AD

The analyses presented in this section were performed in an attempt to determine whether increases in blood pressure were associated with an increased risk of progression to AD. Since there is a relationship between increased blood pressure and the potential for strokes, and strokes can leave patients exhibiting signs of dementia, it was necessary to confirm that the AD diagnosed in this study was not ischemic-related. There were a total of 6 patients with confirmed ischemic strokes and 1 patient with hemorrhagic stroke in the rofecoxib group, and 13 patients with confirmed ischemic strokes and 2 patients with hemorrhagic strokes in the placebo group (Section 8.4.4 Table 65). Of the patients with confirmed AD, 1 patient (AN 1345) in the rofecoxib group and 3 (ANs 0360, 0481, and 0600) in the placebo group had confirmed ischemic cerebrovascular stroke. Of note, brain scans (CT or MRI) conducted at the time of the investigator's diagnosis of AD were reviewed by the EAC, and there was no evidence of significant ischemic cerebrovascular disease in any of the confirmed AD patients.

In prior clinical studies, any increases/changes in blood pressure associated with use of NSAIDs or COX-2 inhibitors generally were seen early and were constant over time. Mean values for diastolic blood pressure in this study decreased postrandomization, but changes were relatively small and constant over time for both treatment groups. Mean values for systolic blood pressure were higher relative to baseline (Figure 4) by 0.4 to 2.2 mm Hg for the rofecoxib group at the first 3 time points (Months 4, 8, and 12), and thereafter the differences from baseline were smaller than that observed at Month 12 [4.8]. For the placebo group, mean values represented a decrease of approximately 2.0 mm Hg or greater at every time point. The differences from placebo were relatively constant over time.

Figure 4

Mean Change From Baseline (95% CI) in Systolic Blood Pressure (mm Hg)
All Patients—Data As Observed



Number of Patients												
Rofecoxib	705	566	492	454	388	327	256	221	200	156	121	71
Placebo	715	612	555	497	448	399	309	281	254	196	151	109

Changes from baseline in the mean arterial pressure (MAP) were calculated as

$$(2 \times DBP+SBP)/3$$

and determined for the Month 4 visit (first scheduled visit). Based on observations in the current and in previous rofecoxib AD clinical studies, any increases in blood pressure would likely have occurred by this time point, and the blood pressure results were available for most of the patients enrolled for this time point.

The odds ratio of converting to AD was fairly consistent across the 3 categories of changes in MAP (Table 33). Within each treatment group, the percentage of those who converted was consistent across the 3 categories of changes in MAP, as evidenced by the treatment-specific odds ratios near one (1) for those with increases of ≥5 mm Hg relative to those with no increase or an increase of <5 mm Hg.

Table 33

Clinically Diagnosed AD Tabulations by Changes in Mean Arterial Pressure
Intention-to-Treat Population

Change in Mean Arterial Pressure (MAP) From Month 0 to 4	Rofecoxib n/N[†] (%)	Placebo n/N[†] (%)	OR[‡] (Rofecoxib: Placebo)
Overall	107/725 (14.8%)	82/732 (11.2%)	1.37
No change or decrease in MAP	59/375 (15.7%)	54/467 (11.6%)	1.43
Increase in MAP ≤5 mmHg	20/159 (12.6%)	13/120 (10.8%)	1.18
Increase in MAP >5 mmHg	28/182 (15.4%)	15/136 (11.0%)	1.47

P = 0.895, Breslow-Day test of homogeneity of the odds ratios (null hypothesis of homogeneity) across BP categories.
[†] n/N = Number of conversions to AD/ Number of patients in the treatment group.
[‡] OR = Odds Ratio of conversion to AD (unadjusted).
MAP = (2xDBP+SBP)/3.

Data Source: [4.2; 4.3]

An additional analysis was conducted to determine if meeting the criteria for a postrandomization predefined limit of change (PDLC) in systolic blood pressure (increase) was related to conversion to AD. This criterion was prespecified in the DAP and was defined as a postrandomization value that was ≥180 mmHg and ≥20 mmHg increase from baseline. The by-treatment results are listed in Table 34. The data do not suggest an increased risk of conversion to AD for patients who experienced a PDLC for increased systolic blood pressure, though the number of patients who experienced a PDLC was relatively low in both treatment groups (16.2 and 10.0% for the rofecoxib and placebo group, respectively)[4.8].

Table 34

Tabulations of Clinically Diagnosed AD
Based on Systolic Blood Pressure Predefined Limits of Change
Intention-to-Treat Population

	Event Counts		
	Rofecoxib	**Placebo**	**HR (Rofecoxib:Placebo)**
Category	**n/N (%)**	**n/N (%)**	**95% CI**
Did Not Meet SBP PDLC	96/657 (14.6%)	78/692 (11.3%)	1.422 (1.055, 1.917)
Met SBP PDLC	11/68 (16.2%)	4/40 (10.0%)	1.532 (0.488, 4.814)

PDLC = Pre-defined limit of change
SBP = Systolic blood pressure
N = Number of patients in the category by treatment group.
n = Number of patients with clinically diagnosed AD.
HR = Hazard ratio.
CI = Confidence Interval

Data Source: [4.2; 4.3]

7.2.1.4 Exploratory Analyses

7.2.1.4.1 Additional Statistical Models

Additional statistical models were fit to the primary endpoint data to investigate the effect of known prognostic covariates, as well as to assess whether increased exposure to study drug influenced risk of conversion to clinically diagnosed AD.

The PP and on-drug analyses were pre-specified in the DAP, whereas the model that adjusted for covariates, as well as the model that was based on the population of patients that were 80% compliant using an on-drug approach were post-hoc. The results from these additional statistical models used to analyze the primary endpoint data described in Section 5.8 are summarized in Table 35. The difference between treatment groups was not statistically significant in the analysis which adjusted for baseline covariates (post-hoc Model # 4).

Stepwise Model Selection

A (post-hoc) stepwise procedure, described in Section 5.8, was used to build the Cox PH regression model using a significance level of 0.10 as the criterion for inclusion of a covariate. The results from the stepwise selection model described in Section 5.8, estimated treatment hazard ratios, 95% CIs, and p-values are presented in Table 35 (Model #2). Statistically significant (at the 0.10 significance level) factors in this model were baseline MMSE stratum, gender, duration of concomitant NSAID use, concomitant statin use (yes/no), age category (<75/≥75), prior ginkgo biloba use (yes/no), and treatment. No other factors were statistically significant (at the 0.10 significance level) in the presence of these factors. The estimate and direction of the treatment effect based on this model was consistent with the primary analysis, though both the magnitude of the effect declined (hazard ratio [rofecoxib:placebo] changed from 1.456 to 1.312) and the nominal p-value was larger (from p=0.011 to p=0.065).

PP Analysis

Results from the PP analysis prespecified in the DAP [3.4] are presented in Table 35 (Model #3). Protocol violations were primarily composed of patients who used prohibited medications either concomitantly during the study or in the washout period (see Section 6.2). The estimated treatment hazard ratio from the PP analysis was similar to that of the ITT analysis, (Table 35 Model #1), with a statistically significant p-value (p=0.005).

PP and 80% Compliant Analysis

An additional PP analysis (post-hoc) was performed that was based on the subset of patients who were 80% compliant during the study participation period, regardless of the length of participation. The estimated treatment hazard ratio from this analysis (Table 35, Model #4) was 1.720 (Rofecoxib:Placebo) with a statistically significant p-value (p=0.002).

On-Drug Analysis

A further analysis, which was prespecified in the DAP, was conducted to determine if, for the subset of follow-up time that patients were actually exposed to study drug, the estimated hazard ratio varied from the ITT approach. Patient time-at-risk for this time-to-event analysis consisted of the date of randomization through 14 days after the last dose of study medication. In effect, this resulted in the

- exclusion of patients who never dosed
- censoring of patients at 14 days after their last dose if they were either

  —censored (in the ITT approach) later than 14 days after their last dose, or

  —had a trigger visit that occurred more than 14 days after the last dose

Estimates of treatment effect for the pre-specified on-drug analysis (Table 35, Model #5) were similar to the ITT and PP analyses, with an estimated treatment hazard ratio (rofecoxib:placebo) of 1.489 (p=0.014). Estimates of treatment effect for these endpoints were similar to the ITT and PP analyses presented in Table 35.

Table 35

Additional Statistical Analysis Models for Time to Clinically Diagnosed AD

Model Number	Covariate Terms Used in the Cox PH Model	Analysis	Conversions to AD		Treatment Hazard Ratio (95% CI)	p-Value
			Rofecoxib n/N (%)	Placebo n/N (%)		
1	MMSE stratum, region	ITT (pre-specified)	107/725 (14.8%)	82/732 (11.2%)	1.456 (1.091, 1.942)	0.011
2	MMSE stratum, gender, age category, prior Ginkgo biloba use, duration of concomitant NSAID use, concomitant statin use	ITT (post-hoc)	107/725 (14.8%)	82/732 (11.2%)	1.312 0.983, 1.751)	0.065
3	MMSE stratum, region	Per protocol (pre-specified)	93/698 (13.3%)	66/696 (9.5%)	1.567 (1.143, 2.149)	0.005
4	MMSE stratum, region	PP & 80% drug compliance (post-hoc)	75/429 (17.5%)	57/496 (11.5%)	1.720 (1.218, 2.429)	0.002
5	MMSE stratum, region	On drug within 14 days of conversion (pre-specified)	85/723 (11.8%)	69/728 (9.5%)	1.489 (1.083, 2.047)	0.014

AD = Alzheimer's disease.
Cox PH = Cox Proportional Hazards.
MMSE = Mini-Mental State Examination.
ITT = Intention to treat.
n = Number of patients with clinically diagnosed AD in each category.
N = Number of randomized patients within each subgroup.
CI = Confidence interval.
NSAID = Nonsteroidal anti-inflammatory drug.
PP = Per protocol.

Data Source: [4.1; 4.2; 4.3]

7.2.1.4.2 Clinically Diagnosed AD (Intention-to-Treat Population, Excluding Sites 019, 023 and 044)

As a result of findings from a Quality Assurance audit, an additional analysis of the primary efficacy endpoint (clinically diagnosed AD) was performed excluding the 137 patients from Sites 019, 023 and 044.

Results from a statistical comparison between rofecoxib and placebo based on a Cox proportional hazards model for time to clinically diagnosed AD, excluding data from study Sites 019, 023 and 044, are summarized in Section 11, Table 82.

The conclusions from this analysis were the same as those from the primary efficacy analysis which included all patients from all sites. For this clinical study report, all study sites were included in all efficacy and safety analyses and conclusions.

7.2.2 Exploratory Efficacy Measures

In light of the uncertainty surrounding whether this primary result was due to a drug effect or to chance, it was important to evaluate the prespecified exploratory efficacy measures to determine if they were consistent with the primary results in the direction of the treatment difference, and supported a conclusion that a true difference existed between rofecoxib and placebo in the rate of progression to AD.

Section 7.2.2.1 describes the results of analyses that were pre-specified in the DAP. Section 7.2.2.2 describes post-hoc summaries of cognitive function tests based on an LOCF approach, described in Section 5.8.

7.2.2.1 Contrast of Treatments for Rate of Change From Baseline

The treatment comparisons in terms of change from baseline based on mixed models (based on an ITT approach for observed data), as specified in the DAP, are in [Section 11, Tables 84 to 88] for the exploratory efficacy measures. The statistical test of the contrast between slopes of annualized change from baseline between treatment groups (Table 36) was performed for SRT-Summed Recall (p=0.8779), SRT-Delayed Recall (p=0.8064), MMSE (p=0.9594), ADAS-Cog (p=0.3106), and CDR Sum of Box scores (p=0.0577). The mixed model included terms for treatment, time, region, MMSE stratum, and time-by-treatment interaction (the last term was included in the model to allow for estimation and testing of treatment-specific slopes).

Unlike the primary endpoint, slope estimates were very similar for the two treatment groups from 3 comparisons based on a repeated measures analysis of the data over time for the exploratory efficacy measures: SRT-Summed Recall, SRT-Delayed Recall, and MMSE. For each of these 3 measures, the 98% CI on the difference in slopes was centered close to zero and the p-value for the treatment comparison was >0.8.

The positive estimate of slope in ADAS-Cog, indicating a progression of disease, was numerically larger for rofecoxib versus placebo (see Table 86 Section 11), though not statistically significant (p=0.3106). In addition, this difference represented an approximately 0.1 higher average increase in ADAS-Cog score (scale of 0 to 70) on an annual basis.

In contrast, the result for the analysis of the CDR Sum of Box scores showed a nonstatistically significant trend (p=0.0577) in favor of placebo, consistent with the primary analysis. The CDR Sum of Box scores was the basis of the criterion used to identify the trigger for the primary endpoint (conversion to AD).

Table 36

Comparison Between Rofecoxib and Placebo
In Terms of Slope of Exploratory Efficacy Measures
Intention–to-Treat Population

Treatment	Slope Difference†	95% CI of the Slope Difference	p-Value‡
SRT summed recall	0.0260	(-0.307, 0.359)	0.8779
SRT delayed recall	-0.0116	(-0.104, 0.081)	0.8064
MMSE	-0.0024	(-0.095, 0.090)	0.9594
ADAS-Cog	-0.0977	(-0.287, 0.091)	0.3106
CDR sum of box scores	-0.0682	(-0.139, 0.002)	0.0577

† Difference in annualized slope (placebo—rofecoxib)
‡ Based on longitudinal mixed model including terms for treatment, time, region, MMSE Stratum, and time by treatment interaction.
SRT = Selective reminding test.
MMSE = Mini-Mental State Examination.
ADAS-Cog = Alzheimer's Disease Assessment Scale—Cognitive subset.
CDR = Clinical dementia rating.
Note: A positive estimate of slope difference would indicate that results favor placebo for SRT-Summed Recall, SRT Delayed Recall, and MMSE. For ADAS-Cog and CDR sum of box scores, a negative estimate of slope difference would indicate that results favor placebo.

Data Source: [4.1; 4.2; 4.3]

7.2.2.2 LOCF Approach To Exploratory Efficacy Measure Changes Over Time

7.2.2.2.1 ADAS-Cog Changes Over Time (0-70 Scale, LOCF Approach)

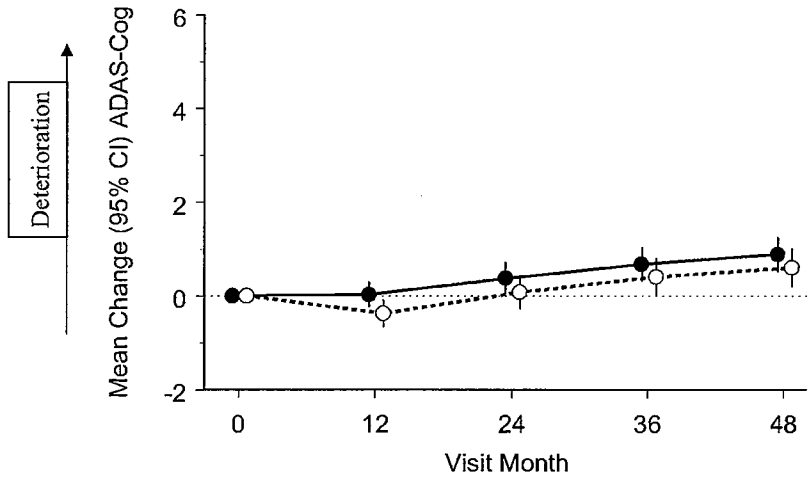
An LOCF approach (post-hoc) was used to investigate the effect of treatment over time on the mean changes in ADAS-Cog. Figure 5 (all patients) contains the graphical representation of the LOCF approach for patient populations described in Section 5.8. Similar trends were observed for both treatment groups. The largest separation between treatments in mean changes from baseline in ADAS-Cog occurred for the patients in the baseline MMSE ≤26 stratum, though the mean difference was less than 1 point (ADAS-Cog scale 0-70) and the 95% CIs overlapped. An analysis by baseline MMSE

stratum of mean changes over time in ADAS-Cog and a comparison to similar data from the Alzheimer's disease treatment protocol [2.1.1] is provided in [2.1.3]. Discussion of this comparison are in Section 9. None of these analyses indicated worsening of scores for rofecoxib relative to placebo.

Overall, the ADAS-Cog results are not consistent with the statistically significant difference in the treatments in the primary analysis of time to clinically diagnosed AD.

Figure 5

Mean Change From Baseline (95% CI) in ADAS-Cog[†](LOCF Approach)
All Patients



Number of Subjects					
● Rofecoxib 25 mg	624	622	624	624	624
○ Placebo	656	651	656	656	656

[†] ADAS-Cog=Alzheimer Disease Assessment Scale-Cognitive subscale, a neuropsychological test battery including memory and praxis tasks; range of scores is 0-70; higher score indicates greater impairment.
LOCF = Last observation carried forward.
CI = Confidence Interval.

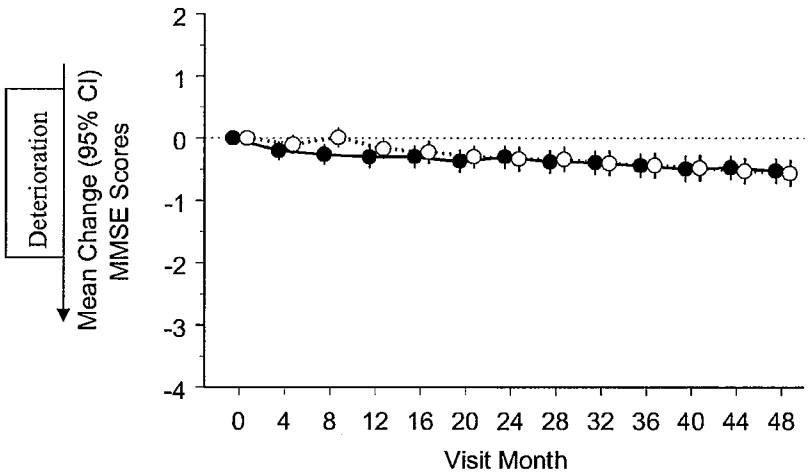
Data Source: [4.2; 4.3]

7.2.2.2.2 MMSE Changes Over Time (LOCF Approach)

An LOCF approach (posthoc) was also used to investigate the effect of treatment over time on the mean changes in MMSE. Figure 6 (all patients) contains the graphical representation of the LOCF approach for patient populations described in Section 5.8. Similar trends were observed for both treatment groups. Overall, the MMSE results are not consistent with the statistically significant difference in the primary analysis of time to clinically diagnosed AD. An analysis by baseline MMSE stratum of mean changes over time in MMSE and a comparison to similar data from the Alzheimer's disease treatment protocol [2.1.1] is provided in [2.1.3]

Figure 6

Mean Change From Baseline (95% CI) in MMSE Scores† (LOCF Approach)
All Patients



Number of Subjects													
● Rofecoxib 25 mg	683	673	683	683	683	683	683	683	683	683	683	683	683
○ Placebo	704	698	704	704	704	704	704	704	704	704	704	704	704

† MMSE = Mini Mental State Exam, an exam of cognitive function; range of possible scores is 0-30, lower score indicates greater impairment

LOCF = Last observation carried forward.
CI = Confidence Interval.

Data Source: [4.2; 4.3]

7.2.3 Investigation of Study Discontinuation Rates and Patient Disposition

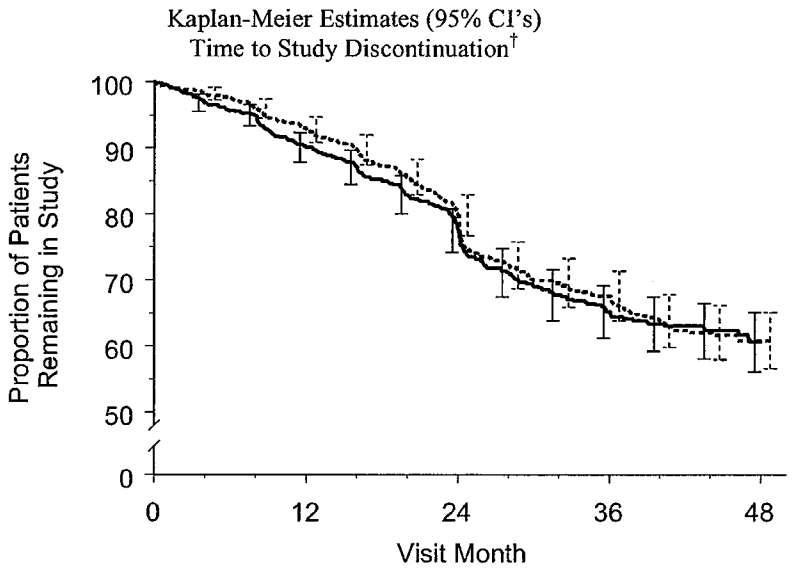
The unexpected result of the primary analysis, as well as high dropout rates for reasons that differed somewhat by treatment group, made it necessary to investigate (through additional post-hoc analyses) patients who withdrew from the study to determine whether the censoring of these patients was related to treatment. Investigation of patients who withdrew from the study was made through these additional post-hoc analyses described in Section 5.8.

7.2.3.1 Analysis of Study Discontinuation Rates

Figure 7 contains a Kaplan-Meier curve for all patients randomized for time to study discontinuation due to the following reasons: withdrawn consent, patient uncooperative, and lost to follow-up. All other outcomes were considered to be a censoring event for this analysis (e.g., completed the study, experienced an endpoint, discontinued due to a clinical adverse experiences). This analysis was performed to determine if rates of study discontinuation for reasons that could be related to the progression of the disease were differential between treatment groups. The cumulative Kaplan-Meier estimated proportion of patients to discontinue the study was approximately 40% for each treatment group, with no differential time course for these dropouts evident from the data or the Kaplan-Meier plot. Note the substantial increase in the proportion of patients who withdrew from the study at the 2-year time point. This was the time point at which patients were requested to sign an additional consent form due to the study being extended (from 2 to 4 years due to the low rate of conversion to Alzheimer's disease in the study).

Kaplan-Meier plots by gender and stratum (Section 11, Figure 26 to Figure 29), showed similar results as for the ITT population.

Figure 7



Number of Subjects													
—— Rofecoxib 25 mg	725	682	642	582	535	486	415	344	311	258	214	159	68
------ Placebo	732	707	666	625	581	528	458	390	359	310	240	177	87

† Includes patients who discontinued due to withdrawn consent, patient uncooperative, or lost to follow-up.

Data Source: [4.1; 4.2]

7.2.3.2 Efficacy Measures: Change From Baseline to Study Discontinuation or Completion

An analysis of change from baseline to the last measured time point for ADAS-Cog, MMSE, and CDR Sum of Box scores by treatment group and patient status (Table 37) was performed (post-hoc) in order to determine if, for either treatment group, there was a fundamental difference between the patients who discontinued and the patients who completed the study. The categories used for status included Endpoint (i.e., any investigator-confirmed dementia), Completed (i.e., completed 48 months of study participation or discontinued for administrative reasons), and Discontinued (premature discontinuation for any reason other than an administrative reason or a confirmed endpoint).

Consistently within both treatment groups, these three measures capture the decline in cognitive function for individuals who experienced an endpoint, as well as the relatively stable condition of those who completed the study. Also consistently within both treatment groups, patients who discontinued from the study were more similar to those who completed than those who had an endpoint (true for all 3 efficacy measures).

Table 37

Change From Baseline to Last Time point for Exploratory Efficacy Measures
by Patient Status
Intention-to-Treat Population

Measure	Rofecoxib (N=725)					Placebo (N=732)				
Status	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
ADAS-Cog										
Endpoint†	111	4.9	6.7	-11	30	83	5.4	6.9	-4	32
Completed‡	288	-0.0	3.7	-10	14	318	-0.4	3.9	-12	21
Discontinued §	225	0.1	3.6	-12	11	255	0.3	5.4	-21	45
MMSE										
Endpoint†	112	-3.1	3.4	-15	3	83	-3.9	3.8	-15	2
Completed‡	288	0.2	2.1	-10	6	318	0.2	2.3	-12	5
Discontinued §	283	-0.2	2.2	-10	4	303	-0.4	2.5	-16	6
CDR Sum of Box										
Endpoint †	112	3.3	1.4	0.0	8.5	83	3.6	1.8	0.5	10.5
Completed‡	288	0.1	1.0	-2.5	4.0	318	0.1	1.0	-3.5	3.5
Discontinued§	280	0.1	1.0	-3.0	6.0	299	0.2	1.1	-3.0	7.0

† Endpoint is defined as having a status of any investigator-confirmed dementia.
‡ Completed is defined as completed 48 months of study participation, or discontinued for administrative reasons
§ Discontinued is defined as premature discontinuation for any reason other than an administrative reason or a confirmed endpoint.
Note: Increases for ADAS-Cog and CDR Sum of Box scores, and decreases for MMSE scores, are indicative of a decline in cognitive function.
ADAS-Cog = Alzheimer's Disease Assessment Scale—Cognition subset.
N = Number of randomized patients.
n = Number of patients in each category.
SD = Standard deviation.
MMSE = Mini-Mental State Examination.
CDR = Clinical Dementia Rating.

Data Source: [4.1; 4.3]

8. Safety Evaluation

Clinical and laboratory adverse experiences occurring postrandomization are summarized in the following sections. Specific adverse experiences and related clinical information are discussed. The primary safety objective for this study was to examine the safety and tolerability of rofecoxib 25 mg in relation to placebo in patients with MCI. This was assessed by statistical and/or clinical review of all safety parameters, including adverse experiences, vital signs, and laboratory values.

Two approaches were used for the adverse experience summaries. First, a primary analysis included all adverse experiences occurring when patients were on treatment and up to 14 days following discontinuation of study drug (referred to subsequently as "on-drug"). Second, a summary based on the ITT approach included all adverse experiences regardless of whether patients were on or off study drug. Each safety subsection presents the on-drug results followed by the respective ITT results.

All safety analyses were based on the APaT population, which included randomized patients who received one or more doses of test drug therapy. Of the 1457 patients randomized, 6 never dosed with study medication and were excluded from analyses; 723 of 725 patients randomized to receive rofecoxib 25 mg, and 728 of 732 patients randomized to receive placebo were included in the APaT safety analyses. The patients who never dosed with study drug and whose data were not included in the safety analyses are ANs 0062, 0390, 0787, 1023, 1099, 1496.

The percentage of patients with adverse experiences by body system was tabulated by treatment group. In order to further characterize the most common adverse experiences, the difference in proportions of patients with adverse experiences between treatment groups and associated 95% CIs have been provided for the adverse experiences which occurred in ≥2% of patients in any treatment group. Miettinen and Nurminen's method was used to calculate the 95% CI for the difference in proportions [1.2.19].

Statistical comparison of the differences in proportions of patients with adverse experiences was conducted using the Fisher's exact test for the following clinical adverse experiences: (1) at least one adverse experience; (2) drug-related adverse experiences; (3) serious adverse experiences; (4) serious and drug-related adverse experiences; (5) deaths; (6) discontinuations from study therapy due to an adverse experience; and for tables of special interest including (7) discontinuation of study therapy due to GI adverse experiences, (8) edema-related adverse experiences, (9) hypertension-related adverse experiences, and (10) adverse experiences associated with CHF. The selections of terms used to define the adverse experiences of special interest can be found in [4.5]. The corresponding risk differences and 95% CIs were also provided. No formal hypotheses were prespecified for statistical testing for individual adverse experience types within a category.

Suspected upper GI PUBs, serious cardiovascular thrombotic adverse experiences, and deaths were reviewed and adjudicated prior to unblinding the database according to the respective SOP for the rofecoxib Phase III program [3.11.1; 3.11.2; 3.11.3]. The tabulation of deaths for the "on-drug" analysis included 3 patients who had fatal adverse experiences with an onset date greater than 14 days after the last dose of

study drug and had precursor adverse experiences that may have been related to the fatal off-drug adverse experiences (see Sections 8.3.1.1 and 8.3.1.1.4). Summary statistics of adjudicated results are provided in Section 8.4.3 for PUBs and in 8.4.4 for cardiovascular events.

No multiplicity adjustment was used for the safety analysis. Therefore, the nominal p-values reported in this context should be interpreted with caution. All tests of significance were based upon the Fisher's exact test. The Fisher's exact test is strictly a hypothesis test; no equivalent estimation procedure exists. Asymptotic CIs were provided to indicate the precision of the study sample estimates of treatment differences as population values. These CIs observed in the study represent the range of truly existing treatment differences that might be observed in a larger, similar population. Exclusion of zero by a CI does not always correspond with statistical significance by the Fisher's exact test.

8.1 Extent of Exposure

The duration of exposure to rofecoxib 25 mg and placebo for the duration of the study is shown in Table 38. The first patient in the trial (FPI), based on the first dose of study drug, was on 29-April-1998. The last patient out of the study (LPO) was on 23-April-2003. The mean duration of exposure to drug was 656.6 and 753.9 days for rofecoxib and placebo, respectively. The maximum numbers of days for dosing were 1478 and 1482 days, respectively.

Table 38

Number of Patients by Treatment Group and Actual Duration of Treatment
Grouped by 4 Month Intervals

Treatment Group	1 to 120 Days	121 to 241 Days	242 to 362 Days	363 to 483 Days	484 to 604 Days	605 to 725 Days	726 to 846 Days	847 to 967 Days	968 to 1088 Days	1089 to 1209 Days	1210 to 1330 Days	1331 to 1451 Days	≥1452 Days	Total	Range of Days on Drug	Mean Number of Days on Drug
Rofecoxib 25 mg	107	69	69	56	51	82	55	22	41	42	51	68	10	723	1 to 1478	656.6
Placebo	71	58	62	51	52	72	66	30	42	53	52	97	22	728	1 to 1482	753.9

Data Source: [4.2]

8.2 Clinical Adverse Experiences

The following sections consist of safety analyses of patients who were exposed to at least one dose of study drug (the APaT population). Based on the APaT population, the total number of patients depicted in the safety tables is 1451; there were 6 additional patients who were randomized but never dosed with study drug: 2 in the rofecoxib group and 4 in the placebo group. For all safety tables, patients were counted according to their randomized assigned treatment group, i.e., rofecoxib or placebo.

Patients were allowed to continue participating in the study whether or not they were taking study drug. Patients were considered to be counted in the "on-drug" patient population if an adverse experience occurred while they were taking study drug, or if it occurred within 14 days after the last dose of study drug. The ITT patient population consists of all participating patients; adverse experiences were counted for this population whether or not they were taking study drug. Information on serious adverse experiences is in Section 8.2.2.3 and complete narratives can be found in [4.6].

One patient in the rofecoxib group (AN 0237) inadvertently did not have all of the data from the final study visit (Visit 15.1) entered into the database. When the missing data error was discovered, the decision was made not to enter the data based on criteria in the Clinical Trial System SOP 3.401 Frozen File and Unblinding Procedures [3.11.5]. The patient stopped study drug on Day 1065 of randomization due to a clinical adverse experience of transient ischemic attack. The investigator diagnosed the patient with the study endpoint of AD at Visit 15 (1456 days after randomization), thus the patient had completed the trial off study medication and reached the study endpoint trigger visit. The protocol-specified 2-month follow-up visit for confirmation of Alzheimer's disease was performed at Visit 15.1 (1523 days after randomization). A portion of data from Visit 15.1 that was not entered in the database included the nonserious adverse experiences of sensory loss in toes and sensory disturbances (paranoid delusions) that decreased in intensity from moderate to mild. The patient had repeated episodes of these adverse experiences throughout the study which had been recorded in earlier patient visits. Whereas the verbatim terms were slightly different for each occurrence of the adverse experiences, each mapped to the same preferred dictionary term (terms as displayed in the tables). These adverse experiences are accounted for in the safety tables, which count numbers of patients with the adverse experiences and not the number of occurrences of events.

8.2.1 Summary of Clinical Adverse Experiences

8.2.1.1 Summary of Clinical Adverse Experiences

The summaries of clinical adverse experiences for on-drug and ITT populations are presented in the following sections.

8.2.1.1.1 On-Drug Population Summary

Table 39 shows the summary of clinical and other adverse experiences for patients who were taking study drug (including events occurring within 14 days after the last dose of study drug). Also shown are the p-values (as determined by Fisher's exact test) for prespecified comparisons. Clinical adverse experiences were reported by 1321 (91%) of 1451 randomized patients who dosed with study drug: 651 (90%) patients in the rofecoxib group and 670 (92%) patients in the placebo group. There were no statistically significant differences in the proportions of patients reporting clinical adverse experiences between treatment groups (p=0.199, Fisher's exact test).

Drug-related clinical adverse experiences (determined by the investigator to be possibly, probably, or definitely related to study drug) occurred in 384 patients: 211 (29.2%) in the rofecoxib group and 173 (23.8%) in the placebo group. A significantly greater proportion of patients in the rofecoxib than the placebo group had at least one drug-related adverse experience (p=0.020, Fisher's exact test).

Serious adverse experiences occurred in 453 patients: 217 (30%) in the rofecoxib group and 236 (32.4%) in the placebo group. There were no statistically significant differences between treatment groups (p=0.336, Fisher's exact test).

No statistically significant differences were observed between treatment groups for patients who had serious adverse experiences determined to be drug related: 11 (1.5%) in the rofecoxib group and 10 (1.4%) in the placebo group (p= 0.830, Fisher's exact test).

Counts of patients who died in the on-drug population were based on fatal adverse experiences occurring while the patient was on drug or within 14 days after the last dose of study therapy. Forty-two (2.9%) patients had fatal adverse experiences while on drug: 27 (3.7%) in the rofecoxib group and 15 (2.1%) in the placebo group. This difference was not statistically significant (p= 0.061, Fisher's exact test). This "on-drug" category includes 3 patients

who had fatal adverse experiences that occurred >14 days after last dose of study drug, but who had experienced precursor adverse experiences on-drug that may have been related to the fatal off-drug adverse experiences. Abbreviated death narratives can be found in Section 8.3.1.1 (Deaths).

There were 303 patients (20.9%) who permanently discontinued study therapy due to clinical adverse experiences: 156 (21.6%) in the rofecoxib group and 147 (20.2%) in the placebo group. This difference was not statistically significant (p = 0.519, Fisher's exact test).

Similar percentages of patients taking rofecoxib or placebo discontinued study drug due to serious adverse experiences: 7.9 and 7.8% in the rofecoxib and placebo groups, respectively. A numerically larger percentage of patients in the rofecoxib than the placebo group discontinued study drug due to drug-related adverse experiences: 8.0 and 5.6% in the rofecoxib and placebo groups, respectively. Similar numbers of patients in each group discontinued study drug due to serious drug-related adverse experiences: 5 (0.7%) in the rofecoxib and 6 (0.8%) in the placebo group. Statistical analyses were not performed for these summary statistics.

Table 39

Clinical Adverse Experience Summary
On-Drug† Population

Adverse Experience Term	Treatment Group: Rofecoxib (N=723) n	Rofecoxib (N=723) (%)	Placebo (N=728) n	Placebo (N=728) (%)	p-Value
With one or more adverse experiences	651	(90.0)	670	(92.0)	0.199
With no adverse experiences	72	(10.0)	58	(8.0)	
With drug-related adverse experiences‡	211	(29.2)	173	(23.8)	0.020
With serious adverse experiences	217	(30.0)	236	(32.4)	0.336
With serious drug-related adverse experiences	11	(1.5)	10	(1.4)	0.830
Who died§	27	(3.7)	15	(2.1)	0.061
Discontinued therapy due to adverse experiences	156	(21.6)	147	(20.2)	0.519
Discontinued therapy due to drug-related adverse experiences	58	(8.0)	41	(5.6)	nps
Discontinued therapy due to serious adverse experiences	57	(7.9)	57	(7.8)	nps
Discontinued therapy due to serious drug-related adverse experiences	5	(0.7)	6	(0.8)	nps

† On drug includes the period through 14 days after discontinuation of study drug.
‡ Determined by the investigator to be possibly, probably, or definitely drug related.
§ Includes 3 patients in the rofecoxib group who had fatal adverse experiences that occurred >14 days after last dose of study drug, but had precursor adverse experiences on-drug that may have been related to the fatal off-drug adverse experiences.
nps = Not prespecified for statistical analysis.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.
p-Value is from Fisher's exact test.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.2.1.1.2 Intention-to-Treat Population Summary

A summary of events for the ITT population is shown in Table 40. There were a total of 61 deaths (4.2%) over the course of the study: 41 (5.7%) in the rofecoxib group and 20 (2.7%) in the placebo group; the difference between treatment groups is statistically significant (p=0.006, Fisher's exact test). Of the 19 patient who died off-drug, 15 died > 1 year after stopping study therapy (see Section 8.3.1.1.2).

Table 40

Clinical Adverse Experience Summary
Intention-to-Treat Population

	Treatment Group				
	Rofecoxib (N=723)		Placebo (N=728)		
Adverse Experience Term	n	(%)	n	(%)	p-Value
With one or more adverse experiences	665	(92.0)	678	(93.1)	0.425
With no adverse experiences	58	(8.0)	50	(6.9)	
With drug-related adverse experiences[†]	211	(29.2)	173	(23.8)	0.020
With serious adverse experiences	268	(37.1)	270	(37.1)	0.999
With serious drug-related adverse experiences	11	(1.5)	11	(1.5)	0.999
Who died	41	(5.7)	20	(2.7)	0.006
Discontinued therapy due to adverse experiences	160	(22.1)	151	(20.7)	0.523
Discontinued therapy due to drug-related adverse experiences	58	(8.0)	41	(5.6)	nps
Discontinued therapy due to serious adverse experiences	59	(8.2)	59	(8.1)	nps
Discontinued therapy due to serious drug-related adverse experiences	5	(0.7)	6	(0.8)	nps

[†] Determined by the investigator to be possibly, probably, or definitely drug related.
nps = Not prespecified for statistical analysis.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.
p-Value is from Fisher's exact test.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.2.2 Display and Analysis of Overall Clinical Adverse Experiences

8.2.2.1 Clinical Adverse Experiences by Body System

8.2.2.1.1 On-Drug Population

The distribution of patients with clinical adverse experiences with a frequency of at least 2% in any treatment group by body system is shown in Table 41. The 95% CIs on the difference of proportions of patients with adverse experiences between treatment groups did not include zero in 3 body systems: infections and infestations; neoplasms (benign, malignant, and unspecified); and vascular disorders. A smaller proportion of patients in the rofecoxib group reported clinical adverse experiences in the categories of infections/infestations and neoplasms (benign, malignant, and unspecified) compared with the placebo group. A greater proportion of patients in the rofecoxib group compared with the placebo group had vascular disorder adverse experiences. Further details of the adverse experiences within these body systems are described below. The 95% CIs included zero for all other body systems, and the differences in proportions between treatment groups were ± 2.61 percentage points in magnitude.

For the category of infections and infestations, 40% of patients in the rofecoxib group and 46.3% patients in the placebo group reported at least one adverse experience of this type. The difference in proportions between treatment groups for this category was -6.32 (95% CI [-11.4, -1.2]). Three adverse experiences were reported most frequently and accounted for most of the difference between treatment groups: nasopharyngitis (11.3 and 13.5%, respectively), upper respiratory tract infection (10.2 and 11.7%), and urinary tract infection (5.5 and 9.2%). The 95% CIs included zero for all adverse experiences except for the adverse experiences of tooth caries (-1.91, 95% CI [-3.7, -0.3]) and urinary tract infection (-3.67, 95% CI [-6.4,-1.0]).

There were fewer patients in the rofecoxib group (10.1%) than in the placebo group (15.0%) who had at least one adverse experience referable to neoplasms (benign, malignant, and unspecified) category. The difference in proportion between treatment groups for this body system category was -4.88 (-8.3,-1.5). Three adverse experiences were reported most frequently and accounted for the difference between treatment groups: basal cell carcinoma (2.5 and 5.1%, respectively), prostate cancer (1.9 and 2.2%), and squamous cell carcinoma of the skin (1.5 and 2.3%). The difference in proportions for the adverse experience of basal cell carcinoma was -2.59 with the 95% CI at [-4.7, -0.7]. The 95% CIs included zero for the other adverse experiences in this category.

More patients on rofecoxib than placebo had at least one adverse experience in the vascular disorders category: 165 (22.8%) in the rofecoxib group and 124 (17.0%) in the placebo group. The difference in proportions between treatment groups for this body system category was 5.79 percentage points (95% CI [1.7, 9.9]. Hypertension was the only adverse experience reported at an incidence of greater than 2% within this category and consisted of 133 patients in the rofecoxib group (18.4%) and 84 patients in the placebo group (11.5%). The difference in proportions between treatment groups for hypertension was 6.86 (95% CI [3.2, 10.5]).

Similar percentages of patients in the rofecoxib group and the placebo group reported adverse experiences of gastrointestinal disorders (42.3 and 41.5%, respectively). The most common adverse experiences in this category were constipation (8.0 and 5.2%, respectively), diarrhea (8.4 and 7.7%), dyspepsia (7.6 and 6.0%), and nausea (6.5 and 6.7%). The difference in proportions between treatment groups for the adverse experience of constipation was 2.8 (95% CI [0.3, 5.4]). The 95% CIs for all other adverse experiences reported in the gastrointestinal category included zero.

Fewer patients in the rofecoxib group than the placebo group reported adverse experiences of the musculoskeletal and connective tissue (36.9 and 39%, respectively). The most frequent adverse experiences in this category were arthralgia (13.4 and 14.3%, respectively) and back pain (8.2 and 10.6%). Of note, 20 (2.8%) patients in the rofecoxib group and 9 (1.2%) in the placebo group reported osteoporosis; the difference between proportions was 1.53 percentage points (95% CI [0.1, 3.1]). With the exception of osteoporosis, the 95% CIs for all other adverse experiences reported in this category included zero. (See section 8.4.5 for additional details for osteoporosis.)

Nervous system disorders were reported for similar numbers of patients in each treatment group: 264 (36.5%) patients in the rofecoxib group and 277 (38.0%) patients in the placebo group. Transient ischemic attack was a reported adverse experience for 15 patients in each treatment group (2.1%). The 95% CIs for all adverse experiences reported in this category included zero.

Fewer patients in the rofecoxib group reported anxiety than in the placebo group (2.1 and 4.0%, respectively). The difference between proportions was -1.91 percentage points (95% CI [-3.8, -0.2]). The 95% CIs for all other adverse experiences reported in the psychiatric disorders category included zero.

Skin lesions were reported in fewer patients in the rofecoxib group than the placebo group (1.1 and 2.9%, respectively); the difference between proportions was -1.78 percentage points (95% CI [-3.4,-0.4]). The 95% CIs for all other adverse experiences reported with the skin and subcutaneous tissue disorder category included zero.

Table 41

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
On-Drug† Population
(Incidence ≥2.0% in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	N	(%)	n	(%)	(A-B)% 95% CI
Patient with at least one Adverse Experience	651	(90.0)	670	(92.0)	-1.99 (-5.0, 1.0)
Patient with no Adverse Experience	72	(10.0)	58	(8.0)	1.99 (-1.0, 5.0)
Blood and Lymphatic System Disorders	**43**	**(5.9)**	**30**	**(4.1)**	**1.83 (-0.4, 4.2)**
Anemia nos	30	(4.1)	19	(2.6)	1.54 (-0.3, 3.5)
Cardiac Disorders	**126**	**(17.4)**	**117**	**(16.1)**	**1.36 (-2.5, 5.2)**
Angina pectoris	15	(2.1)	17	(2.3)	-0.26 (-1.9, 1.3)
Atrial fibrillation	19	(2.6)	23	(3.2)	-0.53 (-2.3, 1.2)
Cardiac failure congestive	14	(1.9)	18	(2.5)	-0.54 (-2.2, 1.0)
Coronary artery disease nos	24	(3.3)	17	(2.3)	0.98 (-0.8, 2.8)
Ear and Labyrinth Disorders	**43**	**(5.9)**	**54**	**(7.4)**	**-1.47 (-4.1, 1.1)**
Vertigo	24	(3.3)	19	(2.6)	0.71 (-1.1, 2.6)
Endocrine Disorders	**19**	**(2.6)**	**16**	**(2.2)**	**0.43 (-1.2, 2.1)**
Eye Disorders	**92**	**(12.7)**	**97**	**(13.3)**	**-0.60 (-4.1, 2.9)**
Cataract unilateral	29	(4.0)	26	(3.6)	0.44 (-1.6, 2.5)
Glaucoma nos	15	(2.1)	7	(1.0)	1.11 (-0.2, 2.5)
Gastrointestinal Disorders	**306**	**(42.3)**	**302**	**(41.5)**	**0.84 (-4.2, 5.9)**
Abdominal pain nos	31	(4.3)	20	(2.7)	1.54 (-0.4, 3.5)
Colonic polyp	12	(1.7)	17	(2.3)	-0.68 (-2.2, 0.8)
Constipation	58	(8.0)	38	(5.2)	2.80 (0.3, 5.4)
Diarrhea nos	61	(8.4)	56	(7.7)	0.74 (-2.1, 3.6)
Dry mouth	12	(1.7)	17	(2.3)	-0.68 (-2.2, 0.8)
Dyspepsia	55	(7.6)	44	(6.0)	1.56 (-1.1, 4.2)
Flatulence	16	(2.2)	10	(1.4)	0.84 (-0.6, 2.3)
Gastritis nos	15	(2.1)	8	(1.1)	0.98 (-0.3, 2.4)
Gastroesophageal reflux disease	23	(3.2)	36	(4.9)	-1.76 (-3.9, 0.3)
Hemorrhoids	18	(2.5)	13	(1.8)	0.70 (-0.8, 2.3)
Nausea	47	(6.5)	49	(6.7)	-0.23 (-2.8, 2.4)
Toothache	11	(1.5)	17	(2.3)	-0.81 (-2.4, 0.6)
Vomiting nos	24	(3.3)	20	(2.7)	0.57 (-1.2, 2.4)

Table 41 (Cont.)

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
On-Drug† Population
(Incidence ≥2.0% in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) N	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
General Disorders and Administration Site Conditions	**210**	**(29.0)**	**205**	**(28.2)**	**0.89 (-3.8, 5.5)**
Asthenia	44	(6.1)	45	(6.2)	-0.10 (-2.6, 2.4)
Chest pain	45	(6.2)	41	(5.6)	0.59 (-1.9, 3.1)
Gait abnormal	24	(3.3)	17	(2.3)	0.98 (-0.8, 2.8)
Influenza like illness	16	(2.2)	25	(3.4)	-1.22 (-3.0, 0.5)
Edema peripheral	65	(9.0)	56	(7.7)	1.30 (-1.6, 4.2)
Pain nos	17	(2.4)	19	(2.6)	-0.26 (-1.9, 1.4)
Immune System Disorders	**22**	**(3.0)**	**16**	**(2.2)**	**0.85 (-0.8, 2.6)**
Infections and Infestations	**289**	**(40.0)**	**337**	**(46.3)**	**-6.32 (-11.4, -1.2)**
Influenza	24	(3.3)	29	(4.0)	-0.66 (-2.7, 1.3)
Nasopharyngitis	82	(11.3)	98	(13.5)	-2.12 (-5.5, 1.3)
Pneumonia nos	23	(3.2)	31	(4.3)	-1.08 (-3.1, 0.9)
Sinusitis nos	21	(2.9)	27	(3.7)	-0.80 (-2.7, 1.1)
Tooth abscess	12	(1.7)	17	(2.3)	-0.68 (-2.2, 0.8)
Tooth caries nos	12	(1.7)	26	(3.6)	-1.91 (-3.7, -0.3)
Upper respiratory tract infection nos	74	(10.2)	85	(11.7)	-1.44 (-4.7, 1.8)
Urinary tract infection nos	40	(5.5)	67	(9.2)	-3.67 (-6.4, -1.0)
Injury, Poisoning and Procedural Complications	**172**	**(23.8)**	**174**	**(23.9)**	**-0.11 (-4.5, 4.3)**
Excoriation	9	(1.2)	16	(2.2)	-0.95 (-2.4, 0.4)
Joint sprain	9	(1.2)	15	(2.1)	-0.82 (-2.3, 0.5)
Laceration	22	(3.0)	26	(3.6)	-0.53 (-2.5, 1.4)
Post procedural pain	17	(2.4)	22	(3.0)	-0.67 (-2.4, 1.0)
Investigations	**116**	**(16.0)**	**121**	**(16.6)**	**-0.58 (-4.4, 3.2)**
Blood pressure increased	42	(5.8)	30	(4.1)	1.69 (-0.6, 4.0)
Cardiac murmur nos	18	(2.5)	12	(1.6)	0.84 (-0.7, 2.4)
Weight decreased	25	(3.5)	25	(3.4)	0.02 (-1.9, 2.0)
Metabolism and Nutrition Disorders	**45**	**(6.2)**	**40**	**(5.5)**	**0.73 (-1.7, 3.2)**
Musculoskeletal and Connective Tissue Disorders	**267**	**(36.9)**	**284**	**(39.0)**	**-2.08 (-7.1, 2.9)**
Arthralgia	97	(13.4)	104	(14.3)	-0.87 (-4.4, 2.7)
Arthritis nos	25	(3.5)	25	(3.4)	0.02 (-1.9, 2.0)
Back pain	59	(8.2)	77	(10.6)	-2.42 (-5.5, 0.6)
Muscle cramp	18	(2.5)	11	(1.5)	0.98 (-0.5, 2.6)
Osteoarthritis nos	9	(1.2)	17	(2.3)	-1.09 (-2.6, 0.3)
Osteoporosis nos	20	(2.8)	9	(1.2)	1.53 (0.1, 3.1)
Pain In extremity	50	(6.9)	49	(6.7)	0.18 (-2.4, 2.8)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	**73**	**(10.1)**	**109**	**(15.0)**	**-4.88 (-8.3, -1.5)**
Basal cell carcinoma	18	(2.5)	37	(5.1)	-2.59 (-4.7, -0.7)
Prostate cancer nos	14	(1.9)	16	(2.2)	-0.26 (-1.8, 1.3)
Squamous cell carcinoma of skin	11	(1.5)	17	(2.3)	-0.81 (-2.4, 0.6)

Table 41 (Cont.)

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
On-Drug† Population
(Incidence ≥2.0% in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) N	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Nervous System Disorders	**264**	**(36.5)**	**277**	**(38.0)**	**-1.53 (-6.5, 3.4)**
Dizziness	75	(10.4)	76	(10.4)	-0.07 (-3.2, 3.1)
Headache	52	(7.2)	73	(10.0)	-2.84 (-5.8, 0.1)
Hypoesthesia	18	(2.5)	14	(1.9)	0.57 (-1.0, 2.2)
Somnolence	17	(2.4)	12	(1.6)	0.70 (-0.8, 2.3)
Syncope	17	(2.4)	22	(3.0)	-0.67 (-2.4, 1.0)
Transient ischaemic attack	15	(2.1)	15	(2.1)	0.01 (-1.5, 1.6)
Psychiatric Disorders	**157**	**(21.7)**	**141**	**(19.4)**	**2.35 (-1.8, 6.5)**
Anxiety	15	(2.1)	29	(4.0)	-1.91 (-3.8, -0.2)
Confusional state	15	(2.1)	10	(1.4)	0.70 (-0.7, 2.2)
Depression	56	(7.7)	56	(7.7)	0.05 (-2.7, 2.8)
Insomnia	53	(7.3)	45	(6.2)	1.15 (-1.5, 3.8)
Renal and Urinary Disorders	**98**	**(13.6)**	**91**	**(12.5)**	**1.05 (-2.4, 4.5)**
Hematuria	16	(2.2)	11	(1.5)	0.70 (-0.7, 2.2)
Pollakiuria	31	(4.3)	30	(4.1)	0.17 (-2.0, 2.3)
Reproductive System and Breast Disorders	**55**	**(7.6)**	**67**	**(9.2)**	**-1.60 (-4.5, 1.3)**
Benign prostatic hyperplasia	17	(2.4)	26	(3.6)	-1.22 (-3.1, 0.6)
Respiratory, Thoracic and Mediastinal Disorders	**168**	**(23.2)**	**177**	**(24.3)**	**-1.08 (-5.5, 3.3)**
Bronchitis nos	27	(3.7)	23	(3.2)	0.58 (-1.3, 2.5)
Cough	38	(5.3)	45	(6.2)	-0.93 (-3.4, 1.5)
Dyspnea	35	(4.8)	28	(3.8)	0.99 (-1.1, 3.2)
Nasal congestion	20	(2.8)	15	(2.1)	0.71 (-0.9, 2.4)
Pharyngolaryngeal pain	14	(1.9)	18	(2.5)	-0.54 (-2.2, 1.0)
Skin and Subcutaneous Tissue Disorders	**142**	**(19.6)**	**162**	**(22.3)**	**-2.61 (-6.8, 1.6)**
Contusion	29	(4.0)	29	(4.0)	0.03 (-2.0, 2.1)
Pruritus	15	(2.1)	11	(1.5)	0.56 (-0.9, 2.1)
Rash nos	32	(4.4)	33	(4.5)	-0.11 (-2.3, 2.1)
Skin lesion nos	8	(1.1)	21	(2.9)	-1.78 (-3.4, -0.4)
Vascular Disorders	**165**	**(22.8)**	**124**	**(17.0)**	**5.79 (1.7, 9.9)**
Hypertension nos	133	(18.4)	84	(11.5)	6.86 (3.2, 10.5)

† On drug includes the period through 14 days after discontinuation of study drug.

CI = Confidence interval.

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

N = Number of randomized patients in each treatment group who took at least one dose of study drug.

n = Number of patients in each category.

Data Source: [4.2]

8.2.2.1.2 Intention-to-Treat Population

Specific clinical adverse experiences by body system, occurring at an incidence of ≥2% whether or not the patient was on study drug are shown in Table 42.

In the ITT population, the category of vascular disorders only showed differences between treatment groups that were similar to those in the on-drug population: more patients in the rofecoxib than the placebo group had adverse experiences of the vascular system (5.39% difference, 95% CI [1.1, 9.7]). The upper bound of the 95% CI for the differences between treatment groups for adverse experiences within the category of infections and infestations was zero (95% CI [-10.3, 0.0]), and that for neoplasms (benign, malignant, and unspecified) included zero (95% CI [-7.4, 0.1]). The 95% CIs included zero for all other body systems.

Table 42 shows that the number of reported adverse experiences for the ITT and on-drug populations are similar for the specific adverse experiences of constipation, hypertension, anxiety, skin lesion, tooth caries, and basal cell carcinoma; these are the only adverse experiences shown on this table with 95% CIs that do not include zero. More patients in the rofecoxib group than the placebo group reported adverse experiences of constipation and hypertension; fewer patients in the rofecoxib than the placebo group reported adverse experiences of anxiety, skin lesion, tooth caries, and basal cell carcinoma. In comparison to the on-drug population, the 95% CI in the ITT population includes zero for the adverse experience of osteoporosis, with a difference between treatment groups of 1.40% (95% CI [-0.3, 3.2]). The 95% CIs for all other specific adverse experiences reported for the ITT population included zero.

Table 42

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(Incidence ≥2% in One or More Treatment Groups)

	Treatment Group					
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference	
Adverse Experience Term	n	(%)	n	(%)	(A-B)%	95% CI
Patient with at least one adverse experience	665	(92.0)	678	(93.1)	-1.15	(-3.9, 1.6)
Patient with no adverse experience	58	(8.0)	50	(6.9)	1.15	(-1.6, 3.9)
Blood and Lymphatic System Disorders	**55**	**(7.6)**	**41**	**(5.6)**	**1.98**	**(-0.6, 4.6)**
Anemia Nos	42	(5.8)	29	(4.0)	1.83	(-0.4, 4.1)
Cardiac Disorders	**154**	**(21.3)**	**137**	**(18.8)**	**2.48**	**(-1.6, 6.6)**
Angina Pectoris	18	(2.5)	20	(2.7)	-0.26	(-2.0, 1.5)
Atrial Fibrillation	28	(3.9)	30	(4.1)	-0.25	(-2.3, 1.8)
Cardiac Failure Congestive	23	(3.2)	22	(3.0)	0.16	(-1.7, 2.0)
Coronary Artery Disease Nos	32	(4.4)	22	(3.0)	1.40	(-0.6, 3.5)
Myocardial Infarction	19	(2.6)	14	(1.9)	0.70	(-0.9, 2.4)
Ear and Labyrinth Disorders	**52**	**(7.2)**	**59**	**(8.1)**	**-0.91**	**(-3.7, 1.9)**
Vertigo	26	(3.6)	23	(3.2)	0.44	(-1.5, 2.4)
Endocrine Disorders	**22**	**(3.0)**	**18**	**(2.5)**	**0.57**	**(-1.2, 2.4)**
Hypothyroidism	16	(2.2)	13	(1.8)	0.43	(-1.1, 2.0)
Eye Disorders	**108**	**(14.9)**	**113**	**(15.5)**	**-0.58**	**(-4.3, 3.1)**
Cataract unilateral	35	(4.8)	26	(3.6)	1.27	(-0.8, 3.4)
Glaucoma nos	15	(2.1)	9	(1.2)	0.84	(-0.5, 2.3)
Gastrointestinal Disorders	**333**	**(46.1)**	**327**	**(44.9)**	**1.14**	**(-4.0, 6.3)**
Abdominal pain nos	37	(5.1)	25	(3.4)	1.68	(-0.4, 3.9)
Abdominal pain upper	7	(1.0)	15	(2.1)	-1.09	(-2.5, 0.2)
Colonic polyp	14	(1.9)	18	(2.5)	-0.54	(-2.2, 1.0)
Constipation	78	(10.8)	52	(7.1)	3.65	(0.7, 6.6)
Diarrhea nos	71	(9.8)	64	(8.8)	1.03	(-2.0, 4.1)
Dry mouth	12	(1.7)	19	(2.6)	-0.95	(-2.6, 0.6)
Dyspepsia	59	(8.2)	50	(6.9)	1.29	(-1.4, 4.1)
Flatulence	18	(2.5)	12	(1.6)	0.84	(-0.7, 2.4)
Gastritis nos	19	(2.6)	11	(1.5)	1.12	(-0.4, 2.7)
Gastroesophageal reflux disease	26	(3.6)	38	(5.2)	-1.62	(-3.8, 0.5)
Hemorrhoids	21	(2.9)	16	(2.2)	0.71	(-1.0, 2.4)
Hiatus hernia	15	(2.1)	13	(1.8)	0.29	(-1.2, 1.8)
Loose stools	18	(2.5)	10	(1.4)	1.12	(-0.3, 2.7)
Nausea	59	(8.2)	58	(8.0)	0.19	(-2.6, 3.0)
Rectal hemorrhage	15	(2.1)	12	(1.6)	0.43	(-1.0, 1.9)
Toothache	12	(1.7)	17	(2.3)	-0.68	(-2.2, 0.8)
Vomiting nos	30	(4.1)	22	(3.0)	1.13	(-0.8, 3.1)

Table 42 (Cont.)

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(Incidence ≥2% in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)%	95% CI
General Disorders and Administration Site Conditions	**233**	**(32.2)**	**225**	**(30.9)**	**1.32**	**(-3.5, 6.1)**
Asthenia	50	(6.9)	51	(7.0)	-0.09	(-2.7, 2.6)
Chest Pain	52	(7.2)	45	(6.2)	1.01	(-1.6, 3.6)
Gait Abnormal	25	(3.5)	18	(2.5)	0.99	(-0.8, 2.8)
Influenza Like Illness	18	(2.5)	25	(3.4)	-0.94	(-2.8, 0.8)
Edema Peripheral	73	(10.1)	67	(9.2)	0.89	(-2.2, 4.0)
Pain Nos	21	(2.9)	24	(3.3)	-0.39	(-2.3, 1.5)
Pyrexia	12	(1.7)	15	(2.1)	-0.40	(-1.9, 1.1)
Hepatobiliary Disorders	**12**	**(1.7)**	**16**	**(2.2)**	**-0.54**	**(-2.1, 0.9)**
Immune System Disorders	**24**	**(3.3)**	**20**	**(2.7)**	**0.57**	**(-1.2, 2.4)**
Seasonal Allergy	15	(2.1)	11	(1.5)	0.56	(-0.9, 2.1)
Infections and Infestations	**328**	**(45.4)**	**368**	**(50.5)**	**-5.18**	**(-10.3, -0.0)**
Ear Infection Nos	11	(1.5)	16	(2.2)	-0.68	(-2.2, 0.8)
Herpes Zoster	15	(2.1)	9	(1.2)	0.84	(-0.5, 2.3)
Influenza	28	(3.9)	34	(4.7)	-0.80	(-3.0, 1.3)
Nasopharyngitis	88	(12.2)	105	(14.4)	-2.25	(-5.8, 1.3)
Pneumonia Nos	34	(4.7)	36	(4.9)	-0.24	(-2.5, 2.0)
Sinusitis Nos	24	(3.3)	35	(4.8)	-1.49	(-3.6, 0.6)
Tooth Abscess	14	(1.9)	19	(2.6)	-0.67	(-2.3, 0.9)
Tooth Caries Nos	14	(1.9)	27	(3.7)	-1.77	(-3.6, -0.1)
Upper Respiratory Tract Infection Nos	84	(11.6)	95	(13.0)	-1.43	(-4.8, 2.0)
Urinary Tract Infection Nos	51	(7.1)	71	(9.8)	-2.70	(-5.6, 0.2)
Injury, Poisoning and Procedural Complications	**202**	**(27.9)**	**200**	**(27.5)**	**0.47**	**(-4.1, 5.1)**
Excoriation	12	(1.7)	19	(2.6)	-0.95	(-2.6, 0.6)
Fall	18	(2.5)	15	(2.1)	0.43	(-1.2, 2.1)
Joint Sprain	11	(1.5)	15	(2.1)	-0.54	(-2.0, 0.9)
Laceration	27	(3.7)	30	(4.1)	-0.39	(-2.5, 1.7)
Post Procedural Pain	20	(2.8)	24	(3.3)	-0.53	(-2.4, 1.3)
Investigations	**139**	**(19.2)**	**139**	**(19.1)**	**0.13**	**(-3.9, 4.2)**
Blood Pressure Increased	46	(6.4)	33	(4.5)	1.83	(-0.5, 4.2)
Cardiac Murmur Nos	21	(2.9)	16	(2.2)	0.71	(-1.0, 2.4)
Weight Decreased	35	(4.8)	34	(4.7)	0.17	(-2.1, 2.4)
Metabolism and Nutrition Disorders	**55**	**(7.6)**	**43**	**(5.9)**	**1.70**	**(-0.9, 4.3)**
Musculoskeletal and Connective Tissue Disorders	**300**	**(41.5)**	**308**	**(42.3)**	**-0.81**	**(-5.9, 4.3)**
Arthralgia	108	(14.9)	112	(15.4)	-0.45	(-4.2, 3.3)
Arthritis Nos	26	(3.6)	26	(3.6)	0.02	(-2.0, 2.0)
Back Pain	71	(9.8)	88	(12.1)	-2.27	(-5.5, 1.0)
Muscle Cramp	19	(2.6)	14	(1.9)	0.70	(-0.9, 2.4)
Osteoarthritis Nos	12	(1.7)	18	(2.5)	-0.81	(-2.4, 0.7)
Osteoporosis Nos	24	(3.3)	14	(1.9)	1.40	(-0.3, 3.2)
Pain In Extremity	59	(8.2)	55	(7.6)	0.61	(-2.2, 3.4)

Table 42 (Cont.)

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(Incidence ≥2% in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)%	95% CI
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**100**	**(13.8)**	**127**	**(17.4)**	**-3.61**	**(-7.4, 0.1)**
Basal Cell Carcinoma	21	(2.9)	44	(6.0)	-3.14	(-5.4, -1.0)
Prostate Cancer Nos	17	(2.4)	18	(2.5)	-0.12	(-1.8, 1.5)
Squamous Cell Carcinoma Of Skin	16	(2.2)	19	(2.6)	-0.40	(-2.1, 1.2)
Nervous System Disorders	**299**	**(41.4)**	**304**	**(41.8)**	**-0.40**	**(-5.5, 4.7)**
Dizziness	84	(11.6)	85	(11.7)	-0.06	(-3.4, 3.3)
Headache	55	(7.6)	77	(10.6)	-2.97	(-6.0, -0.0)
Hypoesthesia	20	(2.8)	17	(2.3)	0.43	(-1.3, 2.2)
Somnolence	20	(2.8)	12	(1.6)	1.12	(-0.4, 2.8)
Syncope	22	(3.0)	24	(3.3)	-0.25	(-2.1, 1.6)
Transient Ischaemic Attack	19	(2.6)	16	(2.2)	0.43	(-1.2, 2.1)
Tremor	17	(2.4)	10	(1.4)	0.98	(-0.4, 2.5)
Psychiatric Disorders	**183**	**(25.3)**	**160**	**(22.0)**	**3.33**	**(-1.0, 7.7)**
Anxiety	17	(2.4)	34	(4.7)	-2.32	(-4.3, -0.4)
Confusional State	17	(2.4)	11	(1.5)	0.84	(-0.6, 2.4)
Depression	73	(10.1)	69	(9.5)	0.62	(-2.5, 3.7)
Insomnia	63	(8.7)	49	(6.7)	1.98	(-0.8, 4.8)
Irritability	15	(2.1)	11	(1.5)	0.56	(-0.9, 2.1)
Renal and Urinary Disorders	**119**	**(16.5)**	**101**	**(13.9)**	**2.59**	**(-1.1, 6.3)**
Hematuria	18	(2.5)	13	(1.8)	0.70	(-0.8, 2.3)
Pollakiuria	34	(4.7)	34	(4.7)	0.03	(-2.2, 2.3)
Reproductive System and Breast Disorders	**65**	**(9.0)**	**71**	**(9.8)**	**-0.76**	**(-3.8, 2.3)**
Benign Prostatic Hyperplasia	19	(2.6)	29	(4.0)	-1.36	(-3.3, 0.5)
Respiratory, Thoracic and Mediastinal Disorders	**196**	**(27.1)**	**199**	**(27.3)**	**-0.23**	**(-4.8, 4.4)**
Bronchitis Nos	36	(5.0)	31	(4.3)	0.72	(-1.5, 3.0)
Cough	41	(5.7)	47	(6.5)	-0.79	(-3.3, 1.7)
Dyspnea	40	(5.5)	34	(4.7)	0.86	(-1.4, 3.2)
Nasal Congestion	21	(2.9)	16	(2.2)	0.71	(-1.0, 2.4)
Pharyngolaryngeal Pain	17	(2.4)	20	(2.7)	-0.40	(-2.1, 1.3)
Skin and Subcutaneous Tissue Disorders	**164**	**(22.7)**	**183**	**(25.1)**	**-2.45**	**(-6.8, 1.9)**
Actinic Keratosis	8	(1.1)	16	(2.2)	-1.09	(-2.6, 0.2)
Contusion	32	(4.4)	33	(4.5)	-0.11	(-2.3, 2.1)
Pruritus	16	(2.2)	13	(1.8)	0.43	(-1.1, 2.0)
Rash Nos	36	(5.0)	39	(5.4)	-0.38	(-2.7, 1.9)
Skin Lesion Nos	10	(1.4)	23	(3.2)	-1.78	(-3.5, -0.3)
Vascular Disorders	**183**	**(25.3)**	**145**	**(19.9)**	**5.39**	**(1.1, 9.7)**
Hypertension Nos	144	(19.9)	102	(14.0)	5.91	(2.1, 9.8)

CI = Confidence interval.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.2.2.2 Clinical Adverse Experiences Considered by the Investigator to be Drug Related

While blinded, investigators were asked to assess the relationship of adverse experiences to study therapy. This section discusses clinical adverse experiences that were considered possibly, probably, or definitely related to study medication. Separate tables and discussions are described below for patients in the on-drug population and the ITT population. The ITT section highlights only the differences between the populations.

8.2.2.2.1 On-Drug Population

The distribution of patients with clinical adverse experiences that were determined by the investigators to be possibly, probably, or definitely related to study drug, by body system, is presented in Table 43.

Overall, a greater proportion of patients in the rofecoxib group than the placebo group had drug-related clinical adverse experiences, with the 95% CI on the difference in proportions (5.42 percentage points) covering [0.9 to 10.0]. The 95% CIs were performed for adverse experiences with an incidence of ≥2% and covered zero for all body system categories of classification; the differences were ± 1.74 percentage points in magnitude.

Peripheral edema was reported as a drug-related adverse experience of general disorders in 23 (3.2%) patients in the rofecoxib group and in 11 (1.5%) patients in the placebo group. The 95% CIs for this adverse experience did not cross zero, and the difference in percentage points between treatment groups was 1.67% (95% CI [0.1 to 3.4]).

There were 100 (13.8%) patients in the rofecoxib group and 88 (12.1%) in the placebo group that had adverse experiences of gastrointestinal disorders determined to be drug related by the investigators; the most frequent of which were dyspepsia (3.3 and 2.3%, respectively), diarrhea (1.5 and 2.2%), and nausea (1.9 and 2.1%). Gastric ulcer occurred in 4 (0.6%) patients in the rofecoxib group and in 2 (0.3%) patients in the placebo group, and upper GI hemorrhage was reported in 2 (0.3%) patients on rofecoxib and 1 (0.1%) on placebo. Further discussion of episodes of upper GI perforations, ulcers, and bleeds is presented in Section 8.4.3.

Blood pressure increased was reported as a drug-related adverse experience in 16 (2.2%) patients in the rofecoxib group and 14 (1.9%) patients in the placebo group; hypertension was reported in 29 (4.0%) and 25 (3.4%) patients, respectively. The 95% CIs included zero for the differences between proportions for these adverse experiences. These are known side effects of NSAIDs, including selective Cox-2 inhibitors.

Dizziness (2.5 and 1.9%, respectively) and headache (1.0 and 1.9%) were the most frequent drug-related adverse experiences reported as disorders of the nervous system.

Seven patients had adverse experiences related to and including renal impairment. Renal failure considered as a drug-related adverse experience was reported in 3 patients in the rofecoxib group (Allocation Numbers [ANs] 0105, 0451, 1069) and none in the placebo; drug-related renal impairment was reported in 2 patients in the rofecoxib group (ANs 0141 and 0392) and 1 patient in the placebo group (AN 0236). Oliguria was reported as a drug-related adverse experience in 1 patient in the rofecoxib group (AN 0394). Narratives for these patients are described below.

For Site 004, AN 0105, a 78-year-old female in the rofecoxib treatment group, had a nonserious adverse experience of chronic renal failure, which the investigator rated as being possibly related to study drug. Prior medical history revealed hypertension and hypothyroidism. Concomitant medications included diltiazem hydrochloride, dyazide, hydrazaline, levothyroxine sodium (0.1 mg), folic acid , and vitamin B-12. At baseline blood urea nitrogen (BUN) was 16 mg/dL and serum creatinine was 0.8 mg/dL; both were within the normal range. Nutritional supplements of cyanocobalamin and folic acid were started on Day 289. BUN and creatinine levels increased to 41 mg/dL and 1.8 mg/dL, respectively, on Day 629. On Day 658, renal failure was reported as a nonserious adverse experience related to study drug. Dyazide and folic acid use was stopped and levothyroxine sodium (0.125 mg), nifedipine, and ferrous sulfate were prescribed at that time for hypothyroidism, hypertension and anemia, respectively. Study medication was discontinued on Day 663 due to the renal failure. The patient completed the study (1461 days after randomization) and BUN and serum creatinine levels had dropped to 21 mg/dL and 1.1 mg/dL, respectively. The adverse experience was continuing at the time of study completion.

For Site 008, AN 0236, an 82-year-old male in the placebo group, had a nonserious adverse experience of renal impairment, which the investigator rated as being possibly related to study drug. This patient had hypertension and ankle edema as part of his medical history. Concomitant therapies included hydrochlorothiazide and fosinopril sodium, which were stopped approximately 1 month prior to the adverse experience of renal impairment; furosemide was started in place of those therapies on Day 762 after randomization. At baseline, BUN was 27 mg/dL and serum creatinine was 1.2 mg/dL. BUN and serum creatinine fluctuated between 24 mg/dL and 28 mg/dL and 1.3 mg/dL to 1.1 mg/dL, respectively, over a period of 708 days. On Day 805 after randomization, the patient was seen for a study visit; BUN

had increased to 40 mg/dL and serum creatinine to 1.6 mg/dL. The onset of renal impairment was reported at this time. During this visit, the patient was discontinued from the study because he was diagnosed with probable AD, a study endpoint per protocol. The patient took study medication until discontinuation from the study and the renal impairment was continuing.

For Site 013, AN 0392, a 71-year-old male in the rofecoxib treatment group, had a nonserious adverse experience of renal impairment, which the investigator rated as being possibly related to study drug. The patient presented to the study with a history remarkable for hypertension, urinary incontinence, and renal calculus removal. Concomitant therapies at the time of the adverse experience included fosinopril sodium, hydrochlorothiazide, and atenolol (for nonserious adverse experience of palpitations). Baseline BUN was 21 mg/dL and serum creatinine was 1.5 mg/dL. Serum creatine levels were at 1.7 mg/dl and BUN remained within the normal limit at 22 mg/dl on Day 110. Ten days prior to that, the patient had just come off a course of guaifenesin and albuterol for bronchitis, and on Day 103, he had started atenolol for palpitations. On Day 348 after randomization, BUN increased to 33 mg/dL and serum creatinine increased to 2.4 mg/dL; renal impairment was reported at that time as a drug-related adverse experience. Increased serum creatinine was reported as a nonserious laboratory experience on Day 357 with BUN at 32 mg/dl and serum creatinine at 2.4 mg/dl. Study medication was discontinued on Day 379, due to this laboratory adverse experience. On Day 413, levels of BUN and serum creatinine remained high at 32 and 2.2 mg/dl, respectively. The BUN and serum creatinine values remained high for the next 658 days. The patient completed the trial on Day 1353, and the BUN and serum creatinine levels were 35 mg/dL and 1.9 mg/dL, respectively. The renal impairment was continuing at the time the patient completed the study.

For Site 013, AN 394, a 77-year-old male in the rofecoxib treatment group, had a nonserious adverse experience of oliguria, which the investigator rated as being possibly related to study drug. Past medical history was remarkable for hypercholesterolemia, arthritis, chronic obstructive pulmonary disease, urinary incontinence, and nocturia. On Day 30 after randomization the patient experienced abdominal pain rated as possibly related to study medication by the investigator. On Day 36 after randomization, the nonserious adverse experiences of loose dark stools, decreased appetite, increased flatulence, and oliguria were reported. The patient began taking Mylanta on Day 36 for the increased flatulence. The patient had no other concomitant medications. Also on Day 36 after randomization, the patient experienced a nonserious adverse experience of upper GI hemorrhage, which resulted in discontinuation of study drug. All of the adverse experiences that occurred on Day 36 were rated

by the investigator as being possibly drug related. Laboratory results were within the normal ranges for all laboratory tests throughout the study period. The patient discontinued the study within 3 months due to the ongoing adverse experiences.

For Site 015, AN 0451, an 84-year-old male in the rofecoxib treatment group, had a serious adverse experience of renal failure, which the investigator rated as being possibly related to study drug. The patient had no pertinent medical history to this adverse experience. Concomitant therapies included digestive enzymes for heartburn, valerian extract as a nutritional supplement, cephalexin for post-angioplasty infection prophylaxis, and clopidogrel bisulfate. At baseline BUN was 26 mg/dL and serum creatinine was 1.4 mg/dL. The BUN and serum creatinine increased to 35 mg/dL and 1.8 mg/dL (respectively) 118 days after randomization. The investigator indicated these values as nonserious adverse events, which were considered definitely not related to study medication. On Day 125 after randomization, BUN was 36 mg/dL and serum creatinine was 1.6 mg/dL. On Day 370, BUN was 41 mg/dL and serum creatinine was 1.7 mg/dL. The investigator indicated these values as nonserious adverse experiences, which were considered probably not related to study medication. On Day 440, the patient was diagnosed with coronary artery disease and underwent an angioplasty on Day 449. On Day 466 after randomization, the patient was hospitalized for renal failure. Laboratory tests in the hospital revealed high BUN and serum creatinine levels (exact values were not obtained). Study medication was interrupted on Day 467 due to the renal failure and was never restarted. The patient withdrew consent from the study 588 days after randomization. Renal impairment was present when the patient discontinued from the study. A complete WAES narrative for this event can be found in [4.6].

For Site 025, AN 0141, an 83-year-old female in the rofecoxib treatment group, had a nonserious adverse experience of renal impairment, which the investigator rated as being possibly related to study drug. Medical history included hypothyroidism and hypertension. Concomitant therapies included hydrochlorothiazide, lisinopril, and levothyroid. At baseline BUN was 20 mg/dL and serum creatinine was 1.3 mg/dL. On Day 734 after randomization, BUN was 31 mg/dL and serum creatinine was 1.5 mg/dL. On Day 1099, BUN increased to 44 mg/dL and serum creatinine increased to 2 mg/dL. Over the next 28 days, the serum creatinine decreased but was still outside the normal range (1.4 mg/dL); BUN fluctuated between 35 mg/dL and 44 mg/dL. Renal impairment was recorded as an adverse experience with mild intensity on Day 1148 after randomization. Some medications were changed when renal impairment was noted; atenolol (100 mg) and nifedipine (30 mg) were

added, lisinopril was discontinued. Renal impairment was upgraded to an intensity of moderate (Day 1239) for approximately 9 months at which time hypertension medications were again altered; nifedipine dosing was increased to 60 mg daily and furosemide was started. The investigator continued to indicate the relationship of study drug to the adverse experience of renal impairment as possibly related to study drug. Laboratory tests taken at a routine study visit, 1338 days after starting study medication, showed BUN at 65 mg/dL and serum creatinine at 2.6 mg/dL. At this time, the use of study drug was discontinued due to these laboratory adverse experiences. The patient continued to participate in the trial off of study medication. On Day 1531, the patient completed the trial and the BUN and serum creatinine levels were 27 mg/dL and 1.5 mg/dL, respectively. The renal impairment was still continuing at the time the patient completed the study.

For Site 034, AN 1069, a 78-year-old male in the rofecoxib treatment group, had a nonserious adverse experience of chronic renal failure, which the investigator rated as being possibly related to study drug. The patient had a prior history of chronic renal failure and prostatomegaly. Upon study entry, the patient was taking terazosin for the enlarged prostate. At baseline, BUN was 17 mg/dL and serum creatinine was 1.3 mg/dL. On Day 120 after randomization, BUN was 36 mg/dL and serum creatinine was 1.3 mg/dL. On Day 728, BUN was 37 mg/dL and serum creatinine was 1.3 mg/dL. On Day 1078, the onset of the drug-related adverse experience of renal impairment was reported, with BUN at 35 mg/dL and serum creatinine at 1.4 mg/dL. On Day 1093, BUN was 43 mg/dL and serum creatinine was 1.5 mg/dL. The adverse experience of renal impairment stopped on Day 1112 with BUN level at 22 mg/dL and serum creatinine at 1.5 mg/dL. The patient continued taking study medication and completed the study on Day 1463.

Table 43

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)%	95% CI
Patients with at least one adverse experience	211	(29.2)	173	(23.8)	5.42	(0.9, 10.0)
Patient with no adverse experience	512	(70.8)	555	(76.2)	-5.42	(-10.0, -0.9)
Blood and Lymphatic System Disorders	**7**	**(1.0)**	**6**	**(0.8)**		**ND**
Anemia nos	6	(0.8)	6	(0.8)		ND
Iron deficiency anemia	1	(0.1)	0	(0.0)		ND
Cardiac Disorders	**8**	**(1.1)**	**6**	**(0.8)**		**ND**
Acute myocardial infarction	1	(0.1)	0	(0.0)		ND
Age indeterminate myocardial infarction	1	(0.1)	0	(0.0)		ND
Angina pectoris	1	(0.1)	3	(0.4)		ND
Atrial fibrillation	1	(0.1)	0	(0.0)		ND
Atrioventricular block first degree	0	(0.0)	1	(0.1)		ND
Bradycardia nos	0	(0.0)	1	(0.1)		ND
Bundle branch block left	1	(0.1)	0	(0.0)		ND
Cardiac failure congestive	0	(0.0)	1	(0.1)		ND
Hypertrophic cardiomyopathy	1	(0.1)	0	(0.0)		ND
Myocardial infarction	0	(0.0)	1	(0.1)		ND
Supraventricular extrasystoles	1	(0.1)	0	(0.0)		ND
Ventricular bigeminy	1	(0.1)	0	(0.0)		ND
Ventricular extrasystoles	1	(0.1)	0	(0.0)		ND
Ventricular tachycardia	1	(0.1)	0	(0.0)		ND
Congenital, Familial and Genetic Disorders	**1**	**(0.1)**	**0**	**(0.0)**		**ND**
Epidermolysis Bullosa	1	(0.1)	0	(0.0)		ND
Ear and Labyrinth Disorders	**5**	**(0.7)**	**3**	**(0.4)**		**ND**
Tinnitus	2	(0.3)	2	(0.3)		ND
Vertigo	3	(0.4)	1	(0.1)		ND
Eye Disorders	**2**	**(0.3)**	**0**	**(0.0)**		**ND**
Blindness	1	(0.1)	0	(0.0)		ND
Visual disturbance nos	1	(0.1)	0	(0.0)		ND
Gastrointestinal Disorders	**100**	**(13.8)**	**88**	**(12.1)**	**1.74**	**(-1.7, 5.2)**
Abdominal discomfort	2	(0.3)	0	(0.0)		ND
Abdominal distension	4	(0.6)	4	(0.5)		ND
Abdominal pain lower	0	(0.0)	1	(0.1)		ND
Abdominal pain nos	9	(1.2)	3	(0.4)		ND
Abdominal pain upper	1	(0.1)	3	(0.4)		ND
Abdominal tenderness	1	(0.1)	0	(0.0)		ND
Aphthous stomatitis	2	(0.3)	1	(0.1)		ND
Aptyalism	0	(0.0)	1	(0.1)		ND
Change in bowel habit nos	0	(0.0)	1	(0.1)		ND
Colitis ischaemic	1	(0.1)	0	(0.0)		ND
Colonic polyp	1	(0.1)	0	(0.0)		ND
Constipation	6	(0.8)	4	(0.5)		ND

Table 43 (Cont.)

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Diarrhea hemorrhagic	0	(0.0)	1	(0.1)	ND
Diarrhea nos	11	(1.5)	16	(2.2)	-0.68 (-2.2, 0.8)
Dry mouth	4	(0.6)	6	(0.8)	ND
Duodenal ulcer	2	(0.3)	0	(0.0)	ND
Duodenal ulcer perforation	0	(0.0)	1	(0.1)	ND
Dyspepsia	24	(3.3)	17	(2.3)	0.98 (-0.8, 2.8)
Dysphagia	2	(0.3)	1	(0.1)	ND
Enterocolitis	1	(0.1)	0	(0.0)	ND
Eructation	0	(0.0)	2	(0.3)	ND
Fecal incontinence	1	(0.1)	0	(0.0)	ND
Feces discolored	2	(0.3)	1	(0.1)	ND
Feces hard	1	(0.1)	0	(0.0)	ND
Flatulence	8	(1.1)	5	(0.7)	ND
Frequent bowel movements	3	(0.4)	2	(0.3)	ND
Gastric erosions	0	(0.0)	2	(0.3)	ND
Gastric ulcer	4	(0.6)	2	(0.3)	ND
Gastric ulcer hemorrhage	1	(0.1)	1	(0.1)	ND
Gastritis atrophic	0	(0.0)	1	(0.1)	ND
Gastritis nos	6	(0.8)	3	(0.4)	ND
Gastrointestinal hemorrhage nos	2	(0.3)	0	(0.0)	ND
Gastrointestinal PAIN NOS	0	(0.0)	1	(0.1)	ND
Gastroesophageal reflux disease	6	(0.8)	13	(1.8)	ND
Hemorrhoids	1	(0.1)	0	(0.0)	ND
Hyperacidity	0	(0.0)	1	(0.1)	ND
Lip dry	0	(0.0)	2	(0.3)	ND
Loose stools	10	(1.4)	4	(0.5)	ND
Lower gastrointestinal hemorrhage	0	(0.0)	1	(0.1)	ND
Melena	1	(0.1)	1	(0.1)	ND
Mouth ulceration	2	(0.3)	1	(0.1)	ND
Nausea	14	(1.9)	15	(2.1)	-0.12 (-1.7, 1.4)
Esophageal ulcer	1	(0.1)	0	(0.0)	ND
Esophageal ulcer hemorrhage	0	(0.0)	1	(0.1)	ND
Oral pain	1	(0.1)	0	(0.0)	ND
Pruritus ani	0	(0.0)	1	(0.1)	ND
Rectal hemorrhage	2	(0.3)	0	(0.0)	ND
Reflux esophagitis	1	(0.1)	0	(0.0)	ND
Retching	0	(0.0)	1	(0.1)	ND
Stomach discomfort	2	(0.3)	0	(0.0)	ND
Stomatitis	3	(0.4)	0	(0.0)	ND
Swollen tongue	1	(0.1)	0	(0.0)	ND
Tongue disorder nos	0	(0.0)	1	(0.1)	ND
Upper gastrointestinal hemorrhage	2	(0.3)	1	(0.1)	ND
Vomiting nos	3	(0.4)	2	(0.3)	ND

Table 43 (Cont.)

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)%	95% CI
General Disorders and Administration Site Conditions	**37**	**(5.1)**	**31**	**(4.3)**	**0.86**	**(-1.4, 3.1)**
Anasarca	0	(0.0)	1	(0.1)		ND
Asthenia	6	(0.8)	4	(0.5)		ND
Chest pain	1	(0.1)	3	(0.4)		ND
Fatigue	1	(0.1)	4	(0.5)		ND
Feeling abnormal	0	(0.0)	1	(0.1)		ND
Gait abnormal	1	(0.1)	2	(0.3)		ND
Gravitational edema	1	(0.1)	0	(0.0)		ND
Impaired healing	1	(0.1)	0	(0.0)		ND
Lethargy	1	(0.1)	2	(0.3)		ND
Malaise	0	(0.0)	2	(0.3)		ND
Edema nos	1	(0.1)	3	(0.4)		ND
Edema peripheral	23	(3.2)	11	(1.5)	1.67	(0.1, 3.4)
Pain nos	1	(0.1)	0	(0.0)		ND
Sensation of pressure nos	0	(0.0)	1	(0.1)		ND
Infections and Infestations	**2**	**(0.3)**	**1**	**(0.1)**		**ND**
Gastroenteritis nos	1	(0.1)	1	(0.1)		ND
Nasopharyngitis	1	(0.1)	0	(0.0)		ND
Injury, Poisoning and Procedural Complications	**1**	**(0.1)**	**0**	**(0.0)**		**ND**
Procedural complication	1	(0.1)	0	(0.0)		ND
Investigations	**28**	**(3.9)**	**26**	**(3.6)**	**0.30**	**(-1.7, 2.3)**
Blood in stool	1	(0.1)	1	(0.1)		ND
Blood pressure abnormal	1	(0.1)	0	(0.0)		ND
Blood pressure diastolic increased	2	(0.3)	1	(0.1)		ND
Blood pressure increased	16	(2.2)	14	(1.9)	0.29	(-1.2, 1.9)
Blood pressure systolic increased	1	(0.1)	2	(0.3)		ND
Electrocardiogram St-T change nos	0	(0.0)	1	(0.1)		ND
Fecal occult blood positive	6	(0.8)	2	(0.3)		ND
Heart rate decreased	0	(0.0)	1	(0.1)		ND
Weight decreased	2	(0.3)	2	(0.3)		ND
Weight increased	3	(0.4)	3	(0.4)		ND
Metabolism and Nutrition Disorders	**8**	**(1.1)**	**1**	**(0.1)**		**ND**
Anorexia	3	(0.4)	0	(0.0)		ND
Appetite decreased nos	3	(0.4)	1	(0.1)		ND
Fluid retention	2	(0.3)	0	(0.0)		ND
Musculoskeletal and Connective Tissue Disorders	**9**	**(1.2)**	**4**	**(0.5)**		**ND**
Back pain	2	(0.3)	2	(0.3)		ND
Bursitis	1	(0.1)	0	(0.0)		ND
Joint swelling	1	(0.1)	0	(0.0)		ND
Muscle cramp	2	(0.3)	2	(0.3)		ND
Muscle twitching	1	(0.1)	0	(0.0)		ND
Muscle weakness nos	1	(0.1)	0	(0.0)		ND
Polymyalgia rheumatica	1	(0.1)	0	(0.0)		ND

Table 43 (Cont.)

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)%	95% CI
Nervous System Disorders	**33**	**(4.6)**	**37**	**(5.1)**	**-0.52**	**(-2.8, 1.7)**
Balance impaired nos	1	(0.1)	1	(0.1)		ND
Cerebrovascular accident	0	(0.0)	1	(0.1)		ND
Dizziness	18	(2.5)	14	(1.9)	0.57	(-1.0, 2.2)
Dysgeusia	0	(0.0)	1	(0.1)		ND
Dyskinesia	0	(0.0)	1	(0.1)		ND
Headache	7	(1.0)	14	(1.9)		ND
Hypoesthesia	0	(0.0)	1	(0.1)		ND
Intention tremor	1	(0.1)	0	(0.0)		ND
Migraine nos	2	(0.3)	1	(0.1)		ND
Paraesthesia	1	(0.1)	0	(0.0)		ND
Reversible ischaemic neurological deficit	0	(0.0)	1	(0.1)		ND
Sedation	0	(0.0)	1	(0.1)		ND
Somnolence	4	(0.6)	4	(0.5)		ND
Syncope	1	(0.1)	1	(0.1)		ND
Transient ischaemic attack	1	(0.1)	0	(0.0)		ND
Tremor	1	(0.1)	0	(0.0)		ND
Psychiatric Disorders	**11**	**(1.5)**	**13**	**(1.8)**		**ND**
Abnormal dreams	0	(0.0)	1	(0.1)		ND
Anxiety	1	(0.1)	0	(0.0)		ND
Change in sustained attention	0	(0.0)	1	(0.1)		ND
Confusional state	3	(0.4)	1	(0.1)		ND
Depression	2	(0.3)	1	(0.1)		ND
Insomnia	3	(0.4)	9	(1.2)		ND
Irritability	2	(0.3)	1	(0.1)		ND
Nervousness	0	(0.0)	1	(0.1)		ND
Nightmare	1	(0.1)	0	(0.0)		ND
Sleep disorder nos	1	(0.1)	1	(0.1)		ND
Renal and Urinary Disorders	**8**	**(1.1)**	**2**	**(0.3)**		**ND**
Hematuria	1	(0.1)	0	(0.0)		ND
Micturition urgency	0	(0.0)	1	(0.1)		ND
Oliguria	1	(0.1)	0	(0.0)		ND
Pollakiuria	1	(0.1)	0	(0.0)		ND
Renal failure chronic	2	(0.3)	0	(0.0)		ND
Renal failure nos	1	(0.1)	0	(0.0)		ND
Renal impairment nos	2	(0.3)	1	(0.1)		ND
Reproductive System and Breast Disorders	**1**	**(0.1)**	**2**	**(0.3)**		**ND**
Benign prostatic hyperplasia	0	(0.0)	1	(0.1)		ND
Breast engorgement	1	(0.1)	0	(0.0)		ND
Genital pruritus female	0	(0.0)	1	(0.1)		ND

Table 43 (Cont.)

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Respiratory, Thoracic and Mediastinal Disorders	**4**	**(0.6)**	**6**	**(0.8)**	**ND**
Dyspnea	2	(0.3)	2	(0.3)	ND
Epistaxis	1	(0.1)	3	(0.4)	ND
Hemoptysis	0	(0.0)	1	(0.1)	ND
Rhinitis nos	1	(0.1)	0	(0.0)	ND
Skin and Subcutaneous Tissue Disorders	**8**	**(1.1)**	**14**	**(1.9)**	**ND**
Contusion	1	(0.1)	0	(0.0)	ND
Dermatitis exfoliative nos	1	(0.1)	0	(0.0)	ND
Dermatitis nos	0	(0.0)	1	(0.1)	ND
Ecchymosis	0	(0.0)	1	(0.1)	ND
Erythema	0	(0.0)	1	(0.1)	ND
Night sweats	0	(0.0)	2	(0.3)	ND
Pruritus	1	(0.1)	1	(0.1)	ND
Rash erythematous	1	(0.1)	0	(0.0)	ND
Rash maculo-papular	0	(0.0)	1	(0.1)	ND
Rash nos	3	(0.4)	5	(0.7)	ND
Seborrheic dermatitis	1	(0.1)	0	(0.0)	ND
Stasis dermatitis	0	(0.0)	1	(0.1)	ND
Sweating increased	0	(0.0)	1	(0.1)	ND
Surgical and Medical Procedures	**1**	**(0.1)**	**0**	**(0.0)**	**ND**
Nasal sinus drainage	1	(0.1)	0	(0.0)	ND
Vascular Disorders	**33**	**(4.6)**	**30**	**(4.1)**	**0.44 (-1.7, 2.6)**
Flushing	0	(0.0)	4	(0.5)	ND
Hypertension nos	29	(4.0)	25	(3.4)	0.58 (-1.4, 2.6)
Intermittent claudication	1	(0.1)	0	(0.0)	ND
Labile hypertension	1	(0.1)	0	(0.0)	ND
Orthostatic hypotension	0	(0.0)	1	(0.1)	ND
Pallor	0	(0.0)	1	(0.1)	ND
Peripheral coldness	1	(0.1)	0	(0.0)	ND
Systolic hypertension	1	(0.1)	0	(0.0)	ND

† On drug includes the period through 14 days after discontinuation of study drug.
CI = Confidence interval.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.2.2.2.2 Intention-to-Treat Population

The distribution of patients with clinical adverse experiences that were determined by the investigators to be possibly, probably, or definitely related to study drug by body system for the ITT population is shown in Table 44.

There were no clinically important differences in the ITT and on-drug population, except for renal and urinary disorders where 2 additional patients in the rofecoxib group (ANs 1444 and 1652) had renal impairment reported by the investigator as a drug-related adverse experience. Full narratives for these are discussed below.

For Site 046, AN 1444, an 81-year-old male in the rofecoxib treatment group, had a nonserious adverse experience of renal impairment, which the investigator rated as being possibly related to study drug. Medical history included pacemaker placement. Concomitant therapy included quinine sulfate for leg cramps and clonazepam for sleep disorder. Baseline BUN was 22 mg/dL and serum creatinine was 1.4 mg/dL. Laboratory test results from Day 459 after randomization showed increased BUN t(30 mg/dL) and increased serum creatinine (1.7 mg/dL). Over the next 197 days, the BUN went from 34 mg/dL to 30 mg/dL and serum creatinine went from 2 mg/dL to 2.1 mg/dL. Study medication was discontinued due to the laboratory adverse experience of increased creatinine after dosing for 660 days. Renal impairment was reported as a drug-related adverse experience on Day 677, 17 days after the last dose of study drug. BUN and serum creatinine values decreased after discontinuing study drug. On Day 791, the patient was seen for a study visit. During this visit, the patient was discontinued from the study since he was diagnosed with probable Alzheimer's disease, a study endpoint per protocol. Renal impairment as a drug-related adverse experience was continuing at the final visit with BUN at 24 mg/dL and serum creatinine at 1.5 mg/dL.

For Site 011, AN 1652, a 73-year-old male in the rofecoxib treatment group, had a nonserious adverse experience of renal impairment, which the investigator rated as being possibly related to study drug. The patient had a medical history of hypertension. From entry into the study up to Day 346 the patient had been on a succession of several medications for the hypertension, including valsartan, amlodipine besylate (5, then 10 mg), metoprolol succinate, amlodipine besylate (5 mg again), then concomitant furosemide (80 mg) and labetalol hydrochloride (400 mg) on Day 346 of the study. At baseline BUN was 25 mg/dL and serum creatinine was 1.7 mg/dL. On Day 224 after randomization, BUN was 36 mg/dL and serum creatinine was 1.9 mg/dL (serum creatinine was reported as a nonserious adverse experience at

that time). The labetalol hydrochloride dosage was decreased to 200 mg on Day 348. The nonserious laboratory adverse experience of increased BUN was reported over a period of 15 days beginning with BUN levels at 44 mg/dL and serum creatinine at 2 mg/dL (Day 356) with BUN increasing to 53 mg/dL and serum creatinine increasing to 2.7 mg/dL by Day 371. Study drug was discontinued, 370 days after randomization. The dosage of furosemide was decreased to 40 mg on Day 434. On Day 485, the nonserious adverse experience of renal impairment was indicated. Between Days 695 and 1028, BUN values continued to increase from 28 mg/dL to 29 mg/dL and serum creatinine values from 1.8 mg/dL to 2.3 mg/dL. By the final study visit on Day 1044, BUN was 35 mg/dL and serum creatinine was 1.8 mg/dL. The renal impairment was still continuing as an adverse experience at the time the patient completed the study.

Table 44

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n	(%)	n	(%)	(A-B)% 95% CI
Patient with at least one Adverse Experience	211	(29.2)	173	(23.8)	5.42 (0.9, 10.0)
Patient with no Adverse Experience	512	(70.8)	555	(76.2)	-5.42 (-10.0, -0.9)
Blood and Lymphatic System Disorders	**7**	**(1.0)**	**7**	**(1.0)**	**ND**
Anemia nos	6	(0.8)	7	(1.0)	ND
Iron deficiency anemia	1	(0.1)	0	(0.0)	ND
Cardiac Disorders	**8**	**(1.1)**	**6**	**(0.8)**	**ND**
Acute myocardial infarction	1	(0.1)	0	(0.0)	ND
Age indeterminate myocardial infarction	1	(0.1)	0	(0.0)	ND
Angina pectoris	1	(0.1)	3	(0.4)	ND
Atrial fibrillation	1	(0.1)	0	(0.0)	ND
Atrioventricular block first degree	0	(0.0)	1	(0.1)	ND
Bradycardia nos	0	(0.0)	1	(0.1)	ND
Bundle branch block left	1	(0.1)	0	(0.0)	ND
Cardiac failure congestive	0	(0.0)	1	(0.1)	ND
Hypertrophic cardiomyopathy	1	(0.1)	0	(0.0)	ND
Myocardial infarction	0	(0.0)	1	(0.1)	ND
Supraventricular extrasystoles	1	(0.1)	0	(0.0)	ND
Ventricular bigeminy	1	(0.1)	0	(0.0)	ND
Ventricular extrasystoles	1	(0.1)	0	(0.0)	ND
Ventricular tachycardia	1	(0.1)	0	(0.0)	ND

Table 44 (Cont.)

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Congenital, Familial and Genetic Disorders	**1**	**(0.1)**	**0**	**(0.0)**	**ND**
Epidermolysis bullosa	1	(0.1)	0	(0.0)	ND
Ear and Labyrinth Disorders	**5**	**(0.7)**	**3**	**(0.4)**	**ND**
Tinnitus	2	(0.3)	2	(0.3)	ND
Vertigo	3	(0.4)	1	(0.1)	ND
Eye Disorders	**2**	**(0.3)**	**0**	**(0.0)**	**ND**
Blindness	1	(0.1)	0	(0.0)	ND
Visual disturbance nos	1	(0.1)	0	(0.0)	ND
Gastrointestinal Disorders	**100**	**(13.8)**	**89**	**(12.2)**	**1.61 (-1.9, 5.1)**
Abdominal discomfort	2	(0.3)	0	(0.0)	ND
Abdominal distension	4	(0.6)	4	(0.5)	ND
Abdominal pain lower	0	(0.0)	1	(0.1)	ND
Abdominal pain nos	9	(1.2)	3	(0.4)	ND
Abdominal pain upper	1	(0.1)	3	(0.4)	ND
Abdominal tenderness	1	(0.1)	0	(0.0)	ND
Aphthous stomatitis	2	(0.3)	1	(0.1)	ND
Aptyalism	0	(0.0)	1	(0.1)	ND
Change in bowel habit nos	0	(0.0)	1	(0.1)	ND
Colitis ischaemic	1	(0.1)	0	(0.0)	ND
Colonic polyp	1	(0.1)	0	(0.0)	ND
Constipation	6	(0.8)	4	(0.5)	ND
Diarrhea hemorrhagic	0	(0.0)	1	(0.1)	ND
Diarrhea nos	11	(1.5)	16	(2.2)	-0.68 (-2.2, 0.8)
Dry mouth	4	(0.6)	6	(0.8)	ND
Duodenal ulcer	2	(0.3)	1	(0.1)	ND
Duodenal ulcer perforation	0	(0.0)	1	(0.1)	ND
Dyspepsia	24	(3.3)	17	(2.3)	0.98 (-0.8, 2.8)
Dysphagia	2	(0.3)	1	(0.1)	ND
Enterocolitis	1	(0.1)	0	(0.0)	ND
Eructation	0	(0.0)	2	(0.3)	ND
Fecal incontinence	1	(0.1)	0	(0.0)	ND
Feces discolored	2	(0.3)	1	(0.1)	ND
Feces hard	1	(0.1)	0	(0.0)	ND
Flatulence	8	(1.1)	5	(0.7)	ND
Frequent bowel movements	3	(0.4)	2	(0.3)	ND
Gastric erosions	0	(0.0)	3	(0.4)	ND
Gastric ulcer	4	(0.6)	2	(0.3)	ND
Gastric ulcer hemorrhage	1	(0.1)	1	(0.1)	ND
Gastritis atrophic	0	(0.0)	1	(0.1)	ND
Gastritis nos	6	(0.8)	4	(0.5)	ND
Gastrointestinal hemorrhage nos	2	(0.3)	0	(0.0)	ND
Gastrointestinal pain nos	0	(0.0)	1	(0.1)	ND
Gastroesophageal reflux disease	6	(0.8)	13	(1.8)	ND

Table 44 (Cont.)

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Hemorrhoids	1	(0.1)	0	(0.0)	ND
Hyperacidity	0	(0.0)	1	(0.1)	ND
Lip dry	0	(0.0)	2	(0.3)	ND
Loose stools	10	(1.4)	4	(0.5)	ND
Lower gastrointestinal hemorrhage	0	(0.0)	1	(0.1)	ND
Melena	1	(0.1)	1	(0.1)	ND
Mouth ulceration	2	(0.3)	1	(0.1)	ND
Nausea	14	(1.9)	15	(2.1)	-0.12 (-1.7, 1.4)
Esophageal ulcer	1	(0.1)	0	(0.0)	ND
Esophageal ulcer hemorrhage	0	(0.0)	1	(0.1)	ND
Oral pain	1	(0.1)	0	(0.0)	ND
Pruritus ani	0	(0.0)	1	(0.1)	ND
Rectal hemorrhage	2	(0.3)	0	(0.0)	ND
Reflux esophagitis	1	(0.1)	0	(0.0)	ND
Retching	0	(0.0)	1	(0.1)	ND
Stomach discomfort	2	(0.3)	0	(0.0)	ND
Stomatitis	3	(0.4)	0	(0.0)	ND
Swollen tongue	1	(0.1)	0	(0.0)	ND
Tongue disorder nos	0	(0.0)	1	(0.1)	ND
Upper gastrointestinal hemorrhage	2	(0.3)	1	(0.1)	ND
Vomiting nos	3	(0.4)	2	(0.3)	ND
General Disorders and Administration Site Conditions	**37**	**(5.1)**	**31**	**(4.3)**	**0.86 (-1.4, 3.1)**
Anasarca	0	(0.0)	1	(0.1)	ND
Asthenia	6	(0.8)	4	(0.5)	ND
Chest pain	1	(0.1)	3	(0.4)	ND
Fatigue	1	(0.1)	4	(0.5)	ND
Feeling abnormal	0	(0.0)	1	(0.1)	ND
Gait abnormal	1	(0.1)	2	(0.3)	ND
Gravitational edema	1	(0.1)	0	(0.0)	ND
Impaired healing	1	(0.1)	0	(0.0)	ND
Lethargy	1	(0.1)	2	(0.3)	ND
Malaise	0	(0.0)	2	(0.3)	ND
Edema nos	1	(0.1)	3	(0.4)	ND
Edema peripheral	23	(3.2)	11	(1.5)	1.67 (0.1, 3.4)
Pain nos	1	(0.1)	0	(0.0)	ND
Sensation of pressure nos	0	(0.0)	1	(0.1)	ND
Infections and Infestations	**2**	**(0.3)**	**1**	**(0.1)**	**ND**
Gastroenteritis nos	1	(0.1)	1	(0.1)	ND
Nasopharyngitis	1	(0.1)	0	(0.0)	ND

Table 44 (Cont.)

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Injury, Poisoning and Procedural Complications	**1**	**(0.1)**	**0**	**(0.0)**	**ND**
Procedural complication	1	(0.1)	0	(0.0)	ND
Investigations	**28**	**(3.9)**	**26**	**(3.6)**	**0.30 (-1.7, 2.3)**
Blood in stool	1	(0.1)	1	(0.1)	ND
Blood pressure abnormal	1	(0.1)	0	(0.0)	ND
Blood pressure diastolic increased	2	(0.3)	1	(0.1)	ND
Blood pressure increased	16	(2.2)	14	(1.9)	0.29 (-1.2, 1.9)
Blood pressure systolic increased	1	(0.1)	2	(0.3)	ND
Electrocardiogram St-T change nos	0	(0.0)	1	(0.1)	ND
Fecal occult blood positive	6	(0.8)	2	(0.3)	ND
Heart rate decreased	0	(0.0)	1	(0.1)	ND
Weight decreased	2	(0.3)	2	(0.3)	ND
Weight increased	3	(0.4)	3	(0.4)	ND
Metabolism and Nutrition Disorders	**8**	**(1.1)**	**1**	**(0.1)**	**ND**
Anorexia	3	(0.4)	0	(0.0)	ND
Appetite decreased nos	3	(0.4)	1	(0.1)	ND
Fluid retention	2	(0.3)	0	(0.0)	ND
Musculoskeletal and Connective Tissue Disorders	**9**	**(1.2)**	**4**	**(0.5)**	**ND**
Back pain	2	(0.3)	2	(0.3)	ND
Bursitis	1	(0.1)	0	(0.0)	ND
Joint swelling	1	(0.1)	0	(0.0)	ND
Muscle cramp	2	(0.3)	2	(0.3)	ND
Muscle twitching	1	(0.1)	0	(0.0)	ND
Muscle weakness nos	1	(0.1)	0	(0.0)	ND
Polymyalgia rheumatica	1	(0.1)	0	(0.0)	ND
Nervous System Disorders	**33**	**(4.6)**	**37**	**(5.1)**	**-0.52 (-2.8, 1.7)**
Balance impaired nos	1	(0.1)	1	(0.1)	ND
Cerebrovascular accident	0	(0.0)	1	(0.1)	ND
Dizziness	18	(2.5)	14	(1.9)	0.57 (-1.0, 2.2)
Dysgeusia	0	(0.0)	1	(0.1)	ND
Dyskinesia	0	(0.0)	1	(0.1)	ND
Headache	7	(1.0)	14	(1.9)	ND
Hypoesthesia	0	(0.0)	1	(0.1)	ND
Intention tremor	1	(0.1)	0	(0.0)	ND
Migraine nos	2	(0.3)	1	(0.1)	ND
Paraesthesia	1	(0.1)	0	(0.0)	ND
Reversible ischaemic neurological deficit	0	(0.0)	1	(0.1)	ND
Sedation	0	(0.0)	1	(0.1)	ND
Somnolence	4	(0.6)	4	(0.5)	ND
Syncope	1	(0.1)	1	(0.1)	ND
Transient ischaemic attack	1	(0.1)	0	(0.0)	ND
Tremor	1	(0.1)	0	(0.0)	ND

Table 44 (Cont.)

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Psychiatric Disorders	**11**	**(1.5)**	**13**	**(1.8)**	**ND**
Abnormal dreams	0	(0.0)	1	(0.1)	ND
Anxiety	1	(0.1)	0	(0.0)	ND
Change in sustained attention	0	(0.0)	1	(0.1)	ND
Confusional state	3	(0.4)	1	(0.1)	ND
Depression	2	(0.3)	1	(0.1)	ND
Insomnia	3	(0.4)	9	(1.2)	ND
Irritability	2	(0.3)	1	(0.1)	ND
Nervousness	0	(0.0)	1	(0.1)	ND
Nightmare	1	(0.1)	0	(0.0)	ND
Sleep disorder nos	1	(0.1)	1	(0.1)	ND
Renal and Urinary Disorders	**10**	**(1.4)**	**2**	**(0.3)**	**ND**
Hematuria	1	(0.1)	0	(0.0)	ND
Micturition urgency	0	(0.0)	1	(0.1)	ND
Oliguria	1	(0.1)	0	(0.0)	ND
Pollakiuria	1	(0.1)	0	(0.0)	ND
Renal failure chronic	2	(0.3)	0	(0.0)	ND
Renal failure nos	1	(0.1)	0	(0.0)	ND
Renal impairment nos	4	(0.6)	1	(0.1)	ND
Reproductive System and Breast Disorders	**1**	**(0.1)**	**2**	**(0.3)**	**ND**
Benign prostatic hyperplasia	0	(0.0)	1	(0.1)	ND
Breast engorgement	1	(0.1)	0	(0.0)	ND
Genital pruritus female	0	(0.0)	1	(0.1)	ND
Respiratory, Thoracic and Mediastinal Disorders	**4**	**(0.6)**	**6**	**(0.8)**	**ND**
Dyspnea	2	(0.3)	2	(0.3)	ND
Epistaxis	1	(0.1)	3	(0.4)	ND
Hemoptysis	0	(0.0)	1	(0.1)	ND
Rhinitis Nos	1	(0.1)	0	(0.0)	ND
Skin and Subcutaneous Tissue Disorders	**8**	**(1.1)**	**14**	**(1.9)**	**ND**
Contusion	1	(0.1)	0	(0.0)	ND
Dermatitis exfoliative nos	1	(0.1)	0	(0.0)	ND
Dermatitis nos	0	(0.0)	1	(0.1)	ND
Ecchymosis	0	(0.0)	1	(0.1)	ND
Erythema	0	(0.0)	1	(0.1)	ND
Night sweats	0	(0.0)	2	(0.3)	ND
Pruritus	1	(0.1)	1	(0.1)	ND
Rash erythematous	1	(0.1)	0	(0.0)	ND
Rash maculo-papular	0	(0.0)	1	(0.1)	ND
Rash nos	3	(0.4)	5	(0.7)	ND
Seborrheic dermatitis	1	(0.1)	0	(0.0)	ND
Stasis dermatitis	0	(0.0)	1	(0.1)	ND
Sweating increased	0	(0.0)	1	(0.1)	ND

Table 44 (Cont.)

Number (%) of Patients With Drug-Related Specific Clinical Adverse Experiences
by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Surgical and Medical Procedures	**1**	**(0.1)**	**0**	**(0.0)**	**ND**
Nasal sinus drainage	1	(0.1)	0	(0.0)	ND
Vascular Disorders	**33**	**(4.6)**	**30**	**(4.1)**	**0.44 (-1.7, 2.6)**
Flushing	0	(0.0)	4	(0.5)	ND
Hypertension nos	29	(4.0)	25	(3.4)	0.58 (-1.4, 2.6)
Intermittent claudication	1	(0.1)	0	(0.0)	ND
Labile hypertension	1	(0.1)	0	(0.0)	ND
Orthostatic hypotension	0	(0.0)	1	(0.1)	ND
Pallor	0	(0.0)	1	(0.1)	ND
Peripheral coldness	1	(0.1)	0	(0.0)	ND
Systolic hypertension	1	(0.1)	0	(0.0)	ND

CI = Confidence interval.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.2.2.3 Serious Adverse Experiences

A listing of all serious adverse experiences is found in [4.5]

8.2.2.3.1 On-Drug Population

The distribution of patients who had serious clinical adverse experiences while on drug, or within 14 days of the last dose of study therapy, is presented in Table 45. Complete WAES narratives describing the serious adverse experiences noted below are in [4.6].

The 95% CI for the differences in proportions of patients with serious adverse experiences did not cross zero for the category of neoplasms (benign, malignant, and unspecified). The differences between treatment groups was -4.34 percentage points (95% CI [-7.5 to -1.2]). The CI for percentage point differences in patients with serious adverse experiences for all other body systems included zero, and the differences were ± 1.4 percentage points. Estimated differences and 95% CIs were performed for serious adverse experiences that occurred with an incidence of ≥2% and are shown on Table 45.

Serious adverse experiences of cardiac disorders were reported in 58 (8.0%) patients in the rofecoxib group and 56 (7.7%) patients in the placebo group. The most frequent adverse experiences reported for rofecoxib and placebo groups, by patient counts were: atrial fibrillation (7 and 13, respectively), congestive cardiac failure (5 and 12), coronary artery disease (19 and 14), and myocardial infarction (13 and 11).

Chest pain was the most frequently reported serious adverse experience in the general disorders category for 8 (1.1%) patients in the rofecoxib group and 10 (1.4%) in the placebo group.

Serious gastrointestinal adverse experiences were reported for 31 (4.3%) patients in the rofecoxib group and 21 (2.9%) patients in the placebo group. Upper gastrointestinal hemorrhages were reported for 7 patients in the rofecoxib group and 2 in the placebo group; these were respectively divided between duodenal ulcer hemorrhage (2 and 0 respectively), gastric ulcer hemorrhage (2 and 0), gastrointestinal hemorrhage NOS (2 and 1), and upper gastrointestinal hemorrhage (1 and 1). Three perforations were reported: 1 gastric perforation for a patient in the rofecoxib group, 1 duodenal ulcer perforation for a patient in the placebo group, and one intestinal perforation in the placebo group. A gastric ulcer was reported as a serious adverse experience for a patient in rofecoxib group. Some patients may have had a combination of these adverse experiences. All adverse experiences of upper GI perforations, ulcers, and bleeds were adjudicated (see 3.11.1; 4.7.1) and are discussed in Section 8.4.3.

Twenty-one (2.9%) patients in the rofecoxib group and 27 (3.7%) patients in the placebo group had serious adverse experiences of infections and infestations. Pneumonia was reported for 10 patients in each treatment group (1.4% of each group).

Various types of fractures were reported as serious adverse experiences in the injury, poisoning, and procedural complications category for a total of 20 (2.8%) patients in the rofecoxib group and 19 (2.6%) in the placebo group. Hip fractures, specifically, were reported in 9 (1.2%) patients on rofecoxib and 5 (0.7%) on placebo. An assessment of fractures can be found in Section 8.4.5.

Serious adverse events of benign, malignant, and unspecified neoplasms occurred in 59 (8.2%) patients on drug in the rofecoxib group and 91 (12.5%) patients in the placebo group. Basal cell carcinoma was the most frequently reported neoplasm with 17 (2.4%) patients in the rofecoxib group and 37 (5.1%) in the placebo group. The 95% CI on the difference between treatment

groups for basal cell carcinoma (-2.73 percentage points) was -4.8 to -0.8. Prostate cancer was reported in 16 (2.2%) and 18 (2.5%), and squamous cell carcinoma of the skin in 11(1.5%) and 17 (2.3%), of the patients in the rofecoxib and placebo groups, respectively.

For disorders of the nervous system, cerebrovascular accident occurred in 8 (1.1%) patients in the rofecoxib treatment group and in 12 (1.6%) patients in the placebo group. Transient ischemic attacks were reported as serious adverse events in 10 (1.4%) patients on rofecoxib and 9 (1.2%) patients on placebo. Syncope was reported for 8 patients on rofecoxib and 7 on placebo, and carotid artery stenosis occurred in 1 and 7 patients in the rofecoxib and placebo groups, respectively.

Renal and urinary disorders were reported as serious adverse experiences in 11 (1.5%) patients on rofecoxib and 9 (1.2%) patients on placebo. Two (0.3%) patients in the rofecoxib group and 3 (0.4%) in the placebo group had renal failure; only one in the rofecoxib group was reported as drug related (AN 0451) and is discussed in Section 8.2.2.2.1 (Clinical Adverse Experiences Considered by the Investigator to be Drug Related; On-Drug Population).

Respiratory disorders were reported as serious adverse experiences for 15 (2.1%) patients in the rofecoxib group and 11 (1.5%) in the placebo group. Chronic obstructive airway disease was reported for 5 patients in the rofecoxib group and one patient in the placebo group.

A total of 14 (patients had serious adverse experiences related to vascular disorders: 5 (0.7%) in the rofecoxib group and 9 (1.2%) in the placebo group. Three patients experienced thrombosis: 1 (0.1%) in the rofecoxib group and 2 (0.3%) in the placebo group (reported for the patients on placebo as deep vein thrombosis). Hypertension was reported as a serious adverse experience for 1 (0.1%) patient in the rofecoxib group and 3 (0.4%) patients in the placebo group.

Table 45

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n	(%)	n	(%)	(A-B)% 95% CI
Patient with at least one Adverse Experience	217	(30.0)	236	(32.4)	-2.40 (-7.2, 2.4)
Patient with no Adverse Experience	506	(70.0)	492	(67.6)	2.40 (-2.4, 7.2)
Blood and Lymphatic System Disorders	**3**	**(0.4)**	**4**	**(0.5)**	**ND**
Anemia nos	2	(0.3)	4	(0.5)	ND
Hypercoagulation	1	(0.1)	0	(0.0)	ND
Cardiac Disorders	**58**	**(8.0)**	**56**	**(7.7)**	**0.33 (-2.5, 3.1)**
Acute myocardial infarction	5	(0.7)	4	(0.5)	ND
Angina pectoris	5	(0.7)	6	(0.8)	ND
Angina unstable	3	(0.4)	2	(0.3)	ND
Arrhythmia nos	1	(0.1)	0	(0.0)	ND
Atrial fibrillation	7	(1.0)	13	(1.8)	ND
Atrial flutter	1	(0.1)	0	(0.0)	ND
Atrioventricular block complete	2	(0.3)	0	(0.0)	ND
Atrioventricular block second degree	1	(0.1)	0	(0.0)	ND
Bradyarrhythmia	0	(0.0)	1	(0.1)	ND
Bradycardia nos	2	(0.3)	2	(0.3)	ND
Bundle branch block left	0	(0.0)	1	(0.1)	ND
Cardiac aneurysm	0	(0.0)	1	(0.1)	ND
Cardiac arrest	3	(0.4)	0	(0.0)	ND
Cardiac failure congestive	5	(0.7)	12	(1.6)	ND
Cardiac failure nos	0	(0.0)	1	(0.1)	ND
Cardiac fibrillation nos	1	(0.1)	0	(0.0)	ND
Cardio-respiratory arrest	1	(0.1)	1	(0.1)	ND
Cardiomyopathy nos	1	(0.1)	0	(0.0)	ND
Cardiovascular disorder nos	0	(0.0)	1	(0.1)	ND
Conduction disorder nos	0	(0.0)	1	(0.1)	ND
Coronary artery disease nos	19	(2.6)	14	(1.9)	0.70 (-0.9, 2.4)
Coronary artery occlusion	1	(0.1)	2	(0.3)	ND
Coronary artery stenosis	1	(0.1)	1	(0.1)	ND
Hypertensive heart disease	1	(0.1)	0	(0.0)	ND
Myocardial infarction	13	(1.8)	11	(1.5)	ND
Myocardial ischaemia	1	(0.1)	0	(0.0)	ND
Pericardial effusion	1	(0.1)	0	(0.0)	ND
Sick sinus syndrome	1	(0.1)	1	(0.1)	ND
Sinus bradycardia	0	(0.0)	1	(0.1)	ND
Supraventricular tachycardia	2	(0.3)	3	(0.4)	ND
Tachyarrhythmia	1	(0.1)	0	(0.0)	ND
Tachycardia nos	2	(0.3)	1	(0.1)	ND
Ventricular fibrillation	1	(0.1)	0	(0.0)	ND
Ventricular tachycardia	1	(0.1)	3	(0.4)	ND

Table 45 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Congenital, Familial and Genetic Disorders	**1**	**(0.1)**	**1**	**(0.1)**	**ND**
Congenital atrial septal defect	1	(0.1)	0	(0.0)	ND
Gastrointestinal angiodysplasia	0	(0.0)	1	(0.1)	ND
Ear and Labyrinth Disorders	**0**	**(0.0)**	**3**	**(0.4)**	**ND**
Vertigo	0	(0.0)	3	(0.4)	ND
Endocrine Disorders	**0**	**(0.0)**	**1**	**(0.1)**	**ND**
Goitre	0	(0.0)	1	(0.1)	ND
Eye Disorders	**1**	**(0.1)**	**1**	**(0.1)**	**ND**
Blindness	0	(0.0)	1	(0.1)	ND
Vitreous hemorrhage	1	(0.1)	0	(0.0)	ND
Gastrointestinal Disorders	**31**	**(4.3)**	**21**	**(2.9)**	**1.40 (-0.5, 3.4)**
Abdominal pain nos	2	(0.3)	0	(0.0)	ND
Abdominal pain upper	1	(0.1)	1	(0.1)	ND
Abdominal strangulated hernia	0	(0.0)	1	(0.1)	ND
Acute diverticulitis	0	(0.0)	1	(0.1)	ND
Appendicitis perforated	1	(0.1)	1	(0.1)	ND
Bowel sounds abnormal	0	(0.0)	1	(0.1)	ND
Colitis ischaemic	1	(0.1)	0	(0.0)	ND
Colonic polyp	1	(0.1)	0	(0.0)	ND
Constipation	1	(0.1)	2	(0.3)	ND
Diarrhea nos	3	(0.4)	0	(0.0)	ND
Diverticulitis nos	2	(0.3)	3	(0.4)	ND
Diverticulum intestinal	1	(0.1)	0	(0.0)	ND
Diverticulum intestinal hemorrhagic	2	(0.3)	0	(0.0)	ND
Diverticulum nos	1	(0.1)	1	(0.1)	ND
Duodenal ulcer hemorrhage	2	(0.3)	0	(0.0)	ND
Duodenal ulcer perforation	0	(0.0)	1	(0.1)	ND
Gastric perforation	1	(0.1)	0	(0.0)	ND
Gastric ulcer	1	(0.1)	0	(0.0)	ND
Gastric ulcer hemorrhage	2	(0.3)	0	(0.0)	ND
Gastritis Atrophic	0	(0.0)	1	(0.1)	ND
Gastrointestinal hemorrhage nos	2	(0.3)	1	(0.1)	ND
Gastrointestinal Necrosis	0	(0.0)	1	(0.1)	ND
Hemorrhoidal hemorrhage	2	(0.3)	0	(0.0)	ND
Hiatus hernia	0	(0.0)	1	(0.1)	ND
Ileus paralytic	1	(0.1)	0	(0.0)	ND
Inguinal hernia, obstructive	1	(0.1)	0	(0.0)	ND
Intestinal ischaemia	0	(0.0)	1	(0.1)	ND
Intestinal obstruction nos	1	(0.1)	0	(0.0)	ND
Intestinal perforation nos	0	(0.0)	1	(0.1)	ND
Lower gastrointestinal hemorrhage	3	(0.4)	2	(0.3)	ND
Mallory-Weiss syndrome	1	(0.1)	0	(0.0)	ND
Melena	1	(0.1)	1	(0.1)	ND
Nausea	1	(0.1)	1	(0.1)	ND

Table 45 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Pancreatitis nos	0	(0.0)	2	(0.3)	ND
Proctitis ulcerative	1	(0.1)	0	(0.0)	ND
Rectal hemorrhage	2	(0.3)	1	(0.1)	ND
Small intestinal obstruction nos	2	(0.3)	1	(0.1)	ND
Upper gastrointestinal hemorrhage	1	(0.1)	1	(0.1)	ND
Vomiting nos	3	(0.4)	1	(0.1)	ND
General Disorders and Administration Site Conditions	**12**	**(1.7)**	**14**	**(1.9)**	**ND**
Asthenia	1	(0.1)	2	(0.3)	ND
Chest discomfort	2	(0.3)	0	(0.0)	ND
Chest pain	8	(1.1)	10	(1.4)	ND
Gait abnormal	1	(0.1)	0	(0.0)	ND
Influenza like illness	0	(0.0)	1	(0.1)	ND
Multi-organ failure	0	(0.0)	1	(0.1)	ND
Sudden death	1	(0.1)	0	(0.0)	ND
Hepatobiliary Disorders	**2**	**(0.3)**	**4**	**(0.5)**	**ND**
Bile duct stone	0	(0.0)	1	(0.1)	ND
Cholangitis nos	1	(0.1)	0	(0.0)	ND
Cholecystitis acute nos	0	(0.0)	1	(0.1)	ND
Cholecystitis nos	1	(0.1)	0	(0.0)	ND
Cholelithiasis	1	(0.1)	3	(0.4)	ND
Immune System Disorders	**2**	**(0.3)**	**0**	**(0.0)**	**ND**
Allergy to arthropod sting	1	(0.1)	0	(0.0)	ND
Cryofibrinogenemia	1	(0.1)	0	(0.0)	ND
Infections and Infestations	**21**	**(2.9)**	**27**	**(3.7)**	**-0.80 (-2.7, 1.1)**
Abscess nos	1	(0.1)	0	(0.0)	ND
Appendicitis	1	(0.1)	0	(0.0)	ND
Arthritis infective nos	0	(0.0)	1	(0.1)	ND
Bacterial sepsis	0	(0.0)	1	(0.1)	ND
Brain abscess nos	1	(0.1)	0	(0.0)	ND
Bronchitis acute nos	0	(0.0)	1	(0.1)	ND
Cellulitis	3	(0.4)	4	(0.5)	ND
Coccidioidomycosis	0	(0.0)	1	(0.1)	ND
Empyema nos	1	(0.1)	0	(0.0)	ND
Gastroenteritis nos	2	(0.3)	1	(0.1)	ND
Infection nos	0	(0.0)	1	(0.1)	ND
Labyrinthitis nos	0	(0.0)	1	(0.1)	ND
Lobar pneumonia nos	0	(0.0)	2	(0.3)	ND
Localised infection	0	(0.0)	1	(0.1)	ND
Lung infection nos	1	(0.1)	0	(0.0)	ND
Pneumonia nos	10	(1.4)	10	(1.4)	ND
Pneumonia primary atypical	0	(0.0)	1	(0.1)	ND
Pyelonephritis nos	1	(0.1)	0	(0.0)	ND
Sepsis nos	1	(0.1)	0	(0.0)	ND
Urinary tract infection nos	0	(0.0)	2	(0.3)	ND
Viral infection nos	0	(0.0)	1	(0.1)	ND
Wound infection	1	(0.1)	0	(0.0)	ND

Table 45 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n	(%)	n	(%)	(A-B)% 95% CI
Injury, Poisoning and Procedural Complications	**23**	**(3.2)**	**25**	**(3.4)**	**-0.25 (-2.2, 1.6)**
Ankle fracture	1	(0.1)	1	(0.1)	ND
Back injury nos	0	(0.0)	1	(0.1)	ND
Brain contusion	0	(0.0)	1	(0.1)	ND
Cerebrospinal fluid leakage	0	(0.0)	1	(0.1)	ND
Clavicle fracture	0	(0.0)	1	(0.1)	ND
Closed head injury	0	(0.0)	1	(0.1)	ND
Compression fracture	0	(0.0)	1	(0.1)	ND
Electric shock	1	(0.1)	0	(0.0)	ND
Excoriation	0	(0.0)	1	(0.1)	ND
Facial bones fracture	0	(0.0)	1	(0.1)	ND
Fall	0	(0.0)	1	(0.1)	ND
Femoral neck fracture	0	(0.0)	1	(0.1)	ND
Femur fracture	0	(0.0)	1	(0.1)	ND
Fractured pelvis nos	1	(0.1)	0	(0.0)	ND
Head injury	1	(0.1)	0	(0.0)	ND
Hip fracture	9	(1.2)	5	(0.7)	ND
Humerus fracture	1	(0.1)	1	(0.1)	ND
Injury	1	(0.1)	0	(0.0)	ND
Intervertebral disc injury	0	(0.0)	1	(0.1)	ND
Multiple fractures	0	(0.0)	1	(0.1)	ND
Muscle injury nos	1	(0.1)	0	(0.0)	ND
Polytraumatism	1	(0.1)	0	(0.0)	ND
Post procedural complication	1	(0.1)	0	(0.0)	ND
Post procedural hemorrhage	1	(0.1)	0	(0.0)	ND
Pubic rami fracture	0	(0.0)	1	(0.1)	ND
Rib Fracture	2	(0.3)	2	(0.3)	ND
Scapula fracture	1	(0.1)	0	(0.0)	ND
Skull fracture nos	0	(0.0)	1	(0.1)	ND
Spinal compression fracture	1	(0.1)	0	(0.0)	ND
Sternal fracture	0	(0.0)	1	(0.1)	ND
Subdural hematoma	0	(0.0)	1	(0.1)	ND
Tendon rupture	0	(0.0)	1	(0.1)	ND
Therapeutic agent poisoning	1	(0.1)	0	(0.0)	ND
Traumatic amputation nos	0	(0.0)	1	(0.1)	ND
Traumatic chest injury nos	1	(0.1)	0	(0.0)	ND
Upper limb fracture nos	2	(0.3)	0	(0.0)	ND
Wound dehiscence	0	(0.0)	1	(0.1)	ND
Wrist fracture	2	(0.3)	1	(0.1)	ND
Investigations	**1**	**(0.1)**	**2**	**(0.3)**	**ND**
Blood in stool	0	(0.0)	1	(0.1)	ND
Blood pressure increased	0	(0.0)	1	(0.1)	ND
Heart rate irregular	1	(0.1)	0	(0.0)	ND
Metabolism and Nutrition Disorders	**1**	**(0.1)**	**2**	**(0.3)**	**ND**
Dehydration	1	(0.1)	1	(0.1)	ND
Failure to thrive	0	(0.0)	1	(0.1)	ND

Table 45 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Musculoskeletal and Connective Tissue Disorders	**14**	**(1.9)**	**9**	**(1.2)**	**ND**
Arthralgia	3	(0.4)	3	(0.4)	ND
Back Pain	1	(0.1)	1	(0.1)	ND
Fracture malunion	1	(0.1)	0	(0.0)	ND
Hemarthrosis	0	(0.0)	1	(0.1)	ND
Intervertebral disc displacement	0	(0.0)	1	(0.1)	ND
Intervertebral disc herniation	2	(0.3)	0	(0.0)	ND
Localised osteoarthritis	2	(0.3)	2	(0.3)	ND
Monoarthritis	1	(0.1)	1	(0.1)	ND
Osteoarthritis nos	1	(0.1)	0	(0.0)	ND
Pain In extremity	1	(0.1)	0	(0.0)	ND
Pain in jaw	1	(0.1)	0	(0.0)	ND
Rotator cuff syndrome	2	(0.3)	0	(0.0)	ND
Synovial cyst	1	(0.1)	0	(0.0)	ND
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**59**	**(8.2)**	**91**	**(12.5)**	**-4.34 (-7.5, -1.2)**
Acute myeloid leukemia nos	1	(0.1)	1	(0.1)	ND
Adenocarcinoma nos	0	(0.0)	1	(0.1)	ND
Adenoma benign nos	0	(0.0)	1	(0.1)	ND
Basal cell carcinoma	17	(2.4)	37	(5.1)	-2.73 (-4.8, -0.8)
Bladder cancer nos	2	(0.3)	3	(0.4)	ND
Bladder cancer stage IV	0	(0.0)	1	(0.1)	ND
Bone cancer metastatic	1	(0.1)	0	(0.0)	ND
Bone neoplasm malignant	1	(0.1)	0	(0.0)	ND
Bowen's disease	1	(0.1)	2	(0.3)	ND
Breast cancer nos	3	(0.4)	2	(0.3)	ND
Chronic lymphocytic leukemia nos	1	(0.1)	0	(0.0)	ND
Colon cancer metastatic	0	(0.0)	1	(0.1)	ND
Colon cancer nos	0	(0.0)	2	(0.3)	ND
Intraocular melanoma nos	0	(0.0)	1	(0.1)	ND
Lung adenocarcinoma nos	1	(0.1)	1	(0.1)	ND
Lung neoplasm malignant	1	(0.1)	5	(0.7)	ND
Lymph node cancer metastatic	0	(0.0)	1	(0.1)	ND
Lymphoma nos	0	(0.0)	1	(0.1)	ND
Malignant melanoma	2	(0.3)	2	(0.3)	ND
Malignant neoplasm nos	1	(0.1)	0	(0.0)	ND
Meningioma	0	(0.0)	1	(0.1)	ND
Metastases to liver	0	(0.0)	1	(0.1)	ND
Metastatic neoplasm nos, primary site unknown	0	(0.0)	1	(0.1)	ND
Multiple myeloma	1	(0.1)	1	(0.1)	ND
Esophageal carcinoma nos	0	(0.0)	2	(0.3)	ND

Table 45 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Pancreatic carcinoma nos	1	(0.1)	1	(0.1)	ND
Pancreatic neoplasm nos	1	(0.1)	0	(0.0)	ND
Parathyroid tumour benign	1	(0.1)	0	(0.0)	ND
Pituitary tumour nos	0	(0.0)	1	(0.1)	ND
Prostate cancer metastatic	1	(0.1)	0	(0.0)	ND
Prostate cancer nos	14	(1.9)	16	(2.2)	-0.26 (-1.8, 1.3)
Prostate cancer recurrent	1	(0.1)	2	(0.3)	ND
Renal cell carcinoma stage unspecified	0	(0.0)	1	(0.1)	ND
Squamous cell carcinoma of skin	11	(1.5)	17	(2.3)	-0.81 (-2.4, 0.6)
Throat cancer nos	0	(0.0)	1	(0.1)	ND
Thyroid gland cancer	1	(0.1)	0	(0.0)	ND
Ureteric cancer nos	1	(0.1)	0	(0.0)	ND
Nervous System Disorders	**42**	**(5.8)**	**49**	**(6.7)**	**-0.92 (-3.5, 1.6)**
Abasia	0	(0.0)	1	(0.1)	ND
Amyotrophic lateral sclerosis	1	(0.1)	0	(0.0)	ND
Aphasia	0	(0.0)	1	(0.1)	ND
Ataxia	1	(0.1)	0	(0.0)	ND
Carotid artery occlusion	0	(0.0)	2	(0.3)	ND
Carotid artery stenosis	1	(0.1)	7	(1.0)	ND
Carotid sinus syndrome	0	(0.0)	1	(0.1)	ND
Cerebral disorder	0	(0.0)	1	(0.1)	ND
Cerebral hemorrhage	0	(0.0)	1	(0.1)	ND
Cerebrovascular accident	8	(1.1)	12	(1.6)	ND
Cervical spinal stenosis	1	(0.1)	0	(0.0)	ND
Convulsions nos	1	(0.1)	1	(0.1)	ND
Dizziness	3	(0.4)	2	(0.3)	ND
Grand mal convulsion	1	(0.1)	0	(0.0)	ND
Hypoesthesia	1	(0.1)	1	(0.1)	ND
Iiird nerve disorder	0	(0.0)	1	(0.1)	ND
Intracranial hemorrhage nos	1	(0.1)	1	(0.1)	ND
Loss of consciousness	1	(0.1)	1	(0.1)	ND
Metabolic encephalopathy Nos	0	(0.0)	1	(0.1)	ND
Neuralgia Nos	0	(0.0)	1	(0.1)	ND
Normal pressure hydrocephalus	1	(0.1)	0	(0.0)	ND
Paresis	1	(0.1)	0	(0.0)	ND
Pneumocephalus	0	(0.0)	1	(0.1)	ND
Radiculopathy nos	1	(0.1)	0	(0.0)	ND
Reversible ischaemic neurological deficit	0	(0.0)	1	(0.1)	ND
Spinal stenosis nos	4	(0.6)	0	(0.0)	ND
Subarachnoid hemorrhage nos	0	(0.0)	1	(0.1)	ND
Syncope	8	(1.1)	7	(1.0)	ND
Transient ischaemic attack	10	(1.4)	9	(1.2)	ND
Tremor	1	(0.1)	0	(0.0)	ND
Vertebrobasilar insufficiency	0	(0.0)	1	(0.1)	ND
Vocal cord paralysis	0	(0.0)	1	(0.1)	ND

Table 45 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Psychiatric Disorders	**6**	**(0.8)**	**5**	**(0.7)**	**ND**
Aggression	1	(0.1)	0	(0.0)	ND
Agitation	1	(0.1)	0	(0.0)	ND
Confusional state	2	(0.3)	1	(0.1)	ND
Delirium	0	(0.0)	1	(0.1)	ND
Depression	1	(0.1)	0	(0.0)	ND
Disorientation	1	(0.1)	0	(0.0)	ND
Mental status changes	0	(0.0)	2	(0.3)	ND
Psychotic disorder nos	0	(0.0)	1	(0.1)	ND
Suicide attempt	1	(0.1)	0	(0.0)	ND
Renal and Urinary Disorders	**11**	**(1.5)**	**9**	**(1.2)**	**ND**
Bladder neck obstruction	1	(0.1)	0	(0.0)	ND
Calculus bladder	2	(0.3)	0	(0.0)	ND
Calculus urinary	0	(0.0)	1	(0.1)	ND
Hematuria	3	(0.4)	1	(0.1)	ND
Nephrolithiasis	1	(0.1)	0	(0.0)	ND
Renal failure acute on chronic	0	(0.0)	1	(0.1)	ND
Renal failure nos	2	(0.3)	2	(0.3)	ND
Renal impairment nos	2	(0.3)	1	(0.1)	ND
Urate nephropathy	0	(0.0)	1	(0.1)	ND
Urinary incontinence	1	(0.1)	1	(0.1)	ND
Urinary retention	1	(0.1)	2	(0.3)	ND
Reproductive System and Breast Disorders	**4**	**(0.6)**	**10**	**(1.4)**	**ND**
Benign prostatic hyperplasia	3	(0.4)	6	(0.8)	ND
Epididymitis nos	0	(0.0)	1	(0.1)	ND
Perineal pain nos	1	(0.1)	0	(0.0)	ND
Prostatic hypertrophy	0	(0.0)	2	(0.3)	ND
Prostatitis	0	(0.0)	1	(0.1)	ND
Respiratory, Thoracic and Mediastinal Disorders	**15**	**(2.1)**	**11**	**(1.5)**	**0.56 (-0.9, 2.1)**
Acute respiratory failure	0	(0.0)	1	(0.1)	ND
Aspiration	0	(0.0)	1	(0.1)	ND
Asthma nos	0	(0.0)	1	(0.1)	ND
Atelectasis	0	(0.0)	1	(0.1)	ND
Bronchitis nos	2	(0.3)	2	(0.3)	ND
Bronchopleural fistula	1	(0.1)	0	(0.0)	ND
Bronchospasm nos	1	(0.1)	0	(0.0)	ND
Chronic obstructive airways disease	5	(0.7)	1	(0.1)	ND
Dyspnea	1	(0.1)	0	(0.0)	ND
Emphysema	1	(0.1)	0	(0.0)	ND
Hemopneumothorax	1	(0.1)	0	(0.0)	ND
Hypoxia	0	(0.0)	1	(0.1)	ND

Table 45 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
On Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Pharyngeal edema	0	(0.0)	1	(0.1)	ND
Pleural effusion	1	(0.1)	1	(0.1)	ND
Pneumonia aspiration	0	(0.0)	1	(0.1)	ND
Pneumothorax nos	0	(0.0)	1	(0.1)	ND
Pulmonary embolism	2	(0.3)	1	(0.1)	ND
Pulmonary fibrosis	1	(0.1)	0	(0.0)	ND
Pulmonary edema nos	1	(0.1)	0	(0.0)	ND
Respiratory distress	0	(0.0)	1	(0.1)	ND
Respiratory failure	0	(0.0)	2	(0.3)	ND
Skin and Subcutaneous Tissue Disorders	**1**	**(0.1)**	**0**	**(0.0)**	**ND**
Skin ulcer	1	(0.1)	0	(0.0)	ND
Vascular Disorders	**5**	**(0.7)**	**9**	**(1.2)**	**ND**
Aneurysm	0	(0.0)	1	(0.1)	ND
Aortic aneurysm	1	(0.1)	0	(0.0)	ND
Aortic stenosis	0	(0.0)	1	(0.1)	ND
Atherosclerosis	1	(0.1)	0	(0.0)	ND
Deep vein thrombosis	0	(0.0)	2	(0.3)	ND
Femoral artery aneurysm	1	(0.1)	0	(0.0)	ND
Hemorrhage nos	0	(0.0)	1	(0.1)	ND
Hypertension nos	1	(0.1)	3	(0.4)	ND
Hypovolemic shock	0	(0.0)	1	(0.1)	ND
Phlebitis nos	0	(0.0)	1	(0.1)	ND
Thrombosis	1	(0.1)	0	(0.0)	ND

† On drug includes the period through 14 days after discontinuation of study drug.
CI = Confidence interval.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of patients in each treatment group.
n = Number of patients in each category.

Data Source: [4.2]

8.2.2.3.2 Intention-to-Treat Population

The distribution of patients with serious clinical adverse experiences in the ITT population are shown in Table 46.

There were no clinically significant differences between the ITT and on-drug analyses. The 95% CIs for the differences in percentage of patients experiencing serious adverse experiences in the ITT population cover zero for all body systems, except neoplasms benign, malignant, and unspecified. The differences in percentage points between treatment groups was 3.77 percentage points (95% CI [-7.3, -0.3]). The differences for all other body systems were ± 1.86 percentage points.

Descriptions of two serious adverse experiences that were not counted in Table 46 can be found in the WAES narratives [4.6]. Both adverse experiences occurred after the baseline visit, but prior to the randomization visit: patient AN 0146 had asthma, and patient AN 0648 was diagnosed with basal cell carcinoma. Both patients were subsequently randomized in blinded fashion to the rofecoxib treatment group.

Table 46

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n	(%)	n	(%)	(A-B)% 95% CI
Patient with at least one Adverse Experience	268	(37.1)	270	(37.1)	-0.02 (-5.0, 5.0)
Patient with no Adverse Experience	455	(62.9)	458	(62.9)	0.02 (-5.0, 5.0)
Blood and Lymphatic System Disorders	**8**	**(1.1)**	**5**	**(0.7)**	**ND**
Anemia nos	7	(1.0)	5	(0.7)	ND
Hypercoagulation	1	(0.1)	0	(0.0)	ND
Refractory anemia	1	(0.1)	0	(0.0)	ND
Cardiac Disorders	**75**	**(10.4)**	**62**	**(8.5)**	**1.86 (-1.2, 4.9)**
Acute myocardial infarction	8	(1.1)	5	(0.7)	ND
Angina pectoris	5	(0.7)	7	(1.0)	ND
Angina unstable	5	(0.7)	3	(0.4)	ND
Aortic valve incompetence	0	(0.0)	1	(0.1)	ND
Arrhythmia nos	2	(0.3)	0	(0.0)	ND
Atrial fibrillation	9	(1.2)	15	(2.1)	-0.82 (-2.3, 0.5)
Atrial flutter	1	(0.1)	0	(0.0)	ND
Atrioventricular block complete	2	(0.3)	0	(0.0)	ND
Atrioventricular block nos	0	(0.0)	1	(0.1)	ND
Atrioventricular block second degree	1	(0.1)	0	(0.0)	ND
Bradyarrhythmia	0	(0.0)	2	(0.3)	ND
Bradycardia nos	2	(0.3)	2	(0.3)	ND
Bundle branch block left	0	(0.0)	1	(0.1)	ND

Table 46 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Cardiac aneurysm	0	(0.0)	1	(0.1)	ND
Cardiac arrest	5	(0.7)	0	(0.0)	ND
Cardiac failure congestive	9	(1.2)	14	(1.9)	ND
Cardiac failure nos	0	(0.0)	1	(0.1)	ND
Cardiac fibrillation nos	1	(0.1)	0	(0.0)	ND
Cardio-respiratory arrest	1	(0.1)	1	(0.1)	ND
Cardiomyopathy nos	2	(0.3)	0	(0.0)	ND
Cardiovascular disorder nos	0	(0.0)	1	(0.1)	ND
Conduction disorder nos	0	(0.0)	1	(0.1)	ND
Coronary artery disease nos	25	(3.5)	16	(2.2)	1.26 (-0.5, 3.1)
Coronary artery occlusion	1	(0.1)	3	(0.4)	ND
Coronary artery stenosis	1	(0.1)	1	(0.1)	ND
Hypertensive heart disease	1	(0.1)	0	(0.0)	ND
Mitral valve incompetence	0	(0.0)	1	(0.1)	ND
Mitral valve prolapse	1	(0.1)	0	(0.0)	ND
Myocardial infarction	19	(2.6)	11	(1.5)	1.12 (-0.4, 2.7)
Myocardial ischaemia	3	(0.4)	0	(0.0)	ND
Pericardial effusion	1	(0.1)	0	(0.0)	ND
Sick sinus syndrome	1	(0.1)	2	(0.3)	ND
Sinus bradycardia	1	(0.1)	1	(0.1)	ND
Supraventricular tachycardia	2	(0.3)	3	(0.4)	ND
Tachyarrhythmia	1	(0.1)	0	(0.0)	ND
Tachycardia nos	3	(0.4)	1	(0.1)	ND
Tricuspid valve incompetence	0	(0.0)	1	(0.1)	ND
Ventricular fibrillation	2	(0.3)	0	(0.0)	ND
Ventricular tachycardia	2	(0.3)	3	(0.4)	ND
Congenital, Familial and Genetic Disorders	**1**	**(0.1)**	**2**	**(0.3)**	**ND**
Congenital atrial septal defect	1	(0.1)	0	(0.0)	ND
Congenital skull malformation nos	0	(0.0)	1	(0.1)	ND
Gastrointestinal angiodysplasia	0	(0.0)	1	(0.1)	ND
Ear and Labyrinth Disorders	**0**	**(0.0)**	**3**	**(0.4)**	**ND**
Vertigo	0	(0.0)	3	(0.4)	ND
Endocrine Disorders	**0**	**(0.0)**	**1**	**(0.1)**	**ND**
Goitre	0	(0.0)	1	(0.1)	ND
Eye Disorders	**1**	**(0.1)**	**1**	**(0.1)**	**ND**
Blindness	0	(0.0)	1	(0.1)	ND
Vitreous hemorrhage	1	(0.1)	0	(0.0)	ND

Table 46 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Gastrointestinal Disorders	**38**	**(5.3)**	**26**	**(3.6)**	**1.68 (-0.4, 3.9)**
Abdominal pain lower	1	(0.1)	0	(0.0)	ND
Abdominal pain nos	2	(0.3)	0	(0.0)	ND
Abdominal pain upper	1	(0.1)	1	(0.1)	ND
Abdominal strangulated hernia	0	(0.0)	1	(0.1)	ND
Acute diverticulitis	0	(0.0)	1	(0.1)	ND
Appendicitis perforated	1	(0.1)	1	(0.1)	ND
Bowel sounds abnormal	0	(0.0)	1	(0.1)	ND
Colitis ischaemic	1	(0.1)	0	(0.0)	ND
Colonic Polyp	1	(0.1)	0	(0.0)	ND
Constipation	1	(0.1)	3	(0.4)	ND
Diarrhea nos	3	(0.4)	0	(0.0)	ND
Diverticulitis nos	2	(0.3)	3	(0.4)	ND
Diverticulum intestinal	1	(0.1)	0	(0.0)	ND
Diverticulum intestinal hemorrhagic	2	(0.3)	0	(0.0)	ND
Diverticulum nos	1	(0.1)	1	(0.1)	ND
Duodenal ulcer	0	(0.0)	2	(0.3)	ND
Duodenal ulcer hemorrhage	2	(0.3)	0	(0.0)	ND
Duodenal ulcer perforation	0	(0.0)	1	(0.1)	ND
Dysphagia	0	(0.0)	1	(0.1)	ND
Gastric perforation	1	(0.1)	0	(0.0)	ND
Gastric ulcer	1	(0.1)	0	(0.0)	ND
Gastric ulcer hemorrhage	2	(0.3)	0	(0.0)	ND
Gastritis atrophic	0	(0.0)	1	(0.1)	ND
Gastritis nos	1	(0.1)	0	(0.0)	ND
Gastrointestinal hemorrhage nos	5	(0.7)	3	(0.4)	ND
Gastrointestinal necrosis	0	(0.0)	1	(0.1)	ND
Gastroesophageal reflux disease	1	(0.1)	0	(0.0)	ND
Hematochezia	1	(0.1)	0	(0.0)	ND
Hemorrhoidal hemorrhage	2	(0.3)	0	(0.0)	ND
Hiatus hernia	0	(0.0)	1	(0.1)	ND
Ileus paralytic	1	(0.1)	0	(0.0)	ND
Inguinal hernia, obstructive	1	(0.1)	0	(0.0)	ND
Intestinal ischaemia	0	(0.0)	1	(0.1)	ND
Intestinal obstruction nos	2	(0.3)	0	(0.0)	ND
Intestinal perforation nos	0	(0.0)	1	(0.1)	ND
Lower gastrointestinal hemorrhage	3	(0.4)	2	(0.3)	ND
Mallory-Weiss syndrome	1	(0.1)	1	(0.1)	ND
Melena	1	(0.1)	1	(0.1)	ND
Nausea	1	(0.1)	1	(0.1)	ND
Esophagitis ulcerative	1	(0.1)	0	(0.0)	ND
Pancreatitis nos	0	(0.0)	2	(0.3)	ND
Proctitis ulcerative	1	(0.1)	0	(0.0)	ND
Rectal hemorrhage	3	(0.4)	2	(0.3)	ND
Rectocele	1	(0.1)	0	(0.0)	ND
Retroperitoneal hemorrhage	1	(0.1)	0	(0.0)	ND
Small Intestinal obstruction nos	3	(0.4)	1	(0.1)	ND
Upper Gastrointestinal hemorrhage	1	(0.1)	1	(0.1)	ND
vomiting nos	3	(0.4)	1	(0.1)	ND

Table 46 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
General Disorders and Administration Site Conditions	**16**	**(2.2)**	**18**	**(2.5)**	**-0.26 (-1.9, 1.4)**
Asthenia	1	(0.1)	3	(0.4)	ND
Chest discomfort	2	(0.3)	0	(0.0)	ND
Chest pain	12	(1.7)	12	(1.6)	ND
Gait abnormal	1	(0.1)	0	(0.0)	ND
Influenza like illness	0	(0.0)	1	(0.1)	ND
Multi-organ failure	0	(0.0)	1	(0.1)	ND
Edema peripheral	0	(0.0)	1	(0.1)	ND
Pyrexia	1	(0.1)	1	(0.1)	ND
Sudden death	1	(0.1)	0	(0.0)	ND
Hepatobiliary Disorders	**4**	**(0.6)**	**5**	**(0.7)**	**ND**
Bile duct stone	0	(0.0)	1	(0.1)	ND
Cholangitis nos	1	(0.1)	0	(0.0)	ND
Cholecystitis acute nos	0	(0.0)	1	(0.1)	ND
Cholecystitis nos	3	(0.4)	0	(0.0)	ND
Cholelithiasis	4	(0.6)	4	(0.5)	ND
Immune System Disorders	**3**	**(0.4)**	**0**	**(0.0)**	**ND**
Allergy to arthropod sting	1	(0.1)	0	(0.0)	ND
Cryofibrinogenemia	1	(0.1)	0	(0.0)	ND
Hypersensitivity nos	1	(0.1)	0	(0.0)	ND
Infections and Infestations	**32**	**(4.4)**	**30**	**(4.1)**	**0.31 (-1.8, 2.5)**
Abscess nos	1	(0.1)	0	(0.0)	ND
Appendicitis	1	(0.1)	0	(0.0)	ND
Arthritis infective nos	0	(0.0)	1	(0.1)	ND
Bacteriemia	1	(0.1)	0	(0.0)	ND
Bacterial sepsis	1	(0.1)	1	(0.1)	ND
Brain abscess nos	1	(0.1)	0	(0.0)	ND
Bronchitis acute nos	0	(0.0)	1	(0.1)	ND
Cellulitis	3	(0.4)	4	(0.5)	ND
Cellulitis gangrenous	1	(0.1)	0	(0.0)	ND
Coccidioidomycosis	0	(0.0)	1	(0.1)	ND
Empyema nos	1	(0.1)	0	(0.0)	ND
Gastroenteritis nos	3	(0.4)	1	(0.1)	ND
Infection nos	0	(0.0)	1	(0.1)	ND
Labyrinthitis nos	0	(0.0)	1	(0.1)	ND
Lobar pneumonia nos	0	(0.0)	2	(0.3)	ND
Localised infection	0	(0.0)	1	(0.1)	ND
Lung Infection nos	1	(0.1)	0	(0.0)	ND
Pneumonia nos	17	(2.4)	12	(1.6)	0.70 (-0.8, 2.3)
Pneumonia primary atypical	0	(0.0)	1	(0.1)	ND
Pyelonephritis nos	1	(0.1)	0	(0.0)	ND
Sepsis nos	1	(0.1)	0	(0.0)	ND
Staphylococcal infection	0	(0.0)	1	(0.1)	ND
Urinary tract infection nos	0	(0.0)	2	(0.3)	ND

Table 46 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Urosepsis	1	(0.1)	0	(0.0)	ND
Viral infection nos	1	(0.1)	1	(0.1)	ND
Wound infection	1	(0.1)	1	(0.1)	ND
Injury, Poisoning and Procedural Complications	**31**	**(4.3)**	**32**	**(4.4)**	**-0.11 (-2.3, 2.0)**
Accidental overdose	1	(0.1)	0	(0.0)	ND
Ankle fracture	2	(0.3)	1	(0.1)	ND
Back injury nos	0	(0.0)	1	(0.1)	ND
Brain contusion	0	(0.0)	1	(0.1)	ND
Cerebrospinal fluid leakage	0	(0.0)	1	(0.1)	ND
Clavicle fracture	0	(0.0)	1	(0.1)	ND
Closed head injury	0	(0.0)	1	(0.1)	ND
Compression fracture	0	(0.0)	1	(0.1)	ND
Concussion	1	(0.1)	0	(0.0)	ND
Electric Shock	1	(0.1)	0	(0.0)	ND
Excoriation	0	(0.0)	1	(0.1)	ND
Facial bones fracture	0	(0.0)	1	(0.1)	ND
Fall	1	(0.1)	1	(0.1)	ND
Femoral neck fracture	0	(0.0)	1	(0.1)	ND
Femur fracture	1	(0.1)	1	(0.1)	ND
Fractured pelvis nos	1	(0.1)	1	(0.1)	ND
Head injury	1	(0.1)	2	(0.3)	ND
Hip fracture	11	(1.5)	6	(0.8)	ND
Humerus fracture	1	(0.1)	1	(0.1)	ND
Injury	1	(0.1)	0	(0.0)	ND
Intervertebral disc injury	0	(0.0)	1	(0.1)	ND
Medical device complication	1	(0.1)	0	(0.0)	ND
Multiple fractures	0	(0.0)	1	(0.1)	ND
Muscle injury nos	1	(0.1)	0	(0.0)	ND
Polytraumatism	1	(0.1)	0	(0.0)	ND
Post procedural complication	1	(0.1)	0	(0.0)	ND
Post procedural hemorrhage	1	(0.1)	0	(0.0)	ND
Postoperative ileus	1	(0.1)	0	(0.0)	ND
Pubic rami fracture	0	(0.0)	1	(0.1)	ND
Radiation pneumonitis	0	(0.0)	1	(0.1)	ND
Rib fracture	2	(0.3)	2	(0.3)	ND
Scapula fracture	1	(0.1)	0	(0.0)	ND
Skull fracture nos	0	(0.0)	1	(0.1)	ND
Spinal compression fracture	1	(0.1)	1	(0.1)	ND
Sternal fracture	0	(0.0)	1	(0.1)	ND
Subdural hematoma	0	(0.0)	1	(0.1)	ND
Tendon injury	1	(0.1)	0	(0.0)	ND
Tendon rupture	0	(0.0)	1	(0.1)	ND
Therapeutic agent poisoning	1	(0.1)	1	(0.1)	ND
Traumatic amputation nos	0	(0.0)	1	(0.1)	ND
Traumatic chest injury nos	1	(0.1)	0	(0.0)	ND
Upper limb fracture nos	2	(0.3)	0	(0.0)	ND
Wound dehiscence	0	(0.0)	1	(0.1)	ND
Wrist fracture	2	(0.3)	1	(0.1)	ND

Table 46 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Investigations	**2**	**(0.3)**	**2**	**(0.3)**	**ND**
Blood in stool	0	(0.0)	1	(0.1)	ND
Blood pressure increased	0	(0.0)	1	(0.1)	ND
Coagulation time nos prolonged	1	(0.1)	0	(0.0)	ND
Heart rate irregular	1	(0.1)	0	(0.0)	ND
Metabolism and Nutrition Disorders	**5**	**(0.7)**	**3**	**(0.4)**	**ND**
Dehydration	3	(0.4)	1	(0.1)	ND
Diabetic ketoacidosis	1	(0.1)	0	(0.0)	ND
Failure to thrive	0	(0.0)	2	(0.3)	ND
Fluid retention	1	(0.1)	0	(0.0)	ND
Musculoskeletal and Connective Tissue Disorders	**18**	**(2.5)**	**16**	**(2.2)**	**0.29 (-1.3, 1.9)**
Arthralgia	3	(0.4)	5	(0.7)	ND
Back pain	1	(0.1)	2	(0.3)	ND
Fracture Malunion	1	(0.1)	0	(0.0)	ND
Hemarthrosis	0	(0.0)	1	(0.1)	ND
Intervertebral disc disorder nos	0	(0.0)	1	(0.1)	ND
Intervertebral disc displacement	0	(0.0)	1	(0.1)	ND
Intervertebral disc herniation	2	(0.3)	0	(0.0)	ND
Limb discomfort nos	1	(0.1)	0	(0.0)	ND
Localised osteoarthritis	3	(0.4)	3	(0.4)	ND
Monoarthritis	2	(0.3)	1	(0.1)	ND
Osteoarthritis nos	2	(0.3)	1	(0.1)	ND
Pain in extremity	1	(0.1)	0	(0.0)	ND
Pain in jaw	1	(0.1)	0	(0.0)	ND
Rotator cuff syndrome	2	(0.3)	0	(0.0)	ND
Synovial cyst	1	(0.1)	0	(0.0)	ND
Toe deformities nos	0	(0.0)	1	(0.1)	ND
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**80**	**(11.1)**	**108**	**(14.8)**	**-3.77 (-7.3, -0.3)**
Acute lymphocytic leukemia	1	(0.1)	0	(0.0)	ND
Acute myeloid leukemia nos	1	(0.1)	1	(0.1)	ND
Adenocarcinoma nos	0	(0.0)	1	(0.1)	ND
Adenoma benign nos	0	(0.0)	1	(0.1)	ND
B-Cell lymphoma nos	0	(0.0)	1	(0.1)	ND
Basal cell carcinoma	20	(2.8)	43	(5.9)	-3.14 (-5.4, -1.1)
Bladder cancer nos	3	(0.4)	3	(0.4)	ND
Bladder cancer recurrent	0	(0.0)	1	(0.1)	ND
Bladder cancer stage IV	0	(0.0)	1	(0.1)	ND
Bone cancer metastatic	1	(0.1)	0	(0.0)	ND
Bone neoplasm malignant	1	(0.1)	0	(0.0)	ND
Bowen's Disease	1	(0.1)	2	(0.3)	ND
Breast cancer nos	4	(0.6)	4	(0.5)	ND

Table 46 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Chronic lymphocytic leukemia nos	1	(0.1)	0	(0.0)	ND
Colon cancer metastatic	0	(0.0)	1	(0.1)	ND
Colon cancer nos	3	(0.4)	3	(0.4)	ND
Gastrointestinal tract cancer nos	0	(0.0)	1	(0.1)	ND
Hepatic neoplasm malignant nos	0	(0.0)	1	(0.1)	ND
Intraocular melanoma nos	0	(0.0)	1	(0.1)	ND
Lung adenocarcinoma nos	1	(0.1)	1	(0.1)	ND
Lung neoplasm malignant	2	(0.3)	5	(0.7)	ND
Lymph node cancer metastatic	0	(0.0)	1	(0.1)	ND
Lymphoma nos	0	(0.0)	1	(0.1)	ND
Malignant melanoma	2	(0.3)	2	(0.3)	ND
Malignant neoplasm nos	1	(0.1)	0	(0.0)	ND
Meningioma	1	(0.1)	1	(0.1)	ND
Metastases to liver	1	(0.1)	1	(0.1)	ND
Metastases to lymph nodes	0	(0.0)	1	(0.1)	ND
Metastatic neoplasm nos, primary site unknown	1	(0.1)	1	(0.1)	ND
Multiple myeloma	1	(0.1)	2	(0.3)	ND
Myelodysplastic syndrome nos	2	(0.3)	0	(0.0)	ND
Non-Hodgkin's lymphoma nos	0	(0.0)	1	(0.1)	ND
Non-small cell lung cancer nos	0	(0.0)	1	(0.1)	ND
Esophageal carcinoma nos	0	(0.0)	2	(0.3)	ND
Ovarian cancer metastatic	1	(0.1)	0	(0.0)	ND
Pancreatic carcinoma nos	1	(0.1)	2	(0.3)	ND
Pancreatic neoplasm nos	1	(0.1)	0	(0.0)	ND
Parathyroid tumour benign	1	(0.1)	0	(0.0)	ND
Pituitary tumour nos	0	(0.0)	1	(0.1)	ND
Prostate cancer metastatic	1	(0.1)	0	(0.0)	ND
Prostate cancer nos	17	(2.4)	18	(2.5)	-0.12 (-1.8, 1.5)
Prostate cancer recurrent	1	(0.1)	2	(0.3)	ND
Renal cell carcinoma stage Unspecified	0	(0.0)	2	(0.3)	ND
Squamous cell carcinoma of skin	16	(2.2)	19	(2.6)	-0.40 (-2.1, 1.2)
Throat cancer nos	0	(0.0)	1	(0.1)	ND
Thyroid gland cancer	1	(0.1)	0	(0.0)	ND
Ureteric cancer nos	1	(0.1)	0	(0.0)	ND
Nervous System Disorders	**56**	**(7.7)**	**55**	**(7.6)**	**0.19 (-2.6, 3.0)**
Abasia	0	(0.0)	1	(0.1)	ND
Amyotrophic lateral sclerosis	1	(0.1)	0	(0.0)	ND
Aphasia	0	(0.0)	1	(0.1)	ND
Ataxia	1	(0.1)	0	(0.0)	ND
Brain stem infarction	1	(0.1)	0	(0.0)	ND

Table 46 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Carotid artery occlusion	1	(0.1)	3	(0.4)	ND
Carotid artery stenosis	1	(0.1)	7	(1.0)	ND
Carotid sinus syndrome	0	(0.0)	1	(0.1)	ND
Cerebral disorder	0	(0.0)	1	(0.1)	ND
Cerebral hemorrhage	1	(0.1)	1	(0.1)	ND
Cerebrovascular accident	11	(1.5)	13	(1.8)	ND
Cervical spinal stenosis	1	(0.1)	0	(0.0)	ND
Cognitive disorder	0	(0.0)	1	(0.1)	ND
Coma	1	(0.1)	0	(0.0)	ND
Convulsions nos	1	(0.1)	1	(0.1)	ND
Dementia nos	1	(0.1)	0	(0.0)	ND
Depressed level of consciousness	1	(0.1)	0	(0.0)	ND
Dizziness	4	(0.6)	3	(0.4)	ND
Grand mal convulsion	1	(0.1)	0	(0.0)	ND
Hypoesthesia	1	(0.1)	1	(0.1)	ND
Iiird nerve disorder	0	(0.0)	1	(0.1)	ND
Intracranial hemorrhage nos	1	(0.1)	1	(0.1)	ND
Lacunar infarction	1	(0.1)	0	(0.0)	ND
Loss of consciousness	2	(0.3)	2	(0.3)	ND
Lumbar spinal stenosis	0	(0.0)	1	(0.1)	ND
Metabolic encephalopathy nos	0	(0.0)	1	(0.1)	ND
Neuralgia nos	0	(0.0)	1	(0.1)	ND
Normal pressure hydrocephalus	1	(0.1)	1	(0.1)	ND
Paraplegia	1	(0.1)	0	(0.0)	ND
Paresis	1	(0.1)	0	(0.0)	ND
Parkinson's disease nos	1	(0.1)	0	(0.0)	ND
Pneumocephalus	0	(0.0)	1	(0.1)	ND
Radiculopathy nos	1	(0.1)	0	(0.0)	ND
Reversible ischaemic neurological deficit	0	(0.0)	1	(0.1)	ND
Spinal stenosis nos	5	(0.7)	0	(0.0)	ND
Subarachnoid hemorrhage nos	1	(0.1)	2	(0.3)	ND
Syncope	8	(1.1)	7	(1.0)	ND
Transient ischaemic attack	12	(1.7)	10	(1.4)	ND
Tremor	1	(0.1)	0	(0.0)	ND
Vertebrobasilar insufficiency	0	(0.0)	1	(0.1)	ND
Vocal cord paralysis	0	(0.0)	1	(0.1)	ND
Psychiatric Disorders	**7**	**(1.0)**	**6**	**(0.8)**	**ND**
Aggression	1	(0.1)	0	(0.0)	ND
Agitation	1	(0.1)	0	(0.0)	ND
Completed suicide	0	(0.0)	1	(0.1)	ND
Confusional state	2	(0.3)	1	(0.1)	ND
Delirium	0	(0.0)	1	(0.1)	ND
Depression	1	(0.1)	0	(0.0)	ND
Disorientation	1	(0.1)	0	(0.0)	ND
Mental status changes	1	(0.1)	2	(0.3)	ND
Psychotic disorder nos	0	(0.0)	1	(0.1)	ND
Suicide attempt	1	(0.1)	0	(0.0)	ND

Table 46 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Renal and Urinary Disorders	**18**	**(2.5)**	**10**	**(1.4)**	**1.12 (-0.3, 2.7)**
Bladder neck obstruction	1	(0.1)	0	(0.0)	ND
Calculus bladder	2	(0.3)	0	(0.0)	ND
Calculus urinary	0	(0.0)	1	(0.1)	ND
Cystocele	1	(0.1)	0	(0.0)	ND
Hematuria	3	(0.4)	1	(0.1)	ND
Nephrolithiasis	1	(0.1)	0	(0.0)	ND
Pollakiuria	1	(0.1)	0	(0.0)	ND
Renal failure acute	3	(0.4)	0	(0.0)	ND
Renal failure acute on chronic	0	(0.0)	1	(0.1)	ND
Renal failure nos	2	(0.3)	2	(0.3)	ND
Renal impairment nos	2	(0.3)	2	(0.3)	ND
Urate nephropathy	0	(0.0)	1	(0.1)	ND
Urethral polyp	1	(0.1)	0	(0.0)	ND
Urinary incontinence	1	(0.1)	1	(0.1)	ND
Urinary retention	3	(0.4)	2	(0.3)	ND
Reproductive System and Breast Disorders	**6**	**(0.8)**	**11**	**(1.5)**	**ND**
Benign prostatic hyperplasia	3	(0.4)	7	(1.0)	ND
Epididymitis nos	0	(0.0)	1	(0.1)	ND
Perineal pain nos	1	(0.1)	0	(0.0)	ND
Prostatic hypertrophy	1	(0.1)	2	(0.3)	ND
Prostatitis	0	(0.0)	1	(0.1)	ND
Uterine prolapse	1	(0.1)	0	(0.0)	ND
Respiratory, Thoracic and Mediastinal Disorders	**20**	**(2.8)**	**14**	**(1.9)**	**0.84 (-0.8, 2.5)**
Acute respiratory distress syndrome	1	(0.1)	0	(0.0)	ND
Acute respiratory failure	0	(0.0)	1	(0.1)	ND
Aspiration	0	(0.0)	1	(0.1)	ND
Asthma nos	0	(0.0)	1	(0.1)	ND
Atelectasis	0	(0.0)	1	(0.1)	ND
Bronchitis nos	2	(0.3)	2	(0.3)	ND
Bronchopleural fistula	1	(0.1)	0	(0.0)	ND
Bronchospasm nos	1	(0.1)	1	(0.1)	ND
Chronic obstructive airways disease	5	(0.7)	1	(0.1)	ND
Dyspnea	3	(0.4)	2	(0.3)	ND
Emphysema	1	(0.1)	0	(0.0)	ND
Epistaxis	1	(0.1)	0	(0.0)	ND
Hemopneumothorax	1	(0.1)	0	(0.0)	ND
Hypoxia	1	(0.1)	1	(0.1)	ND
Pharyngeal edema	0	(0.0)	1	(0.1)	ND
Pleural effusion	1	(0.1)	3	(0.4)	ND
Pneumonia aspiration	0	(0.0)	2	(0.3)	ND
Pneumothorax nos	0	(0.0)	1	(0.1)	ND

Table 46 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Pulmonary embolism	3	(0.4)	1	(0.1)	ND
Pulmonary fibrosis	1	(0.1)	0	(0.0)	ND
Pulmonary edema nos	2	(0.3)	1	(0.1)	ND
Respiratory distress	0	(0.0)	1	(0.1)	ND
Respiratory failure	0	(0.0)	3	(0.4)	ND
Skin and Subcutaneous Tissue Disorders	**1**	**(0.1)**	**0**	**(0.0)**	**ND**
Skin ulcer	1	(0.1)	0	(0.0)	ND
Vascular Disorders	**11**	**(1.5)**	**10**	**(1.4)**	**ND**
Aneurysm	0	(0.0)	1	(0.1)	ND
Aortic aneurysm	2	(0.3)	0	(0.0)	ND
Aortic stenosis	0	(0.0)	1	(0.1)	ND
Atherosclerosis	1	(0.1)	0	(0.0)	ND
Deep vein thrombosis	2	(0.3)	3	(0.4)	ND
Femoral artery aneurysm	1	(0.1)	0	(0.0)	ND
Hemorrhage nos	0	(0.0)	1	(0.1)	ND
Hypertension nos	2	(0.3)	3	(0.4)	ND
Hypotension nos	2	(0.3)	0	(0.0)	ND
Hypovolemic shock	0	(0.0)	1	(0.1)	ND
Phlebitis nos	0	(0.0)	1	(0.1)	ND
Thrombosis	1	(0.1)	0	(0.0)	ND

CI = Confidence interval.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.2.2.4 Serious and Drug Related Adverse Experiences

8.2.2.4.1 On-Drug Population

The distribution of patients who were taking drug, or within 14 days of the last dose of study drug who had serious adverse experiences considered to be drug related is presented in Table 47. Complete WAES narratives for serious adverse experiences are found in [4.6].

A total of 21 patients had serious drug-related adverse experiences: 11 (1.5%) in the rofecoxib group and 10 (1.4%) in the placebo group. Numerically, the most common drug-related serious adverse experiences were reported for the categories of blood disorders (no patients on rofecoxib and 3 patients in the placebo group [ANs 0874, 1017, and 1475]); cardiac disorders (3 patients in the rofecoxib group [ANs 0128, 1365, 1478] and 2 in the placebo group [ANs 0538 and 0882]); and gastrointestinal disorders (6 patients in the rofecoxib group [ANs 0297 (had gastric hemorrhage and colitis), 0425, 0690 (had gastric ulcer and gastric hemorrhage), 1077, 1221, and 1338 (had colonic polyp and rectal hemorrhage)] and 4 in the placebo group [ANs 0360, 0600, 1475, and 1525]). Other serious drug-related adverse experiences are: 1 patient in the rofecoxib group had chest pain; 2 patients in the placebo group had nervous system disorders; and 1 patient in the rofecoxib group experienced renal failure. Brief narratives for each of these patients follows.

For Site 007, AN 0128, an 84-year-old male in the rofecoxib group, was hospitalized for ventricular tachycardia, which was considered possibly related to study medication, disabling, and life-threatening. Past medical history was remarkable for valvular heart disease, Paget's disease, atrial fibrillation, angina pectoris, age-indeterminate inferior myocardial infarction, congestive heart failure, and coronary artery disease. The patient had a heart valve replaced in 1989 and in 1994. Concomitant therapy included warfarin sodium and metoprolol tartrate. A nonserious adverse experience of hypertension was listed from Day 28 to Day 119 after randomization. On Day 130, the patient experienced paroxysmal ventricular tachycardia. The patient took study medication for 130 days; study medication was discontinued at the time of hospitalization.

For Site 010, AN 0297, a 74-year-old male in the rofecoxib group, had ischemic colitis and gastrointestinal hemorrhage (determined by the site not to be an upper GI bleed and was therefore not adjudicated; the bleed was from the lower bowel) reported on Day 730 after randomization; both adverse experiences were considered by the investigator to be possibly related to study medication. Past medical history was remarkable for hypercholesterolemia, rectal prolapse, and benign prostatic hyperplasia. Concomitant therapy included vitamin E, atorvastatin calcium, aspirin, and metoprolol tartrate. Study medication was discontinued 12 days prior to those events on Day 718, due to a nonserious adverse experience of dyspnea (reported by the investigator as definitely not related to study medication).

For Site 012, AN 0360, an 82-year-old male in the placebo group, had a serious adverse experience of duodenal ulcer perforation, which was considered probably related to study medication. Past medical history was remarkable for urinary incontinence, urinary tract infection, renal cell carcinoma, and meningioma. Concomitant therapy included echinacea, tolterodine tartrate, and ciprofloxacin. The patient started taking aspirin on Day 358 as a prophylactic for the serious adverse experience of a CVA reported on Day 356. On Day 380, the patient stopped aspirin and started clopidogrel bisulfate. On Day 426 after randomization, the patient had a nonserious adverse experience of perforated duodenal ulcer, which was considered probably related to study medication. On Day 444 the patient was hospitalized for the perforated duodenal ulcer, reported as a serious adverse experience (probably related). This was also considered as life-threatening by the investigator. Study medication was taken until Day 444 and was discontinued due to the serious adverse experience of perforated duodenal ulcer.

For Site 014, AN 0425, a 78-year-old female in the rofecoxib group, a bleeding gastric ulcer, which was considered possibly related to study medication, was reported. Past medical history was remarkable for MCI, anemia, diverticulosis, constipation, gastritis, anorexia, heartburn, hiatal hernia, cystocele, and rectocele. Concomitant therapy included famotidine, ferrous sulfate, cimetidine, and aspirin. On Day 52 after randomization, the patient had a nonserious adverse experience of worsening anorexia (considered possibly related). Nonserious adverse experiences of microscopic hematuria (Day 51) and abdominal bloating (Day 128) were also reported. Study medication was taken for 127 days and was discontinued due to the patient being uncooperative; the patient remained in the study for follow-up. On Day 139 after randomization, 12 days after discontinuing study medication, the patient was hospitalized for a bleeding gastric ulcer. A nonserious adverse event of anemia (considered possibly related) was also reported on Day 139.

For Site 015, AN 0451, an 84-year-old male in the rofecoxib group, had renal failure, which was considered possibly related to study medication. This was discussed in Section 8.2.2.2.1 (Drug-Related Clinical Adverse Experiences) and a complete narrative can be found in [4.6].

For Site 017, AN 0538, a 75-year-old female in the placebo group, was hospitalized for a myocardial infarction on Day 1076 after randomization, which the investigator considered possibly related to study medication. Past medical history was remarkable for MCI, angina pectoris, myocardial

infarction, hypertension, and stress incontinence. Concomitant therapy included hydrochlorothiazide, nadolol, acetaminophen, atorvastatin calcium, and nitroglycerin. A nonserious adverse experience of worsening hypertension was listed from Day 31 to Day 52 (considered possibly related) and then again from Day 1076 to Day 1221 (considered probably not related). A nonserious adverse experience of worsening angina (considered possibly related) was also listed from Day 1046 to Day 1076. Study medication was taken for 1076 days and was discontinued due to the myocardial infarction.

For Site 019, AN 0600, an 86-year-old male in the placebo group, had atrophic gastritis, which was considered possibly related to study medication. Past medical history was remarkable for MCI, chronic obstructive pulmonary disease, heartburn, hypertension, and constipation. Concomitant therapy included nifedipine, hydrochlorothiazide, vitamin E, ranitidine, albuterol, beclomethasone dipropionate, and docusate sodium (+) phenolphthalein. On Day 383 after randomization, the patient was hospitalized for the atrophic gastritis. Study medication was taken until Day 382 and was interrupted for 8 days. Study medication resumed on Day 391 and was taken until the patient was discontinued from the study on Day 617. The patient was discontinued from the study since he was diagnosed with probable AD, a study endpoint per protocol.

For Site 023, AN 0690, a 77-year-old female in the rofecoxib group, reported a gastrointestinal bleed and a pyloric ulcer on Day 612 after randomization; both adverse experiences were considered possibly related to study medication. Past medical history was remarkable for MCI, gastric ulcer, "gastrointestinal distress," hypertension, hypothyroidism, and cholecystitis. Concomitant therapy included levothyroxine sodium, diltiazem hydrochloride, vitamin E, ginkgo biloba extract, and amlodipine besylate. The patient experienced nonserious adverse experiences of abdominal discomfort (Day 596), decreased hemoglobin and hematocrit (Day 611), and iron deficiency anemia (Day 611) all of which were considered possibly related to study drug. Study medication was taken for 611 days and was discontinued due to the gastrointestinal bleed and pyloric ulcer.

For Site 027, AN 0839, a 72-year-old male in the rofecoxib group, chest pain was reported as a serious adverse and considered as possibly related to study medication. Past medical history was remarkable for MCI and coronary artery disease. The patient was not dosing with any concomitant medications prior to the serious adverse event of chest pain. On Day 34 after randomization, the patient was hospitalized for the chest pain. Study medication was interrupted for one day due to the chest pain and resumed on Day 35. Study medication was taken until the patient completed the study on Day 1462.

For Site 034, AN 1077, an 81-year-old female in the rofecoxib group, the serious adverse experience of upper abdominal pain was reported which was considered as possibly related to study medication. Past medical history was remarkable for MCI, hiatal hernia, reflux esophagitis, and urinary incontinence. Concomitant therapy included vitamin E, tolterodine, omeprazole, and acetaminophen. The onset of upper abdominal pain occurred 49 days after randomization. Study medication was interrupted from Day 40 to Day 49 and resumed on Day 50. Study medication was taken until Day 85 and was interrupted due to a nonserious adverse event of worsening arthritis (probably not related); study medication was not resumed because the patient moved and discontinued the study.

For Site 039, AN 1221, a 72-year-old male in the rofecoxib group, was hospitalized on Day 492 after randomization for the adverse experience of upper gastrointestinal bleeding, considered as possibly related to study medication. Past medical history was remarkable for MCI, malnutrition, benign prostatic hypertrophy, and general discomfort. Concomitant therapy included acetaminophen. Study medication was taken for 491 days and was discontinued due to the gastrointestinal bleeding. Nonserious adverse experiences of anemia, hiatal hernia, and gastric ulcer were also reported on Day 492. The nonserious adverse experience of gastric ulcer was considered possibly related to study drug.

For Site 039, AN 1240, a 77-year-old male in the placebo group, had dizziness, hypoesthesia, and a cerebrovascular accident, which were all considered possibly related to study medication. Past medical history was remarkable for MCI, pancreatitis, hiatal hernia, abdominal hernia, left ventricular and atrial hypertrophy, spondylosis, and acid reflux. Concomitant therapy included ranitidine, acetaminophen, and pancrelipase. On Day 515 after randomization, the patient experienced dizziness and was hospitalized. On Day 516, the patient experienced numbness in his right arm and both legs which led to a diagnosis of cerebrovascular accident. Study medication was taken for 515 days and was discontinued due to the dizziness, arm and leg numbness, and cerebrovascular accident. The patient discontinued the study 539 days after randomization due to these serious adverse experiences.

For Site 043, AN 1365, a 79-year-old female in the rofecoxib group, had an acute myocardial infarction which resulted in death and is fully discussed in Section 8.3.1.1.1 (Narratives of Death) and a complete narrative is in [4.6].

For Site 043, AN 1525, a 72-year-old male in the placebo group, had two episodes of lower gastrointestinal hemorrhage, both were considered as possibly related to study medication and life-threatening. Past medical history was remarkable for MCI, diabetes mellitus, irritable bowel syndrome, nocturia, and obesity. Concomitant therapy included metformin hydrochloride, glyburide, rosiglitazone maleate, and pantoprazole sodium. On Day 758 after randomization, the patient was hospitalized for lower gastrointestinal hemorrhage. The patient continued dosing with study medication and no action was taken on study medication due to the hemorrhage. On Day 798, the patient was hospitalized again for lower gastrointestinal hemorrhage. No action was taken on study medication due to this hemorrhage and the patient dosed for a total of 819 days before the trial was terminated by Merck & Co., Inc.

For Site 045, AN 0874, an 82-year-old female in the placebo group, had anemia which was reported 735 days after randomization. Past medical history was remarkable for MCI, hypercholesterolemia, urinary incontinence, constipation, gastroesophageal reflux disease, Hodgkin's disease, basal cell carcinoma, osteoporosis, diverticulosis, chronic obstructive pulmonary disease, and hypothyroidism. Concomitant therapy included levothyroxine sodium, vitamin E, acetaminophen, and vitamin C. The patient experienced a nonserious adverse experiences of increased blood pressure (considered possibly related) from Day 147 to Day 489 and then again from Day 609 to Day 734. The patient's hematocrit and hemoglobin values were within normal range from baseline until laboratory tests drawn on Day 609 indicated a drop in hematocrit to 32.9% (hemoglobin was 11.1 gm/dL). On Day 735 hematocrit was 25% and hemoglobin was 8.2 gm/dL. The patient was hospitalized on Day 738 after randomization. The patient received two units of packed red blood cells and on Day 744 the hematocrit was 31.2%. Study medication was taken for 741 days, but was discontinued due to the anemia.

For Site 045, AN 0882, a 78-year-old male in the placebo group, had two episodes of the serious adverse experience of congestive cardiac failure, which were both considered to be possibly related to study medication. Past medical history was remarkable for MCI, myocardial infarction, coronary artery disease, arrhythmia, aortic aneurysm, hypercholesterolemia, angina pectoris, and hypertension. The patient had past procedures of coronary artery bypass graft (1989), angioplasty (1997), and aortic aneurysm repair (1991). Concomitant therapy included nitroglycerin, atorvastatin calcium, aspirin, amiodarone, metoprolol, hydrochlorothiazide, and furosemide. During the study, the patient experienced serious adverse experiences of myocardial infarction, paroxysmal atrial fibrillation, unstable angina, worsening coronary

artery disease, and carotid artery stenosis. The nonserious adverse experiences of hypertension, paroxysmal atrial fibrillation, cardiomegaly, congestive cardiac failure, angina, bradycardia, sinus arrhythmia, and premature ventricular contractions were reported during the study. The first episode of the serious adverse experience of congestive cardiac failure occurred 759 days after randomization. Study medication was interrupted for two days due to this adverse experience, but was restarted on Day 761. The second serious adverse experience of congestive cardiac failure occurred 773 days after randomization. Study medication was discontinued the same day as a result of this episode.

For Site 045, AN 1338, a 72-year-old male in the rofecoxib group, colonic polyp and rectal bleeding were reported; both adverse experiences were considered as possibly related to study medication. Past medical history was remarkable for MCI, benign prostatic hypertrophy, intestinal diverticulum, ulcerative proctitis, hemorrhoids, and colon polyps. Concomitant therapy included vitamin E, ginkgo biloba extract, and mesalamine. The patient experienced the following serious adverse experiences all of which were considered probably not related to study drug: rectal hemorrhage (Day 37), diverticulosis (Day 41), ulcerative proctitis (Day 41), hemorrhoidal bleeding (Day 83), rectal bleeding (Day 725), and intestinal diverticulum (Day 725). On Day 938 after randomization, the patient was hospitalized for the colonic polyp and rectal bleeding. Study medication was interrupted on Day 939 and resumed on Day 940. Study medication was taken until Day 947 and then discontinued due to the colonic polyp and rectal bleeding.

For Site 046, AN 1461, a 65-year-old male in the placebo group, had a reversible ischemic neurological deficit on Day 854 after randomization; this adverse experience was considered as possibly related to study medication. Past medical history was remarkable for MCI, depression, and benign prostatic hypertrophy. Concomitant therapy included paroxetine hydrochloride, doxazosin mesylate, vitamin E, and aspirin. Study medication was taken until Day 1197 and was discontinued due to a nonserious adverse event of ankle pain (probably not related).

For Site 047, AN 1475, a 74-year-old male in the placebo group, had two episodes of anemia and melena which were considered to be serious and possibly related to study medication. Past medical history was remarkable for MCI, congestive heart failure, diabetes mellitus non-insulin-dependent, coronary artery disease, thrombocytopenia, atherosclerosis, and hypertension. Concomitant therapy included glipizide, lisinopril, digoxin, warfarin, furosemide, aspirin, gabapentin, and lansoprazole. Baseline hemoglobin and

hematocrit values were within the normal range at 13.3 gm/dl and 40.2%, respectively. Laboratory tests drawn on Day 232 revealed low hemoglobin and hematocrit values (11.2 mg/dL and 34.8%, respectively). On Day 338 after randomization, the patient was hospitalized for a serious adverse experience of blood in the stool (probably not related). An esophagogastroduodenoscopy was performed which revealed mild gastritis, but no upper GI source for the guaiac positive stools. A colonoscopy revealed a mass in the rectum and colonic polyps, all of which were removed. Study medication was interrupted for 8 days due to the melena and was restarted on Day 897. The first episode of anemia and the melena was recorded 889 days after randomization. Study medication was then discontinued on Day 918 due to anemia. Laboratory results obtained on Day 927 indicated that the hemoglobin and hematocrit values dropped to 7.7 gm/dL and 25% respectively. A second episode of anemia was recorded on Day 942, 24 days after discontinuing study medication. Hemoglobin on Day 942 was 7.4 gm/dL.

For Site 047, AN 1478, a 76-year-old male in the rofecoxib group, had angina pectoris, which the investigator indicated as being disabling and possibly related to study medication. Past medical history was remarkable for MCI, diabetes mellitus non-insulin-dependent, hypertension, coronary artery disease, and angina pectoris. Angioplasty was performed in 1992. Concomitant therapy included isosorbide dinitrate, nitroglycerin, hydrochlorothiazide, clopidogrel bisulfate, glyburide, pioglitazone hydrochloride, hydrochlorothiazide (+) irbesartan, atorvastatin calcium, atenolol, celecoxib, and verapamil hydrochloride. On Day 971, coronary artery stenosis was listed as a nonserious adverse experience. On Day 1184, increased hypertension was captured as a nonserious adverse experience. Study medication was taken for 1184 days and was discontinued due to a nonserious adverse event of hip pain. The next day the patient experienced angina pectoris and was hospitalized.

For Site 048, AN 1017, a 66-year-old male in the placebo group, had anemia, noted on the final study visit (Day 1224 after randomization). Past medical history was remarkable for MCI, congestive heart failure, diabetes mellitus, hypertension, emphysema, hypercholesterolemia, depression, and constipation. Concomitant therapy included warfarin, acetaminophen, atenolol, prazosin, amlodipine besylate, lisinopril, simvastatin, casanthranol, docusate sodium, and fluoxetine hydrochloride. Laboratory tests drawn on Days 726 and 1224 yielded hematocrit values that dropped from 37.6% to 24.3%, respectively; hemoglobin values also dropped from 12.7 gm/dL to 7.9 gm/dL. On Day 1232 after randomization, the patient was hospitalized for anemia and was given two blood transfusions. During the hospitalization

(Day 1238 after randomization) the patient experienced exacerbation of congestive heart failure which was listed as a serious adverse event. Study medication was taken up until the time of the final study visit.

Table 47

Number (%) of Patients With Serious and Drug-Related Clinical Adverse Experiences by Body System
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=723)		Placebo (N=728)	
	n	(%)	n	(%)
Patients with one or more adverse experience	11	(1.5)	10	(1.4)
Patients with no adverse experience	712	(98.5)	718	(98.6)
Blood and Lymphatic System Disorders	**0**	**(0.0)**	**3**	**(0.4)**
Anemia nos	0	(0.0)	3	(0.4)
Cardiac Disorders	**3**	**(0.4)**	**2**	**(0.3)**
Acute myocardial infarction	1	(0.1)	0	(0.0)
Angina pectoris	1	(0.1)	0	(0.0)
Cardiac failure congestive	0	(0.0)	1	(0.1)
Myocardial infarction	0	(0.0)	1	(0.1)
Ventricular tachycardia	1	(0.1)	0	(0.0)
Gastrointestinal Disorders	**6**	**(0.8)**	**4**	**(0.5)**
Abdominal pain upper	1	(0.1)	0	(0.0)
Colitis ischaemic	1	(0.1)	0	(0.0)
Colonic polyp	1	(0.1)	0	(0.0)
Duodenal ulcer perforation	0	(0.0)	1	(0.1)
Gastric ulcer	1	(0.1)	0	(0.0)
Gastric ulcer hemorrhage	1	(0.1)	0	(0.0)
Gastritis atrophic	0	(0.0)	1	(0.1)
Gastrointestinal hemorrhage nos	2	(0.3)	0	(0.0)
Lower gastrointestinal hemorrhage	0	(0.0)	1	(0.1)
Melena	0	(0.0)	1	(0.1)
Rectal hemorrhage	1	(0.1)	0	(0.0)
Upper gastrointestinal hemorrhage	1	(0.1)	0	(0.0)
General Disorders and Administration Site Conditions	**1**	**(0.1)**	**0**	**(0.0)**
Chest pain	1	(0.1)	0	(0.0)

Table 47 (Cont.)

Number (%) of Patients With Serious and Drug-Related
Clinical Adverse Experiences by Body System
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=723)		Placebo (N=728)	
	n	(%)	n	(%)
Patients with one or more adverse experience	11	(1.5)	10	(1.4)
Patients with no adverse experience	712	(98.5)	718	(98.6)
Nervous System Disorders	**0**	**(0.0)**	**2**	**(0.3)**
Cerebrovascular accident	0	(0.0)	1	(0.1)
Dizziness	0	(0.0)	1	(0.1)
Hypoesthesia	0	(0.0)	1	(0.1)
Reversible ischaemic neurological deficit	0	(0.0)	1	(0.1)
Renal and Urinary Disorders	**1**	**(0.1)**	**0**	**(0.0)**
Renal failure nos	1	(0.1)	0	(0.0)

† On drug includes the period through 14 days after discontinuation of study drug.
Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.2.2.4.2 Intention-to-Treat Population

The distribution of patients in the ITT population with serious clinical adverse experiences considered to be drug related is shown in Table 48. There were no differences in the on-drug and the ITT populations with respect to serious drug-related adverse experiences, with the exception of one more patient in the placebo group with reported anemia (AN 0411; see [4.6] for narrative).

Table 48

Number (%) of Patients With Serious and Drug-Related
Clinical Adverse Experiences by Body System
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

	Rofecoxib 25 mg (N=723)		Placebo (N=728)	
	n	(%)	n	(%)
Patients with one or more adverse experience	11	(1.5)	11	(1.5)
Patients with no adverse experience	712	(98.5)	717	(98.5)
Blood and Lymphatic System Disorders	**0**	**(0.0)**	**4**	**(0.5)**
Anemia Nos	0	(0.0)	4	(0.5)
Cardiac Disorders	**3**	**(0.4)**	**2**	**(0.3)**
Acute myocardial infarction	1	(0.1)	0	(0.0)
Angina pectoris	1	(0.1)	0	(0.0)
Cardiac failure congestive	0	(0.0)	1	(0.1)
Myocardial infarction	0	(0.0)	1	(0.1)
Ventricular tachycardia	1	(0.1)	0	(0.0)
Gastrointestinal Disorders	**6**	**(0.8)**	**4**	**(0.5)**
Abdominal pain upper	1	(0.1)	0	(0.0)
Colitis ischaemic	1	(0.1)	0	(0.0)
Colonic polyp	1	(0.1)	0	(0.0)
Duodenal ulcer	0	(0.0)	1	(0.1)
Duodenal ulcer perforation	0	(0.0)	1	(0.1)
Gastric ulcer	1	(0.1)	0	(0.0)
Gastric ulcer hemorrhage	1	(0.1)	0	(0.0)
Gastritis atrophic	0	(0.0)	1	(0.1)
Gastrointestinal hemorrhage nos	2	(0.3)	0	(0.0)
Lower gastrointestinal hemorrhage	0	(0.0)	1	(0.1)
Melena	0	(0.0)	1	(0.1)
Rectal hemorrhage	1	(0.1)	0	(0.0)
Upper gastrointestinal hemorrhage	1	(0.1)	0	(0.0)
General Disorders and Administration Site Conditions	**1**	**(0.1)**	**0**	**(0.0)**
Chest pain	1	(0.1)	0	(0.0)
Nervous System Disorders	**0**	**(0.0)**	**2**	**(0.3)**
Cerebrovascular accident	0	(0.0)	1	(0.1)
Dizziness	0	(0.0)	1	(0.1)
Hypoesthesia	0	(0.0)	1	(0.1)
Reversible ischaemic neurological deficit	0	(0.0)	1	(0.1)
Renal and Urinary Disorders	**1**	**(0.1)**	**0**	**(0.0)**
Renal failure nos	1	(0.1)	0	(0.0)

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.2.3 Listing of Clinical Adverse Experiences by Patient

Information for patients with clinical adverse experiences are provided as SAS files in. [4.2].

8.3 Deaths, Nonfatal Serious Clinical Adverse Experiences, and Other Significant Clinical Adverse Experiences

The following section provides an assessment of deaths, nonfatal serious clinical adverse events, and other significant events causing discontinuation of either the study medication or the trial.

8.3.1 Listing of Deaths, Nonfatal Serious Clinical Adverse Experiences, and Other Significant Clinical Adverse Experiences

A listing table for all patient deaths is in Section 11, Table 88.

8.3.1.1 Deaths

During the course of the study there were 61 patient deaths: 42 were considered to have occurred on-drug, 27 in the rofecoxib group and 15 in the placebo group. The accounting for on-drug mortality includes 3 patients (ANs 0290, 0536, and 1113) whose deaths were the result of adverse experiences with onset dates more than 14 days after the last dose of study drug, but who had precursor adverse experiences while on study drug that may have been related to the fatal off-drug adverse experiences.

A tabulation of patients with fatal adverse experiences while dosing with study drug or within 14 days of the last dose of study drug are shown in Table 49; this tabulation, however, does not include the 3 patients in the rofecoxib group (ANs 0290, 0536, and 1113) who had fatal off-drug adverse experiences that may have been related to precursor on-drug adverse experiences; only the on-drug adverse experiences that resulted in death are shown in the table.

A listing table for all patient deaths is in [Section 11, Table 88]. Complete WAES narratives for all deaths are in [4.6]. Abbreviated narratives for on-drug mortality can be found in Section 8.3.1.1.3.

All deaths were adjudicated, whether they occurred on or off study medication, per the procedures described in the Acute Thromboembolic Vascular Events SOP [3.11.2]. A complete discussion of adjudication results can be found in 8.3.1.1.4; adjudication results are mentioned in the following sections as deemed relevant.

8.3.1.1.1 On-Drug Population

The distribution of patients who died while dosing with study medication, or within 14 days after the last dose of study drug, is presented in Table 49. As shown, there is no specific pattern as to the cause of death in either treatment group.

Numerically, most on-drug deaths were reported as due to cardiac disorders and includes a total of 14 patients: 9 patients in the rofecoxib group and 5 patients in the placebo group. Myocardial infarction was the most common adverse experience resulting in death (4 patients in the rofecoxib group and 3 in the placebo group). Two patients in the rofecoxib group and none in the placebo group had cardiac arrest. There were a total of 12 patient deaths that were adjudicated as due to thrombotic events: 8 (1.1%) patients in the rofecoxib group and 4 (0.5%) patients in the placebo group (see Section 8.3.1.1.4).

Thirteen patients died from a variety of benign, malignant, and unspecified neoplasms: 6 (0.8%) in the rofecoxib treatment group and 7 (1.0%) in the placebo group.

Injury, poisoning and procedural complications resulted in death for 5 (0.7%) patients in the rofecoxib group and none in the placebo group.

Adverse experiences of gastrointestinal disorders resulted in death for 3 patients: 2 (0.3%) in the rofecoxib group and 1 (0.1%) in the placebo group.

Three patients died from renal failure: 1 (0.1%) in the rofecoxib treatment group and 2 (0.3) on placebo.

MK-0966 Prot. No. 078
MK-0966 Alzheimer's Disease Prevention Study
-189-

Table 49

Counts of Patient Deaths by Body System
On Drug† Population

Adverse Experience Term	Rofecoxib 25 mg (N=723)		Placebo (N=728)	
	n	(%)	n	(%)
Patients with one or more adverse experience	24‡	(3.3)	15	(2.1)
Patients with no adverse experience	699	(96.7)	713	(97.9)
Blood and Lymphatic System Disorders	**1**	**(0.1)**	**0**	**(0.0)**
Hypercoagulation	1	(0.1)	0	(0.0)
Cardiac Disorders	**9**	**(1.2)**	**5**	**(0.7)**
Acute myocardial infarction	2	(0.3)	3	(0.4)
Cardiac arrest	2	(0.3)	0	(0.0)
Cardiac failure nos	0	(0.0)	1	(0.1)
Cardio-respiratory arrest	1	(0.1)	1	(0.1)
Hypertensive heart disease	1	(0.1)	0	(0.0)
Myocardial infarction	2	(0.3)	0	(0.0)
Ventricular fibrillation	1	(0.1)	0	(0.0)
Gastrointestinal Disorders	**2**	**(0.3)**	**1**	**(0.1)**
Bowel sounds abnormal	0	(0.0)	1	(0.1)
Duodenal ulcer hemorrhage	1	(0.1)	0	(0.0)
Gastric perforation	1	(0.1)	0	(0.0)
Intestinal ischaemia	0	(0.0)	1	(0.1)
Pancreatitis nos	0	(0.0)	1	(0.1)
General Disorders and Administration Site Conditions	**1**	**(0.1)**	**1**	**(0.1)**
Multi-organ failure	0	(0.0)	1	(0.1)
Sudden death	1	(0.1)	0	(0.0)
Infections and Infestations	**2**	**(0.3)**	**0**	**(0.0)**
Empyema nos	1	(0.1)	0	(0.0)
Pneumonia nos	2	(0.3)	0	(0.0)
Injury, Poisoning and Procedural Complications	**5**	**(0.7)**	**0**	**(0.0)**
Electric shock	1	(0.1)	0	(0.0)
Head injury	1	(0.1)	0	(0.0)
Polytraumatism	1	(0.1)	0	(0.0)
Post procedural complication	1	(0.1)	0	(0.0)
Traumatic chest injury nos	1	(0.1)	0	(0.0)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**6**	**(0.8)**	**7**	**(1.0)**
Acute myeloid leukemia nos	1	(0.1)	1	(0.1)
Adenocarcinoma nos	0	(0.0)	1	(0.1)
Bladder cancer nos	0	(0.0)	1	(0.1)
Bone cancer metastatic	1	(0.1)	0	(0.0)
Chronic lymphocytic leukemia nos	1	(0.1)	0	(0.0)
Colon cancer metastatic	0	(0.0)	1	(0.1)
Lymphoma nos	0	(0.0)	1	(0.1)

Table 49 (Cont.)

Counts of Patient Deaths by Body System
On Drug† Population

Adverse Experience Term	Rofecoxib 25 mg (N=723)		Placebo (N=728)	
	n	(%)	n	(%)
Malignant melanoma	0	(0.0)	1	(0.1)
Metastases to liver	0	(0.0)	1	(0.1)
Metastatic neoplasm nos, primary site unknown	0	(0.0)	1	(0.1)
Pancreatic carcinoma nos	1	(0.1)	0	(0.0)
Pancreatic neoplasm nos	1	(0.1)	0	(0.0)
Squamous cell carcinoma of skin	1	(0.1)	0	(0.0)
Nervous System Disorders	**0**	**(0.0)**	**1**	**(0.1)**
Intracranial hemorrhage nos	0	(0.0)	1	(0.1)
Renal and Urinary Disorders	**1**	**(0.1)**	**2**	**(0.3)**
Renal failure nos	1	(0.1)	2	(0.3)
Respiratory, Thoracic and Mediastinal Disorders	**1**	**(0.1)**	**1**	**(0.1)**
Acute respiratory failure	0	(0.0)	1	(0.1)
Pulmonary fibrosis	1	(0.1)	0	(0.0)
Vascular Disorders	**1**	**(0.1)**	**1**	**(0.1)**
Atherosclerosis	1	(0.1)	0	(0.0)
Hypertension nos	0	(0.0)	1	(0.1)

† On drug includes the period through 14 days after discontinuation of study drug.
Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
‡ This count does not include 3 patients (ANs 0290, 0536, and 1113) with fatal off-drug adverse experiences that may have been related to precursor non-fatal, nonserious adverse experiences.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.3.1.1.2 Intention-to-Treat Population

The distribution of patients who died in the ITT population are shown in Table 50 and Section 11, Table 89. Compared to the on-drug population, an additional 19 patients died off-drug: 14 in the rofecoxib group and 5 in the placebo group. Fifteen of these deaths occurred >1 year after stopping study therapy: 10 in rofecoxib and 5 in the placebo group. Only 1 patient died within 28 days of stopping study therapy (AN 1202, rofecoxib group, died of cerebral hemorrhage 17 days off drug). Over the entire study, a total of 61 patients died: 41 in the rofecoxib treatment group and 20 in the placebo treatment group. A total of 24 patients died due to cardiac disorders: 18

(2.5%) in the rofecoxib group and 6 (0.8%) in the placebo group. Upon further comparison to the on-drug population, an additional 3 patients in the rofecoxib group died as a result of infections and infestations, 6 additional patients died from neoplasms (4 in the rofecoxib group and 2 in the placebo group), and 4 additional patients in the rofecoxib group had nervous system disorders that resulted in death (2 cerebrovascular accidents, 1 cerebral hemorrhage, and 1 subarachnoid hemorrhage).

Table 50

Counts of Patient Deaths by Body System
Intention-to-Treat Population

Adverse Experience Term	Rofecoxib 25 mg (N=723)		Placebo (N=728)	
	n	(%)	n	(%)
Patients with one or more adverse experience	41	(5.7)	20	(2.7)
Patients with no adverse experience	682	(94.3)	708	(97.3)
Blood and Lymphatic System Disorders	**1**	**(0.1)**	**0**	**(0.0)**
Hypercoagulation	1	(0.1)	0	(0.0)
Cardiac Disorders	**18**	**(2.5)**	**6**	**(0.8)**
Acute myocardial infarction	4	(0.6)	3	(0.4)
Arrhythmia nos	1	(0.1)	0	(0.0)
Cardiac arrest	4	(0.6)	0	(0.0)
Cardiac failure congestive	1	(0.1)	1	(0.1)
Cardiac failure nos	0	(0.0)	1	(0.1)
Cardio-respiratory arrest	1	(0.1)	1	(0.1)
Coronary artery disease nos	2	(0.3)	0	(0.0)
Hypertensive heart disease	1	(0.1)	0	(0.0)
Myocardial infarction	5	(0.7)	0	(0.0)
Ventricular fibrillation	2	(0.3)	0	(0.0)
Gastrointestinal Disorders	**2**	**(0.3)**	**1**	**(0.1)**
Bowel sounds abnormal	0	(0.0)	1	(0.1)
Duodenal ulcer hemorrhage	1	(0.1)	0	(0.0)
Gastric perforation	1	(0.1)	0	(0.0)
Intestinal ischaemia	0	(0.0)	1	(0.1)
Pancreatitis nos	0	(0.0)	1	(0.1)
General Disorders and Administration Site Conditions	**1**	**(0.1)**	**1**	**(0.1)**
Multi-organ failure	0	(0.0)	1	(0.1)
Sudden death	1	(0.1)	0	(0.0)
Infections and Infestations	**5**	**(0.7)**	**0**	**(0.0)**
Bacterial sepsis	1	(0.1)	0	(0.0)
Empyema nos	1	(0.1)	0	(0.0)
Pneumonia nos	4	(0.6)	0	(0.0)
Urosepsis	1	(0.1)	0	(0.0)

Table 50 (Cont.)

Counts of Patient Deaths by Body System
Intention-to-Treat Population

Adverse Experience Term	Rofecoxib 25 mg (N=723)		Placebo (N=728)	
	n	(%)	n	(%)
Injury, Poisoning and Procedural Complications	**5**	**(0.7)**	**1**	**(0.1)**
Electric shock	1	(0.1)	0	(0.0)
Head injury	1	(0.1)	0	(0.0)
Polytraumatism	1	(0.1)	0	(0.0)
Post procedural complication	1	(0.1)	0	(0.0)
Therapeutic agent poisoning	0	(0.0)	1	(0.1)
Traumatic chest injury nos	1	(0.1)	0	(0.0)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**10**	**(1.4)**	**9**	**(1.2)**
Acute lymphocytic leukemia	1	(0.1)	0	(0.0)
Acute myeloid leukemia nos	1	(0.1)	1	(0.1)
Adenocarcinoma nos	0	(0.0)	1	(0.1)
Bladder cancer nos	0	(0.0)	1	(0.1)
Bone cancer metastatic	1	(0.1)	0	(0.0)
Chronic lymphocytic leukemia nos	1	(0.1)	0	(0.0)
Colon cancer metastatic	0	(0.0)	1	(0.1)
Hepatic neoplasm malignant nos	0	(0.0)	1	(0.1)
Lung neoplasm malignant	1	(0.1)	0	(0.0)
Lymphoma nos	0	(0.0)	1	(0.1)
Malignant melanoma	0	(0.0)	1	(0.1)
Metastases to liver	0	(0.0)	1	(0.1)
Metastatic neoplasm nos, primary site unknown	1	(0.1)	1	(0.1)
Ovarian cancer metastatic	1	(0.1)	0	(0.0)
Pancreatic carcinoma nos	1	(0.1)	1	(0.1)
Pancreatic neoplasm nos	1	(0.1)	0	(0.0)
Squamous cell carcinoma of skin	1	(0.1)	0	(0.0)
Nervous System Disorders	**4**	**(0.6)**	**1**	**(0.1)**
Cerebral hemorrhage	1	(0.1)	0	(0.0)
Cerebrovascular accident	2	(0.3)	0	(0.0)
Intracranial hemorrhage nos	0	(0.0)	1	(0.1)
Subarachnoid hemorrhage nos	1	(0.1)	0	(0.0)
Psychiatric Disorders	**0**	**(0.0)**	**1**	**(0.1)**
Completed suicide	0	(0.0)	1	(0.1)
Renal and Urinary Disorders	**3**	**(0.4)**	**3**	**(0.4)**
Renal failure acute	2	(0.3)	0	(0.0)
Renal failure nos	1	(0.1)	2	(0.3)
Renal impairment nos	0	(0.0)	1	(0.1)

Table 50 (Cont.)

Counts of Patient Deaths by Body System
Intention-to-Treat Population

Adverse Experience Term	Rofecoxib 25 mg (N=723)		Placebo (N=728)	
	n	(%)	n	(%)
Respiratory, Thoracic and Mediastinal Disorders	**3**	**(0.4)**	**1**	**(0.1)**
Acute respiratory failure	0	(0.0)	1	(0.1)
Emphysema	1	(0.1)	0	(0.0)
Hypoxia	1	(0.1)	0	(0.0)
Pulmonary embolism	1	(0.1)	0	(0.0)
Pulmonary fibrosis	1	(0.1)	0	(0.0)
Vascular Disorders	**2**	**(0.3)**	**1**	**(0.1)**
Atherosclerosis	1	(0.1)	0	(0.0)
Deep vein thrombosis	1	(0.1)	0	(0.0)
Hypertension nos	0	(0.0)	1	(0.1)

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.3.1.1.3 Narratives of On-Drug Deaths

Following are summaries of the clinically important features of the adverse experiences which resulted in death while the patient was dosing with study drug or within 14 days of last dose of drug, and includes 3 patients who had precursor adverse experiences that may have been related to the fatal off-drug adverse experiences Complete narratives for all patient deaths can be found in [4.6].

8.3.1.1.3.1 Rofecoxib Group

Deaths Due to Serious Adverse Experiences That Began On-Drug or Within 14 Days of Last Dose of Study Drug

From Site 003, AN 1577, an 82-year-old male, died of a myocardial infarction. Past medical history was remarkable for MCI, hypertension, hypercholesterolemia, and benign prostatic hyperplasia. Concomitant medications included finasteride, amlodipine besylate, vitamin E, and atorvastatin calcium. Following 707 days of study therapy, the patient was mowing the lawn when he began to feel tired and went to lie down. The

patient was then found unresponsive. A death certificate could not be obtained. The patient's physician indicated that the patient died of a massive myocardial infarction. The myocardial infarction was considered probably not related to study drug. The death was adjudicated as a thromboembolic event of sudden cardiac death.

For Site 007, AN 0205, an 85-year-old male, died of postoperative complications from hip surgery. Past medical history was remarkable for MCI, coronary artery disease, anxiety, and myasthenia gravis. Concomitant therapy included clopidogrel bisulfate, alprazolam, and sertraline hydrochloride. On Day 494 after randomization, the patient fell and fractured his hip and study medication was discontinued. The next day the patient underwent an open reduction with internal fixation of fracture. On Day 496 after randomization, the patient had a seizure and did not regain consciousness and subsequently became less responsive to painful stimuli. The patient's family opted for conservative treatment. The patient's condition continued to deteriorate. On Day 497 after randomization, an arterial blood gas revealed mild hypoxia and primary acidosis. The patient continued to have diminished responses to painful stimuli throughout the day. The physician thought the patient either had a seizure postoperatively or an acute pulmonary embolism. On Day 497 after randomization, 3 days after the discontinuation of study medication, the patient died. The investigator felt that the patient died due to post-operative complications from the hip surgery (no autopsy was performed). The hip fracture, possible pulmonary embolism, and seizure were considered definitely not related to study drug. The post-operative complications were considered probably not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 008, AN 0233, an 81-year-old male, died of "generalized bone metastases from prostate cancer". Past medical history was remarkable for MCI, prostate cancer, and basal cell carcinoma. Concomitant therapy included donepezil hydrochloride and vitamin E. On Day 1155 after randomization, the patient was diagnosed with worsening prostate cancer during a urology visit. The patient began a 6 week radiation treatment and was placed in hospice care. Study medication was discontinued after 1161 days of dosing due to the prostate cancer. The patient decided to stop the radiation therapy since there was no clinical benefit. On Day 1202, 42 days after discontinuing study drug, the patient died. The death certificate lists the cause of death as cancer metastases secondary to prostate cancer. The bone metastases from prostate cancer were considered definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 008, AN 0248, a 71-year-old female, had sudden death. Past medical history was remarkable for MCI, low back pain, hypertension, alcohol abuse with successful treatment, urinary tract infections, and onychomycosis. Concomitant therapy included acetaminophen, cyanocobalamin, and calcium carbonate. On Day 747 after randomization, the patient died in her sleep. The immediate cause of death listed on the death certificate was "undetermined natural causes." An autopsy was not performed. The sudden death was considered definitely not related to study drug. The death was adjudicated as a thromboembolic event of sudden cardiac death.

For Site 008, AN 0799, an 85-year-old male, died three days after resection of the abdominal aortic aneurysm from cardiac arrest which was attributed to a pre-existing asymptomatic coronary artery disease. Past medical history was remarkable for MCI, prostate carcinoma, systolic murmur, hypercholesterolemia, hypertension, and pneumothorax. Concomitant therapy included fluvastatin sodium, methyclothiazide, and naproxen sodium. The baseline electrocardiogram revealed premature atrial contraction, sinus bradycardia, left axis deviation, and right bundle branch block. On Day 54 after randomization, the patient was hospitalized for a complete heart block. Two days later, the patient had a cardiac pacemaker implanted. The patient developed "cardiac symptoms" and had a cardiac work-up performed which revealed an abdominal aortic aneurysm. Study medication was discontinued 308 days after randomization. The next day, the patient underwent an elective procedure to resect the abdominal aortic aneurysm which was successful. The patient developed cardiac arrest 312 days post-randomization and died. The final cause of death was cardiac arrest which was attributed to the pre-existing asymptomatic coronary artery disease. The abdominal aortic aneurysm and cardiac arrest were considered definitely not related to study drug. The death was adjudicated as a thromboembolic event of sudden cardiac death.

From Site 009, AN 0257, a 76-year-old male, died of "squamous cell carcinoma of the skin." Past medical history was remarkable for MCI, benign prostatic hypertrophy, basal cell carcinoma with excision, seborrheic dermatitis, and actinic keratosis. Concomitant medications included terazosin hydrochloride, vitamin E, and ascorbic acid. Following 1083 days of study therapy, the patient had a skin lesion removed from behind his left ear that was determined to be squamous cell cancer. On Day 1112, an outpatient surgical procedure was performed to remove additional tissue behind his left ear. On Day 1208, the patient began radiation treatment for

the squamous cell carcinoma. Study medication was discontinued 1441 days after randomization due to the cancer. On Day 1442, the patient underwent a left lateral temporal bone resection. The surgery was successful, but the cancer was more invasive than expected. After the surgery, the patient was transferred to the ICU and subsequently died 3 days later. The death certificated listed the cause of death as "recurrent squamous cell carcinoma of the skin", which was considered definitely not related to study therapy. The death was adjudicated as a non-thromboembolic event.

From Site 009, AN 0263, a 79-year-old male, died of pulmonary fibrosis. Past medical history was remarkable for MCI, hypertension, prostate cancer, rosacea, myopia, and pneumonia. Concomitant medications included hydrochlorothiazide/losartan potassium, metronidazole, vitamin E and pramipexole dihydrochloride for Parkinson's disease symptoms, considered a nonserious adverse experience. On Day 696 post randomization, the patient was diagnosed with pulmonary fibrosis and was started on concomitant prednisone. The patient discontinued study medication on Day 882 due to the pulmonary fibrosis. On Day 884, the patient began experiencing shortness of breath due to pulmonary fibrosis and was taken to the hospital. The patient's family requested a "do not resuscitate order" and the patient expired the next day, 885 days after randomization. The cause of death was listed as pulmonary fibrosis which was considered definitely not related to study therapy. The death was adjudicated as a non-thromboembolic event.

For Site 012, AN 0359, a 68-year-old male, died of atherosclerotic and hypertensive cardiovascular disease. Past medical history was remarkable for MCI, hypertension, and spondylosis. Concomitant therapy included lisinopril and multivitamins. On Day 624 after randomization, the patient died unexpectedly in his home. The death certificate listed the cause of death as atherosclerotic and hypertensive cardiovascular disease. These adverse experiences were considered definitely not related to study drug. The death was adjudicated as a thromboembolic event of sudden cardiac death.

For Site 013, AN 1423, an 83-year-old male, died of blunt trauma to the chest. Past medical history was remarkable for MCI, chronic obstructive pulmonary disease, hypertension, venous insufficiency, orthostatic hypotension, emphysema, benign prostatic hypertrophy, and hypercholesterolemia. Concomitant therapy included quinapril hydrochloride, albuterol, ipratropium bromide, tamsulosin hydrochloride, and terazosin hydrochloride. On Day 611 after randomization, the patient

was in a car accident and sustained a blunt trauma to the chest. The patient was taken to the emergency room and shortly after his arrival was pronounced dead from the injuries he sustained in the car accident. The cause of death was blunt force chest trauma. The blunt trauma to the chest was reported as definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 014, AN 0352, a 67-year-old male, died of a bleeding duodenal ulcer. Past medical history was remarkable for MCI, chronic obstructive pulmonary disease, and right lower lung mass. Concomitant therapy included albuterol, flunisolide, salmeterol xinafoate, and vitamin E. On Day 12 after randomization, the patient was diagnosed with lung cancer. Computed axial tomography scans were performed every three months after the patient was diagnosed with lung cancer. On Day 319, a routine computed axial tomography scan revealed a pulmonary embolism. The patient was placed on enoxaparin sodium and warfarin sodium. The patient was experiencing rectal bleeding and an endoscopy was performed 322 days after randomization, which revealed a bleeding duodenal ulcer. Laboratory values included: red blood cell count (RBC) 2.2 M/mm^3, hematocrit 21.8%, hemoglobin 7.4 g/dL, and prothrombin time 14.8 seconds. Endoscopic hemostasis was performed and the patient received seven units of packed RBCs, 4 units of fresh frozen plasma, vitamin K, and IV hydration. On Day 323 after randomization, laboratory values included: RBC count 3.19 M/mm^3, hematocrit 28.3%, and hemoglobin 9.3 gm/dl. The patient's condition continued to deteriorate and he died 323 days after randomization. The cause of death was the bleeding duodenal ulcer, which was considered probably not related to study drug. The death was adjudicated as a hemorrhagic event.

For Site 016, AN 1506, an 81-year-old male, died of pancreatic cancer. Past medical history was remarkable for MCI, hypertension, coronary artery disease, hypokalemia, and diabetes mellitus. Concomitant therapy included glyburide, hydrochlorothiazide (+) losartan potassium, nifedipine, vitamin E, pentoxifylline, and aspirin. On Day 1030 after randomization, the patient was seen by his urologist who noted that the patient was jaundiced. The patient was hospitalized the same day with severe jaundice. The last dose of study medication was taken 1029 days after randomization and was discontinued due to the jaundice. On Day 1030 after randomization, a CT scan suggested that the patient had pancreatic cancer. An endoscopic retrograde cholangiopancreatography was performed 1036 days after randomization which revealed a mass in the head of the pancreas obstructing the common bile duct. On Day 1037 after randomization, 9 days after

discontinuing study medication, percutaneous biliary drainage was established and an open biopsy was performed. On Day 1051 after randomization, the patient was unresponsive to voice, shaking, or sternal rub. The patient died the same day due to pancreatic cancer. The cancer was considered as definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

For site 019, AN 0583, a 70-year-old male, died of hypoxia, pancreatic cancer, pulmonary embolism, and hypercoagulable state. Past medical history was remarkable for MCI, hypertension, and seborrheic keratosis. Concomitant therapy included vitamin E, insulin, glipizide, acetaminophen (+) hydrocodone bitartrate, and fentanyl. Following 303 days of study therapy, the patient developed weight loss, discomfort when eating, and high serum glucose. The patient started glipizide 10 mg on day 322 following the serum glucose increase. The patient's serum glucose level on day 344 was 300 mg/dl, and the levels ranged between 201 mg/dl and 357 mg/dl on day 357 and day 358. Study medication was discontinued after dosing for 312 days. On Day 324 after randomization, a computed axial tomography scan suggested that the patient had pancreatic cancer. The patient also developed a hypercoagulable state. On day 357 after randomization, the patient developed a pulmonary embolism and hypoxia. The patient died two days later due to the hypoxia, pulmonary embolism, hypercoagulable stated, and pancreatic cancer. These adverse experiences were considered definitely not related to study drug. The adjudication committee determined that a final adjudication as either thrombotic or non-thromboembolic could not be provided.

For Site 025, AN 0158, an 82-year-old male, died of a myocardial infarction. Past medical history was remarkable for MCI, hypertension, abdominal aortic aneurysm, chronic obstructive pulmonary disease, rhinitis, cardiomegaly, hypercholesterolemia, right bundle branch block, and first degree atrioventricular block. Concomitant therapy included albuterol, beclomethasone dipropionate, fluvastatin sodium, and lisinopril. On Day 313 after randomization, a malignant tumor was discovered in the patient's right breast. An electrocardiogram was performed 10 days later in preparation for surgery and an atrial flutter was noted. A cardiac pacemaker was placed in the patient on Day 325. On Day 427 after randomization, the patient experienced trouble breathing and a chest x-ray revealed fluid in the lungs. The patient continued to have difficulty breathing and pain in his back. The patient died 3 days later. The death certificate listed the cause of death as terminal ventricular arrhythmia; however, the primary investigator felt the serious adverse experience term should remain as myocardial infarction. This adverse experience was considered definitely not related to study drug. Due to insufficient data, this death could not be adjudicated.

For Site 025, AN 0737, an 84-year-old male, died of cardiac arrest. Past medical history was remarkable for MCI, congestive heart failure, myocardial infarction, non-specific intraventricular block, and left ventricular hypertrophy. Concomitant therapy included lisinopril, isosorbide, furosemide, atenolol, isosorbide dinitrate, and warfarin. On Day 146 after randomization, the patient developed worsening congestive heart failure which was treated with multiple doses of furosemide. On Day 184 after randomization, the patient was treated with IV furosemide and sent home. The next day, the patient fell and hit his head and had external blood loss. Paramedics tried to revive the patient; however he was pronounced dead upon arrival to the emergency room. The death certificate listed the primary cause of death as cardiac arrest with a secondary cause of death as congestive heart failure. Study medication was taken until the time of death. The cardiac arrest was considered definitely not related to study drug. The death was adjudicated as a thromboembolic event of sudden cardiac death.

For Site 025, AN 0762, an 87-year-old male, died of renal failure. Past medical history was remarkable for MCI, right bundle branch block, diabetes mellitus non-insulin-dependent, and hypertension. Concomitant therapy of glyburide for diabetes was started 699 days after randomization. Aspirin (325 mg daily) was started 168 days after randomization for cardiac prophylaxis, but reduced to 81 mg daily on Day 358. On Day 666 after randomization, the patient was diagnosed with prostate cancer. The patient underwent a renal ultrasound 29 days later and bilateral hydronephrosis secondary to the prostate cancer was noted. Study medication was interrupted for 28 days beginning 696 days after randomization. Laboratory values for the time period from baseline to discontinuation from the study were noted as follows: serum aspartate aminotransferase (AST) 26 IU to 17 IU; serum alanine aminotransferase (ALT) 21 IU to 10 IU; serum glucose 172 mg/dL to 216 mg/dL; serum BUN 26 mg/dL to 43 mg/dL; serum creatinine 1.0 mg/dL to 1.8 mg/dL. Laboratory values on admission (695 days after randomization) were creatinine of 10 mg/dL, potassium 8.3 mEq/L, and bicarbonate of 15 mEq/L. The patient had a nephrectomy performed and his high potassium level resolved. On Day 708 after randomization, the patient was hospitalized with kidney failure. On Day 743 the patient was hospitalized for dehydration and for the metastatic prostate cancer. Laboratory results on admission were: potassium 5.1 mEq/L, BUN 124 mg/dL, creatinine 5.1 mg/dL. The liver function tests were noted to be mildly elevated (values were not available). On Day 744 after randomization, the patient was hospitalized for complications from the

prostate cancer and was undergoing radiation therapy. On Day 760, study medication was discontinued due to the renal failure. The patient died 20 days later due to the renal failure. The prostate cancer and renal failure were considered definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 025, AN 0821, an 85-year-old male, died of a closed head injury due to a single car automobile rollover. Past medical history was remarkable for MCI, prostate cancer, and hypertension. Concomitant therapy included doxazosin mesylate and vitamin E. On Day 271 after randomization, the patient was in an automobile accident and died immediately. The death certificate lists the immediate cause of death as a closed head injury due to a single car automobile rollover. An autopsy was not performed. The head trauma was considered definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 025, AN 0823, a 78-year-old male, died of empyema and pneumonia. Past medical history was remarkable for MCI, myocardial infarction, vascular occlusion disease, bacterial pneumonia, hypercholesterolemia, deep vein thrombosis, and asthma. The patient underwent a triple coronary bypass in 1992 and a vascular bypass in both legs in 1995. Concomitant therapy included pentoxifylline, digoxin, atorvastatin calcium, amlodipine besylate, warfarin, vitamin E, ipratropium bromide, and beclomethasone dipropionate. On Day 547 after randomization, the patient was admitted to the hospital with pneumonia and study medication was discontinued due to the pneumonia. Laboratory values on admission included: white blood count of 20,000 mm^3 and hemoglobin 10 gm/dL. The patient was given blood transfusions for anemia. A chest x-ray revealed pleural effusion. A computed tomography scan of the chest and abdomen revealed a left empyema and gallstones. An ultrasound guided thoracentesis was performed and bloody fluid was removed from the left pleural space. Blood cultures revealed positive gram cocci. A pleural fluid culture was positive for alpha strep plus gram negative rods. The patient's condition continued to deteriorate and cardiopulmonary arrest occurred 559 days after randomization (12 days after discontinuing study medication) and the patient died. Medical records indicated that empyema was the probable cause of death. The empyema and pneumonia were considered definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 026, AN 0815, a 75-year-old male, died of ventricular fibrillation. Past medical history was remarkable for MCI, hypertension, hypercholesterolemia, venous thrombosis, and five-vessel coronary bypass surgery. Concomitant therapy included lisinopril, hydrochlorothiazide, simvastatin, vitamin E, and clopidogrel bisulfate. On Day 754 after randomization, the patient's wife found the patient dead on the couch. The death certificate listed ventricular fibrillation as the cause of death which was considered probably not related to study drug. The death was adjudicated as a thromboembolic event of sudden cardiac death.

For Site 030, AN 0935, a 75-year-old male, died as a result of multiple traumatic injuries. Past medical history was remarkable for MCI, hypercholesterolemia, and hypertension. Concomitant therapy included acetaminophen and atorvastatin calcium. After dosing with study medication for 94 days, the patient discontinued the medication for an unknown reason. Twelve days later, the patient was in a car accident and died due to traumatic injuries. The trauma was considered definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 033, AN 1025, an 83-year-old male, died of acute myocardial infarction. Past medical history was remarkable for MCI, hypertension, angina, coronary artery bypass graft, prostate cancer, and hypercholesterolemia. Concomitant therapy included atenolol, isosorbide mononitrate, flutamide, simvastatin, and vitamin E. On Day 125 after randomization, the patient experienced severe chest pain and was admitted to the hospital. The next day, the patient underwent a cardiac catheterization and was noted to be vein graft dependent with critical atherosclerotic degenerative disease in all three bypass veins. Study therapy was discontinued 128 days after randomization. On Day 129, the patient underwent coronary artery bypass grafting. The patient subsequently had recurrent atrial fibrillation and received multiple cardioversions since it was difficult to maintain normal sinus rhythm. Anticoagulation therapy was started but the patient developed a gastrointestinal bleed which was thought to be related to a stress ulcer. The patient developed renal failure on Day 137. The patient had cardiac arrest the next day and died. Primary cause of death was listed as acute myocardial infarction which was considered probably not related to study therapy. The renal insufficiency, atrial fibrillation, worsening chest pain, worsening coronary artery disease, hemorrhagic gastric ulcer, and unstable angina were considered probably not related to study therapy. The death was adjudicated as a thromboembolic event of fatal acute myocardial infarction.

For Site 035, AN 1097, a 69-year-old male, died of electrical shock. Past medical history was remarkable for MCI, benign prostatic hypertrophy, and acid reflux. Concomitant therapy included finasteride, ranitidine hydrochloride, and vitamin E. On Day 248 after randomization, the patient was in his basement working. The patient's wife found the patient dead in the basement from an accidental electrocution. Study medication was taken until the time of death. The electrical shock (resulting in death) was considered definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 043, AN 1365, an 83-year-old female, died of an acute myocardial infarction. Past medical history was remarkable for MCI, hypertension, ankle edema, and arrhythmia. Concomitant therapy included doxazosin mesylate, amlodipine besylate, and furosemide. Study medication was interrupted from Day 212 to Day 361 due to a herniated disc and radiculopathy. Study medication was resumed on Day 362 and was taken until the time of death. On Day 1450 after randomization, the patient suffered a sudden massive heart attack and died. The cause of death was an acute myocardial infarction, which was considered possibly related to study drug. The death was adjudicated as a thromboembolic event of sudden cardiac death.

From Site 045, AN 1419, a 74-year-old male, died from chronic lymphocytic leukemia, gastric perforation, and pneumonia. Past medical history was remarkable for MCI, lymphadenopathy, irregular heart rate, basal cell carcinoma and rosacea. Concomitant medications included metronidazole and vitamin E. Laboratory results at screening revealed a white blood cell count of 15,100 microL and a platelet count of 116,000/mm^3. Following 41 days of study therapy, the patient was seen by a hematologist. Laboratory results were WBC 15.7 X 10 ^{9}/L, platelets 104 10 ^{9}/L, and lymphocyte count 11.78 10 ^{9}/L. Blood for morphology and cell maker studies revealed that the lymphocytes were increased in absolute numbers. The lymphocytosis was consistent with chronic lymphocytic anemia. Cell marker studies were positive for CD_5, CD_{19}, CD_{20}, CD_{23}, and Kappa-positive. The patient was diagnosed with chronic lymphocytic leukemia. Study medication continued without interruption. He was treated with prednisone and chlorambucil which was given over various periods of time throughout the study. On Day 676 after randomization, the patient was hospitalized for bilateral pneumonia. Arterial blood gas showed a pCO_2 of 33 (low); pO_2 of 60 (low); and a HCO_3 of 22.4 (low). Lab results showed a white blood count of 66,600/microL (high); red blood count of 3.2 X 10^{12}/L (low); hemoglobin of 9.9 gm/dL (low); hematocrit of 29.8% (low); RDW of

19.8 (high); and lymphocytes of 62,600/microL (high). The patient was treated with oxygen and ceftriaxone. Study therapy was continued. Six days later, a chest x-ray revealed a right pleural effusion which was treated successfully. Two days later, the patient was discharged and was doing well until Day 689 postrandomization. On Day 689, he was rushed to the hospital for emergency stomach surgery where a ¼-inch perforation was found. Biopsy revealed the lesion hole was caused by the chronic lymphocytic leukemia. The tumor masses were found in the lungs. Study therapy was discontinued as of day 688. Patient was treated with antibiotics and oxygen. The patient subsequently died 27 days later. The cause of death was chronic lymphocytic leukemia, gastric perforation and pneumonia. The adverse experiences of chronic lymphocytic leukemia, gastric perforation and pneumonia were considered definitely not related to study therapy. The death was adjudicated as a non-thromboembolic event.

From Site 046, AN 1453, an 80-year-old male, died of acute myeloid leukemia and bacterial sepsis. Past medical history was remarkable for MCI, non-insulin dependent diabetes mellitus, malignant melanoma, atrial fibrillation, congestive heart failure, hypertension, coronary artery disease, cerebrovascular disorder, Legionnaire's disease, and osteoarthritis. Concomitant medications included nitroglycerin, glyburide, captopril, warfarin, digoxin, furosemide, aluminum hydroxide/magnesium carbonate and acetaminophen. After 4 days on study drug, the patient was experiencing worsening symptoms of congestive heart failure, gastritis, and worsening hypertension and atrial fibrillation. Study therapy was discontinued on Day 36. On Day 36 postrandomization, 2 days after discontinuing study therapy, bloodwork was performed which revealed; WBC 1.4/mm^3 (normal range 3.8-10.8); segmented neutrophils, 33.8%; lymphocytes, 55%; and platelet count 90,000/mm^3. On Days 42, 46, and 50, repeat blood serology revealed progressive pancytopenia. On Day 50, a bone marrow biopsy was done and the patient was diagnosed with acute myelogenous leukemia. The patient declined treatment. The individual subsequently developed sepsis and expired 56 days after randomization. The cause of death was recorded as acute myelogenous leukemia and sepsis. Both adverse experiences were considered definitely not related to study therapy. The death was adjudicated as a non-thromboembolic event.

Deaths Due To Adverse experiences With Onset More Than 14 Days After the Last Dose of Study Drug, but Related to Non-fatal Adverse Experiences in the On-Drug Period

Patients ANs 0290, 0536, and 0113, all in the rofecoxib group, had non-fatal adverse experiences that began on study drug and may have been precursor events related to the off-drug fatal adverse experience:

For Site 010, AN 0290, an 87-year-old male, died of lung cancer. Past medical history was remarkable for MCI, hypertension, benign prostatic hypertrophy, systolic murmur, and sinus bradycardia. Upon study entry patient had history of smoking but stopped 1 year prior to study start. Concomitant therapy included enalapril maleate. On Day 569 after randomization, the nonserious adverse experiences of cough and bloody sputum were reported. Cephalexin monohydrate was started 9 days later. On Day 579, the patient was seen for a study visit and was discontinued from the study since he was diagnosed with probable AD, a study endpoint per protocol. Study medication was discontinued that day and the patient was referred to his primary care physician for treatment. The patient's wife reported to the site that the patient was diagnosed with lung cancer 594 days after randomization, 15 days after discontinuing the study. On Day 625 after randomization, 46 days after discontinuing the study, the patient died of lung cancer. This adverse experience was considered definitely not related to study therapy. The patient death was counted as an on-drug death since the fatal off-drug adverse experience (lung cancer) may have been related to the earlier nonfatal on-drug adverse experiences (bloody sputum and cough). The death was adjudicated as a non-thromboembolic event.

For Site 017, AN 0536, a 91-year-old female, died of metastatic ovarian cancer. Past medical history was remarkable for MCI, aortic sclerosis, chronic interstitial pulmonary disease, and osteoarthritis. The patient developed hypertension on Day 801 and atrial fibrillation on Day 836 and subsequently was treated with digoxin, warfarin, metoprolol, and lisinopril. On Day 850 after randomization, the patient developed a nonserious adverse experience of abdominal pain and discontinued dosing with study medication. On Day 954 after randomization, 104 days after discontinuing study medication, the patient underwent an ultrasound and computed tomography scan of the abdomen and pelvis to evaluate persistent abdominal pain. A left adnexal mass was found and the patient was diagnosed with ovarian cancer. The patient had a hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and debulking on Day 969. Intraoperative findings were remarkable for a large amount of ascites, a 2-cm metastatic right liver lobe lesion, a 7 to 8-cm mass in the mesentery of the transverse colon, pelvic mass involving bilateral ovaries, uterus, and cul-de-sac. The patient died 1021 days after randomization 171 days after discontinuing study medication due to the metastatic ovarian cancer. This adverse experience was considered definitely not related to study therapy. The abdominal pain occurred within 14 days of the last dose of study medication. The patient death was counted as an on-drug death since the fatal off-drug adverse experience (metastatic ovarian cancer) may have been related to the earlier nonfatal on-drug adverse experience (abdominal pain). The death was adjudicated as a non-thromboembolic event.

For Site 013, AN 1113, a 79-year-old male, died of acute lymphocytic leukemia. Past medical history was remarkable for MCI, arrhythmia, hyperlipidemia, benign prostatic hypertrophy, and chronic obstructive pulmonary disease. Concomitant therapy included tamsulosin hydrochloride 0.4 to 0.8 mg daily and simvastatin 20 mg daily. At the screening visit the following laboratory values were noted: white blood count (WBC) 3,500/microL, hematocrit 46.7%, hemoglobin 16.1 gm/dL, and platelet count 186,000/mm^3. On Day 28 after randomization, a nonserious adverse experience of decreased WBC count (2200/microL) was reported. On Day 41, the WBC count was 1,900/microL. The last dose of study drug was taken on Day 40; study drug was discontinued due to the progressive leukopenia. On Day 102 after randomization, 62 days after discontinuing study medication, the patient was reevaluated for neutropenia and anemia. The laboratory values on the same day were: WBC 2,400/microL, hemoglobin 10.5 gm/dL, hematocrit 31%, mean corpuscular volume 98/mm^3, and platelets 93,000/mm^3. A biopsy and bone marrow aspiration were performed which revealed stage IV small B-cell non-Hodgkin's lymphoma. The patient was treated with prednisone and cyclophosphamide. On Day 123 the patient was hospitalized for a syncopal episode secondary to pancytopenia. A flow cytometry was reviewed by the pathologist who revised the cancer diagnosis to pre-B-cell acute lymphocytic leukemia. During hospitalization, the patient slowly improved and his blood counts improved. He was given blood transfusions and epoetin alfa (Procrit) support. On Day 207 after randomization, he received his final treatment of chemotherapy. On Day 221, the patient was considered to be in remission. On Day 362, the patient's leukemia re-emerged. Laboratory values on Day 388 were WBC 1,500 microL, Hemoglobin 9.6 gm/dL, and platelets 25,000/mm^3. The patient was admitted to the hospital for a second induction treatment with daunomycin, vincristine, and prednisone. The patient also received 4 units of packed red blood cells and platelet transfusions. On Day 419, the patient was discharged and laboratory values were: WBC 1,100/microL, neutrophils 70%, lymphocytes 27%, monocytes 4%, hemoglobin 10.1 gm/dL, hematocrit 30%, and platelets 69,000/mm^3. On Day 459, 419 days after discontinuing study medication, the patient died of acute lymphocytic leukemia. The two recorded serious adverse experiences of lymphocytic leukemia were considered definitely not related to study therapy. The patient death was counted as an on-drug death since the fatal off-drug adverse experience (acute lymphocytic leukemia) may have been related to the earlier nonfatal on-drug adverse experience (decreased white blood cell count). The death was adjudicated as a non-thromboembolic event.

8.3.1.1.3.2 **Placebo Group**

Deaths Due to Serious Adverse Experiences That Began On-Drug or Within 14 Days of Last Dose of Study Drug

From Site 004, AN 0111, a 78-year-old female, died of lymphoma. Past medical history was remarkable for MCI and osteoporosis. On Day 607 after randomization, the patient was seen for a site visit and a CBC revealed all values within normal limits except the following: segmented neutrophils 85.2%, lymphocyte 6.6%, platelet count 470 $10^3/mm^3$, and decreased hemoglobin with a value of 11.6 gm/dL. On Day 617 after randomization, the patient was found at home on the floor complaining of stomach pain, general malaise, weakness, tiredness, difficulty walking, and in diffuse pain. The patient was hospitalized the same day for what turned out to be intra-abdominal lymphoma and study medication was discontinued. On Day 620 after randomization, exploratory surgery was performed and revealed widespread large B-cell lymphoma. The patient was treated with opioids and chemotherapy was planned. The patient was discharged to a nursing home 628 days after randomization. The patient died 12 days later from complications related to metastatic lymphoma. The lymphoma was considered definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

From Site 006, AN 0188, an 82-year-old male, died of acute myocardial infarction due to hypertension. Past medical history was remarkable for MCI, coronary artery disease, benign prostatic hypertrophy, and arrhythmia. Concomitant medications included isosorbide, and vitamin E. On Day 945 after randomization, the patient developed a nonserious adverse event of hypertension and began dosing with quinapril hydrochloride. On Day 1260 after randomization, the patient experienced a serious adverse event of chest pain and study medication was discontinued because of this event. An EKG indicated that the patient had a possible acute inferior and lateral myocardial infarction. On Day 1262 after randomization, the patient underwent left heart catheterization and coronary angiography. The patient died 2 days later. The death certificate noted the immediate cause of death as "acute myocardial infarction due to hypertension". The chest pain and acute inferior lateral wall myocardial infarction were considered probably not related to study drug. The death was adjudicated as a thromboembolic event.

For Site 007, AN 1543, an 85-year-old female, died of respiratory failure. Past medical history was remarkable for MCI, osteoporosis, hypothyroidism, atrial fibrillation, anemia, transient ischemic attack, and pseudogout. Concomitant therapy included warfarin sodium, levothyroxine sodium, alendronate sodium, diltiazem hydrochloride, and acetaminophen (+) propoxyphene napsylate. After 954 days of dosing with study medication, the patient discontinued since she wanted to dose with rofecoxib. The patient began dosing with rofecoxib 966 days after randomization. The next day the patient developed "acute respiratory failure" and died. The acute respiratory failure was considered probably not related to study drug and not related to marketed rofecoxib therapy. The death was adjudicated and was not a confirmed thromboembolic event.

For Site 007, AN 1547, an 82-year-old male, died of metastatic adenocarcinoma. Past medical history was remarkable for MCI, occasional back pain, basal and squamous cell carcinoma, anxiety, depression, and Non-Hodgkin's lymphoma. Concomitant therapy included vitamin E, acetaminophen (+) hydrocodone bitartrate, sertraline hydrochloride, amphetamine aspartate (+) amphetamine sulfate (+) dextroamphetamine saccharate (+) dextroamphetamine sulfate, and alprazolam. On Day 36 after randomization, the patient had a stroke and was started on warfarin. Study medication was discontinued 84 days after randomization due to high prothrombin time. On Day 93 after randomization, 9 days after discontinuing study medication, the patient fell, strained his back, and was hospitalized. A bone scan was performed which showed multiple defects raising the question of metastatic disease. On Day 102 after randomization, the patient fell again injuring his lower back and was hospitalized. An MRI was performed the same day which suggested metastatic disease of the right sacroiliac joint. A carcinoembryonic antigen test was also elevated. A CT-guided aspirate of the right sacroiliac joint revealed malignant cells consistent with adenocarcinoma. On Day 112 after randomization, the patient was discharged. On Day 163, the patient died from the metastatic adenocarcinoma. The back strain, back pain, and metastatic adenocarcinoma were considered definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

From Site 009, AN 0264, a 76-year-old male, died of metastatic colon cancer. Past medical history was remarkable for MCI, congestive heart failure, hypertension, atrial fibrillation, emphysema, BPH, non-insulin dependent diabetes mellitus and colon cancer. Concomitant therapy included finasteride, clonidine, furosemide, nisoldipine, digoxin, glyburide, and metformin hydrochloride. On Day 430 post randomization, an elevated

serum carcinoembryonic antigen level lead to a CT scan of the abdomen which revealed diffuse hepatic metastases. A needle guided biopsy was consistent with metastatic adenocarcinoma colon cancer. Because the cancer was very widespread and present in both lobes of the liver, the patient was not considered a surgical candidate. Treatment included chemotherapy of leucovorin calcium and fluorouracil weekly. Study medication was discontinued on day 457 due to chemotherapy treatment. On Day 818, the patient discontinued from the study because developed generalized weakness from his illness. The patient died 882 days after randomization, 426 days after discontinuing study medication, of metastatic colon cancer. The metastatic colon cancer was considered probably not related to study therapy. The death was adjudicated as a non-thromboembolic event.

For Site 010, AN 0294, a 77-year-old male, died of metastatic malignant melanoma. Past medical history was remarkable for MCI, seizure disorder, and benign prostatic hypertrophy. Concomitant therapy included phenytoin and vitamin B12. The patient had a suspicious mole removed from his back and was diagnosed with melanoma 556 days after randomization. On Day 584, a computed tomography scan of the chest demonstrated two soft tissue masses with associated multiple lesions in the liver which were consistent with metastatic disease. Seven days later the oncologist informed the patient that he had metastatic disease which was incurable. The patient was to undergo a course of single agent alfa-interferon; however, 615 days after randomization the patient died. The malignant melanoma was considered probably not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 010, AN 0308, an 85-year-old male, died of renal failure with a secondary condition of leukemia. Past medical history was remarkable for MCI, diabetes mellitus, and hypertension. Concomitant therapy included irbesartan, hydrochlorothiazide, and glipizide. Baseline laboratory values included: platelet count 120,000 mm[3], white blood cell count 9,400/ microL, hemoglobin 15.6 gm/dL, BUN 31 mg/dL, and creatinine 1.2 mg/dL. On Day 407 after randomization, the patient had laboratory tests performed by his primary care physician and the results were found to be strikingly abnormal. Laboratory values were: platelet count 48,000/mm^3, white blood cell count 52,400/microL (with 69% blasts), hemoglobin 13.8 gm/dL, BUN 53 mg/dL, creatinine 3.0 mg/dL, uric acid 13.6 mg/dL, and lactate dehydrogenase 2054 U/L. The patient was diagnosed with acute myelogenous leukemia, uric acid nephropathy, and renal failure. Study medication was discontinued 406 days after randomization due to these

events. On Day 411, laboratory values were: white blood cell count 44,100/microL, hemoglobin 12.0 gm/dL, and platelet count of 57,000/mm^3. A central venous catheter was placed and the patient was treated with hydration and alkalization of urine for the uric acid nephropathy. On Day 413, the patient developed pneumonia. The patient's condition declined and oxygen support was required. During hospitalization, the patient developed worsening acute renal failure and the leukemia continued to progress. On Day 416 after randomization, 10 days after discontinuing study medication, the patient died. Immediate cause of death was renal failure with an underlying condition of leukemia. The acute myelogenous leukemia, uric acid nephropathy, and renal failure were considered probably not related to study drug. The pneumonia was considered definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 011, AN 0323, an 81-year-old male, died of heart failure due to renal failure. Past medical history was remarkable for MCI, hypertension, and pernicious anemia. Concomitant therapy included verapamil, Vitamin E, and cyanocobalamin. On Day 716 after randomization, the patient developed atrial fibrillation and began dosing with enoxaparin sodium and subsequently dosed with digoxin, diltiazem hydrochloride, benazepril hydrochloride, and warfarin sodium. On Day 1067, the patient developed diabetes and began dosing with glyburide. The patient had flu-like symptoms 1193 days after randomization and discontinued study drug at this time. The patient was admitted to the hospital 3 days later with an absence of bowel sounds. On Day 1197, the patient developed renal failure, pancreatitis, heart failure, and an ischemic bowel and died. The death certificate listed the cause of death as heart failure due to renal failure which was a consequence of pancreatitis. The investigator also identified ischemic bowel as a cause of death. The absence of bowel sounds and the presence of heart failure, renal failure, ischemic bowel, and pancreatitis were considered definitely not related to study therapy. The death was adjudicated and was a non-thromboembolic event.

For Site 017, AN 0539, a 72-year-old male, died of hypertension. Past medical history was remarkable for MCI, hypertension, atrial tachycardia, and rhinitis. Concomitant therapy included loratadine, terazosin hydrochloride, benazepril hydrochloride, atenolol, and digoxin. On the morning of Day 243 after randomization, the patient was found dead in bed. The death certificate listed the cause of death as "hypertension". No further information was obtained regarding this event. Study medication was taken until the time of death. The hypertension was probably not related to study drug. This death was adjudicated as having insufficient data to make consensus agreement as to the type of event.

For Site 021, AN 0621, a 77-year-old male, died of an acute myocardial infarction. Past medical history was remarkable for MCI, arrhythmia, and kidney stones. Concomitant therapy included benazepril hydrochloride for hypertension which began 82 days after dosing with study medication. On Day 692 after randomization, the patient went home after shopping and complained of chest pain. The patient laid down and passed away. The death certificate states the cause of death as acute myocardial infarction. Study medication was taken until the time of death. The acute myocardial infarction was considered probably not related to study drug. The death was adjudicated as a thromboembolic event of sudden cardiac death.

For Site 040, AN 1256, an 82-year-old female, died of cardiopulmonary arrest. Past medical history was remarkable for MCI and hypertension. Concomitant therapy included amlodipine besylate, lisinopril, and furosemide. The patient had been placed in an assisted care facility after a fall that resulted in a compressed vertebrae. On Day 611 after randomization, "coronary artery disease" was recorded as a serious adverse experience; the patient died 63 days later. The patient continued dosing with study medication until the time of death. The death certificate listed the primary cause of death as cardio-pulmonary arrest. No further information was obtained regarding this event. The coronary artery disease and cardio-pulmonary arrest were considered definitely not related to study drug. The death was adjudicated as a thromboembolic event of sudden cardiac death.

For Site 043, AN 1350, a 79-year-old female, died of multiple organ failure and metastatic cancer to the liver. Past medical history was remarkable for MCI, bladder cancer, hypercholesterolemia, depression, and hypertension. Concomitant therapy included atorvastatin calcium and sertraline. The patient was complaining of low back pain and fatigue and was admitted to the hospital 702 days after randomization for further evaluation. Study medication was discontinued 5 days later. A urine culture showed greater than 100,000 hemolytic streptococci and greater than 100,000 staphylococcal species. A blood culture revealed gram positive bacillus. An abdominal computed axial tomography scan revealed multiple lesions in the liver, lung, and periaortic/retroperitoneal lymph nodes. A liver biopsy on Day 702 was consistent with metastatic bladder cancer. The patient discontinued study medication 6 days later due to the metastatic bladder cancer. The patient refused chemotherapy and was discharged to home 710 days after randomization. The patient died 8 days later secondary to multiple organ failure related to metastatic cancer. The bladder cancer, metastasis to the liver, and multiple organ failure were considered definitely not related to study drug. The death was adjudicated as a non-thromboembolic event.

For Site 044, AN 1378, a 74-year-old male, died of an acute myocardial infarction. Past medical history was remarkable for MCI, hypertension, peripheral vascular disease, and bilateral ankle edema. Concomitant therapy included ibuprofen, testosterone, loratadine, timolol maleate, latanoprost, ascorbic acid (+) ferrous sulfate (+) vitamin B complex, potassium chloride, dorzolamide hydrochloride, hydrochlorothiazide, propranolol hydrochloride, quinapril hydrochloride, pentoxifylline, and vitamin E. The patient began dosing with metolazone (Day 99) and sildenafil citrate (Day 265) during the study. On Day 361 after randomization, the patient had an electrocardiogram performed which showed sinus bradycardia (considered not clinically significant). On Day 392 after randomization, the patient died in his sleep. Study medication was taken up until the time of death. The death certificate listed the cause of death as acute myocardial infarction, considered probably not related to study drug. The death was adjudicated as a thromboembolic event of sudden cardiac death.

From Site 046, AN 1445, a 77-year-old female, died of an intracranial hemorrhage. Past medical history was remarkable for MCI, depression, hypertension, migraine, hypercholesterolemia, left ventricular hypertrophy, sinus bradycardia, heart murmur, systolic bruit, mitral insufficiency, aortic stenosis, angina pectoris, aortic insufficiency, myocardial infarction, congestive heart failure, atrial fibrillation, and edema (site unspecified). Concomitant medications included warfarin sodium, acetaminophen/ dichloralphenazone/isometheptene mucate, fluoxetine hydrochloride, fosinopril sodium, atorvastatin calcium, nitroglycerin, and vitamin E. On Day 839 after randomization, the patient was hospitalized for worsening bradycardia. On Day 884, the patient complained of the "worst headache of her life" and began having difficulty with speech, developed hemiparesis, followed by nausea and vomiting, and very quickly became unresponsive. She was taken to the hospital and CT scan showed a right basal ganglion bleed. Glasgow Coma Scale was 3 to 4, and pupils were not reactive. Family requested do not resuscitate (DNR) status and the patient expired that same day. Date of last dose of study therapy was not determined. Cause of death was listed as large right frontal basal ganglia hemorrhage. The hemorrhage was considered probably not related to study therapy. The death was adjudicated as a hemorrhagic event.

From Site 046, AN 1472, a 68-year-old male, died of metastatic adenocarcinoma (unknown primary site). Past medical history was remarkable for MCI, hypercholesterolemia, osteoarthritis, onychomycosis and history of hepatitis B. Concomitant therapy included acetaminophen. On Day 482 post randomization blood serology revealed an elevated platelet count. On Day 591, a bone marrow aspiration was performed and the

patient was diagnosed with metastatic adenocarcinoma (unknown primary site). Study medication was discontinued on day 607. The patient expired on day 656, 49 days after discontinuing study medication. The cause of death was metastatic adenocarcinoma (unknown primary site). The investigator felt the cancer was probably not related to study medication. The death was adjudicated as a non-thromboembolic event.

8.3.1.1.4 Death Adjudication Results

All deaths were adjudicated, whether they occurred on or off of study medication, per the procedures described in the Acute Thromboembolic Vascular Events SOP [3.11.2]. Statistical analyses of all-cause mortality and thrombotic cardiovascular mortality, however, were performed only for patients on-drug, as defined in Section 5.5.1.2.7 and by the analyses described in Section 5.8.1.8.

Crude proportions, patient-year-adjusted incidence rates, and 95% CIs are given in Table 51 for all-cause and thrombotic cardiovascular mortality. There were 27 (3.7%) all cause deaths in the rofecoxib arm and 15 (2.1%) in the placebo arm. The patient-year adjusted incidence rates were 1.96 and 0.95 per 100 patient-years for the rofecoxib and placebo arms, respectively. The 95% CI for all-cause mortality for the rofecoxib group was (1.34, 2.85) and for the placebo group (0.57, 1.57). There were 8 (1.1%) thrombotic cardiovascular deaths in the rofecoxib arm and 4 (0.6%) in the placebo arm. The patient-year adjusted incidence rates were 0.58 and 0.25 per 100 patient-years for the rofecoxib and placebo arms, respectively. The 95% CI for thrombotic cardiovascular mortality for the rofecoxib group was (0.29, 1.16), and for the placebo group (0.10, 0.68).

Table 51

All-Cause and Thrombotic Cardiovascular Mortality
On-Drug[†]

Endpoint	Rofecoxib (N=723)		Placebo (N=728)	
	n (%)[‡]	Rate[§] (95% CI)	n (%)[‡]	Rate[§] (95% CI)
All-cause mortality	27 (3.73)	1.957 (1.342, 2.853)	15 (2.06)	0.949 (0.572, 1.574)
Thrombotic cardiovascular mortality	8 (1.11)	0.581 (0.290, 1.161)	4 (0.55)	0.253 (0.095, 0.675)

Note: Patient with multiple events may be counted more than once in different terms, but only once in one term.
[†] On drug includes the period through 14 days after discontinuation of study drug.
[‡] Crude incidence (n/Nx100).
[§] Events per 100 patient-years, where patient-years at risk (PYR) were calculated based on the overall endpoint.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.
CI = Confidence Interval

Data Source: [4.2]

8.3.1.2 Nonfatal Serious Clinical Adverse Experiences

Both nonfatal and fatal serious clinical adverse experiences reported during the trial are accounted for in Section 8.2.2. Serious adverse experiences occurred in 452 patients in the on-drug population: 217 (30.0%) in the rofecoxib group and 236 (32.4%) in the placebo group (see Table 45 and Table 46 for display of serious adverse experiences for the On-Drug and ITT populations, respectively). Two patients had nonfatal serious adverse experiences which occurred after the baseline visit, but prior to the randomization visit (ANs 0146 and 0648) and were described in Section 8.2.2.3.2. Complete narratives of all serious adverse experiences can be found in [4.6].

8.3.1.3 Patients Who Discontinued Study Medication Due to Clinical Adverse Experiences

The summary and statistical analysis for patients who discontinued study medication due to clinical adverse experiences, drug-related, serious, and serious drug-related adverse experiences, for the on-drug and ITT populations are shown in the Clinical Adverse Experience Summary tables (Section 8.2.1.1.1, Table 39 and Section 8.2.1.1.2, Table 40, respectively).

Data for the on-drug and ITT populations for clinical adverse experiences by body system which led to discontinuation of study drug are shown in the following sections.

8.3.1.3.1 On-Drug Population

Table 52 shows patients on study drug, or whose adverse experience occurred within 14 days of last dose and who discontinued study drug due to the adverse experiences. A total of 303 patients discontinued study medication due to clinical adverse experiences: 156 (21.6%)in the rofecoxib group and 147 (20.2%) in the placebo group. The 95% CIs for the difference between treatment groups were performed for incidences of adverse experiences occurring at ≥2%. The 95% CIs did not include zero for two body system categories: cardiac disorders and neoplasms (benign, malignant, and unspecified). The 95% CIs included zero for all other body systems; the difference was ± 1.36 percentage points in magnitude.

Discontinuation of study therapy due to cardiac disorders occurred in a total of 33 patients: 23 (3.2%) in the rofecoxib treatment group and 10 (1.4%) in the placebo group. The 95% CIs on the difference between proportions (1.81 percentage points) was [0.3 and 3.5]. Nine (1.2%) patients on rofecoxib

and 4 (0.5%) patients on placebo discontinued study medication due to myocardial infarction. Five (0.7%) patients in the rofecoxib group and 3 (0.4%) in the placebo group discontinued study medication due to coronary artery disease. A discussion of serious cardiac events and results of adjudication can be found in Section 8.4.4.

Fifty-five patients discontinued from study drug due to gastrointestinal disorders: 32 (4.4%) in the rofecoxib group and 23 (3.2%) in the placebo group. Numerically, the most common reasons for discontinuation from study drug were: diarrhea (6 and 2 respectively), dyspepsia (3 and 4), and nausea (4 and 5). Discontinuation of study medication due to investigator reported upper GI perforations, ulcers, and bleeds occurred for a total of 8 (1.1%) patients in the rofecoxib group and 1 (0.1%) patient in the placebo group: duodenal ulcer (ANs 0826 and 0851 in the rofecoxib group), duodenal ulcer hemorrhage (AN 0352 in the rofecoxib group), duodenal ulcer perforation (AN 0360 in the placebo group), gastric perforation (AN 1419 in the rofecoxib group), gastric ulcer (ANs 0690, 1221, and 1650, all in the rofecoxib group), and gastrointestinal hemorrhage (ANs 0394, 0690, 1221 all in the rofecoxib group). All upper GI perforations, ulcers, and bleeds were adjudicated by the rofecoxib Phase III Clinical Event Monitoring Case Review Committee according to procedures described in [3.11.1]. Results of adjudication are in Section 8.4.3.

Fourteen (1.9%) patients in the rofecoxib group and 11 (1.5%) patients in the placebo group discontinued study medication due to general disorders. Seven patients discontinued drug due to chest pain (3 and 4, respectively). Four patients, all in the rofecoxib group, discontinued drug due to peripheral edema.

Thirty-four patients discontinued study drug due to musculoskeletal and connective tissue disorders: 12 (1.7%) in the rofecoxib group and 22 (3.0%) in the placebo group. The most common adverse experiences in this category were: arthralgia (3 and 5, respectively), arthritis (2 and 4), and osteoarthritis, 0 and 6).

Five (0.7%) patients in the rofecoxib group and 17 (2.3%) patients in the placebo group discontinued study drug due to benign, malignant, or unspecified neoplasms. The 95% CIs on the difference between proportions (-1.64 percentage points) was -3.1 and -0.4. The most common neoplasm reported in this category was malignant lung neoplasm in 4 patients in the placebo group.

Forty-four patients discontinued study medication due to nervous system disorders: 25 (3.5%) patients in the rofecoxib group and 19 (2.6%) patients in the placebo group. Eight patients experienced cerebrovascular accident and discontinued study drug: 4 in each treatment group (0.6 and 0.5% in the rofecoxib and placebo groups, respectively). Nine patients experienced dizziness: 4 (0.6%) in the rofecoxib group and 5 (0.7%) in the placebo group.

Three patients on rofecoxib and 5 on placebo discontinued study drug due to renal and urinary disorders. Of these, 2 patients in each treatment group discontinued drug due to renal failure (ANs 0105 and 0762 in the rofecoxib group, and ANs 0308 and 0800 in the placebo group). Two patients, one in each treatment group, discontinued study drug due to renal impairment (ANs 1025 and 1564, in the rofecoxib and placebo groups, respectively). Brief narratives follow below:

From Site 004, AN 0105, a 78-year-old female in the rofecoxib group, had a nonserious adverse experience of acute renal failure. Medical history was remarkable for osteoporosis, hypertension, and hypothyroidism. Concomitant therapies included captopril and diltiazem hydrochloride for hypertension. Blood pressure upon screening for the study was 160/74 mm/Hg. Baseline BUN was 16 mg/dl and creatinine was 0.8 mg/dl. Hydralazine was also started for hypertension on Day 63 after randomization (blood pressure had been remaining steady around 160/68 mm/Hg). The patient was also started on dyazide on Day 217. The patient developed increased blood pressure (184/68 mm/Hg) on Day 489. On Day 658 after randomization, laboratory results yielded blood urea nitrogen level at 41 mg/dl and serum creatinine at 1.8 mg/dl. Study drug was discontinued on Day 663 due to chronic renal failure rated as possibly related to study drug. By Day 733, BUN was 21 mg/dL and serum creatinine was 1.2 mg/dL and remained stable throughout the rest of the study. The patient continued in the study off study drug and completed the trial.

From Site 008, AN 0800, a 71-year-old male in the placebo group, discontinued study drug due to the nonserious adverse experience of acute renal failure on Day 258. The patient's medical history was unremarkable, except for asthma and bronchitis. Concomitant medications were taken for the asthma and bronchitis (methylprednisone and prednisone). Baseline laboratory values for BUN were 18 mg/dL and for serum creatinine, 0.7 mg/dL. On Day 258, the patient had adverse experiences of dry mouth, urinary frequency, and renal failure. Laboratory results at Day 310 yielded BUN at 58 mg/dL and serum creatinine at 3.9 mg/dL. Study drug was discontinued on Day 311. By Day 366, BUN dropped to 27 mg/dL and serum creatinine levels dropped to 1.6 mg/dl. The patient continued in the study until the trial was terminated by the sponsor.

From Site 010, AN 0308, an 84-year-old male in the placebo group, discontinued study drug due to the serious adverse experiences of acute myeloid leukemia, renal failure, and uric acid nephropathy. The patient died as a result of renal failure with acute myeloid leukemia being a secondary cause. A brief narrative can be found in Section 8.3.1.1.3.2 and a complete WAES narrative is in [4.6].

From Site 025, AN 0762, an 85-year-old male in the rofecoxib group, discontinued study drug due to a serious adverse experience of renal failure which resulted in death. A brief narrative can be found in Section 8.3.1.1.3.1 and a complete WAES narrative is in [4.6].

From Site 033, AN 1025, an 82-year-old male in the rofecoxib group, had acute MI as the primary cause of his death, with secondary causes related to coronary artery disease, chest pain, renal impairment, and lung infection. Study drug was discontinued when . A brief narrative can be found in Section 8.3.1.1.3.1 and a complete narrative in [4.6].

From Site 037, AN 1564, a 76-year-old male in the placebo group, discontinued study medication due to renal impairment. Medical history was remarkable for hypercholesterolemia and dyspepsia. Baseline BUN was 15 mg/dL and serum creatinine was above the normal range at 1.6 mg/dL. Baseline blood pressure was 146/94 mm/Hg. Lisinopril (10 mg) was started as a concomitant therapy on Day 101 after randomization due to the adverse experience of hypertension. On Day 121 and 373, BUN was at 25 and 27 mg/dL, respectively, and serum creatinine was at 1.7 mg/dL at both draws, but this was considered as not clinically significant by the investigator. Renal impairment was reported as a nonserious adverse experience on Day 568 (serum creatinine levels not reported) and study drug was discontinued. On Day 626, the dosage of lisinopril was decreased to 2.5 mg. By Day 737, serum creatinine was at 1.8 mg/dl. Levels of BUN were within the normal range throughout this time period. The patient continued in the study until it was terminated by Merck & Co., Inc. On the final study visit (Day 1212) serum creatinine levels were at 1.6 mg/dL and BUN was at 31 mg/dl.

Study drug was discontinued for 23 patients due to vascular disorders: 14 in the rofecoxib group and 9 in the placebo group. Ten patients in the rofecoxib group and 7 in the placebo group discontinued study drug due to hypertension.

Table 52

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Patient with at least one Adverse Experience	156	(21.6)	147	(20.2)	1.38 (-2.8, 5.6)
Patient with no Adverse Experience	567	(78.4)	581	(79.8)	-1.38 (-5.6, 2.8)
Blood and Lymphatic System Disorders	**2**	**(0.3)**	**4**	**(0.5)**	**ND**
Anemia nos	1	(0.1)	4	(0.5)	ND
Iron deficiency anemia	1	(0.1)	0	(0.0)	ND
Cardiac Disorders	**23**	**(3.2)**	**10**	**(1.4)**	**1.81 (0.3, 3.5)**
Acute myocardial infarction	4	(0.6)	2	(0.3)	ND
Angina unstable	2	(0.3)	0	(0.0)	ND
Atrial fibrillation	2	(0.3)	0	(0.0)	ND
Bradyarrhythmia	0	(0.0)	1	(0.1)	ND
Bradycardia nos	0	(0.0)	1	(0.1)	ND
Bundle branch block left	0	(0.0)	1	(0.1)	ND
Cardiac arrest	3	(0.4)	0	(0.0)	ND
Cardiac failure congestive	2	(0.3)	1	(0.1)	ND
Cardio-respiratory arrest	0	(0.0)	1	(0.1)	ND
Coronary artery disease nos	5	(0.7)	3	(0.4)	ND
Myocardial infarction	5	(0.7)	2	(0.3)	ND
Ventricular fibrillation	1	(0.1)	0	(0.0)	ND
Ventricular tachycardia	1	(0.1)	0	(0.0)	ND
Congenital, Familial and Genetic Disorders	**1**	**(0.1)**	**0**	**(0.0)**	**ND**
Epidermolysis bullosa	1	(0.1)	0	(0.0)	ND
Ear and Labyrinth Disorders	**2**	**(0.3)**	**4**	**(0.5)**	**ND**
Hearing impaired	0	(0.0)	1	(0.1)	ND
Tinnitus	2	(0.3)	1	(0.1)	ND
Vertigo	1	(0.1)	2	(0.3)	ND
Eye Disorders	**3**	**(0.4)**	**1**	**(0.1)**	**ND**
Amblyopia	1	(0.1)	0	(0.0)	ND
Diplopia	0	(0.0)	1	(0.1)	ND
Macular degeneration	2	(0.3)	0	(0.0)	ND
Gastrointestinal Disorders	**32**	**(4.4)**	**23**	**(3.2)**	**1.27 (-0.7, 3.3)**
Abdominal discomfort	1	(0.1)	1	(0.1)	ND
Abdominal distension	2	(0.3)	1	(0.1)	ND
Abdominal pain nos	4	(0.6)	2	(0.3)	ND
Abdominal pain upper	0	(0.0)	1	(0.1)	ND
Aphthous stomatitis	1	(0.1)	0	(0.0)	ND
Bowel sounds abnormal	0	(0.0)	1	(0.1)	ND

Table 52 (Cont.)

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Colonic Polyp	1	(0.1)	0	(0.0)	ND
Constipation	0	(0.0)	2	(0.3)	ND
Diarrhea nos	6	(0.8)	2	(0.3)	ND
Dry mouth	0	(0.0)	1	(0.1)	ND
Duodenal ulcer	2	(0.3)	0	(0.0)	ND
Duodenal ulcer hemorrhage	1	(0.1)	0	(0.0)	ND
Duodenal ulcer perforation	0	(0.0)	1	(0.1)	ND
Dyspepsia	3	(0.4)	4	(0.5)	ND
Enterocolitis	1	(0.1)	0	(0.0)	ND
Epigastric discomfort	1	(0.1)	0	(0.0)	ND
Gastric perforation	1	(0.1)	0	(0.0)	ND
Gastric ulcer	3	(0.4)	0	(0.0)	ND
Gastritis nos	1	(0.1)	0	(0.0)	ND
Gastrointestinal hemorrhage nos	1	(0.1)	0	(0.0)	ND
Gastrointestinal pain nos	0	(0.0)	1	(0.1)	ND
Gastroesophageal reflux disease	2	(0.3)	2	(0.3)	ND
Lip dry	0	(0.0)	1	(0.1)	ND
Loose stools	1	(0.1)	0	(0.0)	ND
Mallory-Weiss syndrome	1	(0.1)	0	(0.0)	ND
Mouth ulceration	1	(0.1)	0	(0.0)	ND
Nausea	4	(0.6)	5	(0.7)	ND
Rectal hemorrhage	1	(0.1)	1	(0.1)	ND
Upper gastrointestinal hemorrhage	2	(0.3)	0	(0.0)	ND
Vomiting nos	1	(0.1)	2	(0.3)	ND
General Disorders and Administration Site Conditions	**14**	**(1.9)**	**11**	**(1.5)**	**ND**
Asthenia	1	(0.1)	3	(0.4)	ND
Chest pain	3	(0.4)	4	(0.5)	ND
Chest tightness	0	(0.0)	1	(0.1)	ND
Fatigue	1	(0.1)	1	(0.1)	ND
Gait abnormal	1	(0.1)	0	(0.0)	ND
Gravitational edema	1	(0.1)	0	(0.0)	ND
Lethargy	1	(0.1)	0	(0.0)	ND
Malaise	0	(0.0)	1	(0.1)	ND
Edema peripheral	4	(0.6)	0	(0.0)	ND
Pain nos	1	(0.1)	0	(0.0)	ND
Pyrexia	0	(0.0)	1	(0.1)	ND
Sudden death	1	(0.1)	0	(0.0)	ND
Hepatobiliary Disorders	**1**	**(0.1)**	**1**	**(0.1)**	**ND**
Cholecystitis nos	1	(0.1)	0	(0.0)	ND
Cholelithiasis	1	(0.1)	1	(0.1)	ND

Table 52 (Cont.)

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Infections and Infestations	**7**	**(1.0)**	**3**	**(0.4)**	**ND**
Brain abscess nos	1	(0.1)	0	(0.0)	ND
Gastroenteritis nos	1	(0.1)	1	(0.1)	ND
Labyrinthitis nos	0	(0.0)	1	(0.1)	ND
Lung Infection nos	1	(0.1)	0	(0.0)	ND
Osteomyelitis nos	0	(0.0)	1	(0.1)	ND
Parasitic infection intestinal	1	(0.1)	0	(0.0)	ND
Pneumonia nos	1	(0.1)	0	(0.0)	ND
Upper respiratory tract infection nos	1	(0.1)	0	(0.0)	ND
Urinary tract infection nos	1	(0.1)	0	(0.0)	ND
Injury, Poisoning and Procedural Complications	**5**	**(0.7)**	**6**	**(0.8)**	**ND**
Burns second degree	0	(0.0)	1	(0.1)	ND
Compression fracture	0	(0.0)	1	(0.1)	ND
Electric shock	1	(0.1)	0	(0.0)	ND
Head injury	1	(0.1)	0	(0.0)	ND
Hip fracture	1	(0.1)	2	(0.3)	ND
Intervertebral disc injury	0	(0.0)	1	(0.1)	ND
Rib fracture	0	(0.0)	1	(0.1)	ND
Spinal compression fracture	1	(0.1)	0	(0.0)	ND
Traumatic chest injury nos	1	(0.1)	0	(0.0)	ND
Investigations	**6**	**(0.8)**	**3**	**(0.4)**	**ND**
Blood pressure increased	3	(0.4)	3	(0.4)	ND
Fecal occult blood positive	2	(0.3)	0	(0.0)	ND
Weight decreased	1	(0.1)	0	(0.0)	ND
Metabolism and Nutrition Disorders	**2**	**(0.3)**	**1**	**(0.1)**	**ND**
Diabetes mellitus nos	0	(0.0)	1	(0.1)	ND
Fluid retention	2	(0.3)	0	(0.0)	ND
Musculoskeletal and Connective Tissue Disorders	**12**	**(1.7)**	**22**	**(3.0)**	**-1.36 (-3.1, 0.2)**
Arthralgia	3	(0.4)	5	(0.7)	ND
Arthritis nos	2	(0.3)	4	(0.5)	ND
Back pain	3	(0.4)	2	(0.3)	ND
Bursitis	0	(0.0)	1	(0.1)	ND
Facial pain	0	(0.0)	1	(0.1)	ND
Localised osteoarthritis	0	(0.0)	2	(0.3)	ND
Muscle spasms	0	(0.0)	1	(0.1)	ND
Musculoskeletal pain	1	(0.1)	0	(0.0)	ND
Neck pain	0	(0.0)	1	(0.1)	ND
Osteoarthritis nos	0	(0.0)	6	(0.8)	ND
Pain in extremity	2	(0.3)	0	(0.0)	ND
Polymyalgia rheumatica	1	(0.1)	0	(0.0)	ND

Table 52 (Cont.)

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**5**	**(0.7)**	**17**	**(2.3)**	**-1.64 (-3.1, -0.4)**
Acute myeloid leukemia nos	0	(0.0)	1	(0.1)	ND
Bladder cancer nos	0	(0.0)	2	(0.3)	ND
Bone cancer metastatic	1	(0.1)	0	(0.0)	ND
Chronic lymphocytic leukemia nos	1	(0.1)	0	(0.0)	ND
Colon cancer metastatic	0	(0.0)	1	(0.1)	ND
Lung neoplasm malignant	0	(0.0)	4	(0.5)	ND
Lymphoma nos	0	(0.0)	1	(0.1)	ND
Malignant melanoma	0	(0.0)	1	(0.1)	ND
Metastases to liver	0	(0.0)	1	(0.1)	ND
Metastatic neoplasm nos, primary site unknown	0	(0.0)	1	(0.1)	ND
Multiple myeloma	1	(0.1)	0	(0.0)	ND
Esophageal carcinoma nos	0	(0.0)	2	(0.3)	ND
Pancreatic carcinoma nos	0	(0.0)	1	(0.1)	ND
Pancreatic neoplasm nos	1	(0.1)	0	(0.0)	ND
Prostate cancer nos	0	(0.0)	1	(0.1)	ND
Renal cell carcinoma stage unspecified	0	(0.0)	1	(0.1)	ND
Squamous cell carcinoma of skin	1	(0.1)	0	(0.0)	ND
Throat cancer nos	0	(0.0)	1	(0.1)	ND
Nervous System Disorders	**25**	**(3.5)**	**19**	**(2.6)**	**0.85 (-1.0, 2.7)**
Aphasia	0	(0.0)	1	(0.1)	ND
Balance impaired nos	1	(0.1)	0	(0.0)	ND
Cerebral hemorrhage	0	(0.0)	1	(0.1)	ND
Cerebrovascular accident	4	(0.6)	4	(0.5)	ND
Dizziness	4	(0.6)	5	(0.7)	ND
Dysphasia	1	(0.1)	0	(0.0)	ND
Extrapyramidal disorder	1	(0.1)	0	(0.0)	ND
Headache	1	(0.1)	1	(0.1)	ND
Hemiparesis	1	(0.1)	0	(0.0)	ND
Hypoesthesia	0	(0.0)	1	(0.1)	ND
Intention tremor	0	(0.0)	1	(0.1)	ND
Intracranial hemorrhage nos	1	(0.1)	1	(0.1)	ND
Migraine nos	1	(0.1)	0	(0.0)	ND
Neuralgia nos	0	(0.0)	1	(0.1)	ND
Paraesthesia	0	(0.0)	1	(0.1)	ND
Somnolence	2	(0.3)	0	(0.0)	ND
Spinal stenosis nos	1	(0.1)	0	(0.0)	ND
Syncope	3	(0.4)	2	(0.3)	ND
Transient ischaemic attack	4	(0.6)	2	(0.3)	ND

Table 52 (Cont.)

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Psychiatric Disorders	**7**	**(1.0)**	**12**	**(1.6)**	**ND**
Abnormal behavior nos	0	(0.0)	1	(0.1)	ND
Abnormal dreams	0	(0.0)	1	(0.1)	ND
Agitation	1	(0.1)	0	(0.0)	ND
Anorgasmia	0	(0.0)	1	(0.1)	ND
Anxiety	0	(0.0)	1	(0.1)	ND
Confusional state	1	(0.1)	2	(0.3)	ND
Delirium	0	(0.0)	1	(0.1)	ND
Depression	1	(0.1)	2	(0.3)	ND
Hypomania	1	(0.1)	0	(0.0)	ND
Insomnia	0	(0.0)	1	(0.1)	ND
Irritability	1	(0.1)	0	(0.0)	ND
Libido decreased	0	(0.0)	1	(0.1)	ND
Nightmare	1	(0.1)	0	(0.0)	ND
Panic attack	0	(0.0)	1	(0.1)	ND
Psychotic disorder nos	0	(0.0)	1	(0.1)	ND
Suicide attempt	1	(0.1)	0	(0.0)	ND
Renal and Urinary Disorders	**3**	**(0.4)**	**5**	**(0.7)**	**ND**
Renal failure acute	0	(0.0)	1	(0.1)	ND
Renal failure chronic	1	(0.1)	0	(0.0)	ND
Renal failure nos	1	(0.1)	1	(0.1)	ND
Renal impairment nos	1	(0.1)	1	(0.1)	ND
Urate nephropathy	0	(0.0)	1	(0.1)	ND
Urinary retention	0	(0.0)	2	(0.3)	ND
Reproductive System and Breast Disorders	**0**	**(0.0)**	**1**	**(0.1)**	**ND**
Erectile dysfunction nos	0	(0.0)	1	(0.1)	ND
Respiratory, Thoracic and Mediastinal Disorders	**5**	**(0.7)**	**5**	**(0.7)**	**ND**
Aspiration	0	(0.0)	1	(0.1)	ND
Dyspnea	2	(0.3)	0	(0.0)	ND
Emphysema	0	(0.0)	1	(0.1)	ND
Epistaxis	0	(0.0)	1	(0.1)	ND
Hemoptysis	0	(0.0)	1	(0.1)	ND
Nasal Polyps	0	(0.0)	1	(0.1)	ND
Pharyngolaryngeal pain	1	(0.1)	0	(0.0)	ND
Pulmonary fibrosis	2	(0.3)	0	(0.0)	ND

Table 52 (Cont.)

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Skin and Subcutaneous Tissue Disorders	**8**	**(1.1)**	**4**	**(0.5)**	**ND**
Ecchymosis	1	(0.1)	0	(0.0)	ND
Pigmentation disorder nos	1	(0.1)	0	(0.0)	ND
Pruritus	3	(0.4)	1	(0.1)	ND
Rash maculo-papular	0	(0.0)	1	(0.1)	ND
Rash Nos	4	(0.6)	2	(0.3)	ND
Vascular Disorders	**14**	**(1.9)**	**9**	**(1.2)**	**ND**
Aortic aneurysm	1	(0.1)	0	(0.0)	ND
Atherosclerosis	1	(0.1)	0	(0.0)	ND
Hematoma nos	1	(0.1)	0	(0.0)	ND
Hypertension nos	10	(1.4)	7	(1.0)	ND
Hypotension nos	1	(0.1)	0	(0.0)	ND
Phlebitis nos	0	(0.0)	1	(0.1)	ND
Thrombosis	1	(0.1)	1	(0.1)	ND

† On drug includes the period through 14 days after discontinuation of study drug.
CI = Confidence interval.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.3.1.3.2 Intention-to-Treat Population

Table 53 shows the patients in the ITT population who discontinued study therapy due to clinical adverse experiences. There were no significant differences between the ITT and on-drug populations. Similar to the on-drug population, the 95% CIs for the differences in proportions for the ITT population did not include zero for the categories of cardiac disorders or neoplasms (benign, malignant, and unspecified); more patients in the rofecoxib than the placebo group discontinued therapy due to cardiac disorders (1.67 percentage point difference, 95% CI [0.1,3.4]) and fewer patients in the rofecoxib than placebo group discontinued study therapy due to neoplasms (-1.37 percentage point difference, 95% CI [-2.9,-0.1]). The 95% CIs included zero for all other body systems; the difference was ± 1.5 percentage points in magnitude. Table 53 includes four additional patients in

each treatment group who had interrupted study drug dosing for more than 14 days prior to the onset of the adverse experience (therefore patients were counted in this off-drug [ITT] period) and who subsequently discontinued the study or the study medication.

Table 53

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n	(%)	n	(%)	(A-B)% 95% CI
Patient with at least one adverse experience	160	(22.1)	151	(20.7)	1.39 (-2.8, 5.6)
Patient with no adverse experience	563	(77.9)	577	(79.3)	-1.39 (-5.6, 2.8)
Blood and Lymphatic System Disorders	**2**	**(0.3)**	**4**	**(0.5)**	**ND**
Anemia nos	1	(0.1)	4	(0.5)	ND
Iron deficiency anemia	1	(0.1)	0	(0.0)	ND
Cardiac Disorders	**23**	**(3.2)**	**11**	**(1.5)**	**1.67 (0.1, 3.4)**
Acute myocardial infarction	4	(0.6)	2	(0.3)	ND
Angina unstable	2	(0.3)	0	(0.0)	ND
Aortic valve incompetence	0	(0.0)	1	(0.1)	ND
Atrial fibrillation	2	(0.3)	1	(0.1)	ND
Bradyarrhythmia	0	(0.0)	1	(0.1)	ND
Bradycardia nos	0	(0.0)	1	(0.1)	ND
Bundle branch block left	0	(0.0)	1	(0.1)	ND
Cardiac arrest	3	(0.4)	0	(0.0)	ND
Cardiac failure congestive	2	(0.3)	1	(0.1)	ND
Cardio-respiratory arrest	0	(0.0)	1	(0.1)	ND
Coronary artery disease nos	5	(0.7)	3	(0.4)	ND
Mitral valve incompetence	0	(0.0)	1	(0.1)	ND
Myocardial infarction	5	(0.7)	2	(0.3)	ND
Tricuspid valve incompetence	0	(0.0)	1	(0.1)	ND
Ventricular fibrillation	1	(0.1)	0	(0.0)	ND
Ventricular tachycardia	1	(0.1)	0	(0.0)	ND
Congenital, Familial and Genetic Disorders	**1**	**(0.1)**	**0**	**(0.0)**	**ND**
Epidermolysis bullosa	1	(0.1)	0	(0.0)	ND
Ear and Labyrinth Disorders	**2**	**(0.3)**	**4**	**(0.5)**	**ND**
Hearing impaired	0	(0.0)	1	(0.1)	ND
Tinnitus	2	(0.3)	1	(0.1)	ND
Vertigo	1	(0.1)	2	(0.3)	ND
Eye Disorders	**3**	**(0.4)**	**1**	**(0.1)**	**ND**
Amblyopia	1	(0.1)	0	(0.0)	ND
Diplopia	0	(0.0)	1	(0.1)	ND
Macular degeneration	2	(0.3)	0	(0.0)	ND

Table 53 (Cont.)

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Gastrointestinal Disorders	**32**	**(4.4)**	**23**	**(3.2)**	**1.27 (-0.7, 3.3)**
Abdominal discomfort	1	(0.1)	1	(0.1)	ND
Abdominal distension	2	(0.3)	1	(0.1)	ND
Abdominal pain nos	4	(0.6)	2	(0.3)	ND
Abdominal pain upper	0	(0.0)	1	(0.1)	ND
Aphthous stomatitis	1	(0.1)	0	(0.0)	ND
Bowel sounds abnormal	0	(0.0)	1	(0.1)	ND
Colonic polyp	1	(0.1)	0	(0.0)	ND
Constipation	0	(0.0)	2	(0.3)	ND
Diarrhea nos	6	(0.8)	2	(0.3)	ND
Dry mouth	0	(0.0)	1	(0.1)	ND
Duodenal ulcer	2	(0.3)	0	(0.0)	ND
Duodenal ulcer hemorrhage	1	(0.1)	0	(0.0)	ND
Duodenal ulcer perforation	0	(0.0)	1	(0.1)	ND
Dyspepsia	3	(0.4)	4	(0.5)	ND
Enterocolitis	1	(0.1)	0	(0.0)	ND
Epigastric discomfort	1	(0.1)	0	(0.0)	ND
Gastric perforation	1	(0.1)	0	(0.0)	ND
Gastric ulcer	3	(0.4)	0	(0.0)	ND
Gastritis nos	1	(0.1)	0	(0.0)	ND
Gastrointestinal hemorrhage nos	1	(0.1)	0	(0.0)	ND
Gastrointestinal pain nos	0	(0.0)	1	(0.1)	ND
Gastroesophageal reflux disease	2	(0.3)	2	(0.3)	ND
Lip dry	0	(0.0)	1	(0.1)	ND
Loose stools	1	(0.1)	0	(0.0)	ND
Mallory-Weiss syndrome	1	(0.1)	0	(0.0)	ND
Mouth ulceration	1	(0.1)	0	(0.0)	ND
Nausea	4	(0.6)	5	(0.7)	ND
Rectal hemorrhage	1	(0.1)	1	(0.1)	ND
Upper gastrointestinal hemorrhage	2	(0.3)	0	(0.0)	ND
Vomiting nos	1	(0.1)	2	(0.3)	ND
General Disorders and Administration Site Conditions	**14**	**(1.9)**	**11**	**(1.5)**	**ND**
Asthenia	1	(0.1)	3	(0.4)	ND
Chest pain	3	(0.4)	4	(0.5)	ND
Chest tightness	0	(0.0)	1	(0.1)	ND
Fatigue	1	(0.1)	1	(0.1)	ND
Gait abnormal	1	(0.1)	0	(0.0)	ND
Gravitational edema	1	(0.1)	0	(0.0)	ND
Lethargy	1	(0.1)	0	(0.0)	ND
Malaise	0	(0.0)	1	(0.1)	ND
Edema peripheral	4	(0.6)	0	(0.0)	ND
Pain nos	1	(0.1)	0	(0.0)	ND
Pyrexia	0	(0.0)	1	(0.1)	ND
Sudden death	1	(0.1)	0	(0.0)	ND

Table 53 (Cont.)

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Hepatobiliary Disorders	**1**	**(0.1)**	**1**	**(0.1)**	**ND**
Cholecystitis nos	1	(0.1)	0	(0.0)	ND
Cholelithiasis	1	(0.1)	1	(0.1)	ND
Infections and Infestations	**8**	**(1.1)**	**3**	**(0.4)**	**ND**
Brain abscess nos	1	(0.1)	0	(0.0)	ND
Gastroenteritis nos	1	(0.1)	1	(0.1)	ND
Labyrinthitis nos	0	(0.0)	1	(0.1)	ND
Lung Infection nos	1	(0.1)	0	(0.0)	ND
Osteomyelitis nos	0	(0.0)	1	(0.1)	ND
Parasitic infection intestinal	1	(0.1)	0	(0.0)	ND
Pneumonia nos	1	(0.1)	0	(0.0)	ND
Upper respiratory tract infection nos	1	(0.1)	0	(0.0)	ND
Urinary tract infection nos	2	(0.3)	0	(0.0)	ND
Injury, Poisoning and Procedural Complications	**5**	**(0.7)**	**6**	**(0.8)**	**ND**
Burns second degree	0	(0.0)	1	(0.1)	ND
Compression fracture	0	(0.0)	1	(0.1)	ND
Electric shock	1	(0.1)	0	(0.0)	ND
Head injury	1	(0.1)	0	(0.0)	ND
Hip fracture	1	(0.1)	2	(0.3)	ND
Intervertebral disc injury	0	(0.0)	1	(0.1)	ND
Rib fracture	0	(0.0)	1	(0.1)	ND
Spinal compression fracture	1	(0.1)	0	(0.0)	ND
Traumatic chest injury nos	1	(0.1)	0	(0.0)	ND
Investigations	**7**	**(1.0)**	**3**	**(0.4)**	**ND**
Blood pressure increased	3	(0.4)	3	(0.4)	ND
Electrocardiogram abnormal nos	1	(0.1)	0	(0.0)	ND
Fecal occult blood positive	2	(0.3)	0	(0.0)	ND
Weight decreased	1	(0.1)	0	(0.0)	ND
Metabolism and Nutrition Disorders	**2**	**(0.3)**	**1**	**(0.1)**	**ND**
Diabetes Mellitus Nos	0	(0.0)	1	(0.1)	ND
Fluid Retention	2	(0.3)	0	(0.0)	ND
Musculoskeletal and Connective Tissue Disorders	**12**	**(1.7)**	**23**	**(3.2)**	**-1.50 (-3.2, 0.1)**
Arthralgia	3	(0.4)	5	(0.7)	ND
Arthritis nos	2	(0.3)	4	(0.5)	ND
Back pain	3	(0.4)	2	(0.3)	ND
Bursitis	0	(0.0)	1	(0.1)	ND
Facial pain	0	(0.0)	1	(0.1)	ND
Intervertebral disc disorder nos	0	(0.0)	1	(0.1)	ND
Localised osteoarthritis	0	(0.0)	2	(0.3)	ND

Table 53 (Cont.)

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Muscle spasms	0	(0.0)	1	(0.1)	ND
Musculoskeletal pain	1	(0.1)	0	(0.0)	ND
Neck pain	0	(0.0)	1	(0.1)	ND
Osteoarthritis nos	0	(0.0)	6	(0.8)	ND
Pain in extremity	2	(0.3)	0	(0.0)	ND
Polymyalgia rheumatica	1	(0.1)	0	(0.0)	ND
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**7**	**(1.0)**	**17**	**(2.3)**	**-1.37 (-2.9, -0.1)**
Acute myeloid leukemia nos	0	(0.0)	1	(0.1)	ND
Bladder cancer nos	0	(0.0)	2	(0.3)	ND
Bone cancer metastatic	1	(0.1)	0	(0.0)	ND
Chronic lymphocytic leukemia nos	1	(0.1)	0	(0.0)	ND
Colon cancer metastatic	0	(0.0)	1	(0.1)	ND
Lung neoplasm malignant	0	(0.0)	4	(0.5)	ND
Lymphoma nos	0	(0.0)	1	(0.1)	ND
Malignant melanoma	0	(0.0)	1	(0.1)	ND
Meningioma	1	(0.1)	0	(0.0)	ND
Metastases to liver	0	(0.0)	1	(0.1)	ND
Metastatic neoplasm nos, primary site unknown	0	(0.0)	1	(0.1)	ND
Multiple myeloma	1	(0.1)	0	(0.0)	ND
Esophageal carcinoma nos	0	(0.0)	2	(0.3)	ND
Pancreatic carcinoma nos	0	(0.0)	1	(0.1)	ND
Pancreatic neoplasm nos	1	(0.1)	0	(0.0)	ND
Prostate cancer nos	1	(0.1)	1	(0.1)	ND
Renal cell carcinoma stage unspecified	0	(0.0)	1	(0.1)	ND
Squamous cell carcinoma of skin	1	(0.1)	0	(0.0)	ND
Throat cancer nos	0	(0.0)	1	(0.1)	ND
Nervous System Disorders	**26**	**(3.6)**	**20**	**(2.7)**	**0.85 (-1.0, 2.7)**
Aphasia	0	(0.0)	1	(0.1)	ND
Balance impaired nos	1	(0.1)	0	(0.0)	ND
Cerebral hemorrhage	1	(0.1)	1	(0.1)	ND
Cerebrovascular accident	4	(0.6)	4	(0.5)	ND
Dizziness	4	(0.6)	5	(0.7)	ND
Dizziness postural	1	(0.1)	0	(0.0)	ND
Dysphasia	1	(0.1)	0	(0.0)	ND
Extrapyramidal disorder	1	(0.1)	0	(0.0)	ND
Headache	1	(0.1)	1	(0.1)	ND
Hemiparesis	1	(0.1)	0	(0.0)	ND
Hypoesthesia	0	(0.0)	1	(0.1)	ND
Intention tremor	0	(0.0)	1	(0.1)	ND
Intracranial hemorrhage nos	1	(0.1)	1	(0.1)	ND

Table 53 (Cont.)

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Migraine nos	1	(0.1)	0	(0.0)	ND
Neuralgia nos	0	(0.0)	1	(0.1)	ND
Paraesthesia	0	(0.0)	1	(0.1)	ND
Somnolence	2	(0.3)	0	(0.0)	ND
Spinal stenosis nos	1	(0.1)	0	(0.0)	ND
Subarachnoid hemorrhage nos	0	(0.0)	1	(0.1)	ND
Syncope	3	(0.4)	2	(0.3)	ND
Transient ischaemic attack	4	(0.6)	2	(0.3)	ND
Psychiatric Disorders	**7**	**(1.0)**	**13**	**(1.8)**	**ND**
Abnormal behavior nos	0	(0.0)	1	(0.1)	ND
Abnormal dreams	0	(0.0)	1	(0.1)	ND
Agitation	1	(0.1)	0	(0.0)	ND
Anorgasmia	0	(0.0)	1	(0.1)	ND
Anxiety	0	(0.0)	1	(0.1)	ND
Confusional state	1	(0.1)	2	(0.3)	ND
Delirium	0	(0.0)	1	(0.1)	ND
Depression	1	(0.1)	3	(0.4)	ND
Hypomania	1	(0.1)	0	(0.0)	ND
Insomnia	0	(0.0)	1	(0.1)	ND
Irritability	1	(0.1)	0	(0.0)	ND
Libido decreased	0	(0.0)	1	(0.1)	ND
Nightmare	1	(0.1)	0	(0.0)	ND
Panic attack	0	(0.0)	1	(0.1)	ND
Psychotic disorder nos	0	(0.0)	1	(0.1)	ND
Suicide attempt	1	(0.1)	0	(0.0)	ND
Renal and Urinary Disorders	**4**	**(0.6)**	**5**	**(0.7)**	**ND**
Hematuria	1	(0.1)	0	(0.0)	ND
Renal failure acute	0	(0.0)	1	(0.1)	ND
Renal failure chronic	1	(0.1)	0	(0.0)	ND
Renal failure nos	1	(0.1)	1	(0.1)	ND
Renal impairment nos	1	(0.1)	1	(0.1)	ND
Urate nephropathy	0	(0.0)	1	(0.1)	ND
Urinary retention	0	(0.0)	2	(0.3)	ND
Reproductive System and Breast Disorders	**0**	**(0.0)**	**1**	**(0.1)**	**ND**
Erectile dysfunction nos	0	(0.0)	1	(0.1)	ND
Respiratory, Thoracic and Mediastinal Disorders	**5**	**(0.7)**	**5**	**(0.7)**	**ND**
Aspiration	0	(0.0)	1	(0.1)	ND
Dyspnea	2	(0.3)	0	(0.0)	ND
Emphysema	0	(0.0)	1	(0.1)	ND
Epistaxis	0	(0.0)	1	(0.1)	ND
Hemoptysis	0	(0.0)	1	(0.1)	ND
Nasal polyps	0	(0.0)	1	(0.1)	ND

Table 53 (Cont.)

Number (%) of Patients Who Discontinued Therapy Due to Clinical Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Pharyngolaryngeal pain	1	(0.1)	0	(0.0)	ND
Pulmonary fibrosis	2	(0.3)	0	(0.0)	ND
Skin and Subcutaneous Tissue Disorders	**8**	**(1.1)**	**4**	**(0.5)**	**ND**
Ecchymosis	1	(0.1)	0	(0.0)	ND
Pigmentation disorder nos	1	(0.1)	0	(0.0)	ND
Pruritus	3	(0.4)	1	(0.1)	ND
Rash maculo-papular	0	(0.0)	1	(0.1)	ND
Rash nos	4	(0.6)	2	(0.3)	ND
Vascular Disorders	**14**	**(1.9)**	**9**	**(1.2)**	**ND**
Aortic aneurysm	1	(0.1)	0	(0.0)	ND
Atherosclerosis	1	(0.1)	0	(0.0)	ND
Hematoma nos	1	(0.1)	0	(0.0)	ND
Hypertension nos	10	(1.4)	7	(1.0)	ND
Hypotension nos	1	(0.1)	0	(0.0)	ND
Phlebitis nos	0	(0.0)	1	(0.1)	ND
Thrombosis	1	(0.1)	1	(0.1)	ND

CI = Confidence interval.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.4 Clinical Adverse Experiences of Special Interest

Both COX-1 and COX-2 are constitutively expressed in the human kidney. Fluid retention, edema formation, increased blood pressure, and decreased glomerular filtration rate are well characterized consequences of therapy with NSAIDS (nonspecific COX-1/COX-2 inhibitors) and COX-2 inhibitors [1.2.25 to 1.2.27]. The following sections review the renal/vascular effects of rofecoxib, a selective inhibitor of COX-2.

8.4.1 Hypertension-, Edema-, and Congestive Heart Failure-Related Adverse Experiences

Statistical comparisons were conducted using Fisher's exact test for the following clinical adverse experiences and related terms: hypertension, edema, and CHF. Tests of significance were performed and the corresponding differences in incidences and 95% CIs are provided.

8.4.1.1 On-Drug Population

Hypertension-Related Adverse Experiences

The distribution of patients with clinical adverse experiences associated with hypertension while on drug or within 14 days from the last dose of study drug is presented in Table 54. Hypertension-related adverse experiences were reported for 176 (24.3%) patients in the rofecoxib treatment group and 116 (15.9%) patients in the placebo group. Patients in the rofecoxib treatment group were significantly more likely to have hypertension-related adverse experiences than those in the placebo group ($p<0.001$, Fisher's exact test). The 95% CI on the difference in percentage of patients who had at least one adverse experience (8.41 percentage points) was [4.3 to 12.5]. The majority of these adverse experiences were mild to moderate in severity. Twenty-three patients discontinued study medication due to hypertension-related adverse experiences: 1.8 and 1.4% of patients in the rofecoxib and placebo groups, respectively. Seventy-eight (10.8%) patients in the rofecoxib and 43 (5.9%) patients in the placebo group, who had a prior history of hypertension, experienced a hypertension-related adverse experience.

Table 54

Number (%) of Patients With Adverse Experiences Related to Hypertension
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)%	95% CI
Patients with at least one adverse experience	176	(24.3)	116	(15.9)	8.41‡	(4.3, 12.5)
Patients with no adverse experience	547	(75.7)	612	(84.1)	-8.41	(-12.5, -4.3)
Investigations	**45**	**(6.2)**	**36**	**(4.9)**	**1.28**	**(-1.1, 3.7)**
Blood pressure diastolic increased	3	(0.4)	4	(0.5)	ND	
Blood pressure increased	42	(5.8)	30	(4.1)	1.69	(-0.6, 4.0)
Blood pressure systolic increased	3	(0.4)	3	(0.4)	ND	
Vascular Disorders	**135**	**(18.7)**	**85**	**(11.7)**	**7.00**	**(3.3, 10.7)**
Diastolic hypertension	0	(0.0)	1	(0.1)	ND	
Hypertension nos	133	(18.4)	84	(11.5)	6.86	(3.2, 10.5)
Labile hypertension	1	(0.1)	0	(0.0)	ND	
Systolic hypertension	1	(0.1)	0	(0.0)	ND	
Patients who discontinued study therapy due to hypertension-related adverse experience	**13**	**(1.8)**	**10**	**(1.4)**	**nps**	
Patients with a hypertension- related adverse experience who had a history of hypertension	**78**	**(10.8)**	**43**	**(5.9)**	**nps**	

† On drug includes the period through 14 days after discontinuation of study drug.
‡ p=<0.001, Fisher's exact test.
CI = Confidence interval.
nps - Not Prespecified for Statistical analysis.
Although a patient may have had 2 or more clinical adverse experiences
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.1; 4.2]

Edema-Related Adverse Experiences

The distribution of patients with clinical adverse experiences associated with edema while on study drug or within 14 days of the last dose is presented in Table 55. There were no statistically significant differences between treatment groups for edema-related adverse experiences (p=0.139, Fisher's exact test). The 95% CI included zero for the percentage point differences between treatments for those patients with at least one adverse experience (difference of 2.27 percentage points, 95% CI [-0.7, 5.2]). A total of 128 patients experienced at lease one edema-related adverse experience: 72 (10.0%) in the rofecoxib and 56 (7.7%) in the placebo group. The majority of these were mild to moderate in intensity. Peripheral edema occurred most frequently with 63 (8.7%) patients in the rofecoxib and 49 (6.7%) patients in the placebo group.

Six patients in the rofecoxib group and none in the placebo group discontinued study drug due to an edema-related adverse experience. AN 0252 discontinued study drug due to gravitational edema; ANs 0694, 0796, 0986, and 1530 due to peripheral edema; and ANs 0796 and 1429 due to fluid retention. The intensity for each of these edema-related adverse experiences were mild to moderate, except for AN 0986, which was rated as severe and probably related to study medication. Patient AN 0986 had onset of peripheral edema on Day 3 after randomization and discontinued medication after 8 days of dosing. The medical history for patient AN 0986 includes hypertension, hypercholesterolemia, osteopenia, and irritable bowel syndrome; medications taken prior to study entry and continuing during study treatment were lisinopril (10 mg), Fosamax, and atropine sulfate (+) diphenoxylate hydrochloride.

Two patients in the rofecoxib group (ANs 0252 and 1530) had a prior history of edema and none in the placebo group had edema-related adverse experiences.

Table 55

Number (%) of Patients With Adverse Experiences Related to Edema
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)%	95% CI
Patients with at least one Adverse Experience	72	(10.0)	56	(7.7)	2.27‡	(-0.7, 5.2)
Patients with no adverse experience	651	(90.0)	672	(92.3)	-2.27	(-5.2, 0.7)
General disorders and administration site conditions	**71**	**(9.8)**	**55**	**(7.6)**	**2.27**	**(-0.6, 5.2)**
Anasarca	0	(0.0)	1	(0.1)	ND	
Gravitational edema	1	(0.1)	0	(0.0)	ND	
Oedema nos	8	(1.1)	7	(1.0)	ND	
Oedema peripheral	63	(8.7)	49	(6.7)	1.98	(-0.8, 4.8)
Metabolism and Nutrition Disorders	**2**	**(0.3)**	**1**	**(0.1)**	**ND**	
Fluid retention	2	(0.3)	1	(0.1)	ND	
Patients who discontinued study therapy due to Edema-Related adverse experience	**6**	**(0.8)**	**0**	**(0.0)**	**nps**	
Patients with an edema-related adverse experience who had a history of edema	**2**	**(0.3)**	**0**	**(0.0)**	**nps**	

† On drug includes the period through 14 days after discontinuation of study drug.
‡ p=0.139, Fisher's exact test.
CI = Confidence interval.
nps - Not Prespecified for Statistical analysis.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.1; 4.2]

Congestive Heart Failure-Related Adverse Experiences

The distribution of patients with clinical adverse experiences related to CHF while on study drug or within 14 days of the last dose is presented in Table 56. There were no statistically significant differences between treatment groups (p=0.733, Fisher's exact test) for the patients who had a CHF-related adverse experience. The 95% CI for the differences in percent of patients experiencing CHF included zero [-2.1, 1.2]. Sixteen (2.2%) patients in the rofecoxib and 19 (2.6%) in the placebo group had at least one adverse experience related to CHF. Twelve of these patients had CHF-related adverse experiences that were severe in intensity: 6 in each treatment group (0.8 and 0.8% in the rofecoxib and placebo groups, respectively). Seven patients with a prior history of CHF had CHF-related adverse experiences: 4 (0.6%) and 3 (0.4%) in the rofecoxib and placebo groups, respectively.

Three patients discontinued study medication due to CHF-related adverse experiences: ANs 1369 and 1412 in the rofecoxib group and AN 0882 in the placebo group. AN 1369 had a serious adverse experience of CHF on Day 187 after randomization, rated as severe intensity and probably not related to study drug, and discontinued study drug. AN 1412 had a nonserious adverse experience of CHF on Day 105 after randomization, rated as severe intensity and definitely not related to study drug, and discontinued study drug. AN 0882, in the placebo group, had a nonserious adverse experience of CHF on Day 776, rated as moderate in intensity and probably not related to study drug; study drug was discontinued due to this adverse experience.

Table 56

Number (%) of Patients With Adverse Experiences Related to Congestive Heart Failure
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)%	95% CI
Patients with at least one adverse experience	16	(2.2)	19	(2.6)	-0.40‡	(-2.1, 1.2)
Patients with no adverse experience	707	(97.8)	709	(97.4)	0.40	(-1.2, 2.1)
Cardiac disorders	**14**	**(1.9)**	**18**	**(2.5)**	**-0.54**	**(-2.2, 1.0)**
Cardiac failure congestive	14	(1.9)	18	(2.5)	-0.54	(-2.2, 1.0)
Cardiac failure nos	0	(0.0)	1	(0.1)	ND	
Respiratory, thoracic and mediastinal disorders	**3**	**(0.4)**	**3**	**(0.4)**	**ND**	
Pulmonary edema nos	3	(0.4)	3	(0.4)	ND	
Patients who discontinued study therapy due to CHF-Related adverse experience	**2**	**(0.3)**	**1**	**(0.1)**	**nps**	
Patients with a CHF-Related adverse experience who had a history of CHF	**4**	**(0.6)**	**3**	**(0.4)**	**nps**	

† On drug includes the period through 14 days after discontinuation of study drug.
‡ p=0.733, Fisher's exact test.
CI = Confidence interval.
nps - Not Prespecified for Statistical analysis.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.1; 4.2]

8.4.1.2 Intention-to-Treat Population

Patients in the ITT population were counted as having adverse experiences whether they were taking study drug or not.

Hypertension-Related Adverse Experiences

Table 57 shows patients in the ITT population who had adverse experiences related to hypertension. Hypertension-related adverse experiences were reported for 191 (26.4%) patients in the rofecoxib treatment group and 135 (18.5%) patients in the placebo group. Patients in the rofecoxib treatment group in the ITT population were statistically significantly more likely to have hypertension-related adverse experiences than those in the placebo group ($p<0.001$, Fisher's exact test). The 95% CI on the difference in percentage points for those patients who had at least one adverse experience was 7.87 percentage points (95% CI [3.6 to 12.2]). There were no clinically significant differences between the on-drug and ITT populations for hypertension-related adverse experiences.

Table 57

Number (%) of Patients with Adverse Experiences Related to Hypertension
Intention-to-Treat
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Patients with at least one Adverse Experience	191	(26.4)	135	(18.5)	7.87† (3.6, 12.2)
Patients with no adverse experience	532	(73.6)	593	(81.5)	-7.87 (-12.2, -3.6)
Investigations	**49**	**(6.8)**	**40**	**(5.5)**	**1.28 (-1.2, 3.8)**
Blood pressure diastolic increased	3	(0.4)	4	(0.5)	ND
Blood pressure increased	46	(6.4)	33	(4.5)	1.83 (-0.5, 4.2)
Blood pressure systolic increased	3	(0.4)	4	(0.5)	ND
Vascular Disorders	**146**	**(20.2)**	**103**	**(14.1)**	**6.05 (2.2, 9.9)**
Diastolic hypertension	0	(0.0)	1	(0.1)	ND
Hypertension nos	144	(19.9)	102	(14.0)	5.91 (2.1, 9.8)
Labile hypertension	1	(0.1)	0	(0.0)	ND
Systolic hypertension	1	(0.1)	0	(0.0)	ND
Patients who discontinued study therapy due to hypertension-related adverse experience	**13**	**(1.8)**	**10**	**(1.4)**	**nps**
Patients with a hypertension-related adverse experience who had a history of Hypertension	**83**	**(11.5)**	**53**	**(7.3)**	**nps**

† p=<0.001, Fisher's exact test.
CI = Confidence interval.
nps - Not Prespecified for Statistical analysis.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.1; 4.2]

Edema-Related Adverse Experiences

The distribution of patients with clinical adverse experiences associated with edema for the ITT population is presented in Table 58. There were no statistically significant differences between treatment groups for edema-related adverse experiences (p=0.225, Fisher's exact test). The 95% CIs included zero for the difference between percents for those patients with at least one adverse experience (2.00 percentage points difference, [-1.1, 5.2]). A total of

148 patients experienced at lease one edema-related adverse experience: 81 (11.2%) in the rofecoxib and 67 (9.2%) in the placebo group. There were no clinically significant differences between the on-drug and ITT populations for edema-related adverse experiences.

Table 58

Number (%) of Patients with Adverse Experiences Related to Edema
Intention-to-Treat
(>0% Incidence in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n	(%)	n	(%)	(A-B)% 95% CI
Patients with at least one adverse experience	81	(11.2)	67	(9.2)	2.00† (-1.1, 5.2)
Patients with no adverse experience	642	(88.8)	661	(90.8)	-2.00 (-5.2, 1.1)
General Disorders and Administration Site Conditions	**80**	**(11.1)**	**66**	**(9.1)**	**2.00 (-1.1, 5.1)**
Anasarca	0	(0.0)	1	(0.1)	ND
Gravitational edema	1	(0.1)	0	(0.0)	ND
Oedema nos	9	(1.2)	10	(1.4)	ND
Oedema peripheral	71	(9.8)	59	(8.1)	1.72 (-1.2, 4.7)
Metabolism and Nutrition Disorders	**3**	**(0.4)**	**1**	**(0.1)**	**ND**
Fluid retention	3	(0.4)	1	(0.1)	ND
Patients who discontinued study therapy due to edema-related adverse experience	**6**	**(0.8)**	**0**	**(0.0)**	**nps**
Patients with an edema-related adverse experience who had a history of edema	**2**	**(3.8)**	**0**	**(0.0)**	**nps**

† p=0.225, Fisher's exact test.
CI = Confidence interval.
nps - Not Prespecified for Statistical analysis.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.1; 4.2]

Congestive Heart Failure-Related Adverse Experiences

The distribution of patients with clinical adverse experiences related to CHF for the ITT population is presented in Table 59. There were no statistically significant differences between treatment groups (p=0.666, Fisher's exact test)

for patients who had a CHF-related adverse experience. The 95% CIs for the differences in percent of patients experiencing CHF covered zero [-1.5, 2.4]. Twenty-six (3.6%) patients in the rofecoxib group and 23 (3.2%) in the placebo group had at least one adverse experience related to CHF. In the ITT population as compared to the on-drug population, two additional patients in the rofecoxib group had a CHF-related adverse experience who had a history of CHF. No other clinically significant differences were shown between the on-drug and ITT populations for patients with CHF-related adverse experiences.

Table 59

Number (%) of Patients with Adverse Experiences Related to Congestive Heart Failure
Intention-to-Treat
(>0% Incidence in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n	(%)	n	(%)	(A-B)% 95% CI
Patients with at least one adverse experience	26	(3.6)	23	(3.2)	0.44† (-1.5, 2.4)
Patients with no adverse experience	697	(96.4)	705	(96.8)	-0.44 (-2.4, 1.5)
Cardiac Disorders	**24**	**(3.3)**	**22**	**(3.0)**	**0.30 (-1.6, 2.2)**
Cardiac failure congestive	23	(3.2)	22	(3.0)	0.16 (-1.7, 2.0)
Cardiac failure nos	0	(0.0)	1	(0.1)	ND
Left ventricular failure	1	(0.1)	0	(0.0)	ND
Respiratory, Thoracic and Mediastinal Disorders	**5**	**(0.7)**	**3**	**(0.4)**	**ND**
Pulmonary edema nos	5	(0.7)	3	(0.4)	ND
Patients who discontinued study therapy due to CHF-Related adverse experience	**2**	**(0.3)**	**1**	**(0.1)**	**nps**
Patients with a CHF-Related adverse experience who had a history of CHF	**6**	**(0.8)**	**3**	**(0.4)**	**nps**

† p=0.666, Fisher's exact test.
CI = Confidence interval.
nps - Not Prespecified for Statistical analysis.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.
CHF = Congestive heart failure

Data Source: [4.1; 4.2]

8.4.2 Discontinuation of Study Therapy Due to Gastrointestinal Adverse Experiences

8.4.2.1 On-Drug Population

The distribution of patients who discontinued study therapy due to clinical adverse experiences associated with GI and abdominal pain while on drug is presented in Table 60. Discontinuation from study therapy due to GI and abdominal pain-related adverse experiences occurred for 33 (4.6%) patients in the rofecoxib treatment group and 22 (3.0%) patients in the placebo group. There was no statistically significant difference between treatment groups (p=0.132, Fisher's exact test). Numerically, the most common adverse experiences for which patients discontinued study therapy were abdominal pain (4 [0.6%] patients in the rofecoxib group and 2 [0.3%] in the placebo group), diarrhea (6 [0.8%] patients and 2 [0.3%], respectively), and nausea (4 [0.6%] and 5 [0.7%]).

Table 60

Number (%) of Patients Who Discontinued Therapy Due to GI Clinical Adverse Experiences >0.0% Incidence in One or More Treatment Groups
On-Drug† Population

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n	(%)	Placebo (B) (N=728) n	(%)	Estimated Difference (A-B)% 95% CI
Patients with at least one adverse experience	33	(4.6)	22	(3.0)	1.54‡ (-0.4, 3.6)
Patients with no adverse experience	690	(95.4)	706	(97.0)	-1.54 (-3.6, 0.4)
Gastrointestinal Disorders	**31**	**(4.3)**	**22**	**(3.0)**	**1.27 (-0.7, 3.3)**
Abdominal discomfort	1	(0.1)	1	(0.1)	ND
Abdominal pain nos	4	(0.6)	2	(0.3)	ND
Abdominal pain upper	0	(0.0)	1	(0.1)	ND
Aphthous stomatitis	1	(0.1)	0	(0.0)	ND
Bowel sounds abnormal	0	(0.0)	1	(0.1)	ND
Colonic polyp	1	(0.1)	0	(0.0)	ND
Constipation	0	(0.0)	2	(0.3)	ND
Diarrhea nos	6	(0.8)	2	(0.3)	ND
Dry mouth	0	(0.0)	1	(0.1)	ND
Duodenal ulcer	2	(0.3)	0	(0.0)	ND
Duodenal ulcer haemorrhage	1	(0.1)	0	(0.0)	ND
Duodenal ulcer perforation	0	(0.0)	1	(0.1)	ND
Dyspepsia	3	(0.4)	4	(0.5)	ND
Enterocolitis	1	(0.1)	0	(0.0)	ND
Epigastric discomfort	1	(0.1)	0	(0.0)	ND
Gastric perforation	1	(0.1)	0	(0.0)	ND
Gastric ulcer	3	(0.4)	0	(0.0)	ND
Gastritis nos	1	(0.1)	0	(0.0)	ND
Gastrointestinal haemorrhage nos	1	(0.1)	0	(0.0)	ND
Gastrointestinal pain nos	0	(0.0)	1	(0.1)	ND
Gastroesophageal reflux disease	2	(0.3)	2	(0.3)	ND
Lip dry	0	(0.0)	1	(0.1)	ND
Loose stools	1	(0.1)	0	(0.0)	ND
Mallory-Weiss syndrome	1	(0.1)	0	(0.0)	ND
Mouth ulceration	1	(0.1)	0	(0.0)	ND
Nausea	4	(0.6)	5	(0.7)	ND
Rectal haemorrhage	1	(0.1)	1	(0.1)	ND
Upper gastrointestinal haemorrhage	2	(0.3)	0	(0.0)	ND
Vomiting nos	1	(0.1)	2	(0.3)	ND
Investigations	**2**	**(0.3)**	**0**	**(0.0)**	**ND**
Fecal occult blood positive	2	(0.3)	0	(0.0)	ND

† On drug includes the period through 14 days after discontinuation of study drug.
‡ p-Value=0.132, Fisher's exact test.
CI = Confidence interval.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
ND = Confidence intervals were not determined.
GI - Gastrointestinal
N = Number of randomized patients in each treatment group who took at least one dose of study therapy.
n = Number of patients in each category.

Data Source: [4.2]

8.4.2.2 Intention-to-Treat Population

Table 61 shows patients in the ITT population who discontinued study therapy due to clinical adverse experiences associated with GI and abdominal pain. The number of patients who discontinued study therapy due to GI and abdominal pain-related clinical adverse experiences for the ITT population was consistent with those of the on-drug population.

Table 61

Number (%) of Patients Who Discontinued Therapy
Due to GI Clinical Adverse Experiences
(>0% Incidence in One or More Treatment Groups)
Intention-to-Treat Population

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n	(%)	n	(%)	(A-B)% 95% CI
Patients with at least one adverse experience	33	(4.6)	22	(3.0)	1.54* (-0.4, 3.6)
Patients with no adverse experience	690	(95.4)	706	(97.0)	-1.54 (-3.6, 0.4)
Gastrointestinal Disorders	**31**	**(4.3)**	**22**	**(3.0)**	**1.27 (-0.7, 3.3)**
Abdominal discomfort	1	(0.1)	1	(0.1)	ND
Abdominal pain nos	4	(0.6)	2	(0.3)	ND
Abdominal pain upper	0	(0.0)	1	(0.1)	ND
Aphthous stomatitis	1	(0.1)	0	(0.0)	ND
Bowel sounds abnormal	0	(0.0)	1	(0.1)	ND
Colonic polyp	1	(0.1)	0	(0.0)	ND
Constipation	0	(0.0)	2	(0.3)	ND
Diarrhea nos	6	(0.8)	2	(0.3)	ND
Dry mouth	0	(0.0)	1	(0.1)	ND
Duodenal ulcer	2	(0.3)	0	(0.0)	ND
Duodenal ulcer haemorrhage	1	(0.1)	0	(0.0)	ND
Duodenal ulcer perforation	0	(0.0)	1	(0.1)	ND
Dyspepsia	3	(0.4)	4	(0.5)	ND
Enterocolitis	1	(0.1)	0	(0.0)	ND
Epigastric discomfort	1	(0.1)	0	(0.0)	ND
Gastric perforation	1	(0.1)	0	(0.0)	ND
Gastric ulcer	3	(0.4)	0	(0.0)	ND
Gastritis nos	1	(0.1)	0	(0.0)	ND
Gastrointestinal haemorrhage nos	1	(0.1)	0	(0.0)	ND
Gastrointestinal pain nos	0	(0.0)	1	(0.1)	ND
Gastroesophageal reflux disease	2	(0.3)	2	(0.3)	ND
Lip dry	0	(0.0)	1	(0.1)	ND
Loose stools	1	(0.1)	0	(0.0)	ND
Mallory-Weiss syndrome	1	(0.1)	0	(0.0)	ND
Mouth ulceration	1	(0.1)	0	(0.0)	ND
Nausea	4	(0.6)	5	(0.7)	ND
Rectal haemorrhage	1	(0.1)	1	(0.1)	ND
Upper gastrointestinal haemorrhage	2	(0.3)	0	(0.0)	ND
Vomiting nos	1	(0.1)	2	(0.3)	ND
Investigations	**2**	**(0.3)**	**0**	**(0.0)**	**ND**
Fecal occult blood positive	2	(0.3)	0	(0.0)	ND

* p-Value=0.132, Fisher's exact test.
CI = Confidence interval.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category and adverse experience term. The patient may appear in different categories and adverse experience terms.
GI = Gastrointestinal
ND = Confidence intervals were not determined.
N = Number of randomized patients in each treatment group who took at least one dose of study therapy.
n = Number of patients in each category.

Data Source: [4.2]

8.4.3 Episodes of Perforations, Ulcers, or Upper GI Bleeding (PUBs)

Suspected upper GI PUBs were reviewed and adjudicated by the rofecoxib Phase III GI Clinical Event Monitoring Case Review Committee, according to procedures described in [3.11.1]. The distribution of patients with adjudicated GI clinical event results and corresponding adjudication results are shown in Table 62. A listing of all PUB and adjudicated events can be found in Table 90 - Section 11, and in [4.5; 4.7]. On-Drug events adjudicated as confirmed episodes of perforations, ulcers, and upper GI bleeding, and the corresponding subgroup of those confirmed events adjudicated as complicated are displayed in Table 62.

Twenty-three patients experienced investigator-reported upper GI clinical events while on-drug: 16 (2.2%) in the rofecoxib group and 7 (1.0%) in the placebo group; of these, the number of patients with confirmed on-drug events was 14 (1.9%) in the rofecoxib group and 4 (0.5%) in the placebo group. Eight patients in the rofecoxib group and 3 patients in the placebo group had more than one type of confirmed event (e.g., both an ulcer and a hemorrhage).

Upper GI hemorrhage was confirmed as an on-drug event for 13 (1.8%) patients in the rofecoxib group and 2 (0.3%) in the placebo group; of these, 9 of the events in the rofecoxib group were adjudicated as complicated, and both in the placebo group were adjudicated as complicated. A total of 9 patients were adjudicated as having confirmed on-drug gastric ulcer: 6 in the rofecoxib group (4 complicated) and 3 in the placebo group (1 complicated). Five patients in the rofecoxib group and 1 in the placebo group had on-drug duodenal ulcers; only 1 event in the rofecoxib group was deemed as complicated and none in the placebo group. The 1 patient in the placebo group who had a duodenal ulcer also had a perforation (complicated) (AN 0360).

Four patients (2 in each treatment group) had investigator reported on-drug GI hemorrhages which were not confirmed as events by the adjudication committee (see [4.7.1]). These patients had no other suspected PUB events.

Nine patients had off-drug upper GI events reported by the investigator: 4 in the rofecoxib group (one patient also had 2 temporally separate hemorrhages on–drug) and 5 in the placebo group; see [Table 90 - Section 11; 4.5; 4.7]. Eight of these patients had confirmed events: 4 in the rofecoxib group and 4 in the placebo group.

Table 62

Adjudication Results for Confirmed Episodes of
Upper GI Perforations, Ulcers, or Bleeds
On-Drug† Population

	Treatment Group	
	Rofecoxib (N=723) n (%)	Placebo N=728) n (%)
GI Clinical Event Term	**Confirmed Events**	
Patients with at least one event	**14 (1.9)**	**4 (0.5)**
GI hemorrhage	13 (1.8)	2 (0.3)
Gastric ulcer	6 (0.8)	3 (0.4)
Gastric or duodenal perforation	0 (0.0)	1 (0.1)
Duodenal ulcer	5 (0.7)	1 (0.1)
	Confirmed Complicated Events	
Patients with at least one event	**10 (1.4)**	**3 (0.4)**
GI hemorrhage	9 (1.2)	2 (0.3)
Gastric ulcer	4 (0.6)	1 (0.1)
Gastric or duodenal perforation	0 (0.0)	1 (0.1)
Duodenal ulcer	1 (0.1)	0 (0.0)

† On drug includes the period through 14 days after discontinuation of study drug.
Patients may be counted in more than one row, but only once within a row.
GI = Gastrointestinal.
n = Number of patients with event.
N= Number of randomized patients who took at least one dose of study medication.

Data Source: [4.2; 4.7]

Table 63 shows the crude proportions (number of patients with events/number of patients) and patient-year adjusted incidence rates (number of patients with events/100 patient-years) for the confirmed and confirmed complicated on-drug PUB events. Fourteen patients in the rofecoxib group had confirmed PUB events; the rate per 100 patient-years was 1.02 and the 95% CI was [0.60,1.72]; for the placebo group, in which 4 patients had a confirmed PUB event, the rate per 100 patient years was 0.25 with 95% CI of [0.10, 0.68].

There were a total of 13 patients with a confirmed on-drug event rated as complicated: 10 in the rofecoxib group (rate per 100 patient years was 0.73; 95% CI was [0.39, 1.35]) and 3 in the placebo group (rate per 100 patient years was 0.19; 95% CI was [0.06, 0.59]).

Table 63

Analyses of Adjudicated Confirmed and Complicated PUB Events
On-Drug[†] Population

Adjudicated Outcome	Rofecoxib (N=723)		Placebo (N=728)	
	n (%)[§]	Rate[‡] (95% CI)	n (%)[§]	Rate[‡] (95% CI)
Confirmed event	14 (1.94)	1.02 (0.60, 1.72)	4 (0.55)	0.25 (0.10, 0.68)
Confirmed complicated event	10 (1.38)	0.73 (0.39, 1.35)	3 (0.41)	0.19 (0.06, 0.59)

[†] On drug includes the period through 14 days after discontinuation of study drug.
[§] Crude incidence (n/Nx100).
[‡] Events per 100 patient-years, where patient-years at risk (PYR) were calculated based on the overall endpoint. Total PYR were 1375.2 for the rofecoxib group and 1578.8 for the placebo group.
PUB = Perforation, Ulcer, Bleed
CI = Confidence interval
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.7]

There were 180 patients in the rofecoxib arm who dosed for at least 7 consecutive days with aspirin while on study drug; of these, 3 (1.7%) patients had a PUB event within 14 days of at least 7 consecutive days of dosing with aspirin. In the placebo group, there were 152 patients who dosed for at least 7 consecutive days with aspirin while on study drug; one (0.7%) patient in the placebo group had a PUB event within 14 days of at least 7 consecutive days of dosing with aspirin [4.1; 4.2].

8.4.4 Serious Cardiovascular, Peripheral Vascular, and Cerebrovascular Events

Suspected serious cardiovascular, cerebrovascular, and peripheral vascular events were reviewed and adjudicated according to the Acute Thromboembolic Vascular Events SOP [3.11.2] to confirm whether events met guidelines for the diagnosis as a thromboembolic event. Events were also adjudicated to determine if they met guidelines for APTC combined endpoint [1.2.28, 1.2.29, 3.11.3]. A listing of adjudicated events can be found in Table 89 – Section 11 [4.7]. The distribution of patients with adjudicated CV events on-drug and corresponding adjudication results are shown in Table 64. Crude proportions (number of patients with events/number of patients) and patient-year adjusted incidence rates (number of patients with events/ patients-years) are also shown in Table 64.

There were 132 patients with investigator-reported suspected thrombotic cardiovascular serious adverse experiences while on drug: 68 (9.4%) in the rofecoxib group and 64 (8.8%) in the placebo group [4.7.2]. Seventy-four patients were adjudicated to have had confirmed thrombotic events: 38 (5.3%) patients in the rofecoxib arm and 36 (4.9%) patients in the placebo arm. The adjusted incidence rates were 2.79 and 2.32 per 100 patient-years for the rofecoxib and placebo arms, respectively.

Forty-five patients were confirmed to have cardiac events: 26 (3.6%) in the rofecoxib group and 19 (2.6%) in the placebo group. The majority of these events were adjudicated to have had acute myocardial infarctions (13 [1.8%] patients in the rofecoxib group and 10 [1.3%] in the placebo group). Seven (1.0%) patients in the rofecoxib group and 3 (0.4%) in the placebo group were adjudicated to have had sudden cardiac death. One patient in each group had fatal acute myocardial infarction and 7 in each group had unstable angina pectoris.

A total of 29 patients were adjudicated with cerebrovascular events: 13 (1.8%) in the rofecoxib group and 16 (2.2%) in the placebo group. The majority were adjudicated as having ischemic cerebrovascular strokes (6 [0.8%] and 13 [1.8%] patients in the rofecoxib and placebo groups, respectively). Seven (1.0%) patients in the rofecoxib group and 3 (0.4%) in the placebo group were adjudicated as having transient ischemic attacks.

Three patients in the placebo group were adjudicated as having peripheral vascular events: 2 as peripheral venous thrombosis and 1 as a pulmonary embolism. No patients in the rofecoxib group had events adjudicated in this category.

Table 64

Confirmed Thrombotic Cardiovascular Events by Class of Event Terms
On-Drug† Population

	Rofecoxib (N=723) 1361 Patient-Years			Placebo (N=728) 1551 Patient-Years		
Thrombotic Cardiovascular Event Terms	**n**	**(%)‡**	**Rate§**	**n**	**(%)‡**	**Rate §**
Total number of patients with Event	38	(5.3)	2.79	36	(5.0)	2.32
Cardiac Events	**26**	**(3.6)**	**1.91**	**19**	**(2.6)**	**1.23**
Acute myocardial infarction	13	(1.8)	0.96	10	(1.4)	0.64
Fatal acute myocardial infarction	1	(0.1)	0.07	1	(0.1)	0.06
Sudden cardiac death	7	(1.0)	0.51	3	(0.4)	0.19
Unstable angina pectoris	7	(1.0)	0.51	7	(1.0)	0.45
Cerebrovascular Events	**13**	**(1.8)**	**0.96**	**16**	**(2.2)**	**1.03**
Ischemic cerebrovascular stroke	6	(0.8)	0.44	13	(1.8)	0.84
Transient ischemic attack	7	(1.0)	0.51	3	(0.4)	0.19
Peripheral Vascular Events	**0**	**(0.0)**	**0.0**	**3**	**(0.4)**	**0.19**
Peripheral venous thrombosis	0	(0.0)	0.0	2	(0.3)	0.13
Pulmonary embolism	0	(0.0)	0.0	1	(0.1)	0.06

Patient with multiple events may be counted more than once in different terms, but only once in one term.
† On drug includes the period through 14 days after discontinuation of study drug.
‡Crude incidence (100×n/N)
§ Events per 100 patient-years, where patient-years at risk (PYR) were calculated based on the overall endpoint.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2; 4.7]

Table 65 summarizes the confirmed APTC events by class of event terms and treatment group.

There were 58 patients with confirmed APTC events: 29 (4.0%) patients in the rofecoxib arm and 29 (4.0%) in the placebo arm. The adjusted incidence rates were 2.12 and 1.86 per 100 patient-years for the rofecoxib and placebo arms, respectively.

There were 37 patients with events adjudicated as APTC cardiac events: 21 (2.9%) in the rofecoxib group and 16 (2.0) in the placebo group. The majority of these patients were adjudicated as having acute myocardial infarction (13 [1.8%] in the rofecoxib group and 10 (1.4%) in the placebo group). Seven (2.0%) patients in the rofecoxib group and 3 (0.4%) in the placebo group were

adjudicated by APTC criteria to have had sudden cardiac death. One patient in each group met criteria for fatal acute myocardial infarction and 2 patients in the placebo group had sudden or unknown causes of death.

Nineteen patients met criteria for cerebrovascular events: 6 (0.8%) in the rofecoxib group and 13 in the placebo group (1.8%); events were all adjudicated as ischemic cerebrovascular strokes.

Two patients in each treatment group met APTC criteria for hemorrhagic events: AN 1445, in the placebo group, had a fatal hemorrhagic stroke; AN 0920, in the rofecoxib group, and AN 1363, in the placebo group, were adjudicated as having had hemorrhagic strokes; and AN 352 in the rofecoxib group had an other fatal hemorrhagic death (fatal hemorrhagic duodenal ulcer).

Table 65

Confirmed APTC Combined Endpoint Events by Body System
On-Drug† Population

	Rofecoxib (N=723) 1369 Patient-Years			Placebo (N=728) 1562 Patient-Years		
APTC Combined Endpoint Event Terms	**n**	**(%)‡**	**Rate§**	**n**	**(%)‡**	**Rate§**
Total number of patients with Event	29	(4.0)	2.12	29	(4.0)	1.86
Cardiac Events	**21**	**(2.9)**	**1.53**	**16**	**(2.2)**	**1.02**
Acute myocardial infarction	13	(1.8)	0.95	10	(1.4)	0.64
Fatal acute myocardial infarction	1	(0.1)	0.07	1	(0.1)	0.06
Sudden cardiac death	7	(1.0)	0.51	3	(0.4)	0.19
Sudden/Unknown cause of death	0	(0.0)	0.00	2	(0.3)	0.13
Cerebrovascular Events	**6**	**(0.8)**	**0.44**	**13**	**(1.8)**	**0.83**
Ischemic cerebrovascular stroke	6	(0.8)	0.44	13	(1.8)	0.83
Hemorrhagic Events	**2**	**(0.3)**	**0.15**	**2**	**(0.3)**	**0.13**
Fatal hemorrhagic stroke	0	(0.0)	0.00	1	(0.1)	0.06
Hemorrhagic stroke	1	(0.1)	0.07	1	(0.1)	0.06
Other fatal hemorrhagic death¶	1	(0.1)	0.07	0	(0.0)	0.00

Patient with multiple events may be counted more than once in different terms, but only once in one term.
† On drug includes the period through 14 days after discontinuation of study drug.
‡ Crude incidence (100×n/N).
§ Events per 100 patient-years, where patient-years at risk (PYR) were calculated based on the overall endpoint.
¶ Fatal hemorrhagic duodenal ulcer.
APTC = Antiplatelet Trialists' Collaboration.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.7]

8.4.5 Osteoporosis/Fractures

In Section 8.2.1.1, it was noted that 20 (2.8%) patients in the rofecoxib group and 9 (1.2%) in the placebo group reported osteoporosis; the 95% CI for the difference between treatment groups in the on-drug population for the incidence of osteoporosis did not include zero (95% CI [0.1, 3.1]). Although the results of statistical tests on any individual adverse experience term need to be interpreted with caution because the tests have not been adjusted for multiplicity, it was nonetheless thought important to further explore the clinical significance of this observation. The listing of patients with osteoporosis and osteopenia reported as an adverse experience while on-drug can be found in Table 91—Section 11. One patient in the rofecoxib group and 2 in the placebo group reported adverse experiences of osteopenia.

Osteoporosis is usually asymptomatic, greatly complicating the determination of its onset; moreover, the presence or absence of osteoporosis was not part of the prespecified baseline evaluation but only obtained in the course of the general interview. The numbers of patients with osteoporosis as a secondary medical diagnosis were similar between treatment groups: 43 (5.9%) in the rofecoxib group and 47 (6.4%) in the placebo group. Only one patient in the rofecoxib group, and none in the placebo group, with osteoporosis as an adverse experience had osteoporosis included in their medical history.

An examination of drugs known to affect rapid bone density loss shows that corticosteroids were taken concomitantly by 156 (21.5%) patients in the rofecoxib group and 158 (21.6%) patients in the placebo group; numerically more patients in the rofecoxib than the placebo group used antiepileptics/anticonvulsants concomitantly (36 [5.0%] and 28 [3.8%], respectively). Within the first 6 months of starting study medication, 13 patients reported the adverse experience of osteoporosis: 9 in the rofecoxib group and 4 in the placebo group.

Adverse experiences of fracture were tabulated by treatment group as a post-hoc exploratory analysis (Table 66). There were 53 (7.3%) patients in the rofecoxib group and 42 (5.8%) patients in the placebo group with fractures. The 95% CI on the difference in percentage of patients who had at least one adverse experience of fracture (1.56 percentage points) was (-1.0 to 4.2). Of the 20 patients in the rofecoxib group with osteoporosis reported as an adverse event on-drug, 2 patients had fractures (one was 2 months prior to the reported osteoporosis onset); 4 of the 9 patients in the placebo group had fractures (one of which was 2 years prior to the reported osteoporosis onset).

Table 66

Number (%) of Patients With Adverse Experiences of Fractures
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

	MK-0966 25 mg (N=723) 1311 Patient-Years		Placebo (N=728) 1528 Patient-Years	
Adverse Experience Terms	**n (%)‡**	**Rate§**	**n (%)‡**	**Rate§**
Patients with at least one Adverse Experience	53 (7.33)	4.04	42 (5.77)	2.75
Ankle fracture	3 (0.41)	0.23	2 (0.27)	0.13
Clavicle fracture	2 (0.28)	0.15	1 (0.14)	0.07
Compression fracture	1 (0.14)	0.08	1 (0.14)	0.07
Femoral neck fracture	0 (0.00)	0.00	1 (0.14)	0.07
Femur fracture	0 (0.00)	0.00	1 (0.14)	0.07
Fibula fracture	0 (0.00)	0.00	2 (0.27)	0.13
Foot fracture	4 (0.55)	0.31	5 (0.69)	0.33
Forearm fracture	0 (0.00)	0.00	1 (0.14)	0.07
Fracture NOS	2 (0.28)	0.15	0 (0.00)	0.00
Fractured pelvis NOS	3 (0.41)	0.23	0 (0.00)	0.00
Hand fracture	4 (0.55)	0.31	3 (0.41)	0.20
Hip fracture	10 (1.38)	0.76	5 (0.69)	0.33
Humerus fracture	2 (0.28)	0.15	2 (0.27)	0.13
Lumbar vertebral fracture	1 (0.14)	0.08	2 (0.27)	0.13
Pubic rami fracture	0 (0.00)	0.00	2 (0.27)	0.13
Rib fracture	11 (1.52)	0.84	7 (0.96)	0.46
Scapula fracture	1 (0.14)	0.08	0 (0.00)	0.00
Spinal compression fracture	2 (0.28)	0.15	1 (0.14)	0.07
Spinal fracture NOS	0 (0.00)	0.00	1 (0.14)	0.07
Stress fracture	1 (0.14)	0.08	1 (0.14)	0.07
Tibia fracture	1 (0.14)	0.08	0 (0.00)	0.00
Upper limb fracture NOS	8 (1.11)	0.61	3 (0.41)	0.20
Wrist fracture	6 (0.83)	0.46	5 (0.69)	0.33

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

† On drug includes the period through 14 days after discontinuation of study drug.

‡ Crude incidence (100×n/N)

§ Events per 100 patient-years, where patient-years at risk(PYR) were calculated based on the overall endpoint.

Data Source: [4.2]

8.5 Laboratory Adverse Experiences

This section reviews laboratory adverse experiences for the on-drug and ITT populations. The frequency of laboratory adverse experiences was summarized in a similar way as for the clinical adverse experiences. Statistical testing was conducted using Fisher's exact test for the following laboratory adverse experiences: (1) at least one laboratory adverse experience; (2) drug-related laboratory adverse experience; (3) serious laboratory adverse experience; and (4) discontinued study therapy due to a laboratory adverse experience.

The difference in proportions of patients with adverse experiences between treatment groups and associated 95% CIs were provided for all laboratory adverse experiences which occurred in ≥2% of patients in any treatment group. CIs were not calculated for those tests with fewer than 10 patients in each treatment group. Miettinen and Nurminen's method was used to calculate the 95% CI for the difference in proportions [1.2.19].

Means and standard deviations of the laboratory measures and their changes from baseline were provided by treatment over time. Graphical representations of mean changes from baseline to treatment visits were provided for BUN, serum creatinine, hemoglobin, hematocrit, ALT, and AST. No formal statistical testing with regard to laboratory measures was performed.

Tabulation of patients whose changes in laboratory values (from baseline to treatment visits) exceeded the predefined limits of change (PDLC) from baseline was presented by treatment group using criteria of the FDA Division of Neuropharmacological Drug Products [3.4; results in Tables 92 and 93 of Section 11] and of the VIGOR study [3.4]. No formal statistical testing was performed.

Means and standard deviations of the vital sign measures by treatment visit and of the changes from baseline to treatment visits were provided by treatment group. Graphical representations of changes from baseline to treatment visits were provided for systolic blood pressure, diastolic blood pressure, and pulse rate. No formal statistical testing with regard to vital signs was performed.

Tabulation of patients whose changes in vital signs (from baseline to treatment visits) exceeded the vital sign PDLC from baseline were presented by treatment group based on criteria of the FDA Division of Neuropharmacological Drug Products [3.4]. No formal statistical testing was performed. In additional analyses, the number and proportion of patients whose changes in systolic blood pressure exceeded the PDLC criteria for 2 consecutive assessments were tabulated by treatment group.

8.5.1 Brief Summary of Laboratory Adverse Experiences

8.5.1.1 On-Drug Population

Table 67 summarizes the results for laboratory adverse experiences for patients dosing, or within 14 days of the last dose of study drug, and the respective p-values on prespecified comparisons.

In order to be considered at risk for a laboratory adverse experience, a patient had to have had at least one laboratory test performed postbaseline. There were 1438 patients who had at least one laboratory test postbaseline: 715 in the rofecoxib group and 723 in the placebo group.

There was a statistically significantly higher proportion of patients in the rofecoxib group who experienced at least one laboratory adverse experience while on-drug than in the placebo group (p=0.036, Fisher's exact test): 191 (26.7%) in the rofecoxib group and 158 (21.9%) in the placebo group.

There was a statistically significantly higher proportion of patients in the rofecoxib group with at least one drug-related adverse experience (p<0.001, Fisher's exact test). Seventy-six patients experienced laboratory adverse experiences that were determined by the investigator to be possibly, probably, or definitely related to study medication: 55 (7.7%) patients in the rofecoxib group and 21 (2.9%) in the placebo group.

Four patients had a serious laboratory adverse experience during the study: 1 (0.1%) in the rofecoxib group (AN 0139), and 3 (0.4%) in the placebo group (ANs 0273, 0508, and 0600); there were no statistically significant differences between treatment groups (p=0.625, Fisher's exact test). AN 0508, in the placebo group, had a serious laboratory adverse experience of decreased platelet count and was the only patient who discontinued study drug due to the serious laboratory adverse experience.

A significantly higher proportion of patients in the rofecoxib than the placebo group discontinued study drug due to laboratory adverse experiences (p<0.001, Fisher's exact test): 23 (3.2%) patients in the rofecoxib group and 5 (0.7%) in the placebo group.

Eighteen patients discontinued study drug due to drug-related adverse experiences: 17 (2.4%) in the rofecoxib group and 1 (0.1%) in the placebo group.

No patients had serious drug-related laboratory adverse experiences or died due to laboratory adverse experiences.

Table 67

Laboratory Adverse Experience Summary
On-Drug† Population

Adverse Experience Term	Rofecoxib (N=723) n	(%)§	Placebo (N=728) n	(%)§	p-Value
With at least one laboratory test post baseline	715		723		
With one or more adverse experience	191	(26.7)	158	(21.9)	0.036
With no Adverse Experience	524	(73.3)	565	(78.1)	
With drug-related adverse experiences‡	55	(7.7)	21	(2.9)	<0.001
With serious adverse experiences	1	(0.1)	3	(0.4)	0.625
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	nps
Who died	0	(0.0)	0	(0.0)	nps
Discontinued therapy due to adverse experiences	23	(3.2)	5	(0.7)	<0.001
Discontinued therapy due to drug-related adverse experiences	17	(2.4)	1	(0.1)	nps
Discontinued therapy due to serious adverse experiences	0	(0.0)	1	(0.1)	nps
Discontinued therapy due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	nps

† On drug includes the period through 14 days after discontinuation of study drug.
‡ Determined by the investigator to be possibly, probably, or definitely drug related.
Although a patient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.
§ % = number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline x100.
"With at least one laboratory test postbaseline" = number of patients for whom a laboratory test was recorded for the given treatment group.
nps - Not prespecified for statistical analysis.
p-Value is from Fisher's exact test.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source: [4.2]

8.5.1.2 Intention-to-Treat Population

Table 68 represents a summary analysis of laboratory adverse experiences, and the respective p-values for prespecified comparisons occurring in the ITT population.

Overall, 1438 patients had at least one laboratory adverse experience for the ITT population: 715 in the rofecoxib group and 723 in the placebo group. There were no clinically important differences between the ITT and on-drug analyses.

Table 68

Laboratory Adverse Experience Summary
Intention-to-Treat Population

Adverse Experience Term	Treatment Group: Rofecoxib (N=723) n	(%)†	Placebo (N=728) N	(%)†	p-Value
With at least one laboratory test post baseline	715		723		
With one or more adverse experiences	220	(30.8)	183	(25.3)	0.022
With no adverse experience	495	(69.2)	540	(74.7)	
With drug-related adverse experiences‡	55	(7.7)	22	(3.0)	<0.001
With serious adverse experiences	2	(0.3)	3	(0.4)	0.999
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	nps
Who died	0	(0.0)	0	(0.0)	nps
Discontinued therapy due to adverse experiences	25	(3.5)	7	(1.0)	0.001
Discontinued therapy due to drug-related adverse experiences	19	(2.7)	3	(0.4)	nps
Discontinued therapy due to serious adverse experiences	0	(0.0)	1	(0.1)	nps
Discontinued therapy due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	nps

† %= number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline x100.
‡ Determined by the investigator to be possibly, probably, or definitely drug related.
Although a patient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.
"With at least one laboratory test postbaseline" = number of patients for whom a laboratory test was recorded for the given treatment group.
nps - Not prespecified for statistical analysis.
p-Value is from Fisher's exact test.
N = Number of randomized patients in each treatment group who took at least one dose of study drug.
n = Number of patients in each category.

Data Source:[4.2]

8.5.2 Display of Laboratory Adverse Experiences

The following sections detail specific laboratory adverse experiences, drug-related laboratory adverse experiences, serious laboratory adverse experiences, and discontinuations of study drug due to laboratory adverse experiences. There were a total of 715 patients in the rofecoxib group and 723 patients in the placebo group who had at least one laboratory test post-baseline. The percentage of patients with laboratory adverse experiences shown in the tables below is based on the number of patients who had laboratory tests performed postbaseline. The 95% CIs were provided for the adverse experiences which occurred in ≥ 2% of patients in any treatment group, unless there were less than 10 patients who had a laboratory test in either treatment group.

8.5.2.1 Specific Laboratory Adverse Experiences

8.5.2.1.1 On-Drug Population

Table 69 displays specific laboratory adverse experiences by test category for patients on drug and the corresponding CIs for those which occurred at ≥ 2% incidence rate. Laboratory adverse experiences were reported for a total of 349 patients while on study drug: 191 (26.7%) patients in the rofecoxib group and 158 (21.9%) in the placebo group. The 95% CIs for the differences in percentage points of patients with blood chemistry adverse experiences did not include zero. The 95% CIs included zero for all other laboratory test categories.

A greater percentage of patients in the rofecoxib group had blood chemistry laboratory adverse experiences compared to the placebo group. The 95% CIs for the differences between treatment groups (4.64%) were [0.8 to 8.5]. Of 244 patients with a blood chemistry adverse experience, 138 (19.3%) were in the rofecoxib group and 106 (14.7%) were in the placebo group. The most frequent blood chemistry laboratory adverse experience was increased cholesterol with 52 (75.4%) patients in the rofecoxib group and 50 (71.4%) in the placebo group.

A greater percentage of patients with increased creatinine was reported for patients in the rofecoxib group; 30 (4.2%) patients in the rofecoxib group and 11 (1.5%) in the placebo group. This difference between treatment groups corresponds to a difference of 2.68% with a 95% CI of (1.0 , 4.6). Thirteen patients in the rofecoxib group discontinued study medication due to the laboratory adverse event of increased creatinine compared to none in the placebo group, and 11 of those patients in the rofecoxib group exceeded the predefined limits of change criteria (PDLC); a further discussion of study therapy discontinuation due to laboratory adverse experiences is in Section 8.5.2.4.1 and PDLC information is in Section 8.6.3. Increased BUN was reported more frequently in the rofecoxib group than placebo (3.4 and 0.8%); six patients in the rofecoxib group, compared with 1 in the placebo group, discontinued study therapy as a result of increased BUN. All six patients in the rofecoxib group who discontinued study therapy for BUN also reported the adverse experience of increased serum creatinine. These types of elevations have been described for all NSAIDs and are consistent with the known effects of NSAIDs.

There was a greater percentage of patients in the rofecoxib group than the placebo group with adverse experiences of increased potassium (15 [2.1%] and 3 [0.4%], respectively); study therapy was discontinued for 1 patient (AN 1103, discussed below) with increased potassium in the rofecoxib group and none in the placebo group. For 8 patients in the rofecoxib group and 2 in the placebo group, the adverse experience of increased potassium resolved while the patients were taking study medication; 2 patients in the rofecoxib group and none in the placebo group received treatment for this adverse experience.

AN 1103 had a baseline level for potassium near the upper limit of normal at 5.2 mEq/L, blood urea nitrogen was high at 31 mg/dL, and serum creatinine was high at 1.9 mg/dL. Laboratory values from Day 32 after randomization showed many values outside of the normal ranges: increased potassium at 6 mEq/L, decreased hematocrit at 32.7%, decreased hemoglobin at 11.1 gm/dL, increased serum glucose at 66 mg/dL, increased serum creatinine at 2.2 mg/dL, and increased blood urea nitrogen at 35 mg/dL; no treatments were prescribed for these nonserious adverse experiences. Study drug was stopped on Day 34 due to these laboratory adverse experiences. Laboratory values at Day 35 revealed a potassium level of 5.7 mEq/L and laboratory results from Day 102 showed serum potassium at 4.7 mEq/L. ECG findings on Day 35 did not show evidence of changes consistent with hyperkalemia.

There were 12 (1.7%) patients in the rofecoxib group and 4 (0.6%) in the placebo group with increased alanine aminotransferase (ALT); 4 patients in the rofecoxib group and one in the placebo group discontinued study medication due to increased ALT. Ten (1.4%) patients in the rofecoxib group had increased aspartate aminotransferase (AST), compared with 3 (0.4%) patients in the placebo group; 4 patients in the rofecoxib group and one in the placebo group discontinued medication due to increased AST. Three of the patients in the rofecoxib group and one in the placebo group discontinued study medication due to both increased ALT and AST. (Refer to Section 8.5.2.4.1 for narratives on patients who discontinued due to LFTs.) Elevations of ALT and/or AST (~3 or more times the upper limit of normal) have been reported in ~1% of patients in clinical trials of rofecoxib [2.1.4] (see Section 8.6.3 for display of laboratory values for predefined limits of change).

A total of 96 patients had hematologic laboratory adverse experiences: 54 (7.6%) patients in the rofecoxib group and 42 (5.8%) patients in the placebo group. The majority of these laboratory adverse experiences included decreased hematocrit and hemoglobin. There were 29 (4.1%) patients in the rofecoxib group and 12 (1.7%) patients in the placebo group that had decreased hematocrit. The 95% CIs for the differences between treatment groups for this adverse experience (2.41%) was (0.7 to 4.3). There were 23 (3.2%) patients in the rofecoxib group and 13 (1.8%) in the placebo group with decreased hemoglobin. The 95% CIs for the differences between treatment groups for decreased hemoglobin included zero. Five patients in the rofecoxib group had upper GI hemorrhage in relation to the decreases in hematocrit and hemoglobin. Rofecoxib has been associated with decreases of hemoglobin and hematocrit. In the absence of evidence for significant GI blood loss with rofecoxib, these observations are consistent with hemodilution, postulated as secondary to fluid retention consequent to COX-2 inhibition in the kidney.

Forty-five patients had laboratory adverse experiences related to urinalysis: 22 (3.3%) in the rofecoxib group and 23 (3.3%) in the placebo group. The most common adverse experience in this category was the presence of protein in the urine occurring in 8 (1.2%) patients in the rofecoxib group and 12 (1.7%) in the placebo group.

Table 69

Number (%) of Patients With Specific Laboratory Adverse Experiences
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n/m	(%) ‡	n/m	(%)‡	(A-B)% 95% CI
Patient with at least one adverse experience	191/715	(26.7)	158/723	(21.9)	4.86 (0.4, 9.3)
Patient with no adverse experience	524/715	(73.3)	565/723	(78.1)	
Blood Chemistry Test	**138/715**	**(19.3)**	**106/723**	**(14.7)**	**4.64 (0.8, 8.5)**
Alanine aminotransferase increased	12/714	(1.7)	4/723	(0.6)	ND
Alkaline phosphatase increased	4/714	(0.6)	2/723	(0.3)	ND
Aspartate aminotransferase increased	10/714	(1.4)	3/723	(0.4)	ND
Blood albumin decreased	0/714	(0.0)	1/723	(0.1)	ND
Blood bilirubin increased	6/714	(0.8)	2/723	(0.3)	ND
Blood bilirubin indirect increased	1/18	(5.6)	0/17	(0.0)	5.56 (-13.9, 26.2)
Blood calcium decreased	3/10	(30.0)	1/9	(11.1)	ND
Blood chloride decreased	2/714	(0.3)	0/723	(0.0)	ND
Blood chloride increased	1/714	(0.1)	0/723	(0.0)	ND
Blood cholesterol increased	52/69	(75.4)	50/70	(71.4)	3.93 (-10.9, 18.6)
Blood creatine phosphokinase mb increased	0/11	(0.0)	1/7	(14.3)	ND
Blood creatinine decreased	1/714	(0.1)	0/723	(0.0)	ND
Blood creatinine increased	30/714	(4.2)	11/723	(1.5)	2.68 (1.0, 4.6)
Blood glucose decreased	3/714	(0.4)	1/723	(0.1)	ND
Blood glucose increased	17/714	(2.4)	26/723	(3.6)	-1.22 (-3.1, 0.6)
Blood homocysteine increased	1/3	(33.3)	0/2	(0.0)	ND
Blood magnesium decreased	4/9	(44.4)	2/5	(40.0)	ND
Blood potassium decreased	6/714	(0.8)	6/723	(0.8)	ND
Blood potassium increased	15/714	(2.1)	3/723	(0.4)	1.69 (0.6, 3.1)
Blood sodium decreased	4/714	(0.6)	2/723	(0.3)	ND
Blood triglycerides increased	4/10	(40.0)	5/14	(35.7)	4.29 (-33.0, 41.9)
Blood Urea nitrogen increased	24/714	(3.4)	6/723	(0.8)	2.53 (1.1, 4.2)
Blood Uric acid increased	1/1	(100.0)	0/3	(0.0)	ND
Calcium ionized increased	1/1	(100.0)	0/1	(0.0)	ND
Creatine phosphokinase increased	0/12	(0.0)	1/12	(8.3)	-8.33 (-36.1, 17.9)
Folate decreased	0/125	(0.0)	1/106	(0.9)	ND
Glycosylated hemoglobin increased	1/2	(50.0)	1/2	(50.0)	ND
High density lipoprotein decreased	1/8	(12.5)	0/11	(0.0)	ND
Low density lipoprotein increased	1/12	(8.3)	0/11	(0.0)	8.33 (-19.6, 36.1)
Total cholesterol/HDL ratio increased	1/4	(25.0)	0/2	(0.0)	ND
Very low density lipoprotein increased	0/3	(0.0)	1/3	(33.3)	ND
Clinical Microbiology Test	**1/7**	**(14.3)**	**1/10**	**(10.0)**	**ND**
Sputum culture positive	0/2	(0.0)	1/3	(33.3)	ND
Clinical Serology Test	**10/27**	**(37.0)**	**9/27**	**(33.3)**	**3.70 (-21.6, 28.6)**
Prostatic specific antigen increased	9/18	(50.0)	9/23	(39.1)	10.87 (-19.4, 39.6)
Endocrine Test	**6/137**	**(4.4)**	**3/107**	**(2.8)**	**1.58 (-4.0, 6.9)**
Testosterone Decreased	3/3	(100.0)	1/2	(50.0)	ND
Thyroid stimulating hormone decreased	1/133	(0.8)	0/105	(0.0)	ND
Thyroid stimulating hormone increased	1/133	(0.8)	1/105	(1.0)	ND

Table 69 (Cont.)

Number (%) of Patients With Specific Laboratory Adverse Experiences
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n/m	(%)‡	n/m	(%)‡	(A-B)% 95% CI
Hematology Laboratory Test	**54/712**	**(7.6)**	**42/723**	**(5.8)**	**1.78 (-0.8, 4.4)**
Blood iron decreased	1/4	(25.0)	0/1	(0.0)	ND
Eosinophil count increased	4/712	(0.6)	1/723	(0.1)	ND
Ferritin increased	0/1	(0.0)	1/1	(100.0)	ND
Hematocrit decreased	29/712	(4.1)	12/723	(1.7)	2.41 (0.7, 4.3)
Hematocrit increased	0/712	(0.0)	1/723	(0.1)	ND
Hemoglobin decreased	23/712	(3.2)	13/723	(1.8)	1.43 (-0.2, 3.2)
Hemoglobin increased	0/712	(0.0)	1/723	(0.1)	ND
Lymphocyte count decreased	4/712	(0.6)	4/723	(0.6)	ND
Lymphocyte count increased	3/712	(0.4)	0/723	(0.0)	ND
Monocyte count increased	1/712	(0.1)	1/723	(0.1)	ND
Neutrophil count decreased	2/712	(0.3)	0/723	(0.0)	ND
Neutrophil count increased	5/712	(0.7)	3/723	(0.4)	ND
Platelet count decreased	12/712	(1.7)	9/723	(1.2)	ND
Platelet count increased	2/712	(0.3)	2/723	(0.3)	ND
Red blood cell count decreased	0/27	(0.0)	1/21	(4.8)	-4.76 (-22.9, 8.3)
Red blood cell hypochromic morphology present	1/3	(33.3)	0/4	(0.0)	ND
Red blood cell sedimentation rate increased	1/2	(50.0)	0/3	(0.0)	ND
Transferrin saturation decreased	1/4	(25.0)	0/1	(0.0)	ND
Vitamin B12 decreased	2/127	(1.6)	2/107	(1.9)	ND
White blood cell count decreased	5/712	(0.7)	5/723	(0.7)	ND
White blood cell count increased	6/712	(0.8)	9/723	(1.2)	ND
Hemostatic Function Test	**3/32**	**(9.4)**	**6/40**	**(15.0)**	**-5.63 (-21.6, 11.4)**
Activated partial thromboplastin time prolonged	2/17	(11.8)	1/24	(4.2)	7.60 (-10.9, 31.2)
International normalised ratio increased	2/27	(7.4)	4/31	(12.9)	-5.50 (-23.0, 12.6)
Prothrombin time prolonged	2/26	(7.7)	5/35	(14.3)	-6.59 (-23.4, 12.0)
Pathology Analysis	**0/1**	**(0.0)**	**2/2**	**(100.0)**	**ND**
Therapeutic Drug Monitoring	**0/2**	**(0.0)**	**1/1**	**(100.0)**	**ND**
Digoxin level decreased	0/1	(0.0)	1/1	(100.0)	ND

Table 69 (Cont.)

Number (%) of Patients With Specific Laboratory Adverse Experiences
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n/m	(%) ‡	Placebo (B) (N=728) n/m	(%)‡	Estimated Difference (A-B)% 95% CI
Urinalysis Test	**22/675**	**(3.3)**	**23/705**	**(3.3)**	**-0.00 (-1.9, 2.0)**
Bacteria nos urine identified	7/77	(9.1)	2/78	(2.6)	6.53 (-1.0, 15.4)
Blood urine present	0/3	(0.0)	1/6	(16.7)	ND
Casts urinary granular	1/37	(2.7)	4/20	(20.0)	-17.30 (-39.5, -1.9)
Casts urinary hyaline	3/84	(3.6)	5/59	(8.5)	-4.90 (-15.2, 3.0)
Crystal urine present	5/197	(2.5)	3/170	(1.8)	0.77 (-2.8, 4.3)
Glucose urine present	3/675	(0.4)	5/704	(0.7)	ND
Protein urine present	8/675	(1.2)	12/705	(1.7)	ND
Red blood cells urine positive	6/266	(2.3)	8/244	(3.3)	-1.02 (-4.4, 2.0)
Urine analysis abnormal nos	4/675	(0.6)	4/704	(0.6)	ND
Urine calcium oxalate crystal present	0/65	(0.0)	1/54	(1.9)	ND
Urine epithelial cells increased	1/142	(0.7)	1/129	(0.8)	ND
Urine uric acid crystals present	0/23	(0.0)	2/13	(15.4)	-15.38 (-42.7, 0.7)
White blood cells urine positive	5/248	(2.0)	4/241	(1.7)	0.36 (-2.4, 3.2)

† On drug includes the period through 14 days after discontinuation of study drug.
‡ % = number of patients with the laboratory adverse experience/ number of patients who had at least one laboratory test postbaseline x100.
Although a patient may have had 2 or more laboratory adverse experiences, the patient is only counted once in a category. The same patient may appear in different categories.
ND = Confidence intervals were not determined because the adverse experience did not occur in ≥2% of patients or there were fewer than 10 patients in either treatment group who had a particular laboratory test.
CI = Confidence interval.
N = Number of patients in each treatment group.
n/m = Number of patients with laboratory adverse experience/number of patients who had at least one laboratory test postbaseline.

Data Source: [4.2]

8.5.2.1.2 Intention-to-Treat Population

Table 70 shows the number of patients with specific laboratory adverse experiences and corresponding confidence intervals for the ITT population. The results of the on-drug and ITT analyses were similar.

A total of 403 patients in the ITT population experienced at least one laboratory adverse experience: 220 (30.8%) patients in the rofecoxib group and 183 (25.3%) in the placebo group. All laboratory adverse events for the ITT population were generally similar to those of the on-drug population.

Table 70

Number (%) of Patients With Specific Laboratory Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n/m	(%)†	Placebo (B) (N=728) n/m	(%)†	Estimated Difference (A-B)% 95% CI
Patients with at least one adverse experience	220/715	(30.8)	183/723	(25.3)	5.46 (0.8, 10.1)
Patients with no adverse experience	495/715	(69.2)	540/723	(74.7)	
Blood Chemistry Test	**159/715**	**(22.2)**	**122/723**	**(16.9)**	**5.36 (1.3, 9.5)**
Alanine aminotransferase increased	13/714	(1.8)	5/723	(0.7)	ND
Alkaline phosphatase increased	4/714	(0.6)	2/723	(0.3)	ND
Aspartate aminotransferase increased	10/714	(1.4)	3/723	(0.4)	ND
Blood albumin decreased	0/714	(0.0)	1/723	(0.1)	ND
Blood bicarbonate decreased	1/3	(33.3)	0/2	(0.0)	ND
Blood bilirubin increased	6/714	(0.8)	2/723	(0.3)	ND
Blood bilirubin indirect increased	1/18	(5.6)	0/17	(0.0)	5.56 (-13.9, 26.2)
Blood calcium decreased	4/10	(40.0)	1/9	(11.1)	ND
Blood chloride decreased	2/714	(0.3)	0/723	(0.0)	ND
Blood chloride increased	1/714	(0.1)	0/723	(0.0)	ND
Blood cholesterol increased	63/69	(91.3)	60/70	(85.7)	5.59 (-5.4, 16.9)
Blood creatine phosphokinase mb increased	0/11	(0.0)	1/7	(14.3)	ND
Blood creatinine decreased	1/714	(0.1)	0/723	(0.0)	ND
Blood creatinine increased	33/714	(4.6)	15/723	(2.1)	2.55 (0.7, 4.5)
Blood glucose decreased	3/714	(0.4)	1/723	(0.1)	ND
Blood glucose increased	23/714	(3.2)	30/723	(4.1)	-0.93 (-3.0, 1.1)
Blood homocysteine increased	1/3	(33.3)	0/2	(0.0)	ND
Blood magnesium decreased	5/9	(55.6)	2/5	(40.0)	ND
Blood potassium decreased	7/714	(1.0)	7/723	(1.0)	ND
Blood potassium increased	17/714	(2.4)	4/723	(0.6)	1.83 (0.7, 3.3)
Blood sodium decreased	6/714	(0.8)	2/723	(0.3)	ND
Blood sodium increased	1/714	(0.1)	0/723	(0.0)	ND
Blood triglycerides increased	4/10	(40.0)	7/14	(50.0)	-10.00 (-46.1, 29.6)
Blood urea nitrogen increased	28/714	(3.9)	8/723	(1.1)	2.82 (1.3, 4.6)
Blood uric acid increased	1/1	(100.0)	0/3	(0.0)	ND
Calcium ionized increased	1/1	(100.0)	0/1	(0.0)	ND
Cardiac troponin increased	1/12	(8.3)	0/7	(0.0)	ND
Creatine phosphokinase increased	0/12	(0.0)	1/12	(8.3)	-8.33 (-36.1, 17.9)
Direct bilirubin increased	2/19	(10.5)	0/20	(0.0)	10.53 (-6.9, 31.7)
Fasting blood glucose increased	1/1	(100.0)	0/2	(0.0)	ND
Folate decreased	1/125	(0.8)	1/106	(0.9)	ND
Glycosylated hemoglobin increased	2/2	(100.0)	1/2	(50.0)	ND
High density lipoprotein decreased	1/8	(12.5)	0/11	(0.0)	ND
Low density lipoprotein increased	1/12	(8.3)	0/11	(0.0)	8.33 (-19.6, 36.1)
Total cholesterol/HDL ratio increased	1/4	(25.0)	0/2	(0.0)	ND
Very low density lipoprotein increased	0/3	(0.0)	1/3	(33.3)	ND
Clinical Microbiology Test	**1/7**	**(14.3)**	**1/10**	**(10.0)**	**ND**
Sputum culture positive	0/2	(0.0)	1/3	(33.3)	ND
Clinical Serology Test	**12/27**	**(44.4)**	**10/27**	**(37.0)**	**7.41 (-18.7, 32.5)**
Prostatic specific antigen increased	11/18	(61.1)	10/23	(43.5)	17.63 (-13.3, 45.3)

Table 70 (Cont.)

Number (%) of Patients With Specific Laboratory Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n/m	(%)†	Placebo (B) (N=728) n/m	(%)†	Estimated Difference (A-B)%	95% CI
Endocrine Test	**6/137**	**(4.4)**	**3/107**	**(2.8)**	**1.58**	**(-4.0, 6.9)**
Testosterone decreased	3/3	(100.0)	1/2	(50.0)	ND	
Thyroid stimulating hormone decreased	1/133	(0.8)	0/105	(0.0)	ND	
Thyroid stimulating hormone increased	1/133	(0.8)	1/105	(1.0)	ND	
Hematology Laboratory Test	**68/712**	**(9.6)**	**53/723**	**(7.3)**	**2.22**	**(-0.7, 5.2)**
Blood iron decreased	1/4	(25.0)	0/1	(0.0)	ND	
Eosinophil count increased	5/712	(0.7)	2/723	(0.3)	ND	
Ferritin increased	0/1	(0.0)	1/1	(100.0)	ND	
Hematocrit decreased	35/712	(4.9)	20/723	(2.8)	2.15	(0.2, 4.3)
Hematocrit increased	0/712	(0.0)	1/723	(0.1)	ND	
Hemoglobin decreased	33/712	(4.6)	20/723	(2.8)	1.87	(-0.1, 3.9)
Hemoglobin increased	0/712	(0.0)	1/723	(0.1)	ND	
Lymphocyte count decreased	4/712	(0.6)	5/723	(0.7)	ND	
Lymphocyte count increased	4/712	(0.6)	0/723	(0.0)	ND	
Monocyte count increased	2/712	(0.3)	1/723	(0.1)	ND	
Neutrophil count decreased	2/712	(0.3)	0/723	(0.0)	ND	
Neutrophil count increased	6/712	(0.8)	3/723	(0.4)	ND	
Platelet count decreased	13/712	(1.8)	10/723	(1.4)	ND	
Platelet count increased	3/712	(0.4)	4/723	(0.6)	ND	
Red blood cell count decreased	0/27	(0.0)	1/21	(4.8)	-4.76	(-22.9, 8.3)
Red blood cell hypochromic morphology present	1/3	(33.3)	1/4	(25.0)	ND	
Red blood cell sedimentation rate increased	1/2	(50.0)	0/3	(0.0)	ND	
Transferrin saturation decreased	1/4	(25.0)	0/1	(0.0)	ND	
Vitamin B12 decreased	2/127	(1.6)	2/107	(1.9)	ND	
White blood cell count decreased	5/712	(0.7)	7/723	(1.0)	ND	
White blood cell count increased	8/712	(1.1)	9/723	(1.2)	ND	
Hemostatic Function Test	**3/32**	**(9.4)**	**6/40**	**(15.0)**	**-5.63**	**(-21.6, 11.4)**
Activated partial thromboplastin time prolonged	2/17	(11.8)	1/24	(4.2)	7.60	(-10.9, 31.2)
International normalised ratio increased	2/27	(7.4)	4/31	(12.9)	-5.50	(-23.0, 12.6)
Prothrombin time prolonged	2/26	(7.7)	5/35	(14.3)	-6.59	(-23.4, 12.0)
Pathology Analysis	**1/1**	**(100.0)**	**2/2**	**(100.0)**	**ND**	
Therapeutic Drug Monitoring	**0/2**	**(0.0)**	**1/1**	**(100.0)**	**ND**	
Digoxin level decreased	0/1	(0.0)	1/1	(100.0)	ND	

Table 70 (Cont.)

Number (%) of Patients With Specific Laboratory Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n/m	(%)†	Placebo (B) (N=728) n/m	(%)†	Estimated Difference (A-B)% 95% CI
Urinalysis Test	**25/675**	**(3.7)**	**27/705**	**(3.8)**	**-0.13 (-2.2, 2.0)**
Bacteria nos urine identified	7/77	(9.1)	2/78	(2.6)	6.53 (-1.0, 15.4)
Blood urine present	0/3	(0.0)	1/6	(16.7)	ND
Casts urinary granular	1/37	(2.7)	4/20	(20.0)	-17.30 (-39.5, -1.9)
Casts urinary hyaline	3/84	(3.6)	5/59	(8.5)	-4.90 (-15.2, 3.0)
Crystal urine present	5/197	(2.5)	4/170	(2.4)	0.19 (-3.7, 3.8)
Glucose urine present	5/675	(0.7)	5/704	(0.7)	ND
Protein urine present	10/675	(1.5)	13/705	(1.8)	ND
Red blood cells urine positive	7/266	(2.6)	9/244	(3.7)	-1.06 (-4.5, 2.1)
Urine analysis abnormal nos	4/675	(0.6)	4/704	(0.6)	ND
Urine calcium oxalate crystal present	0/65	(0.0)	1/54	(1.9)	ND
Urine epithelial cells increased	1/142	(0.7)	1/129	(0.8)	ND
Urine uric acid crystals present	0/23	(0.0)	2/13	(15.4)	-15.38 (-42.7, 0.7)
White blood cells urine positive	6/248	(2.4)	6/241	(2.5)	-0.07 (-3.2, 3.0)

Although a patient may have had 2 or more laboratory adverse experiences, the patient is only counted once in a category. The same patient may appear in different categories.
† % = number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline x100.
ND = Confidence intervals were not determined because the adverse experience did not occur in ≥2% of patients or there were fewer than 10 patients in either treatment group who had a particular laboratory test.
CI = Confidence interval.
N = Number of patients in each treatment group.
n/m = Number of patients with laboratory adverse experience/number of patients for whom the laboratory test was performed postbaseline.

Data Source: [4.2]

8.5.2.2 Laboratory Adverse Experiences Determined by the Investigator to be Drug Related

Below are laboratory adverse experiences determined to be possibly, probably, or definitely related to study drug for the on-drug and ITT populations.

8.5.2.2.1 On-Drug Population

Seventy-six patients were reported to have one or more laboratory adverse experiences determined by the investigator to be possibly, probably, or definitely related to study drug for the on-drug population (Table 71): 55 (7.7%) patients in the rofecoxib group and 21 (2.9%) patients in the placebo group. Most drug-related adverse experiences were reported for the test category of blood chemistry and involved 33 (4.6%) patients in the rofecoxib group and 7 (1.0%) in the placebo group. The 95% CIs for the differences in percentage points of patients with drug-related blood chemistry adverse experiences did not include zero. This difference between treatment groups corresponds to a difference of 3.65% with a 95% CI of (2.1 , 5.5). Increased blood creatinine was considered as drug related for 17 (2.4%) patients in the rofecoxib group and 5 (0.7%) patients in the placebo group. Increased blood urea nitrogen was reported as drug related for 11 (1.5%) patients in the rofecoxib group and 2 (0.3%) in the placebo group.

Twice as many patients in the rofecoxib group reported drug-related laboratory adverse experiences in the hematology category: 24 (3.4%) on rofecoxib and 12 (1.7%) on placebo. Numerically, the most common drug related adverse experience in this category was decreased hematocrit, which was reported in 16 (2.2%) patients on rofecoxib and 5 (0.7%) on placebo. The 95% CI did not cross zero (0.3, 3.0). Decreased hemoglobin was also reported as drug related more frequently for patients in the rofecoxib group (14) than the placebo group (5).

Five patients in each treatment group reported drug-related adverse experiences in the urinalysis category: 3 (0.4%) patients in the rofecoxib group and 2 (0.3%) in the placebo group had protein present in the urine as a drug-related adverse experience.

Table 71

Number (%) of Patients With Drug-Related Laboratory Adverse Experiences
On-Drug† Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n/m	(%)‡	Placebo (B) (N=728) n/m	(%)‡	Estimated Difference (A-B%)
Patients with at least one adverse experience	55/715	(7.7)	21/723	(2.9)	4.79 (2.5, 7.2)
Patients with no adverse experience	660/715	(92.3)	702/723	(97.1)	
Blood Chemistry Test	**33/715**	**(4.6)**	**7/723**	**(1.0)**	**3.65 (2.1, 5.5)**
Alanine Aminotransferase Increased	8/714	(1.1)	2/723	(0.3)	ND
Alkaline Phosphatase Increased	1/714	(0.1)	1/723	(0.1)	ND
Aspartate Aminotransferase Increased	6/714	(0.8)	1/723	(0.1)	ND
Blood Bilirubin Increased	4/714	(0.6)	1/723	(0.1)	ND
Blood Bilirubin Indirect Increased	1/18	(5.6)	0/17	(0.0)	5.56 (-13.9, 26.2)
Blood Chloride Decreased	1/714	(0.1)	0/723	(0.0)	ND
Blood Cholesterol Increased	1/69	(1.4)	0/70	(0.0)	ND
Blood Creatine Phosphokinase Mb Increased	0/11	(0.0)	1/7	(14.3)	ND)
Blood Creatinine Decreased	1/714	(0.1)	0/723	(0.0)	ND
Blood Creatinine Increased	17/714	(2.4)	5/723	(0.7)	1.69 (0.5, 3.2)
Blood Potassium Increased	3/714	(0.4)	0/723	(0.0)	ND
Blood Sodium Decreased	1/714	(0.1)	0/723	(0.0)	ND
Blood Urea Nitrogen Increased	11/714	(1.5)	2/723	(0.3)	ND
Hematology Laboratory Test	**24/712**	**(3.4)**	**12/723**	**(1.7)**	**1.71 (0.1, 3.5)**
Haematocrit Decreased	16/712	(2.2)	5/723	(0.7)	1.56 (0.3, 3.0)
Haemoglobin Decreased	14/712	(2.0)	5/723	(0.7)	ND
Lymphocyte Count Decreased	1/712	(0.1)	2/723	(0.3)	ND
Neutrophil Count Increased	1/712	(0.1)	1/723	(0.1)	ND
Platelet Count Decreased	3/712	(0.4)	1/723	(0.1)	ND
Platelet Count Increased	1/712	(0.1)	1/723	(0.1)	ND
Red Blood Cell Hypochromic Morphology Present	1/3	(33.3)	0/4	(0.0)	ND)
White Blood Cell Count Decreased	2/712	(0.3)	2/723	(0.3)	ND
Urinalysis Test	**5/675**	**(0.7)**	**5/705**	**(0.7)**	**ND**
Casts Urinary Granular	1/37	(2.7)	0/20	(0.0)	2.70 (-13.8, 14.0)
Casts Urinary Hyaline	2/84	(2.4)	0/59	(0.0)	2.38 (-3.8, 8.3)
Crystal Urine Present	2/197	(1.0)	0/170	(0.0)	ND
Protein Urine Present	3/675	(0.4)	2/705	(0.3)	ND
Red Blood Cells Urine Positive	1/266	(0.4)	0/244	(0.0)	ND
Urine Analysis Abnormal Nos	3/675	(0.4)	0/704	(0.0)	ND
Urine Calcium Oxalate Crystal Present	0/65	(0.0)	1/54	(1.9)	ND
Urine Uric Acid Crystals Present	0/23	(0.0)	1/13	(7.7)	-7.69 (-33.8, 7.7)
White Blood Cells Urine Positive	0/248	(0.0)	1/241	(0.4)	ND

† On drug includes the period through 14 days after discontinuation of study drug.
Although a patient may have had 2 or more clinical adverse experiences, the patient is only counted once in a category. The same patient may appear in different categories.
‡ %= number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline x100.
ND = Confidence intervals were not determined because the adverse experience did not occur in ≥2% of patients or there were fewer than 10 patients in either treatment group who had a particular laboratory test.
CI = Confidence interval.
N = Number of patients in each treatment group.
n/m = Number of patients with laboratory adverse experience/number of patients with one or more laboratory tests postbaseline.

Data Source: [4.2]

8.5.2.2.2 Intention-to-Treat Population

The number of drug-related laboratory adverse experiences was similar in both the ITT and the on-drug population. Table 72 shows the drug-related profile for the ITT population.

Table 72

Number (%) of Patients With Drug-Related Laboratory Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

	Treatment Group				
	Rofecoxib (A) (N=723)		Placebo (B) (N=728)		Estimated Difference
Adverse Experience Term	n/m	(%)‡	n/m	(%)‡	(A-B)% 95% CI
Patients with at least one adverse experience	55/715	(7.7)	22/723	(3.0)	4.65 (2.4, 7.1)
Patients with no adverse experience	660/715	(92.3)	701/723	(97.0)	
Blood Chemistry Test	**33/715**	**(4.6)**	**7/723**	**(1.0)**	**3.65 (2.1, 5.5)**
Alanine aminotransferase increased	8/714	(1.1)	2/723	(0.3)	ND
Alkaline phosphatase increased	1/714	(0.1)	1/723	(0.1)	ND
Aspartate aminotransferase increased	6/714	(0.8)	1/723	(0.1)	ND
Blood bilirubin increased	4/714	(0.6)	1/723	(0.1)	ND
Blood bilirubin indirect increased	1/18	(5.6)	0/17	(0.0)	5.56 (-13.9, 26.2)
Blood chloride decreased	1/714	(0.1)	0/723	(0.0)	ND
Blood cholesterol increased	1/69	(1.4)	0/70	(0.0)	ND
Blood creatine phosphokinase mb increased	0/11	(0.0)	1/7	(14.3)	ND
Blood creatinine decreased	1/714	(0.1)	0/723	(0.0)	ND
Blood creatinine increased	17/714	(2.4)	5/723	(0.7)	1.69 (0.5, 3.2)
Blood potassium increased	3/714	(0.4)	0/723	(0.0)	ND
Blood sodium decreased	1/714	(0.1)	0/723	(0.0)	ND
Blood urea nitrogen increased	12/714	(1.7)	2/723	(0.3)	ND
Direct bilirubin increased	1/19	(5.3)	0/20	(0.0)	5.26 (-11.7, 25.0)
Hematology Laboratory Test	**24/712**	**(3.4)**	**13/723**	**(1.8)**	**1.57 (-0.1, 3.4)**
Eosinophil count increased	0/712	(0.0)	1/723	(0.1)	ND
Hematocrit decreased	16/712	(2.2)	6/723	(0.8)	1.42 (0.2, 2.9)
Hemoglobin decreased	14/712	(2.0)	6/723	(0.8)	ND
Lymphocyte count decreased	1/712	(0.1)	3/723	(0.4)	ND
Neutrophil count increased	1/712	(0.1)	1/723	(0.1)	ND
Platelet count decreased	3/712	(0.4)	1/723	(0.1)	ND
Platelet count increased	1/712	(0.1)	1/723	(0.1)	ND
Red blood cell hypochromic morphology present	1/3	(33.3)	0/4	(0.0)	ND
White blood cell count decreased	2/712	(0.3)	2/723	(0.3)	ND

Table 72 (Cont.)

Number (%) of Patients With Drug-Related Laboratory Adverse Experiences
Intention-to-Treat Population
(>0% Incidence in One or More Treatment Groups)

Adverse Experience Term	Treatment Group: Rofecoxib (A) (N=723) n/m	(%)‡	Placebo (B) (N=728) n/m	(%)‡	Estimated Difference (A-B)% 95% CI
Urinalysis Test	**5/675**	**(0.7)**	**6/705**	**(0.9)**	**ND**
Casts urinary granular	1/37	(2.7)	0/20	(0.0)	2.70 (-13.8, 14.0)
Casts urinary hyaline	2/84	(2.4)	0/59	(0.0)	2.38 (-3.8, 8.3)
Crystal urine present	2/197	(1.0)	0/170	(0.0)	ND
Protein urine present	3/675	(0.4)	3/705	(0.4)	ND
Red blood cells urine positive	1/266	(0.4)	0/244	(0.0)	ND
Urine analysis abnormal nos	3/675	(0.4)	0/704	(0.0)	ND
Urine calcium oxalate crystal present	0/65	(0.0)	1/54	(1.9)	ND
Urine uric acid crystals present	0/23	(0.0)	1/13	(7.7)	-7.69 (-33.8, 7.7)
White blood cells urine positive	0/248	(0.0)	1/241	(0.4)	ND

Although a patient may have had 2 or more laboratory adverse experiences, the patient is only counted once in a category. The same patient may appear in different categories.
‡ % = number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline x100.
ND = Confidence intervals were not determined because the adverse experience did not occur in ≥2% of patients or there were fewer than 10 patients in either treatment group who had a particular laboratory test.
CI = Confidence interval.
N = Number of patients in each treatment group.
n/m = Number of patients with laboratory adverse experience/number of patients with one or more laboratory tests postbaseline.

Data Source: [4.2]

8.5.2.3 Serious Laboratory Adverse Experiences

8.5.2.3.1 On-Drug Population

Table 73 lists the patients with specific serious laboratory adverse experiences which occurred while patients were on drug, or within 14 days of dosing with study medication.

One patient in the rofecoxib group (AN 0139, with decreased blood sodium) and 3 patients in the placebo group (ANs 0273 [blood glucose decreased], 0508 [platelets count decreased], and 0600 [blood potassium decreased]) had serious laboratory adverse experiences. A brief narrative for AN 0139 appears below.

From Site 005, AN 0139, an 82-year-old man in the rofecoxib group, had a serious laboratory adverse experience of hyponatremia. Medical history was remarkable for hypertension. The patient was dosing with hydrochlorothiazide for the hypertension upon study entry. On Day 90 after randomization, lisinopril (2.5 mg) was added to his drug regimen and it was

increased to 5 mg on Day 100. Hydrochlorothiazide was stopped on Day 402 and lisinopril was increased to 10 mg on Day 512. On Day 529 after randomization, the patient was hospitalized with GI distress and weakness after dosing with Percocet for left flank pain. During the hospital stay, laboratory results yielded a sodium level of 115 mmol/L and chloride of 78 mmol/L; the decreased chloride level was attributed to the nonserious adverse experience of dehydration. He was admitted for observation and rehydration. Study medication was interrupted for 8 days. The patient resumed study medication and remained in the trial until it was terminated by the sponsor. The study investigator felt that the decreased sodium was definitely not related to study drug.

Table 73

Listing of Serious Laboratory Adverse Experiences
On-Drug† Population

Study Number	AN	Gender	Race	Age	No. Days Off Study Drug	Relative Day of Onset of Adverse Experience	Adverse Experience	Drug Relation-ship	Action Taken on Study Drug
Rofecoxib 25mg									
078005	139	M	White	82	3	531	Blood sodium decreased	Def. not	Interrupted
Placebo									
078009	273	F	White	80	1	123	Blood glucose decreased	Prob. not	Interrupted
078013	508	M	White	86	0	628	Platelet count decreased	Prob. not	Discontinued
078019	600	M	White	86	2	384	Blood potassium decreased	Def. not	Interrupted

†On-drug includes the period through 14 days after discontinuation of study drug.
Def. not = definitely not
Prob. Not = probably not

Data Source: [4.2]

8.5.2.3.2 Intention-to-Treat Population

Table 74 lists the patients with serious laboratory adverse experiences for the ITT population. One additional patient in the ITT population had a serious laboratory adverse experiences compared with the on-drug population: AN 0103 in the rofecoxib group had decreased potassium 594 days after study drug was stopped.

Table 74

Listing of Serious Laboratory Adverse Experiences
Intention-to-Treat Population

Study Number	AN	Gender	Race	Age	No. Days Off Study Drug	Relative Day of Onset of Adverse Experience	Adverse Experience	Drug Relationship	Action Taken on Study Drug
Rofecoxib 25 mg									
078004	103	M	White	85	594	1305	Blood potassium decreased	Def. not	No action
078005	139	M	White	82	3	531	Blood sodium decreased	Def. not	Interrupted
Placebo									
078009	273	F	White	80	1	123	Blood glucose decreased	Prob. not	Interrupted
078013	508	M	White	86	0	628	Platelet count decreased	Prob. not	Discontinued
078019	600	M	White	86	2	384	Blood potassium decreased	Def. not	Interrupted
Def. not = definitely not. Prob. not = probably not.									

Data Source: [4.2]

8.5.2.4 Patients who Discontinued Study Therapy Due to Laboratory Adverse Experiences

A listing of all patients who discontinued study medication due to laboratory adverse experiences is in [4.5].

8.5.2.4.1 On-Drug Population

The distribution of patients who discontinued study therapy due to laboratory adverse experiences which occurred while patients were on drug, or within 14 days of dosing with study medication, are presented in Table 75.

A total of 28 patients discontinued study therapy due to a laboratory adverse experience: 23 (3.2%) patients in the rofecoxib group and 5 (0.7%) in the placebo group.

Twenty-two patients in the on-drug population discontinued study therapy due to adverse experiences in blood chemistry: 20 (2.8%) patients in the rofecoxib group, and 2 (0.3%) in the placebo group. Of these, 13 (1.8%) patients in the rofecoxib group discontinued study therapy due to increased creatinine levels; no patients in the placebo group discontinued due to this laboratory adverse experience. Six patients in the rofecoxib group and none in the placebo group discontinued study medication due to both increased creatinine and increased BUN. Brief narratives for 10 patients in the rofecoxib group who discontinued study medication because of increased creatinine levels and who exceeded the PDLC values (one value with actual increase of serum creatinine level ≥0.5(mg/dL) from baseline and >ULN) and who discontinued the study drug due to the laboratory and/or related adverse experience are below.

From Site 004, AN 0118, an 83-year-old male, discontinued study medication due to the laboratory adverse experience of increased creatinine. Prior medical history was remarkable for non-insulin dependent diabetes mellitus, diabetic neuropathy, and osteoarthritis. Prior and concomitant medications included glipizide and metformin hydrochloride. Baseline serum creatinine levels were 0.9 mg/dL and BUN was 12 mg/dL. By Day 367, creatinine was at 1.1 mg/dL and BUN levels had increased to 25 mg/dL and remained about the same (serum creatinine 1.0 mg/dL and BUN 20 mg/dL) on Day 731. Captopril was started on Day 846 due to the nonserious adverse experience of hypertension. On Day 1081, the patient developed edema and was prescribed triamterene. On Day 1092, the laboratory adverse experiences of increased serum creatinine and proteinuria were reported. At this time, BUN was at 25 mg/dL and serum creatinine was at 1.5 mg/dL. Study drug use was discontinued on Day 1099 due to the elevated creatinine. On Day 1175, serum creatine levels were still elevated at 1.7 mg/dL. The patient completed the trial on Day 1455 and BUN and serum creatinine levels were at 17 and 1.3 mg/dL, respectively.

From Site 008, AN 0243, a 71-year-old-male, had a medical history of lower limb edema, urinary frequency, coronary bypass graft, congestive heart failure, and myocardial infarction. Prior and concomitant therapies included: spironolactone, furosemide, potassium chloride, and metolazone. Baseline BUN and creatine levels were 27 and 1.2 mg/dL, respectively. The BUN was at 24 and serum creatine level was 1.4 mg/dL on Day 731. The patient had adverse experiences of anemia, edema, COPD, chest pain, bronchitis, and hypertension starting on or about Day 780. Lisinopril, nitroglycerin, furosemide, azithromycin, prednisone, methylprednisolone sodium succinate, and morphine sulfate were prescribed during this time frame. The patient suffered an MI on Day 890, and aspirin (325 mg), metoprolol, clopidogrel

were prescribed; adjustments to dosage of lisinopril and furosemide were also made. Blood tests for serum creatinine and BUN were not reported again until Day 1094, when a series of abnormal laboratory values were reported as adverse experiences: increased BUN (50 mg/d), creatinine (2.1 mg/dL), glucose (176 mg/dL), and potassium (6.4 mEq/L). Study drug was discontinued on Day 1099. By Day 1120, serum creatinine was at 1.3 mg/dL and BUN was at 36 mg/dL. The patient had recurrent episodes of worsening congestive heart failure and COPD over the next 10 months. The patient continued in the trial until completion and at the final study visit (Day 1463), serum creatinine was at 0.8 mg/dL and BUN was at 15 mg/dL.

From Site 008, AN 1690, a 79-year-old male, had a past medical history of edema, trigeminal neuralgia, and hypertension. Therapies taken upon study entry and continuing during the study were ramipril, hydrochlorothiazide and carbamazepine. Baseline serum creatine was 1.7 mg/dL and BUN was at 33 mg/dL. One day after dosing with study medicine, serum creatinine was at 2.0 mg/dL and BUN was 32 mg/dL. BUN and serum creatinine levels continued to increase to 44 and 2.5 mg/dL, respectively on Day 265 after randomization. Abnormal laboratory values of BUN and serum creatine remained high and were reported as nonserious adverse experiences on Day 335 with levels at 52 and 2.4 mg/dL, respectively. No other adverse experiences were reported at that time. Concomitant therapies remained as initially prescribed except hydrochlorothiazide, which was increased from 25 to 50 mg on Day 157, and lisinopril (10 mg) was prescribed on Day 258 and reduced in dosage to 5 mg on Day 357. Study drug was discontinued on Day 339 due to the laboratory adverse experiences. On Day 352, creatinine was at 2.1 mg/dL and BUN levels were 49 mg/dL. Blood values for BUN and creatinine continued to rise and on Day 422, serum creatinine was at 2.5 mg/dL and BUN at 63 mg/dL; levels remained above 2.0 mg/dL for serum creatinine and at or above 39 mg/dL until Day 1077, when the study was terminated by the Sponsor.

From Site 009, AN 0272, a 66-year-old male, had a medical history remarkable for diabetes mellitus, increased blood pressure, and hypercholesterolemia. Concomitant therapies included pravastatin sodium, metformin hydrochloride, fosinopril sodium, and glyburide. Baseline BUN was 19 mg/dL and serum creatinine was 1.1 mg/dL. The patient was diagnosed with coronary artery disease on Day 59 after randomization and the dose of pravastatin sodium was increased from 20 mg to 40 mg. Aspirin 325 mg daily was prescribed for cardiac prophylaxis on Day 61. Changes in dosing of pravastatin sodium and atorvastatin calcium were made for the hypercholesterolemia from days 161 to 791. On Day 732 after randomization, serum creatinine was at 1.8 mg/dL and BUN had increased to 35 mg/dL. On

Day 740, serum creatinine was 1.9 mg/dL and was rated by the investigator as being possibly related to study drug, BUN was 32 mg/dL, and study drug was interrupted. By Day 756 study drug had not been resumed, serum creatinine remained high at 1.7 mg/dL, BUN was 28 mg/dL and study drug was discontinued at this time. On Day 778, serum creatinine was at 1.6 mg/dL and BUN was in the normal range at 23 mg/dL. The patient remained in the study until it was terminated by the sponsor. At the final study visit (Day 1343), serum creatinine was at 1.2 mg/dL and BUN was 18 mg/dL.

From Site 010, AN 0319, a 79-year-old male, had no remarkable medical history or prior therapy and was taking no concomitant medications. Baseline serum creatinine was 1.3 mg/dL and BUN was 25 mg/dL. On Day 823, the patient was prescribed hydrochlorothiazide for hypertension which was rated as possible related to study drug. Baseline blood pressure was 162/88 mm/Hg and at the time of the adverse experience of hypertension it was 178/92 mm/Hg. He took the hydrochlorothiazide for 13 days and blood pressure remained around 130/75 mm/Hg for the next 12 months. On Day 1078, the patient had an adverse experience of increased serum creatinine (1.7 mg/dL) rated as probably not related to study drug. On Day 1088, the patient was prescribed lisinopril 10 mg. for hypertension (blood pressure on Day 1078 was 128/76 mm/Hg). By Day 1099, serum creatinine was at 1.9 mg/dL and BUN was at 35 mg/dL; both adverse experiences were rated as possibly related to study drug. Serum creatinine continued to remain high on Day 1113 with results of 1.8 mg/dL and BUN at 31 mg/dL; and study drug was discontinued. Eighteen days later blood chemistry levels were lower for serum creatinine (1.5 mg/dL) and BUN (29 mg/dL). On Day 1473, serum creatinine was 1.5 mg/dL and BUN was 34 mg/dL. The patient completed the study.

From Site 011, AN 1652, a 73-year-old male, had a medical history remarkable for hypertension. Therapies taken upon study start were hydrochlorothiazide and valsartan for hypertension. Baseline BUN was 25 mg/dL and serum creatinine was 1.7 mg/dL. By Day 22 after randomization, BUN was 36 mg/dL and creatinine 1.9 mg/dL. Amlodipine besylate was prescribed for hypertension and valsartan was discontinued by Day 40. On Day 224 after randomization, serum creatinine levels were high at 2.4 mg/dL. Medications for hypertension were modified through Day 348. On Day 356, increased BUN (44 mg/dL) and increased serum creatinine (2.0 mg/dL) were reported as nonserious adverse experiences and again on Day 363, BUN was 43 mg/dL and creatinine was 2.4 mg/dL. Study drug was discontinued on Day 370. Laboratory levels declined between Days 371 and 695 from 2.7 to 1.7 mg/dL for creatinine and 53 to 27 mg/dL for BUN. The patient continued in the trial until the study was stopped by the sponsor on Day 1044; BUN was at 35 mg/dL and creatinine was at 1.8 mg/dL.

From Site 015, AN 0462, an 86-year-old female, had a history of hypertension. Concomitant therapies included hydrochlorothiazide 50 mg for hypertension. Baseline serum creatinine was 0.8 mg/dL and BUN was 17 mg/dL. Baseline blood pressure was 140/80 mm/Hg. On Day 365 after randomization serum creatinine was 1.5 mg/dL and BUN was at 49 mg/dL; these were reported as adverse experiences rated as possibly related to study drug. On Day 752 levels were at 1.7 and 49 mg/dL for serum creatinine and BUN, respectively. On Day 805 nifedipine 30 mg was prescribed in place of hydrochlorothiazide for hypertension, then changed again on Day 1094 back to the originally prescribed hydrochlorothiazide 50 mg. HGB, HCT, BUN, and Creatinine levels remained high and were reported as adverse experiences on Day 1114, rated as probably related to study drug, and for which study drug was discontinued; serum creatinine was at 1.5 mg/dL and BUN was at 40 mg/dL. The last dose of study drug was taken on Day 1124. The patient discontinued the study on Day 1305 due to reaching the protocol specified endpoint of investigator confirmed AD. By Day 1305, serum creatine was at 1.2 mg/dL and BUN was 27 mg/dL.

Brief narratives for patient ANs 0141, 0392, and 1444, with details regarding the abnormal laboratory values for serum creatinine and drug-related adverse experiences of renal impairment, can be found in Section 8.2.2.1.

There were 4 patients in the rofecoxib group (ANs 0482, 0588, 1320, and 1410) and one in the placebo group (AN 0947) who discontinued study medication due to increased ALT. Four patients in the rofecoxib group (ANs 0482, 0154, 0588, and 1320) and AN 0947 in the placebo group discontinued medication due to increased AST.

Brief narratives are below for the patients in the rofecoxib group who discontinued study medication and who met the criteria for the AST and/or ALT PDLC (one value >3 x ULN [if normal baseline] or one value>2 x baseline value and >3 x ULN [if abnormal baseline]); see Section 8.6.3 for complete PDLC results. Patient AN 0588 was the only patient to have discontinued medication due to adverse experiences of both increased AST and ALT, and who also met the PDLC criteria. ANs 0482 and 1320 met the PDLC criteria for ALT, while AN 0154 met the PDLC criteria for AST. AN 1410 discontinued study medication due to increased ALT, but the ALT value did not meet the PDLC criteria and is not included in the discussions below.

From Site 016, AN 0482, a 79-year-old female in the rofecoxib group, had an unremarkable medical history and was taking vitamins upon entry into the study. Baseline AST was 24 IU and ALT was 19 IU which remained steady until results from blood drawn on Day 370 after randomization showed

increases to 92 IU for AST and 172 IU for ALT. No other adverse experiences were reported during that period of time. Nine days later results for blood chemistry revealed levels at 102 IU for AST and 182 IU for ALT. Study drug was discontinued on Day 386. On Day 398, AST levels were in the normal range at 43 IU and ALT was elevated at 66 IU. The patient remained in the study until she reached the protocol specified endpoint of confirmed AD. On the final study visit (Day 1078), AST was at 21 IU and ALT was at 15 IU.

From Site 019, AN 0588, an 81-year-old female in the rofecoxib group, had a past medical history of a thyroidectomy. She was taking iron as a prior therapy upon entering the study. Baseline AST was 19 IU and ALT was 13 IU. On Day 112 the patient reported a urinary tract infection and blood chemistry levels were elevated to 283 IU for AST and 382 IU for ALT and remained so through to Day 131, when it was determined that the patient was reactive for hepatitis A antibody. Study drug was discontinued and by Day 148, AST had decreased to 67 IU and ALT to 96 IU. The patient withdrew consent from study participation on Day 789; AST levels were at 14 IU and ALT was 9 IU.

From Site 025, AN 0154, a 74-year-old female in the rofecoxib group, had a medical history of diverticulitis. Concomitant medicine use included Vicodin, estradiol, and aspirin (81 mg). Baseline AST was 22 IU and ALT was 14 IU. On Day 122, AST had increased to 111 IU and ALT was at 93 IU. Aphasia had been reported as an adverse experience on Day 122 and on Day 129 AST was at 161 IU and ALT was at 146 IU. The patient had a TIA on Day 130. On Day 126 nabumetone was prescribed for knee pain and on Day 130, omeprazole and Plavix were started. On Day 136, AST and ALT had begun to decrease to 83 and 77 IU, respectively. About a month later the patient also had a serious adverse experience of worsening diverticulitis and lower GI hemorrhage and anemia. The AST and ALT remained within the normal range until Day 318 when levels were high at 435 IU and 391 IU for ALT and AST, respectively. On Day 325, the patient was tested for hepatitis, but results showed non-reactive to hepatitis A and B. Study drug was discontinued due to the increased AST on Day 331. The patient remained in the study and on the final visit (Day 1097), ALT was at 11 IU and AST was at 23 IU.

From Site 042, AN 1320, A 73-year-old female in the rofecoxib group, had a medical history of hypertension, hyperlipidemia, diverticulosis, and obesity. Concomitant therapies included nitrofurantoin, amlodipine besylate, and gemfibrozil. Baseline AST and ALT were 14 and 18 IU, respectively. By Day 347, AST was at 108 IU and ALT was at 196 IU. Blood glucose was

also high at 148 mg/dL. Levels were still high on Day 368 (AST at 83 IU and ALT at 154 IU) and study drug was discontinued. Glucose had decreased to 128 mg/dL at that time. Laboratory adverse experiences of increased ALT and AST were reported again at Day 411: levels were at 92 IU for ALT and 67 IU for AST. No other adverse experiences were reported during that period of time. At the patient's last visit on Day 1069, before being lost to follow-up, AST and ALT levels were still above the normal range at 87 IU for ALT and 83 IU for AST.

Table 75

Number (%) of Patients Who Discontinued Therapy
Due to Specific Laboratory Adverse Experiences
On- Drug[†] Population
(Incidence >0% in One or More Treatment Groups)

	Rofecoxib 25 mg N=723		Placebo N=728	
	n/m	(%)[§]	n/m	(%)[§]
Patients with one or more adverse experiences	23/715	(3.2)	5/723	(0.7)
Patients with no adverse experience	692/715	(96.8)	718/723	(99.3)
Blood Chemistry Test	**20/715**	**(2.8)**	**2/723**	**(0.3)**
Alanine aminotransferase increased	4/714	(0.6)	1/723	(0.1)
Alkaline phosphatase increased	0/714	(0.0)	1/723	(0.1)
Aspartate aminotransferase increased	4/714	(0.6)	1/723	(0.1)
Blood bilirubin increased	1/714	(0.1)	0/723	(0.0)
Blood creatinine decreased	1/714	(0.1)	0/723	(0.0)
Blood creatinine increased	13/714	(1.8)	0/723	(0.0)
Blood potassium increased	1/714	(0.1)	0/723	(0.0)
Blood urea nitrogen increased	6/714	(0.8)	1/723	(0.1)
Clinical Serology Test	**1/27**	**(3.7)**	**0/27**	**(0.0)**
Hepatitis A antibody positive	1/4	(25.0)	0/†	
Hepatitis A virus IgM antibody positive	1/3	(33.3)	0/†	
Hematology Laboratory Test	**6/712**	**(0.8)**	**2/723**	**(0.3)**
Hematocrit decreased	2/712	(0.3)	0/723	(0.0)
Hemoglobin decreased	2/712	(0.3)	0/723	(0.0)
Platelet count decreased	2/712	(0.3)	2/723	(0.3)
White blood cell count decreased	2/712	(0.3)	1/723	(0.1)
Hemostatic Function Test	**0/32**	**(0.0)**	**1/40**	**(2.5)**
Prothrombin time prolonged	0/26	(0.0)	1/35	(2.9)

[†] On drug includes the period through 14 days after discontinuation of study drug.
† Indicates there was no associated laboratory test or there were no patients for whom the laboratory test was recorded postbaseline.
[§] %= Number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline x100.
N = Number of patients randomized to each treatment group who took at least one dose of study medication.
n/m = Number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.
Although a patient may have had two or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

Data Source: [4.2]

8.5.2.4.2 Intention-to-Treat Population

Table 76 shows the number of patients who discontinued study therapy due to at least one or more specific laboratory adverse experience for the ITT population. The number of patients who discontinued study therapy due to laboratory adverse events for the ITT population was consistent with those of the on-drug population. Overall, 32 patients in the ITT population discontinued study therapy due to a laboratory adverse experience: 25 (3.5%) patients in the rofecoxib group and 7 (1.0%) in the placebo group.

Table 76

Number (%) of Patients Who Discontinued Therapy
Due to Specific Laboratory Adverse Experiences
Intention-to-Treat Population
(Incidence >0% in One or More Treatment Groups)

	Rofecoxib 25 mg N=723		Placebo N=728	
	n/m	(%)†	n/m	(%)†
Patients with one or more adverse experiences	25/715	(3.5)	7/723	(1.0)
Patients with no adverse experience	690/715	(96.5)	716/723	(99.0)
Blood Chemistry Test	**22/715**	**(3.1)**	**4/723**	**(0.6)**
Alanine aminotransferase increased	4/714	(0.6)	1/723	(0.1)
Alkaline phosphatase increased	0/714	(0.0)	1/723	(0.1)
Aspartate aminotransferase increased	4/714	(0.6)	1/723	(0.1)
Blood bilirubin increased	1/714	(0.1)	0/723	(0.0)
Blood creatinine decreased	1/714	(0.1)	0/723	(0.0)
Blood creatinine increased	15/714	(2.1)	1/723	(0.1)
Blood potassium increased	1/714	(0.1)	0/723	(0.0)
Blood urea nitrogen increased	7/714	(1.0)	2/723	(0.3)
Clinical Serology Test	**1/27**	**(3.7)**	**0/27**	**(0.0)**
Hepatitis A antibody positive	1/4	(25.0)	0/‡	
Hepatitis A virus IgM antibody positive	1/3	(33.3)	0/‡	
Hematology Laboratory Test	**6/712**	**(0.8)**	**2/723**	**(0.3)**
Hematocrit decreased	2/712	(0.3)	0/723	(0.0)
Hemoglobin decreased	2/712	(0.3)	0/723	(0.0)
Platelet count decreased	2/712	(0.3)	2/723	(0.3)
White blood cell count decreased	2/712	(0.3)	1/723	(0.1)
Hemostatic Function Test	**0/32**	**(0.0)**	**1/40**	**(2.5)**
Prothrombin time prolonged	0/26	(0.0)	1/35	(2.9)

†%= Number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline x100.
‡Indicates there was no associated laboratory test or there were no patients for whom the laboratory test was recorded postbaseline.
N = Number of patients randomized to each treatment group who took at least one dose of study medication.
n/m = Number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.
Although a patient may have had two or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

Data Source: [4.2]

8.6 Clinical Evaluation of Laboratory Safety Tests

Clinically significant laboratory abnormalities were tabulated by treatment group over time. Means and standard deviations at baseline and changes from baseline to treatment visits were summarized by treatment groups for laboratory measures.

8.6.1 Listing of Specific Laboratory Safety Tests, Including Abnormal Laboratory Values, by Patient

Records for all patients with laboratory adverse experiences are in [4.2].

8.6.2 Laboratory Values Over Time

The tables for the Summary of Laboratory Tests Over Time for the On-Drug and ITT populations are in [4.8]. Graphical representation of the mean change from baseline for BUN, serum creatinine, hemoglobin, hematocrit, AST and ALT are shown in Figure 8 through Figure 13 for the on-drug population and Figure 14 through Figure 19 for the ITT population.

8.6.2.1 On-Drug Population

The table for the summary of all laboratory tests over 48 months of treatment can be found in [4.8]. Figure 8 through Figure 13 shows the mean change from baseline for BUN, hemoglobin, hematocrit, serum creatinine, AST and ALT for patients in the on-drug population. The 95% CIs did not include zero at any time points for any of the mean changes from baseline, except for the 12-month value for ALT.

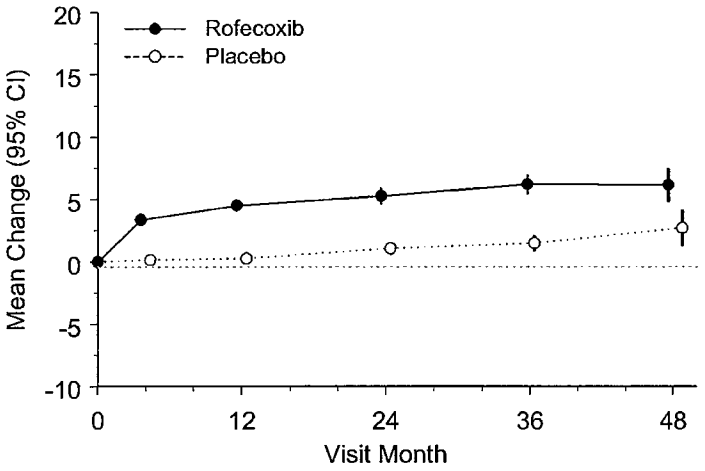
There was a mean (SD) increase of 3.37 (4.26) mg/dL in BUN in the rofecoxib group at Month 4 that gradually increased to 6.15 (5.62) mg/dL at Month 48. Mean changes were smaller in the placebo group with a gradual increase over time to a mean change of 2.72 (7.32) mg/dL at Month 48.

Mean decreases from baseline in hematocrit were ~1 to 2% for rofecoxib and 0 to 1% for placebo across the duration of the study, with similar mean changes at the Month 48 time point. A similar pattern was observed for hemoglobin, with decreases over 48 months of ~0.5 to 0.9 gm/dL for rofecoxib and 0.2 to 0.6 gm/dL for placebo. Rofecoxib has been associated with decreases of hemoglobin and hematocrit. In the absence of evidence for significant GI blood loss with rofecoxib, these observations are consistent with hemodilution, postulated as secondary to fluid retention consequent to COX-2 inhibition in the kidney.

Mean change from baseline for serum creatinine levels increased slightly over time for both treatment groups, with the mean change (SD) at the Month 48 visit of 0.15 (0.24) mg/dL and 0.06 (0.20) mg/dL for the rofecoxib and placebo groups, respectively. Mean changes in the liver test ALT and AST were highly variable, and there were no observed patterns or recognizable differences between treatment groups.

Figure 8

Blood Urea Nitrogen: Mean (95% CI) Change From Baseline
On-Drug Population

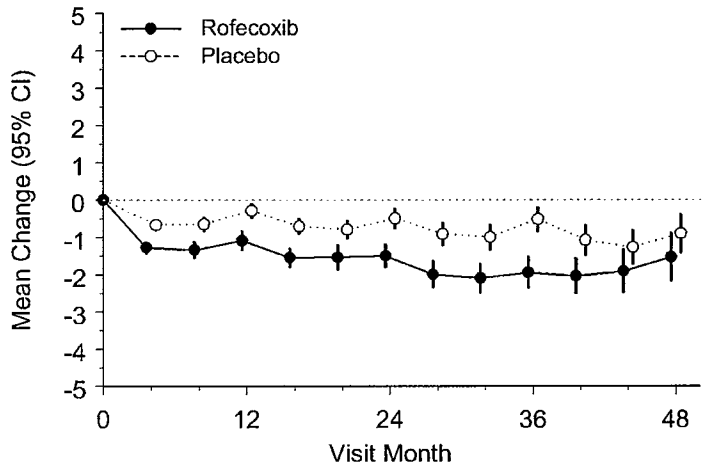


Number of Patients					
Rofecoxib	703	496	324	193	71
Placebo	713	548	393	242	106

Data Source: [4.2]

Figure 9

Hematocrit: Mean (95% CI) Change From Baseline
On-Drug Population



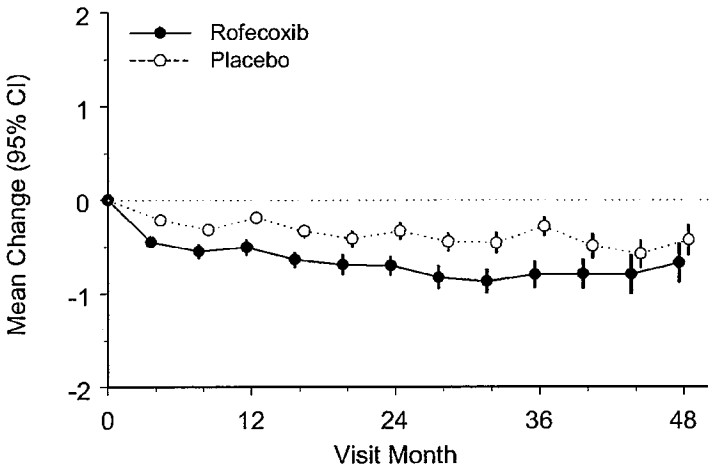
Number of Patients

Rofecoxib	701	564	495	456	386	329	255	218	201	153	118	72
Placebo	711	604	549	491	442	393	303	277	250	194	147	106

Data Source: [4.2]

Figure 10

Hemoglobin: Mean (95% CI) Change From Baseline
On-Drug Population

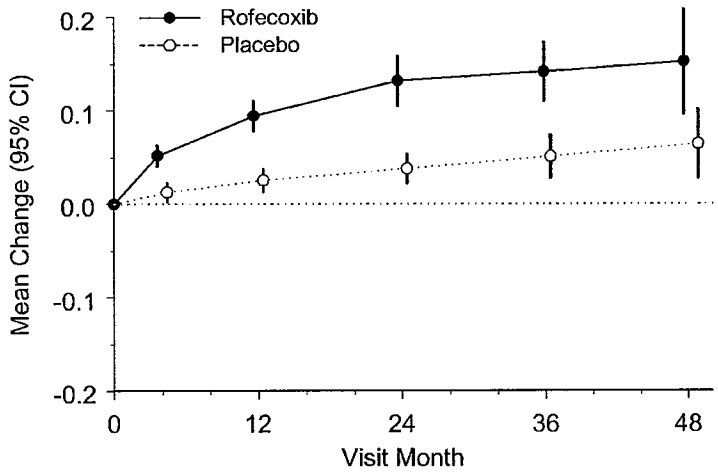


Number of Patients												
Rofecoxib	701	564	495	456	386	329	255	218	201	153	118	72
Placebo	711	604	549	491	442	393	303	277	250	194	147	106

Data Source: [4.2]

Figure 11

Serum Creatinine: Mean (95% CI) Change From Baseline
On-Drug Population

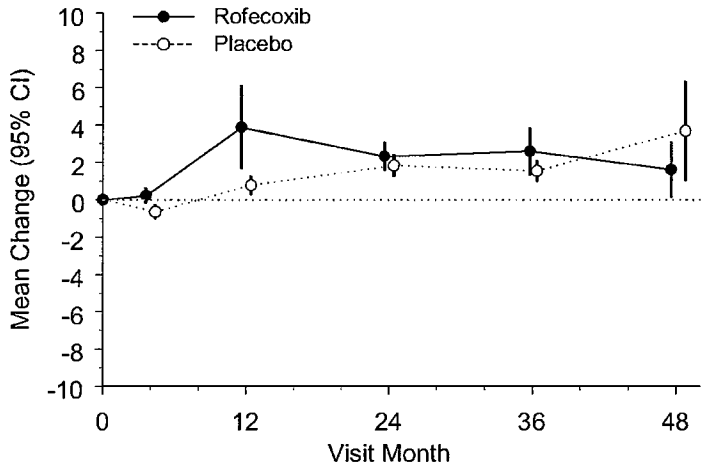


Number of Patients					
Rofecoxib	703	496	324	193	71
Placebo	712	548	393	242	106

Data Source: [4.2]

Figure 12

AST: Mean (95% CI) Change From Baseline
On-Drug Population

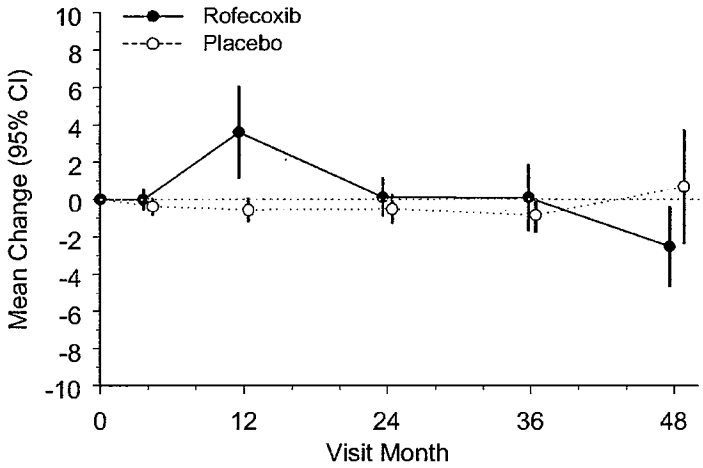


	Number of Patients				
Rofecoxib	703	496	324	193	71
Placebo	713	548	393	242	106

Data Source: [4.2]

Figure 13

ALT: Mean (95% CI) Change From Baseline
On-Drug Population



	Number of Patients				
Rofecoxib	703	496	324	193	71
Placebo	713	548	393	242	106

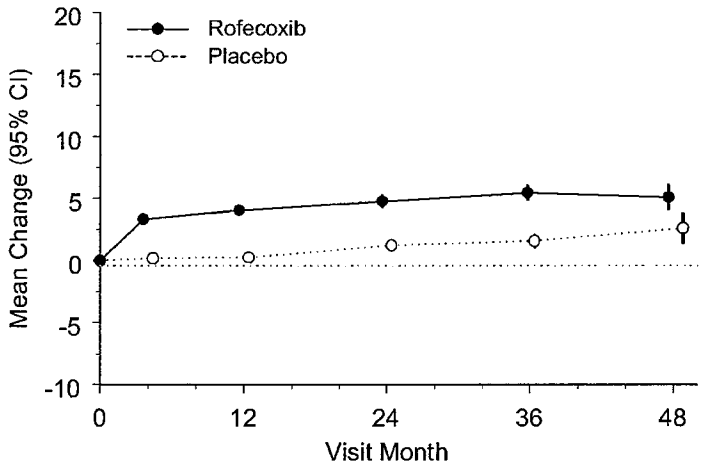
Data Source: [4.2]

8.6.2.2 Intention-to-Treat Population

The summary of laboratory values over time for the ITT population can be found in [4.8]. Graphical representations are shown for BUN, hemoglobin, hematocrit, serum creatinine, AST, and ALT in Figure 14 through Figure 19. Plots of mean changes of laboratory values from baseline to 48 months of treatment for the ITT population were similar to those for the on-drug population.

Figure 14

BUN: Mean (95% CI) Change From Baseline
Intention-to-Treat Population

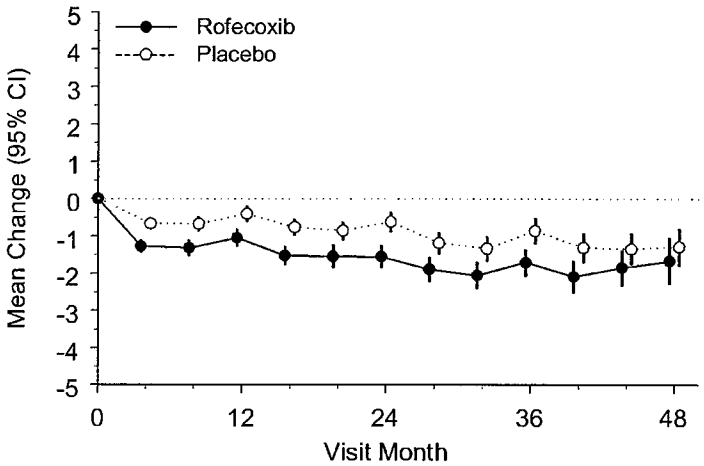


Number of Patients					
Rofecoxib	713	573	410	271	113
Placebo	722	619	465	310	138

Data Source: [4.2]

Figure 15

Hematocrit: Mean (95% CI) Change From Baseline
Intention-to-Treat Population

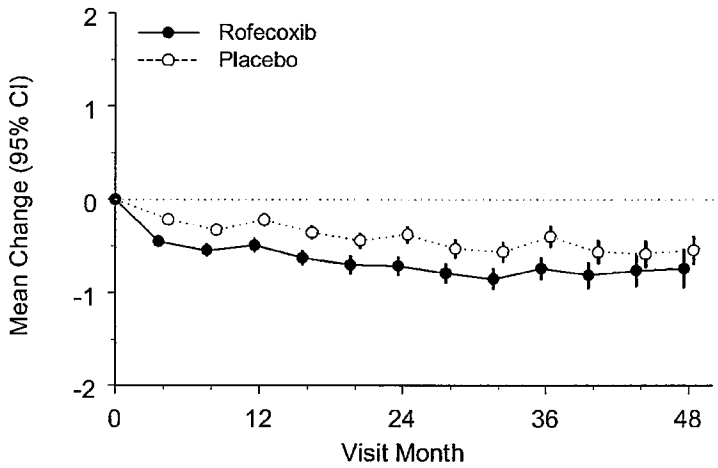


Number of Patients												
Rofecoxib	711	629	572	532	467	415	347	301	284	224	174	114
Placebo	720	651	619	564	509	465	374	342	320	251	192	139

Data Source: [4.2]

Figure 16

Hemoglobin: Mean (95% CI) Change From Baseline
Intention-to-Treat Population

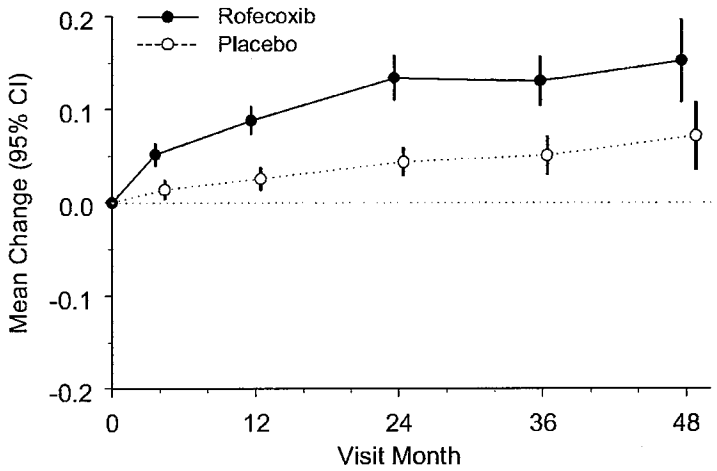


Number of Patients												
Rofecoxib	711	629	572	532	467	415	347	301	284	224	174	114
Placebo	720	651	619	564	509	465	374	342	320	251	192	139

Data Source: [4.2]

Figure 17

Serum Creatinine: Mean (95% CI) Change From Baseline
Intention-to-Treat Population

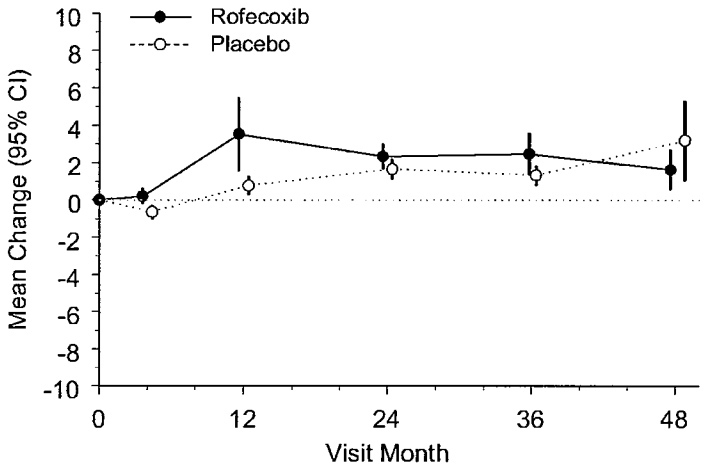


Number of Patients					
Rofecoxib	713	573	410	271	113
Placebo	721	619	464	310	137

Data Source: [4.2]

Figure 18

AST: Mean (95% CI) Change From Baseline
Intention-to-Treat Population

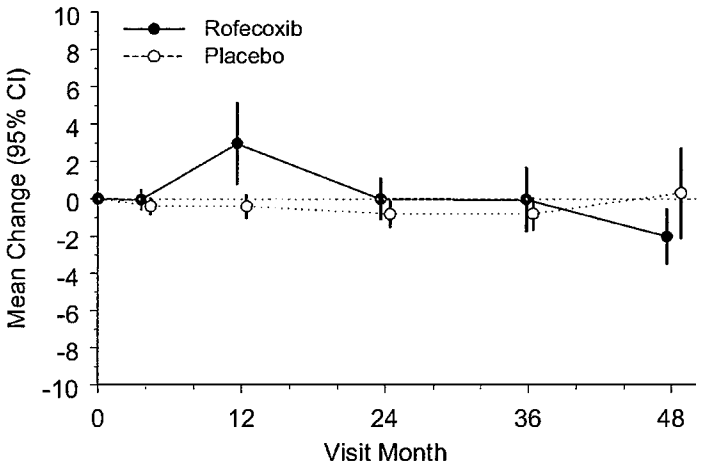


Number of Patients					
Rofecoxib	713	573	410	271	113
Placebo	722	619	465	310	138

Data Source: [4.2]

Figure 19

ALT: Mean (95% CI) Change From Baseline
Intention-to-Treat Population



	Number of Patients				
Rofecoxib	713	573	410	271	113
Placebo	722	619	465	310	138

Data Source: [4.2]

8.6.3 Laboratory Values for Predefined Limits of Change

Counts of patients exceeding the PDLC were obtained for the laboratory parameters used in the VIOXX Rheumatoid Arthritis and Low Back Pain studies and in the VIGOR (VIOXX Gastrointestinal Outcomes Research) studies [2.1.2]. The definition of laboratory parameters for the VIGOR study are in [3.4]. The PDLC tables (on-drug and ITT populations), using the Neuropharmacology Division criteria, are in Section 11 and the definition of parameters is in [3.4]. A patient was classified as "above limit" or "below limit" if a value (actual value, change, or percent change from baseline depending on the definition) fell outside of the predefined limits of change at least once during the treatment period of the study unless the definition specified consecutive occurrences were required. Consecutive values included all scheduled and unscheduled laboratory measures. For some measures, if a value met the criteria on one occasion (instead of consecutive values) and a patient discontinued as a result, then the value could be classified as exceeding the predefined limit of change. For some laboratory parameters, a secondary analysis was performed using the definitions marked as secondary.

8.6.3.1 On-Drug Population

Table 77 shows the number of patients who exceeded the PDLC from baseline laboratory values over the course of the study. There was a decrease in hemoglobin >2 gm/dL and hematocrit ≥5% or a decrease in hemoglobin >1 gm/dL and hematocrit ≥10% for 233 (33.2%) patients in the rofecoxib group and 145 (20.4%) in the placebo group. The secondary analysis performed for a decrease in hemoglobin >2 gm/dL and hematocrit ≥10% resulted in counts of 121 (17.3%) patients in the rofecoxib group and 51 (7.2%) patients in the placebo group. The greater number of patients in the rofecoxib group exhibiting decreases in hemoglobin and hematocrit are most consistent with hemodilution, postulated as secondary to fluid retention consequent to COX-2 inhibition in the kidney.

There were 21 (3.0%) patients in the rofecoxib group and 4 (0.6%) in the placebo group with consecutive serum creatinine values with increases of ≥0.5 mg/dL over baseline and greater than the upper limits of normal. A secondary analysis resulted in 51 (7.3%) patients in the rofecoxib group and 14 (2.0%) in the placebo group with one or more serum creatinine values with increases of ≥0.5 mg/dL over baseline and greater than the upper limits of normal. The majority of these did not lead to discontinuation of study drug. These findings are consistent with the known renal effects of NSAIDs and selective COX-2 inhibitors.

Table 77

Patients Exceeding the Predefined Limits of Change
On-Drug[†] Population

Laboratory Test	Predefined Limit of Change From Baseline[‡]	Treatment	Number[§]/Total[‖] (%)
WBC count (10[3]/microL)	Consecutive values with a decrease ≥20% and <LLN[¶]	Rofecoxib 25 mg	6/701 (0.9)
		Placebo	7/711 (1.0)
	Consecutive values with an increase ≥20% and >ULN[¶]	Rofecoxib 25 mg	6/701 (0.9)
		Placebo	4/711 (0.6)
Hemoglobin (gm/dL) and hematocrit (%)	Decrease in Hgb>2g/dL and Hct ≥5% or Decrease in Hgb >1g/dL and Hct ≥10%[¶#]	Rofecoxib 25 mg	233/701 (33.2)
		Placebo	145/711 (20.4)
	Decrease in Hgb>2g/dL and Hct ≥10%[¶#] (secondary)	Rofecoxib 25 mg	121/701 (17.3)
		Placebo	51/711 (7.2)
Lymphocyte count (10[3]/microL)	Consecutive values with a decrease ≥20% and <LLN[¶]	Rofecoxib 25 mg	13/701 (1.9)
		Placebo	7/711 (1.0)
	Consecutive values with an increase ≥50% and >ULN[¶]	Rofecoxib 25 mg	1/701 (0.1)
		Placebo	0/711 (0.0)
Neutrophil count (10[3]/microL)	Consecutive values with a decrease ≥20% and <LLN[¶]	Rofecoxib 25 mg	7/701 (1.0)
		Placebo	4/710 (0.6)
	Consecutive values with an increase ≥50% and >ULN[¶]	Rofecoxib 25 mg	3/701 (0.4)
		Placebo	3/710 (0.4)

Table 77 (Cont.)

Patients Exceeding the Predefined Limits of Change
On-Drug[†] Population

Laboratory Test	Predefined Limit of Change From Baseline[‡]	Treatment	Number[§]/Total[‖] (%)
Platelet count (10[3]/microL)	Consecutive values with a decrease ≥25% and <LLN[¶]	Rofecoxib 25 mg	8/701 (1.1)
		Placebo	5/711 (0.7)
Serum alanine aminotransferase (IU(aminotransferase))	Consecutive values>3 x ULN(if normal baseline) or Consecutive values>2 x baseline value and >3 x ULN(if abnormal baseline)[¶]	Rofecoxib 25 mg	5/703 (0.7)
		Placebo	1/713 (0.1)
	One or more values>3 x ULN(if normal baseline) or one or more values>2 x baseline value and >3 x ULN(if abnormal baseline) (secondary)	Rofecoxib 25 mg	7/703 (1.0)
		Placebo	2/713 (0.3)
Serum aspartate aminotransferase (IU(aminotransferase))	Consecutive values>3 x ULN(if normal baseline) or Consecutive values>2 x baseline value and >3 x ULN(if abnormal baseline)[¶]	Rofecoxib 25 mg	2/703 (0.3)
		Placebo	0/713 (0.0)
	One or more values>3 x ULN(if normal baseline) or one or more values>2 x baseline value and >3 x ULN(if abnormal baseline) (secondary)	Rofecoxib 25 mg	3/703 (0.4)
		Placebo	0/713 (0.0)
Serum creatinine (mg/dL)	Consecutive values with actual increase ≥0.5 and >ULN[¶]	Rofecoxib 25 mg	21/703 (3.0)
		Placebo	4/712 (0.6)
	Consecutive values>2 x baseline value and >ULN[¶] (secondary)	Rofecoxib 25 mg	0/703 (0.0)
		Placebo	0/712 (0.0)

Table 77 (Cont.)

Patients Exceeding the Predefined Limits of Change
On-Drug[†] Population

Laboratory Test	Predefined Limit of Change From Baseline[‡]	Treatment	Number[§]/Total[‖] (%)
	One or more values with absolute increase ≥0.5 and >ULN (secondary)	Rofecoxib 25 mg	51/703 (7.3)
		Placebo	14/712 (2.0)
	One or more values >2 x baseline value and >ULN (secondary)	Rofecoxib 25 mg	4/703 (0.6)
		Placebo	1/712 (0.1)
Serum potassium (mEq(K)/L)	Consecutive values ≥1.1 x ULN[¶]	Rofecoxib 25 mg	1/703 (0.1)
		Placebo	1/713 (0.1)
	Consecutive values with actual decrease ≥0.8 and <LLN[¶]	Rofecoxib 25 mg	0/703 (0.0)
		Placebo	0/713 (0.0)
	Consecutive values with actual increase ≥0.8 and >ULN[¶]	Rofecoxib 25 mg	10/703 (1.4)
		Placebo	6/713 (0.8)
Serum sodium (mEq(Na)/L)	Actual decrease ≥8 and <LLN[¶]	Rofecoxib 25 mg	13/703 (1.8)
		Placebo	6/713 (0.8)
	Actual increase ≥8 and >ULN[¶]	Rofecoxib 25 mg	4/703 (0.6)
		Placebo	6/713 (0.8)

Table 77 (Cont.)

Patients Exceeding the Predefined Limits of Change
On-Drug† Population

Laboratory Test	Predefined Limit of Change From Baseline‡	Treatment	Number§/Total‖ (%)
Total serum bilirubin (mg/dL) and serum alkaline phosphatase (IU(alk phosphatase)	Bilirubin ≥1.8 x ULN and Alkaline phosphatase ≥3 x ULN¶#	Rofecoxib 25 mg	0/703 (0.0)
		Placebo	0/713 (0.0)
Urine protein	Consecutive values with increase from 0 or trace to: 2, 3, or 4 OR from 1 to: 3 or 4 OR from 2 to: 4¶	Rofecoxib 25 mg	1/622 (0.2)
		Placebo	3/670 (0.4)

† On drug includes the period through 14 days after discontinuation of study drug.
‡ Increases and decreases are compared with baseline, which is defined as the last laboratory value prior to the first randomized dose.
§ Number of patients meeting the pre-defined limit criteria.
‖ Total number of patients with valid values of the laboratory test.
¶ Meeting the criteria (instead of consecutive values) and discontinuing from therapy due to the particular laboratory adverse experience is sufficient to be classified as exceeding the predefined limit of change.
# Changes in the 2 parameters must occur on the same date.
ULN = Upper Limit of Normal
LLN = Lower Limit of Normal

Data Source: [3.4; 4.2]

8.6.3.2 Intention-to-Treat Population

Table 78 shows the patients exceeding the predefined limits of change in the intention-to-treat population. There were no clinically significant differences between the on-drug population and the ITT population for patients who exceeded the predefined limits.

Table 78

Patients Exceeding the Predefined Limits of Change
Intention-to-Treat Population

Laboratory Test	Predefined Limit of Change From Baseline[†]	Treatment	Number[‡]/Total[§] (%)
WBC count (10[3]/microL)	Consecutive values with a decrease ≥20% and <LLN[¶]	Rofecoxib 25 mg	7/712 (1.0)
		Placebo	7/720 (1.0)
	Consecutive values with an increase ≥20% and >ULN[¶]	Rofecoxib 25 mg	7/712 (1.0)
		Placebo	5/720 (0.7)
Hemoglobin (gm/dL) and hematocrit (%)	Decrease in Hgb >2 g m/dL and Hct ≥5% or Decrease in Hgb >1 gm/dL and Hct ≥10%[‖¶]	Rofecoxib 25 mg	264/712 (37.1)
		Placebo	184/720 (25.6)
	Decrease in Hgb >2 gm/dL and Hct ≥10%[‖¶] (secondary)	Rofecoxib 25 mg	140/712 (19.7)
		Placebo	78/720 (10.8)
Lymphocyte count (10[3]/microL)	Consecutive values with a decrease ≥20% and <LLN[¶]	Rofecoxib 25 mg	17/712 (2.4)
		Placebo	11/720 (1.5)
	Consecutive values with an increase ≥50% and >ULN[¶]	Rofecoxib 25 mg	1/712 (0.1)
		Placebo	0/720 (0.0)
Neutrophil count (10[3]/microL)	Consecutive values with a decrease ≥20% and <LLN[¶]	Rofecoxib 25 mg	7/712 (1.0)
		Placebo	4/719 (0.6)
	Consecutive values with an increase ≥50% and >ULN[¶]	Rofecoxib 25 mg	4/712 (0.6)
		Placebo	4/719 (0.6)
Platelet count (10[3]/microL)	Consecutive values with a decrease ≥25% and <LLN[¶]	Rofecoxib 25 mg	8/712 (1.1)
		Placebo	5/720 (0.7)

Table 78 (Cont.)

Patients Exceeding the Predefined Limits of Change
Intention-to-Treat Population

Laboratory Test	Predefined Limit of Change From Baseline[†]	Treatment	Number[‡]/Total[§] (%)
Serum alanine aminotransferase (IU(aminotrans-ferase))	Consecutive values>3 x ULN(if normal baseline) or Consecutive values>2 x baseline value and >3 x ULN(if abnormal baseline)[¶]	Rofecoxib 25 mg	5/714 (0.7)
		Placebo	1/722 (0.1)
	One or more values>3 x ULN(if normal baseline) or one or more values>2 x baseline value and >3 x ULN(if abnormal baseline) (secondary)	Rofecoxib 25 mg	7/714 (1.0)
		Placebo	2/722 (0.3)
Serum aspartate aminotransferase (IU(aminotrans-ferase))	Consecutive values>3 x ULN(if normal baseline) or Consecutive values>2 x baseline value and >3 x ULN(if abnormal baseline)[¶]	Rofecoxib 25 mg	2/714 (0.3)
		Placebo	0/722 (0.0)
	One or more values>3 x ULN(if normal baseline) or one or more values>2 x baseline value and >3 x ULN(if abnormal baseline) (secondary)	Rofecoxib 25 mg	3/714 (0.4)
		Placebo	0/722 (0.0)
Serum creatinine (mg/dL)	Consecutive values with actual increase ≥0.5 and >ULN[¶]	Rofecoxib 25 mg	26/714 (3.6)
		Placebo	6/721 (0.8)
	Consecutive values>2 x baseline value and >ULN[¶] (secondary)	Rofecoxib 25 mg	0/714 (0.0)
		Placebo	0/721 (0.0)
	One or more values with absolute increase ≥0.5 and >ULN (secondary)	Rofecoxib 25 mg	58/714 (8.1)
		Placebo	21/721 (2.9)
	One or more values >2 x baseline value and >ULN (secondary)	Rofecoxib 25 mg	5/714 (0.7)
		Placebo	3/721 (0.4)

Table 78 (Cont.)

Patients Exceeding the Predefined Limits of Change
Intention-to-Treat Population

Laboratory Test	Predefined Limit of Change From Baseline†	Treatment	Number‡/Total§ (%)
Serum potassium (mEq(K)/L)	Consecutive values ≥1.1 x ULN¶	Rofecoxib 25 mg	1/714 (0.1)
		Placebo	1/722 (0.1)
	Consecutive values with actual decrease ≥ 0.8 and <LLN¶	Rofecoxib 25 mg	0/714 (0.0)
		Placebo	0/722 (0.0)
	Consecutive values with actual increase ≥0.8 and >ULN¶	Rofecoxib 25 mg	11/714 (1.5)
		Placebo	6/722 (0.8)
Serum sodium (mEq(Na)/L)	Actual decrease ≥ 8 and <LLN¶	Rofecoxib 25 mg	14/714 (2.0)
		Placebo	7/722 (1.0)
	Actual increase ≥ 8 and >ULN¶	Rofecoxib 25 mg	5/714 (0.7)
		Placebo	7/722 (1.0)
Total serum bilirubin (mg/dL) and serum alkaline phosphatase (IU(alk p	Bilirubin ≥1.8 x ULN and Alkaline phosphatase ≥3 x ULN‖¶	Rofecoxib 25 mg	0/714 (0.0)
		Placebo	0/722 (0.0)
Urine protein	Consecutive values with increase from 0 or trace to: 2, 3, or 4 OR from 1 to: 3 or 4 OR from 2 to: 4¶	Rofecoxib 25 mg	2/671 (0.3)
		Placebo	4/702 (0.6)

† Increases and decreases are compared with baseline, which is defined as the last laboratory value prior to the first randomized dose.
‡ Number of patients meeting the pre-defined limit criteria.
§ Total number of patients with valid values of the laboratory test.
‖ Changes in the 2 parameters must occur on the same date.
¶ Meeting the criteria (instead of consecutive values) and discontinuing from therapy due to the particular laboratory adverse experience is sufficient to be classified as exceeding the predefined limit of change.
ULN = Upper Limit of Normal
LLN = Lower Limit of Normal

Data Source: [3.4; 4.2]

8.7 Vital Signs

Summary statistics of mean change from baseline for vital signs were tabulated by treatment and visit time point and are in [4.8] for the on-drug and ITT populations. Graphical representation of these are in Section 8.7.1. Analysis of patients exceeding the predefined limits of change in vital sign parameters were based on the Neuropharmacology Division standards for clinically significant abnormalities defined in [3.4], and are shown in Section 8.7.2. No formal statistical analyses were performed for vital sign data.

8.7.1 Vital Sign Values Over Time

8.7.1.1 On-Drug Population

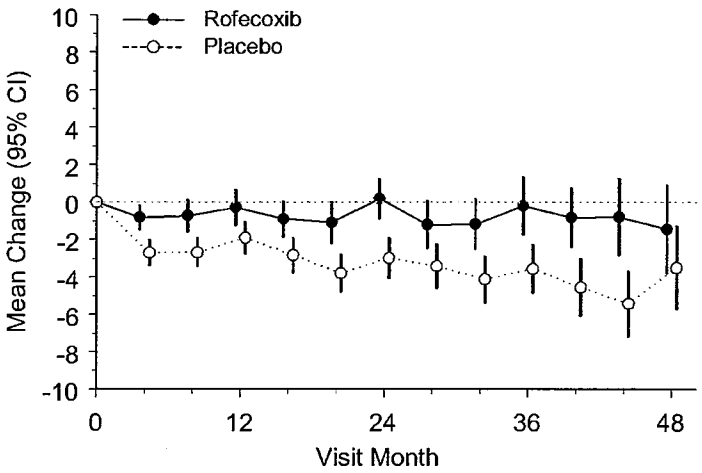
Summary statistics of vital signs for the on-drug population were tabulated by treatment and visit time point and are in [4.8]. Graphical representation of mean changes from baseline to 48 months of treatment are shown for diastolic blood pressure, systolic blood pressure, and pulse rate in Figure 20, Figure 21, and Figure 22, respectively.

Overall, for both diastolic and systolic blood pressure, changes from baseline were small and indistinguishable from 0 (based on 95% CIs) at almost all time points for the rofecoxib group. For the placebo group, initial decreases at the Month 4 time point persisted through Month 48.

Mean changes in pulse rate were highly variable and very similar between treatment group across all time points.

Figure 20

Diastolic Blood Pressure: Mean (95% CI) Change From Baseline
On-Drug Population

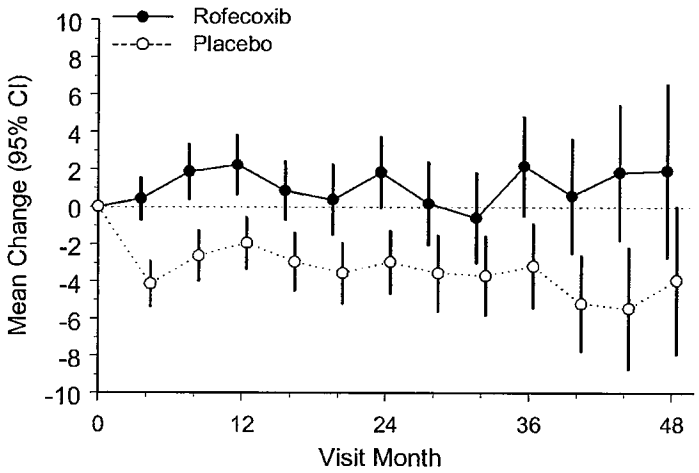


Number of Patients												
Rofecoxib	705	566	492	454	388	327	256	221	200	156	121	71
Placebo	715	612	555	497	448	400	309	281	254	196	151	109

Data Source: [4.2]

Figure 21

Systolic Blood Pressure: Mean (95% CI) Change From Baseline
On-Drug Population

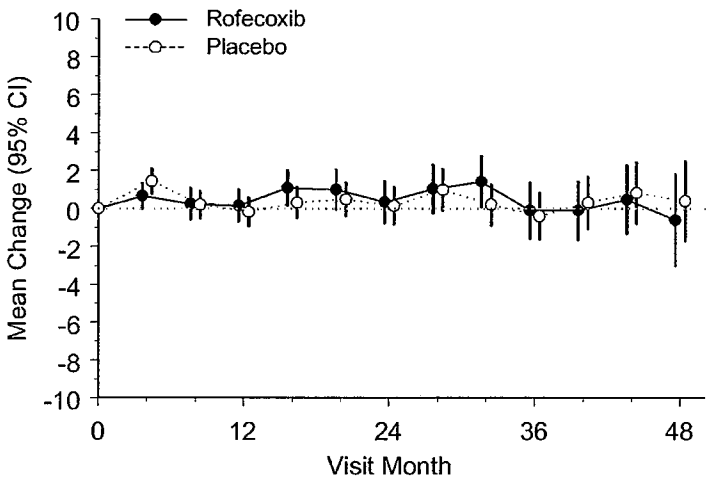


Number of Patients												
Rofecoxib	705	566	492	454	388	327	256	221	200	156	121	71
Placebo	715	612	555	497	448	399	309	281	254	196	151	109

Data Source: [4.2]

Figure 22

Pulse Rate: Mean (95% CI) Change From Baseline
On-Drug Population



Number of Patients												
Rofecoxib	701	565	491	452	386	326	254	220	199	155	120	71
Placebo	711	608	552	495	445	398	309	280	253	196	150	109

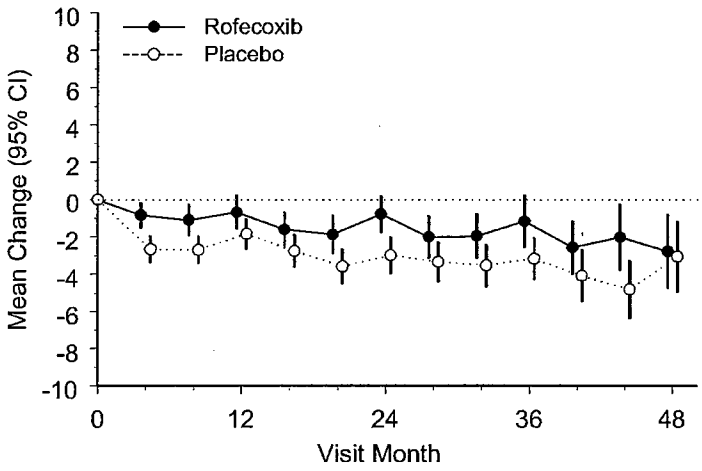
Data Source: [4.2]

8.7.1.2 Intention-to-Treat Population

Summary statistics of vital signs for the ITT population were tabulated by treatment and visit time point and are shown in [4.8]. Graphical representation of mean changes from baseline to 48 months of treatment for the ITT population are shown for diastolic, systolic, and pulse rate in Figure 23, Figure 24, and Figure 25, respectively. Results did not differ significantly in the ITT and on-drug populations.

Figure 23

Diastolic Blood Pressure: Mean (95% CI) Change From Baseline
Intention-to-Treat Population

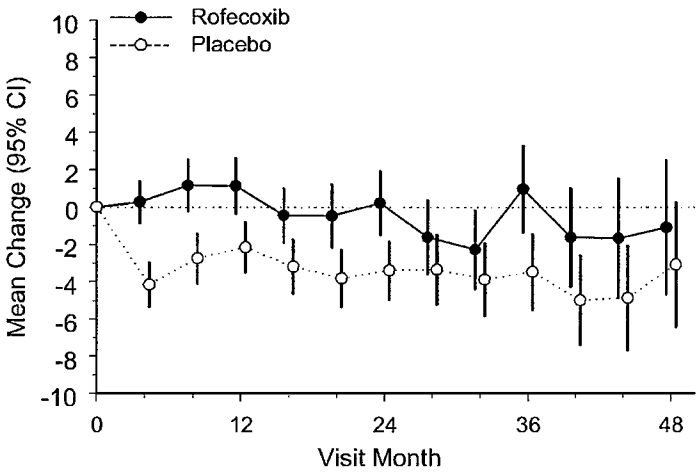


Number of Patients												
Rofecoxib	716	633	573	532	468	415	348	304	285	226	178	112
Placebo	723	659	628	572	517	474	382	349	325	252	196	141

Data Source: [4.2]

Figure 24

Systolic Blood Pressure: Mean (95% CI) Change From Baseline
Intention-to-Treat Population

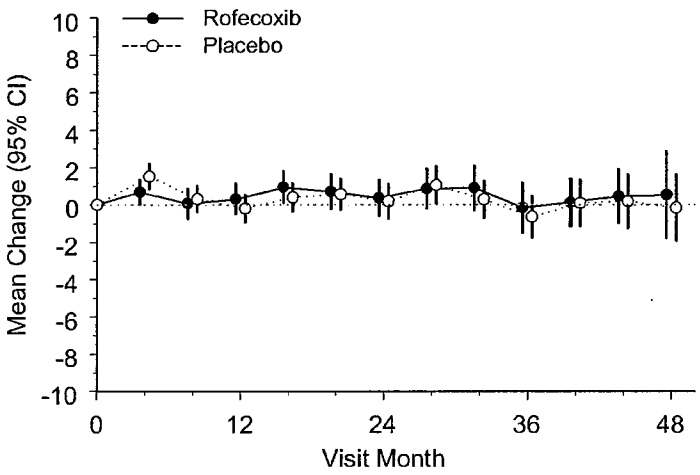


Number of Patients												
Rofecoxib	716	633	573	532	468	415	348	304	285	226	178	112
Placebo	723	659	628	572	517	473	382	349	325	252	196	141

Data Source: [4.2]

Figure 25

Pulse Rate: Mean (95% CI) Change From Baseline
Intention-to-Treat Population



Number of Patients												
Rofecoxib	712	630	570	529	466	414	346	303	283	224	176	112
Placebo	719	655	625	570	515	472	381	348	324	253	195	141

Data Source: [4.2]

8.7.2 Vital Sign Values for Predefined Limits of Change

8.7.2.1 On-Drug Population

The number of patients who exceeded the PDLC for vital signs while on study medication or within 14 days of last dose is shown in Table 79. Criteria were based on the Neuropharmacology Division standards for clinically significant abnormalities, defined in [3.4].

Sixty-one (8.8%) patients in the rofecoxib group exceeded the limits of change for systolic blood pressure (value ≥180 mm Hg and increase ≥20 mm Hg), compared with 37 (5.2%) patients in the placebo group. The majority of these were not persistent increases as evidenced by the fact that only six patients in each treatment group met the predefined limits of change criteria for 2 consecutive measurements (consecutive values ≥180 mm Hg and increase ≥20 mm Hg from baseline). No corresponding differences were seen for the diastolic blood pressure (0.9 and 0.9%, respectively).

Weight loss limits (weight loss of ≥7 %) were exceeded for 79 (11.4%) and 96 (13.7%) patients on rofecoxib and placebo, respectively. Alternatively, a weight gain of ≥7 % was seen in 83 (11.9%) and 81 (11.6%) patients, respectively. The clinical importance of these weight changes is not clear.

Table 79

Patients Exceeding the Predefined Limits of Change—Vital Signs
On-Drug[†] Population

Vital Sign Test	Predefined Limit of Change[‡]	Treatment	Number[§]/Total[‖] (%)
Systolic blood pressure	Value ≤90 and Decrease ≥20	Rofecoxib 25 mg	7/697 (1.0)
		Placebo	4/705 (0.6)
	Value ≥180 and Increase ≥20	Rofecoxib 25 mg	61/697 (8.8)
		Placebo	37/705 (5.2)
	Consecutive values ≤90 mm Hg and 20 mm Hg decrease from baseline	Rofecoxib 25 mg	0/697 (0.0)
		Placebo	1/705 (0.1)
	Consecutive values ≥180 mmHg and 20 mmHg increase from baseline	Rofecoxib 25 mg	6/697 (0.9)
		Placebo	6/705 (0.9)
Diastolic blood pressure	Value ≤50 and Decrease ≥15	Rofecoxib 25 mg	10/697 (1.4)
		Placebo	23/705 (3.3)
	Value ≥105 and Increase ≥15	Rofecoxib 25 mg	6/697 (0.9)
		Placebo	9/705 (1.3)
Pulse Rate	Value ≤50 and Decrease ≥15	Rofecoxib 25 mg	16/693 (2.3)
		Placebo	17/702 (2.4)
	Value ≥120 and Increase ≥15	Rofecoxib 25 mg	0/693 (0.0)
		Placebo	1/702 (0.1)
Weight (kg)	Decrease ≥7%	Rofecoxib 25 mg	79/696 (11.4)
		Placebo	96/701 (13.7)
	Increase ≥7%	Rofecoxib 25 mg	83/696 (11.9)
		Placebo	81/701 (11.6)
Temperature (C)	Value ≥38.33 and Increase ≥1.11	Rofecoxib 25 mg	0/685 (0.0)
		Placebo	0/693 (0.0)

[†] On drug includes the period through 14 days after discontinuation of study drug.
[‡] Increases and decreases are compared with baseline, which is defined as the last vital sign test value prior to the first randomized dose.
[§] Number of patients meeting the predefined limit criteria.
[‖] Total number of patients with valid values of the vital sign test for the given treatment group.

Data Source: [3.4; 4.2]

8.7.2.2 Intention-to-Treat Population

The number of patients taking in the ITT population who exceeded the PDLC for vital signs is shown in Table 80. Criteria were based on the Neuropharmacology Division standards for clinically significant abnormalities defined in [3.4]. Results did not differ significantly from those in the on-drug population.

Table 80

Patients Exceeding the Predefined Limits of Change—Vital Signs
Intention-to-Treat Population

Vital Sign Test	Predefined Limit of Change†	Treatment	Number‡ /Total§ (%)	
Systolic blood pressure	Value ≤90 and Decrease ≥20	Rofecoxib 25 mg	9/716	(1.3)
		Placebo	7/723	(1.0)
	Value ≥180 and Increase ≥20	Rofecoxib 25 mg	68/716	(9.5)
		Placebo	40/723	(5.5)
	Consecutive values ≤90 mmHg and 20 mmHg decrease from baseline	Rofecoxib 25 mg	1/716	(0.1)
		Placebo	1/723	(0.1)
	Consecutive values ≥180 mmHg and 20 mmHg increase from baseline	Rofecoxib 25 mg	7/716	(1.0)
		Placebo	6/723	(0.8)
Diastolic blood pressure	Value ≤50 and Decrease ≥15	Rofecoxib 25 mg	15/716	(2.1)
		Placebo	26/723	(3.6)
	Value ≥105 and Increase ≥15	Rofecoxib 25 mg	9/716	(1.3)
		Placebo	11/723	(1.5)
Pulse rate	Value ≤50 and Decrease ≥15	Rofecoxib 25 mg	25/712	(3.5)
		Placebo	18/720	(2.5)
	Value ≥120 and Increase ≥15	Rofecoxib 25 mg	1/712	(0.1)
		Placebo	1/720	(0.1)
Weight (kg)	Decrease ≥7%	Rofecoxib 25 mg	117/715	(16.4)
		Placebo	135/719	(18.8)
	Increase ≥7%	Rofecoxib 25 mg	92/715	(12.9)
		Placebo	94/719	(13.1)
Temperature (C)	Value ≥38.33 and Increase ≥1.11	Rofecoxib 25 mg	0/704	(0.0)
		Placebo	0/711	(0.0)

† Increases and decreases are compared with baseline, which is defined as the last vital sign test value prior to the first randomized dose.
‡ Number of patients meeting the predefined limit criteria.
§ Total number of patients with valid values of the vital sign test for the given treatment group.

Data Source: [3.4; 4.2]

9. Discussion

Efficacy

In this 4-year study of 1457 patients with MCI, statistically significantly more patients randomized to rofecoxib converted to AD than those who were randomized to placebo; the estimated annual conversion rate to AD was 6.4% in the rofecoxib group versus 4.5% in the placebo group (hazard ratio [rofecoxib:placebo] = 1.46, 95% CI [1.09, 1.94], Wald Chi Square p-value = 0.011). The apparent effect of rofecoxib was unexpected and was not confirmed by exploratory measures of cognition (ADAS-Cog, SRT, MMSE), which found no statistically significant or clinically meaningful differences between treatment groups. The results were unexpected given that two large previous studies in AD patients that included patients with an MMSE score up to 26 (thereby partly overlapping with patients in present study 078 who had a MMSE score of 24 to 26) found that rofecoxib had no effect on the progression of cognitive or functional decline [1.1.1; 1.1.2]. Here, we consider aspects of the conduct of the present study which may have had an influence on the results and discuss the likelihood that the unexpected and unsupported findings on the primary endpoint are not indicative of a true effect of rofecoxib in this population.

A number of aspects of the conduct of the present study should be borne in mind when interpreting the results. It is important to note that this is the first completed randomized, controlled prevention study in MCI patients to be reported, so there are no other studies available to benchmark the study results from a methodological viewpoint. The overall annual conversion rates of 5 to 6% were lower than the anticipated 10 to 15% observed in previous observational or natural history studies, which have typically been performed in specialist research centers [1.2.13]. Since the diagnostic criteria for MCI were, and remain, not clearly defined with regard to the particular tests and score thresholds that should be used to aid in the diagnosis of memory impairment, it is possible that the target population represented by the sample of patients included in our study was more heterogenous than others have described. Furthermore, the diagnosis is heavily dependent on clinical judgment, and investigators in our study (which was initiated at a time when the MCI concept was relatively new) may not have been as skilled as those at specialist research centers at making the diagnosis. It is conceivable, therefore, that the population of patients we studied may have included some patients who did not have genuine memory problems (e.g., patients who initially scored poorly because they were anxious), in addition to "real" MCI patients. The source of the patients, many of whom were identified through advertising campaigns rather than being direct clinical referrals, may have also resulted in greater heterogeneity. These factors may have increased the possibility of some unidentified imbalance existing between the treatment groups at baseline (see below), and raise doubts about the validity of the findings.

The study discontinuation rate is not surprising given the duration of the study, the elderly population being investigated, and the strict criteria used to define discontinuation from the study. The notable decrease in the number of patients who remained in the study at the 2-year time point is probably due to the fact that the original protocol specified a 2-year evaluation period, but was then amended to continue for up to 4 years [3.3.6]. Patients had to sign an additional consent form to agree to this longer evaluation period, but it appears that a number of patients decided to discontinue from the study after completing the original commitment. Overall drop-out rates were similar between the treatment groups, but there were some differences between the groups with regard to specific reasons for discontinuation, suggesting that discontinuation may not have been random but rather may have been related to treatment. For example, a greater proportion of patients in the placebo group discontinued due to withdrawal of consent. Nonetheless, there was not an immediately obvious way in which the differential reasons for discontinuation could have entirely accounted for the results.

In addition to the inconsistency between the exploratory cognitive test measures and the primary endpoint of conversion to AD (discussed below), there are a number of reasons which suggest that the primary findings may not be indicative of a true treatment effect of rofecoxib. A difference between treatment groups in conversion to AD was apparent from 4 months, the earliest time point assessed. This observation supports the suggestion that there may have been a pre-existing imbalance between treatment groups at baseline which was not controlled for by the randomization process. There was, however, no clear evidence of a major imbalance for measured variables. In general, baseline scores for outcome variables were similar between the two treatment groups, so the groups appear to have been adequately matched for severity of cognitive impairment. Overall, patient baseline characteristics were also generally similar, except that there were slightly larger proportions of female patients, patients ≥75 years old and patients previously using ginkgo in the rofecoxib group. These characteristics were shown to be strongly associated with increased risk for conversion to AD. In this regard it is interesting to note that, although analyses were generally consistent across models, the model which adjusted for covariates that were risk factors for AD had the smallest treatment effect and the p-value from this model was not statistically significant at the 0.05 level. It is also important to note that there was no enhancement of the treatment difference in an analysis restricted to those patients on-drug, which might have been expected if rofecoxib truly did increase the risk of developing AD.

A further point to consider in evaluating the validity of the primary results is their scientific plausibility. From a scientific perspective, there is no convincing biological explanation as to why inhibition of COX-2 should lead to an increased risk for AD, especially given the early onset of treatment differences. There was no suggestion that the finding might reflect hypothesized vascular effects of COX-2

inhibitors in analyses which categorized patients according to blood pressure changes. There were a total of 6 patients with confirmed ischemic strokes and 1 patient with hemorrhagic stroke in the rofecoxib group compared to 13 patients with confirmed ischemic strokes and 2 patients with hemorrhagic strokes in the placebo group. Furthermore, CT or MRI scans were performed on all patients who converted to AD, to help exclude the possibility of vascular dementia, and these were taken into account when each endpoint was reviewed by the blinded independent adjudication committee. Therefore it seems unlikely that any vascular changes could have accounted for the observed differences in AD conversion rates.

Another factor which could have influenced the results is differential concomitant use between groups for agents which are thought to be protective for AD. The most likely candidate would be concomitant NSAID use. The motivation for performing the study was based on epidemiological evidence suggesting a protective effect of non-selective NSAIDs. We hypothesized that this might be related to the ability of non-selective NSAIDs to inhibit COX-2. However, the protective effect could instead be related to some other property of nonselective NSAIDs such as their ability to inhibit COX-1, or β-amyloid lowering properties [1.2.30]. There was slightly greater recorded use of concomitant NSAIDs in the placebo group and greater duration of use. It is also possible that there was differential under-reporting of regular NSAID use in the placebo group since chronic NSAID use was prohibited during the study and these agents are available without prescription. Greater NSAID use would certainly be expected in the placebo group, since rofecoxib is an effective analgesic and many elderly patients would be expected to require regular analgesic use. Indeed, 161 (22.2%) patients taking rofecoxib and 178 (24.3%) patients taking placebo reported a baseline diagnosis of osteoarthritis. During the trial, fewer patients in the rofecoxib group than the placebo group reported adverse experiences of the musculoskeletal and connective tissue (36.9 and 39.0%, respectively) and fewer in the rofecoxib group than the placebo group discontinued study drug due to adverse experiences in this category (1.7 and 3.0%, respectively). On the other hand, recent epidemiological studies suggest that NSAIDs used in preventing AD require 2 or more years of treatment before showing an effect [1.2.10; 1.2.16], so this would not explain the apparent early separation between the treatment groups. Other agents which could conceivably have influenced the progression to AD include cholinesterase inhibitors and estrogen. However, reported use of these agents was low and since they are only available with a prescription, under-reporting would be anticipated to be less common than for NSAIDs.

The most important point to consider in evaluating the present data is that, if the results of the primary analysis were due to a true treatment effect, then similar effects would have been expected for the exploratory measures of cognition (ADAS-Cog, MMSE, SRT). However, investigations performed using either a mixed models analysis of slope of decline, or analyses incorporating an LOCF approach,

consistently showed that there were no statistically significant or clinically important differences between rofecoxib and placebo for any of the exploratory efficacy measurements. Furthermore, as noted above, no overall statistically significant nor clinically relevant differences between rofecoxib and placebo were observed in two previous 12-month studies looking at progression of cognitive or functional decline in AD patients [2.1.1; 1.1.2].

We also compared ADAS-Cog, MMSE, and CDR Sum of Box scores in the subgroup of patients who had baseline MMSE scores of 24 to 26 in the present study (i.e., those in the subgroup with the worst prognosis on the primary endpoint) with the subgroup of patients who met the same MMSE criteria in a previous AD study [2.1.1]. Results of this comparison are in [2.1.3]. In both these "overlapping" patient populations, rofecoxib did not show any clinically relevant differences from placebo.

In summary, the unexpected primary findings in the present study, suggesting that rofecoxib accelerates the rate of conversion to AD in "at risk" patients with MCI, are neither supported by data on exploratory efficacy measurements in the same study nor by other data from previous studies which assessed cognitive and functional decline in AD patients. On the basis of these considerations, and those noted above, it does not seem reasonable to conclude that the primary findings indicate a true drug effect. If not a true effect, then the most plausible explanations are that this is either due to chance, or that there was an imbalance between the treatment groups which either existed at baseline or arose during the study (e.g., differences in protective concomitant medication use), resulting in early and sustained difference in treatment groups with respect to conversion to AD. It can, however, be concluded from results of this study and previous studies that rofecoxib was not effective in either the treatment or prevention of AD.

General Safety and Tolerability

Rofecoxib 25 mg was generally well tolerated in this elderly population. The overall frequencies of individual clinical adverse experiences were generally similar between the rofecoxib and placebo groups. There were no statistically significant differences between the treatment groups in the number of patients who had serious clinical adverse experiences or discontinued due to clinical adverse experiences or in the number of deaths during the study. An analysis of results for all-cause mortality showed that there were more deaths in the rofecoxib than the placebo group (3.7 and 2.1%, respectively). However, death is an outcome and not an adverse experience. A review of the adverse experiences resulting in death revealed multiple diverse events without a clear difference among the treatment groups. There were slightly more patients treated with rofecoxib than those with placebo who had adjudicated

events of thrombotic cardiovascular mortality (8 and 4 respectively). Overall, however, mortality was not driven by the these adverse experiences, and these small differences are, therefore, most likely a chance finding. There was a statistically significant difference in the percentage of patients with drug-related clinical adverse experiences, which was higher in the rofecoxib than the placebo group. No single adverse experience or specific group of adverse experiences appeared to account for this difference. There were multiple adverse experiences with small numeric differences. Thus, while patients in the rofecoxib treatment group were significantly more likely to have hypertension-related adverse experiences than those in the placebo group, the 95% CI for drug-related hypertension included zero. The only drug-related adverse experience for which the 95% CI of the difference did not cross zero was peripheral edema (3.2 and 1.5% in the rofecoxib and placebo group, respectively). The body system with the most reported drug-related adverse experiences was the gastrointestinal system (13.8% in the rofecoxib group and 12.1% in the placebo group). Adverse experiences of the GI system are discussed in greater detail below.

The proportions of patients with laboratory adverse experiences and with drug-related laboratory adverse experiences were significantly greater in the rofecoxib group than in the placebo group. The overwhelming majority of laboratory adverse experiences were nonserious, and there was no statistically significant difference between treatment groups in the occurrence of serious laboratory adverse experiences. The greater proportions of patients with laboratory adverse experiences in the rofecoxib group were driven primarily by higher frequencies of increased BUN, increased serum creatinine, increased serum potassium, decreased hemoglobin, and decreased hematocrit. These adverse experiences are consistent with the known renal and hemodilution effects of NSAIDs and selective COX-2 inhibitors. The frequency observed in this study are consistent with previous studies and with product labeling. The proportion of patients who discontinued the study due to a laboratory adverse experience was also significantly greater in the rofecoxib group than in the placebo group, but overall was quite low (3.2 and 0.7% in the rofecoxib and placebo group, respectively).

Clinical Adverse Experiences of Special Interest

Gastrointestinal Clinical Adverse Experiences

Rofecoxib 25 mg had a generally favorable gastrointestinal tolerability profile. The proportion of patients with GI adverse experiences was very similar between the treatment groups (42.3 and 41.5% in the rofecoxib and placebo groups, respectively). There were slightly more discontinuations due to GI and abdominal pain-related adverse experiences in the rofecoxib group (4.3%) than in the placebo group(3.0%), but these differences were not statistically significant.

Episodes of Perforations, Ulcers, or Upper GI Bleeding Events

A total of 16 (2.2%) patients on rofecoxib and 7 (1.0%) on placebo had suspected PUB events while on study drug or within 14 days of the last dose of study therapy. Confirmed PUB events occurred in 14 (1.9%) rofecoxib patients (10 complicated events) and in 4 (0.5%) placebo patients (3 complicated events). The approximate rate of PUBs in the rofecoxib group (1.02 per 100 patient-years) compares favorably with the rates observed in elderly patients taking a higher rofecoxib dose in the VIGOR study (3.3 and 4.5 per 100 patient-years for patients 65 to 75 years old and >75 years old, respectively in the rofecoxib group and 7.4 and 14.5 per 100 patient-years for patients 65 to 75 years old and >75 years old, respectively in the naproxen group) [2.1.2]. Although rofecoxib has been shown to have an improved GI safety and tolerability relative to non-selective NSAIDs, GI adverse experiences and PUBs can occur in patients treated with selective COX-2 inhibitors.

Serious Vascular Events

Suspected serious cardiovascular, peripheral vascular, and cerebrovascular events were reviewed and adjudicated according to the Acute Thromboembolic Vascular Events SOP. Confirmed thrombotic cardiovascular events occurred in 5.3% of the rofecoxib group and in 5.0% of the placebo group. The incidence of cardiac events was slightly higher in the rofecoxib group (3.6%) than the placebo group (2.6%), while the incidences of cerebrovascular (1.8 and 2.2%, respectively) and peripheral vascular events (0.0 and 0.4%, respectively) were slightly higher in the placebo group. APTC events occurred at the same incidence rate (4.0%) for both treatment arms. These data are consistent with the hypothesis that rofecoxib is not associated with an increased risk of thrombotic cardiovascular serious adverse events relative to placebo.

Hypertension, Edema, and CHF-Related Adverse Experiences

Significantly more patients in the rofecoxib (24.3%) than the placebo (15.9%) group had hypertension-related adverse experiences while on drug or within 14 days of the last dose of study drug. However, the number of patients who discontinued therapy due to these events was low in both groups (1.8 and 1.4%, respectively). The proportion of patients with edema-related adverse experiences was not significantly different between the treatment groups (10.0 and 7.7%), nor was the proportion of patients with CHF-related adverse experiences (2.2 and 2.6%). These findings are consistent with the known effects of NSAIDs including selective COX-2 inhibitors and consistent with the rofecoxib product circular.

Osteoporosis / Fractures

While there is an imbalance in the reported incidence of osteoporosis between the treatment group and the placebo group (2.8 and 1.2%, respectively), it is likely that this is a chance observation. Bone mineral density or the presence of osteoporosis were not a specified part of the baseline evaluation in this study. Osteoporosis, unlike some adverse experiences, is usually asymptomatic, greatly complicating the determination of onset date for the adverse experience. Most of the adverse experiences resulted from spontaneous reporting from patients and caretakers and were not associated with any particular medical event (e.g., fractures) which could have been attributed to osteoporosis. Specifically, the fracture group did not have much overlap with the osteoporosis group (of a total of 20 patients in the rofecoxib group who reported osteoporosis while on-drug, only 2 patients reported fractures; 4 patients of 9 with osteoporosis in the placebo group reported fractures). In addition, the incidence of fractures reported during the study was not statistically different between the treatment groups. Because of limitation in the method of collection and categorization of this adverse experience, it is difficult to have confidence that this finding represents a true biological signal as opposed to a sampling error. Furthermore Merck and Co., Inc., conducted a study specifically designed to examine the effect of rofecoxib on bone density [2.1.5]. The study enrolled 305 men and women with a confirmed diagnosis of osteoarthritis. Baseline bone material density was compared with that at 12 months in patients treated with rofecoxib and ibuprofen as an active comparator (NSAID). The rofecoxib to ibuprofen between-group difference (with 95% CI) of the mean percent change from baseline in BMD after 12 months of treatment was -0.12% (-1.29%, 1.04%) at the lumbar spine and 0.16%, (-0.63% to 0.96%) at the hip. The 95% CIs for the comparison was contained within the prespecified equivalence interval of -2.0% to 2.0%. Therefore, at least with the current data, it would appear that the imbalance in reports of osteoporosis in the study is a chance observation.

10. Overall Efficacy and Safety Conclusions

Primary

1. Rofecoxib 25 mg daily was not superior to placebo in reducing the incidence of clinically diagnosed AD (possible or probable by NINCDS-ADRDA criteria) in patients with MCI.

2. Rofecoxib 25 mg was generally well tolerated in patients with MCI.

Exploratory

1. Rofecoxib 25 mg was not superior to placebo in reducing the decline on the SRT Summed Recall Score.

2. Rofecoxib 25 mg was not superior to placebo in reducing the decline on the MMSE.

3. Rofecoxib 25 mg was not superior to placebo in reducing the decline on the ADAS-Cog subscale.

11. Supplemental Tables, Figures, and/or Narratives

Table 81

Summary of Concomitant NSAID Exposure (Weeks)
Intention-to-Treat Population

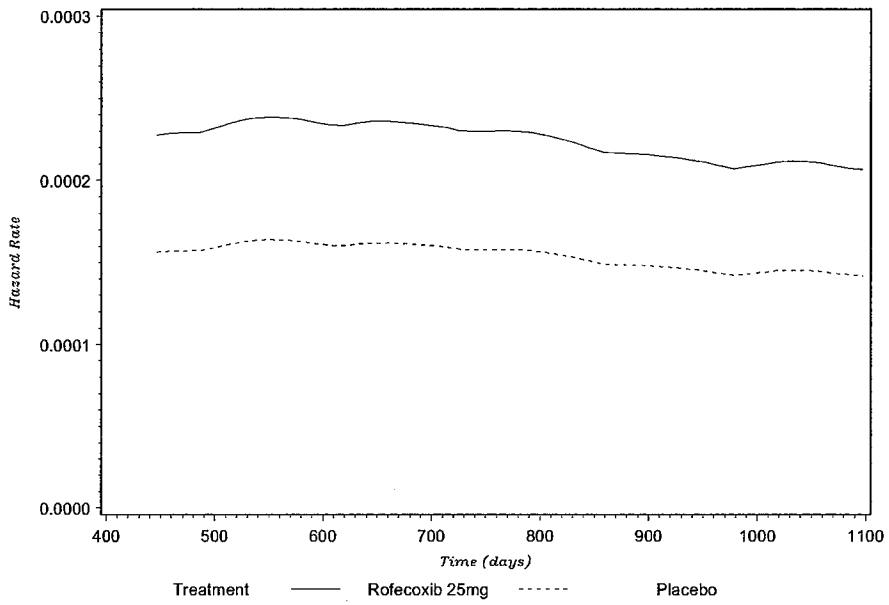
	Rofecoxib ($N^{\dagger}$=725)				Placebo ($N^{\dagger}$=732)			
	$n^{\ddagger}$	Mean (SD)	Median	Range	$n^{\ddagger}$	Mean (SD)	Median	Range
Duration of NSAID Treatment	224	34.3 (45.8)	11.0	0.1-195.1	254	51.6 (61.0)	25.4	0.1-213.1
Actual NSAID treatment exposure	224	20.9 (33.4)	5.6	0.1-177.9	254	29.5 (47.9)	7.4	0.1-213.1

†N = Number of patients in the treatment group
‡n = Number of patients with any concomitant NSAID exposure
SD=Standard deviation

Data Source: [4.1]

Figure 26

Hazard Rates of Time to Clinically Diagnosed AD
VIOXX™



Data Source: [4.3]

Clinically Diagnosed AD (Intention-to-Treat Population, Excluding Sites 019, 023 and 044)

As a result of findings from a Quality Assurance audit, the 137 patients at Sites 019, 023 and 044 were excluded from the primary efficacy analyses of clinically diagnosed AD.

Results from a statistical comparison between rofecoxib and placebo based on a Cox proportional hazards model for time to clinically diagnosed AD, excluding data from study sites 019, 023 and 044, are summarized in Table 82.

In the rofecoxib group, 102 of 657 (15.5%) patients had an event of clinically diagnosed AD versus 78 of 663 (11.8%) placebo patients. The estimated hazard ratio (Rofecoxib:Placebo), adjusting for the effects of stratum and region, was 1.48 (95% CI [1.10 to 1.99]), which was statistically significant (p=0.009) in favor of placebo. Baseline MMSE stratum was highly significant, as the estimated hazard ratio (MMSE ≤26:MMSE >26) was 3.21 (95% CI [2.39,4.31]).

The conclusions from this analysis are the same as those from the primary efficacy analysis which included all patients from all sites.

Table 82

The Results for Time to Clinical Diagnosed AD
Intention to Treat
Excludes Sites 019, 023, and 044

Test	Event Counts: Rofecoxib 25mg n/N(%)	Event Counts: Placebo n/N(%)	Hazard Ratio	95% CI	p-Value
Treatment (rofecoxib: placebo)	102/657 (15.5)	78/663 (11.8)	1.483	(1.104, 1.992)	0.009
Stratum (MMSE ≤26: MMSE > 26)			3.210	(2.390, 4.311)	<0.0001
Region					0.097
Treatment*region					0.274
Treatment*stratum					0.557
Treatment by time					0.282

† Interaction of treatment-by-natural logarithm of time.
CI= confidence interval
MMSE= Mini-Mental State Examination

Data Source [4.1; 4.3]

Table 83

Comparison Between Rofecoxib and Placebo
In Terms of Slope of Decline for SRT Summed Recall
Intention-to-Treat Population

Treatment	Estimated Slope (SE)	Slope Difference†	95% CI of the Slope Difference	p-Value‡
Rofecoxib 25 mg	0.5439 (0.1230)	0.0260	(-0.307, 0.359)	0.8779
Placebo	0.5699 (0.1165)			

† Placebo – Rofecoxib
‡ Based on longitudinal mixed model including terms for treatment, time, region, MMSE Stratum, and time by treatment interaction.
SRT= Selective Reminding Test
CI= Confidence interval
SE= Standard estimate
MMSE= Mini-Mental State Examination
Note: A negative estimate of slope indicates a worsening prognosis

Data Source: [4.3]

Table 84

Comparison Between Rofecoxib and Placebo
In Terms of Slope of Decline for SRT Delayed Recall
Intention-to-Treat Population

Treatment	Estimated Slope (SE)	Slope Difference†	95% CI of the Slope Difference	p-Value‡
Rofecoxib 25mg	0.0738 (0.0343)	-0.0116	(-0.104, 0.081)	0.8064
Placebo	0.0622 (0.0324)			

†Placebo – Rofecoxib
‡Based on longitudinal mixed model including terms for treatment, time, region, MMSE Stratum, and time by treatment interaction.
SRT= Selective Reminding Test
SE= Standard estimate
CI= Confidence interval
MMSE= Mini-Mental State Examination
Note: A negative estimate of slope indicates a worsening prognosis

Data Source: [4.3]

Table 85

Comparison Between Rofecoxib and Placebo
In Terms of Slope of Decline for MMSE
Intention-to-Treat Population

Treatment	Estimated Slope (SE)	Slope Difference†	95% CI of the Slope Difference	p-Value‡
Rofecoxib 25 mg	-0.1326 (0.0341)	-0.0024	(-0.095, 0.090)	0.9594
Placebo	-0.1350 (0.0324)			

† Placebo – Rofecoxib
‡ Based on longitudinal mixed model including terms for treatment, time, region, MMSE Stratum, and time by treatment interaction.
Note: A negative estimate of slope indicates a worsening prognosis
MMSE= Mini-Mental State Examination
SE= Standard estimate
CI= Confidence interval

Data Source: [4.3]

Table 86

Comparison Between Rofecoxib and Placebo
In Terms of Slope of Decline for ADAS-Cog
Intention-to-Treat Population

Treatment	Estimated Slope (SE)	Slope Difference†	95% CI of the Slope Difference	p-Value‡
Rofecoxib 25 mg	0.3480 (0.0697)	-0.0977	(-0.287, 0.091)	0.3106
Placebo	0.2502 (0.0665)			

† Placebo – Rofecoxib
‡ Based on longitudinal mixed model including terms for treatment, time, region, MMSE Stratum, and time by treatment interaction.
ADAS-Cog= Alzheimer's Disease Assessment Scale – Cognitive subset
SE= Standard estimate
CI= Confidence interval
MMSE= Mini-Mental State Examination
Note: A positive estimate of slope indicates a worsening prognosis

Data Source: [4.3]

Table 87

Comparison Between Rofecoxib and Placebo
In Terms of Slope of CDR Sum of Box Scores
Intention-to-Treat Population

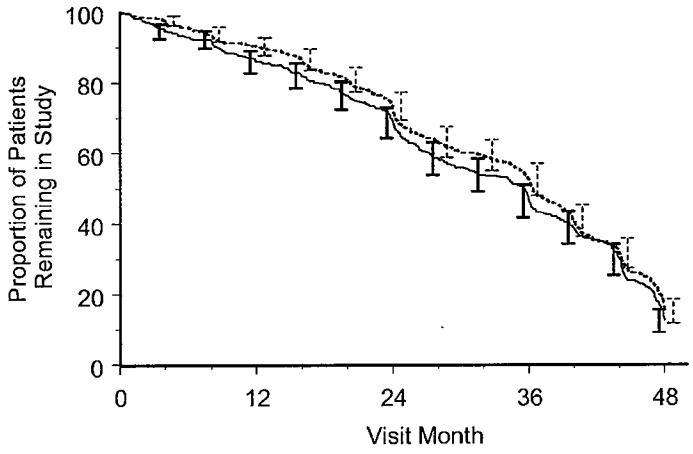
Treatment	Estimated Slope (SE)	Slope Difference	95% CI of the Slope Difference	p-Value†
Rofecoxib	0.2854 (0.0259)	-0.0682	(-0.139, 0.002)	0.0577
Placebo	0.2171 (0.0248)			

† Based on longitudinal mixed model including terms for treatment, time, region, MMSE Stratum, and time by treatment interaction.
Note: A positive estimate of slope indicates a worsening prognosis
CDR= Clinical Dementia Rating
SE= Standard estimate
CI= Confidence interval
MMSE= Mini-Mental State Examination

Data Source: [4.3]

Figure 27

Kaplan-Meier Estimates (95% CI's)
Time to Study Discontinuation†
Males



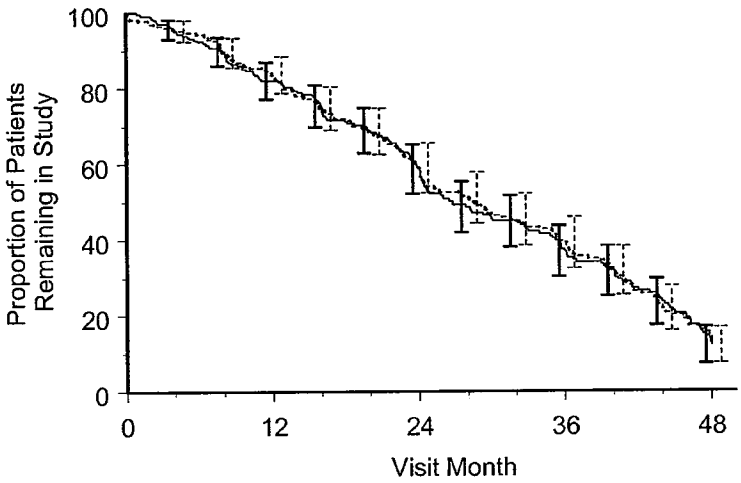
Number of Patients													
—— Rofecoxib 25 mg	476	447	429	393	370	339	296	249	227	194	159	120	48
------ Placebo	504	490	467	442	420	382	338	290	271	235	180	138	65

† Includes patients who discontinued due to withdrawn consent, patient uncooperative, or lost to follow-up.

Data Source: [4.1; 4.2]

Figure 28

Kaplan-Meier Estimates (95% CI's)
Time to Study Discontinuation†
Females



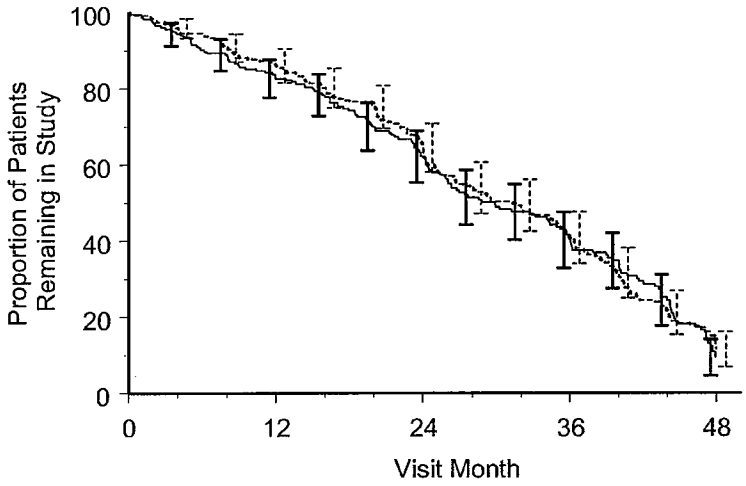
Number of Patients													
—— Rofecoxib 25 mg	249	235	213	189	165	147	119	95	84	64	55	39	20
------ Placebo	228	217	199	183	161	146	120	100	88	75	60	39	21

† Includes patients who discontinued due to withdrawn consent, patient uncooperative, or lost to follow-up.

Data Source: [4.1; 4.2]

Figure 29

Kaplan-Meier Estimates (95% CI's)
Time to Study Discontinuation†
Baseline MMSE ≤26



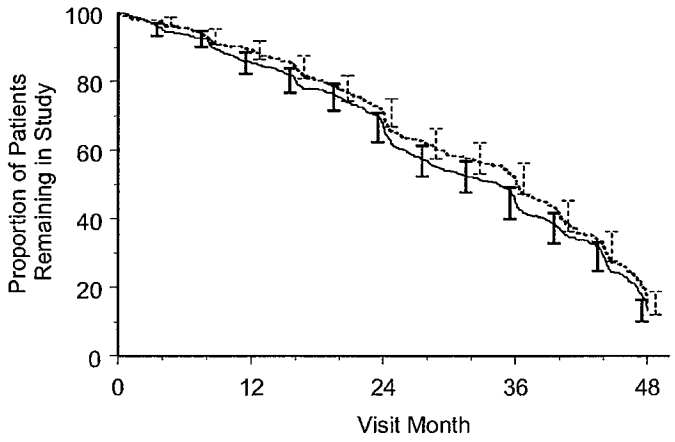
Number of Patients													
—— Rofecoxib 25 mg	229	213	193	172	157	132	107	84	74	60	51	35	12
------ Placebo	242	230	211	195	177	161	130	105	96	76	58	38	20

† Includes patients who discontinued due to withdrawn consent, patient uncooperative, or lost to follow-up.

Data Source: [4.1; 4.2]

Figure 30

Kaplan-Meier Estimates (95% CI's)
Time to Study Discontinuation†
Baseline MMSE >26



Number of Patients													
—— Rofecoxib 25 mg	496	469	449	410	378	354	308	260	237	198	163	124	56
------ Placebo	490	477	455	430	404	367	328	285	263	234	182	139	66

† Includes patients who discontinued due to withdrawn consent, patient uncooperative, or lost to follow-up.

Data Source: [4.1; 4.2]

Table 88

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Rofecoxib 25 mg											
Deaths Due to Serious Adverse Experiences That Began On-Drug or Within 14 Days of Last Dose of Study Drug											
0158	M	82	0	430	Myocardial infarction	1.00 day	430	Def. not	Discontinued	430	Insufficient data
0205	M	83	3	496	Post procedural complication	2.00 day	493	Prob not	No action	497	Other event/fatal non-thromboembolic event
0233	M	78	0	1155	Bone cancer metastatic	1.58 mo	1161	Def not	Discontinued	1202	Other event/fatal non-thromboembolic event
0248	F	69	1	747	Sudden Death	1.00 day	746	Def not	Discontinued	747	Event/sudden cardiac death
0257	M	73	0	1083	Squamous cell carcinoma of skin	11.92 mo	1441	Def not	Discontinued	1445	Non-thromboembolic
0263	M	76	2	884	Pulmonary fibrosis	2.00 day	882	Def not	Discontinued	885	Other event/fatal non-thromboembolic event
0352	M	67	0	322	Duodenal ulcer haemorrhage	2.00 day	323	Prob not	Discontinued	323	Other event†/fatal haemorrhagic duodenal ulcer

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Rofecoxib 25 mg											
Deaths Due to Serious Adverse Experiences That Began On-Drug or Within 14 Days of Last Dose of Study Drug (Cont.)											
0359	M	65	0	624	Atherosclerosis	1.00 hr	624	Def not	Discontinued	624	Event/sudden cardiac death
			0	624	Hypertensive heart disease	1.00 day	624	Def not	No action	624	
0583	M	69	12	324	Hypercoagulation	1.18 mo	312	Def not	No action	359	N/A
			12	324	Pancreatic carcinoma NOS	1.18 mo	312	Def not	No action	359	
			45	357	Hypoxia	3.00 day	312	Def not	No action	359	
			45	357	Pulmonary embolism	3.00 day	312	Def not	No action	359	
0737	M	83	0	185	Cardiac arrest	1.00 day	185	Def not	Discontinued	185	Event/sudden cardiac death
0762	M	85	0	695	Renal failure NOS	2.83 mo	760	Def not	Discontinued	780	Other event/fatal non-thromboembolic event
0799	M	85	4	312	Cardiac arrest	1.00 day	308	Def not	Discontinued	312	Event/sudden cardiac death
0815	M	73	1	754	Ventricular fibrillation	1.00 day	753	Prob not	Discontinued	754	Event/sudden cardiac death

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Rofecoxib 25 mg											
Deaths Due to Serious Adverse Experiences That Began On-Drug or Within 14 Days of Last Dose of Study Drug (Cont.)											
0821	M	84	0	271	Head injury	1.00 day	271	Def not	Discontinued	271	Other event/fatal non-thromboembolic event
0823	M	77	0	547	Empyema NOS	13.00 day	547	Def not	No action	559	Other event/fatal non-thromboembolic event
			0	547	Pneumonia NOS	13.00 day	547	Def not	Discontinued	559	
			12	559	Cardio-respiratory arrest	0.03 hr	547	Def not	No action	559	
0935	M	75	12	106	Polytraumatism	1.00 day	94	Def not	No action	106	Other event/fatal non-thromboembolic event
1025	M	82	10	138	Acute myocardial infarction	1.00 day	128	Prob not	No action	138	Event/fatal acute myocardial infarction
1097	M	68	1	248	Electric shock	0.02 hr	247	Def not	Discontinued	248	Other event/fatal non-thromboembolic event
1365	F	79	0	1450	Acute myocardial infarction	1.00 hr	1450	Poss	Discontinued	1450	Event/sudden cardiac death

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Rofecoxib 25 mg											
Deaths Due to Serious Adverse Experiences That Began On-Drug or Within 14 Days of Last Dose of Study Drug (Cont.)											
1419	M	74	0	41	Chronic lymphocytic leukemia NOS	22.18 mo	688	Def not	Discontinued	715	Other event/fatal non-thromboembolic event
			0	676	Pneumonia NOS	1.31 mo	688	Def not	No action	715	
			1	689	Gastric perforation	27.00 day	688	Def not	Discontinued	715	
1423	M	82	0	611	Traumatic chest injury NOS	0.67 hr	611	Def not	Discontinued	611	Other event/fatal non-thromboembolic event
1453	M	80	0	36	Acute myeloid leukemia NOS	21.00 day	36	Def not	No action	56	Other event/fatal non-thromboembolic event
			17	53	Bacterial sepsis	4.00 day	36	Def not	No action	56	
1506	M	78	0	1030	Pancreatic neoplasm NOS	22.00 day	1029	Def not	Discontinued	1051	Other event/fatal non-thromboembolic event
1577	M	78	0	707	Myocardial infarction	1.00 day	707	Prob not	Discontinued	707	Event/sudden cardiac death

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Rofecoxib 25 mg											
Deaths Due To Adverse experiences With Onset More Than 14 Days After the Last Dose of Study Drug, but Related to Non-fatal Adverse Experiences in the On-Drug Period											
0290[§]	M	85	15	594	Lung neoplasm malignant	1.05 mo	579	Def not	No action	625	Other event/fatal non-thromboembolic event
0536[§]	F	88	104	954	Ovarian cancer metastatic	2.23 mo	850	Def not	No action	1021	Other event/fatal non-thromboembolic event
1113[§]	M	78	62	102	Acute lymphocytic leukemia	11.76 mo	40	Def not	No action	459	Other event/fatal non-thromboembolic event

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Rofecoxib 25 mg											
Off-Drug Deaths											
0002	M	85	335	1463	Cardiac arrest	12.00 hr	1128	Def not	No action	1464	Event/fatal acute myocardial infarction
			336	1464	Emphysema	1.00 day	1128	Def not	No action	1464	
0195	M	81	492	1099	Acute myocardial infarction	0.98 hr	607	Def not	No action	1099	Event/sudden cardiac death
0202	M	85	1238	1257	Cardiac failure congestive	11.00 day	19	Def not	No action	1267	Other event/fatal non-thromboembolic event
0362	M	82	662	1236	Arrhythmia NOS	1.00 day	574	Def not	No action	1236	Event/sudden cardiac death
			662	1236	Coronary artery disease NOS	1.00 day	574	Def not	No action	1236	
0500	M	82	412	457	Cardiac arrest	1.00 day	45	Def not	No action	457	Event/fatal acute myocardial infarction
			412	457	Ventricular fibrillation	1.00 day	45	Def not	No action	457	

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Rofecoxib 25 mg											
Off-Drug Deaths (Cont.)											
0626	F	72	297	787	Metastatic neoplasm NOS, primary site unknown	1.22 mo	490	Def not	No action	823	Other event/fatal non-thromboembolic event
0639	M	68	56	482	Acute myocardial infarction	0.17 hr	426	Def not	No action	482	Event/sudden cardiac death
0796	M	86	709	726	Subarachnoid haemorrhage NOS	10.00 day	17	Def not	No action	735	†Insufficient data
0889	M	83	398	654	Coronary artery disease NOS	6.00 day	256	Def not	No action	659	Event/fatal acute myocardial infarction
			403	659	Myocardial infarction	1.00 day	256	Def not	No action	659	
1068	M	72	952	1330	Cerebrovascular accident	2.00 day	378	Def not	No action	1331	Other event†/fatal haemorrhagic stroke
1202	F	72	17	68	Cerebral haemorrhage	7.00 day	51	Def not	Discontinued	74	Other event†/fatal haemorrhagic stroke

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Rofecoxib 25 mg											
Off-Drug Deaths (Cont.)											
1326	M	78	443	816	Cerebrovascular accident	1.71 mo	373	Def not	No action	867	Other event†/fatal non-thromboembolic event
			484	857	Urosepsis	11.00 day	373	Def not	No action	867	
			494	867	Deep vein thrombosis	1.00 day	373	Def not	No action	867	
			494	867	Pneumonia NOS	1.00 day	373	Def not	No action	867	
			494	867	Renal failure acute	1.00 day	373	Def not	No action	867	
1360	M	80	763	897	Myocardial infarction	0.25 hr	134	Def not	No action	897	Event/sudden cardiac death
1530	M	89	984	1017	Myocardial infarction	3.00 day	33	Def not	No action	1019	Other event/fatal acute myocardial infarction
			984	1017	Pneumonia NOS	3.00 day	33	Def not	No action	1019	
			984	1017	Renal failure acute	3.00 day	33	Def not	No action	1019	

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Placebo											
Deaths Due to Serious Adverse Experiences That Began On-Drug or Within 14 Days of Last Dose of Study Drug											
0111	F	76	0	617	Lymphoma NOS	24.00 day	617	Def not	Discontinued	640	Other event/fatal non-thromboembolic event
0188	M	78	3	1263	Acute myocardial infarction	1.00 day	1260	Prob not	No action	1263	Event/fatal acute myocardial infarction
0264	M	74	0	430	Colon cancer metastatic	1.24 yr	457	Prob not	Discontinued	882	Other event/fatal non-thromboembolic event
0294	M	76	0	556	Malignant melanoma	1.97 mo	615	Prob not	Discontinued	615	Other event/fatal non-thromboembolic event
0308	M	84	1	407	Acute myeloid leukemia NOS	10.00 day	406	Prob not	Discontinued	416	Other event/fatal non-thromboembolic event
			1	407	Renal failure NOS	10.00 day	406	Prob not	Discontinued	416	

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Placebo											
Deaths Due to Serious Adverse Experiences That Began On-Drug or Within 14 Days of Last Dose of Study Drug (Cont.)											
0323	M	79	3	1196	Bowel sounds abnormal	2.00 day	1193	Def not	Discontinued	1197	Other event†/ sudden/unknown cause of death
			4	1197	Cardiac failure NOS	1.00 day	1193	Def not	No action	1197	
			4	1197	Intestinal ischaemia	1.00 day	1193	Def not	No action	1197	
			4	1197	Pancreatitis NOS	1.00 day	1193	Def not	No action	1197	
			4	1197	Renal failure NOS	1.00 day	1193	Def not	No action	1197	
0539	M	71	1	243	Hypertension NOS	1.00 day	242	Prob not	Discontinued	243	Insufficient data
0621	M	75	0	692	Acute myocardial infarction	1.00 day	692	Prob not	Discontinued	692	Event/sudden cardiac death
1256	F	80	0	674	Cardio-respiratory arrest	1.00 day	674	Def not	Discontinued	674	Event/sudden cardiac death

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Placebo											
Deaths Due to Serious Adverse Experiences That Began On-Drug or Within 14 Days of Last Dose of Study Drug (Cont.)											
1350	F	77	0	702	Bladder cancer NOS	17.00 day	707	Def not	Discontinued	718	Other event/fatal non-thromboembolic event
			0	702	Metastases to liver	17.00 day	707	Def not	Discontinued	718	
			11	718	Multi-organ failure	3.00 hr	707	Def not	No action	718	
1378	M	73	1	392	Acute myocardial infarction	1.00 day	391	Prob not	Discontinued	392	Event/sudden cardiac death
1445	F	74	0	884	Intracranial haemorrhage NOS	0.20 hr	884	Prob not	Discontinued	884	Other event†/fatal haemorrhagic stroke
1472	M	66	0	591	Metastatic neoplasm NOS, primary site unknown	2.17 mo	607	Prob not	Discontinued	656	Other event/fatal non-thromboembolic event

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Placebo											
Deaths Due to Serious Adverse Experiences That Began On-Drug or Within 14 Days of Last Dose of Study Drug (Cont.)											
1543	F	82	13	967	Acute respiratory failure	6.00 hr	954	Prob not	No action	967	Other event[†]/ sudden/unknown cause of death
1547	M	82	12	96	Adenocarcinoma NOS	2.27 mo	84	Def not	No action	164	Other event/fatal non-thromboembolic event
Treatment Group: Placebo											
Off-Drug Deaths											
0127	M	84	79	1141	Cardiac failure congestive	1.00 day	1062	Prob not	No action	1141	Non-thromboembolic
0926	M	72	35	1311	Completed suicide	1.00 day	1276	Def not	No action	1311	Other event/fatal non-thromboembolic event
1021	M	78	156	421	Hepatic neoplasm malignant NOS	11.00 day	265	Def not	No action	431	Other event/fatal non-thromboembolic event

Table 88 (Cont.)

Listing of Patient Deaths
Intention-to-Treat Population

AN	Gender	Age	# Days Off Drug When AE Started	Rel Day Of AE Onset	Adverse Experience	Duration of AE	Rel Day of Discon. of Study Med	Drug Relationship	Action Taken on Study Drug	Rel Day of Death	Adjudicated Outcome/Diagnosis
Treatment Group: Placebo											
Off-Drug Deaths (Cont.)											
1144	F	93	376	496	Pancreatic carcinoma NOS	2.14 mo	120	Def not	No action	560	Other event/fatal non-thromboembolic event
1475	M	74	151	1069	Renal impairment NOS	2.00 day	918	Prob not	No action	1070	Non-thromboembolic
			151	1069	Therapeutic agent poisoning	2.00 day	918	Prob not	No action	1070	

AN= Allocation number.
AE= Adverse experience.
Discon = Discontinuation.
Prob not = Probably not.
Def not = Definitely not.
Poss = Possibly.
Rel Day= Day relative to first dose of prime therapy.
APTC=Antiplatelet Trialists' Collaboration
† Antiplatelet Trialists' Collaboration (APTC) event, exclusively. Not a confirmed thrombotic event.
‡ N/A = Not applicable. Could not definitively adjudicate a diagnosis.
§ AN 0290 had cough and bloody sputum, AN 0536 had abdominal pain, and AN 1113 had decreased leukocytes within 14 days of last dose of study medication. Patient deaths were counted as on-drug deaths as the fatal off-drug adverse experiences may have been related to these earlier nonfatal on-drug adverse experiences.

Data Source: [4.2; 4.7]

Table 89

Listing of Cardiovascular Events Intention-to-Treat Population

Case ID	AN	Treatment	Random Date	Last Day on Treatment	Event Day	Investigator Reported Term	Adjudication Term	Throm. Card. Mort.	Conf. Throm. Events	APTC	Invt. Rpt. Throm.
847	2	Rofecoxib 25 mg	10SEP98	1128	1463	Cardiac arrest	Fatal acute myocardial infarction	No	Yes[†]	Yes[†]	Yes[†]
443	9	Rofecoxib 25 mg	23APR99	860	484	Coronary artery disease NOS	Other event	No	No	No	Yes
704	47	Rofecoxib 25 mg	19MAY99	856	856	Transient ischaemic attack	Transient ischemic attack	No	Yes	No	Yes
533	77	Placebo	19DEC98	1467	763	Deep venous thrombosis NOS	Peripheral venous thrombosis	No	Yes	No	Yes
468	104	Placebo	10OCT98	1462	713	Coronary artery disease NOS	Other event	No	No	No	Yes
449	106	Placebo	17SEP98	1097	707	Coronary artery disease NOS and Unstable angina	Unstable angina pectoris	No	Yes	No	Yes
398	109	Placebo	21MAY99	1334	397	Carotid artery stenosis	Other event	No	No	No	Yes
659	111	Placebo	20AUG99	617	617	Lymphoma	Other event	No	No	No	No
811	127	Placebo	30SEP99	1062	957	Pulmonary embolism	Pulmonary embolism	No	Yes	No	Yes
881	127	Placebo	30SEP99	1062	1140	Cardiac failure congestive	Other event	No	No	No	No
606	128	Rofecoxib 25 mg	21SEP99	130	130	Ventricular tachycardia	Other event	No	No	No	Yes
825	130	Placebo	29AUG98	1477	1363	Myocardial infarction, Supraventricular tachycardia	Acute myocardial infarction	No	Yes	Yes	Yes
461	146	Rofecoxib 25 mg	17MAR99	599	85	Transient ischaemic attack	Transient ischemic attack	No	Yes	No	Yes
644	149	Rofecoxib 25 mg	14APR99	767	768	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
605	156	Placebo	29DEC98	1470	791	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
278	158	Rofecoxib 25 mg	12NOV98	430	430	Myocardial infarction	Other event	No	No	No	Yes
224	177	Placebo	10NOV98	1459	401	Coronary artery stenosis	Other event	No	No	No	Yes
553	177	Placebo	10NOV98	1459	758	Ventricular tachycardia	Other event	No	No	No	Yes[‡]
225	186	Placebo	15AUG98	1403	378	Ventricular tachycardia	Other event	No	No	No	Yes
741	188	Placebo	11JUN98	1260	1263	Acute myocardial infarction	Fatal acute myocardial infarction	Yes	Yes	Yes	Yes
361	195	Rofecoxib 25 mg	22AUG98	607	606	Acute myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
697	195	Rofecoxib 25 mg	22AUG98	607	1099	Acute myocardial infarction	Sudden cardiac death	No	Yes[†‡]	Yes[†‡]	Yes[†‡]
750	202	Rofecoxib 25 mg	31MAY98	19	1267	Congestive Heart Failure	Other event	No	No	No	No
497	205	Rofecoxib 25 mg	24NOV98	493	496	Pulmonary embolism	Other event	No	No	No	Yes
303	217	Rofecoxib 25 mg	21NOV98	1468	437	Pulmonary embolism	Other event	No	No	No	Yes

Table 89 (Cont.)

Listing of Cardiovascular Events Intention-to-Treat Population

Case ID	AN	Treatment	Random Date	Last Day on Treatment	Event Day	Investigator Reported Term	Adjudication Term	Throm. Card. Mort.	Conf. Throm. Events	APTC	Invt. Rpt. Throm.
757	233	Rofecoxib25 mg	02SEP98	1161	1155	Prostatic malignant neoplasm	Other event	No	No	No	No
663	243	Rofecoxib25 mg	12JAN99	1099	890	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
486	248	Rofecoxib25 mg	13NOV98	746	747	Sudden death	Sudden cardiac death	Yes	Yes	Yes	Yes
823	257	Rofecoxib25 mg	20JUN98	1441	1083	Squamous cell carciNoma	Other event	No	No	No	No
836	259	Placebo	14NOV98	1463	1347	Carotid artery steNosis	Other event	No	No	No	Yes
816	261	Rofecoxib25 mg	14NOV98	1467	1298	Carotid artery steNosis	Other event	No	No	No	Yes
581	263	Rofecoxib25 mg	13OCT98	882	884	Pulmonary fibrosis	Other event	No	No	No	No
565	264	Placebo	23SEP98	457	430	Metastatic colon carciNoma	Other event	No	No	No	No
733	270	Rofecoxib25 mg	23APR99	924	931	Coronary artery disease NOS	Unstable angina pectoris	No	Yes	No	Yes
262	272	Rofecoxib25 mg	02JUL99	742	59	Coronary artery disease NOS	Other event	No	No	No	Yes
593	283	Rofecoxib25 mg	26JAN00	411	412	Coronary artery disease NOS	Other event	No	No	No	Yes
567	290	Rofecoxib25 mg	15JUN98	579	594	Lung malignant neoplasm	Other event	No	No	No	No
566	294	Placebo	22AUG98	615	556	Malignant melaNoma	Other event	No	No	No	No
480	297	Rofecoxib25 mg	01SEP98	718	721	Coronary artery disease NOS	Other event	No	No	No	Yes
571	308	Placebo	08OCT99	406	407	Acute renal failure, MyelogeNous leukemia	Other event	No	No	No	No
76	320	Placebo	08OCT98	1471	130	Carotid artery occlusion	Other event	No	No	No	Yes
807	323	Placebo	13JAN99	1193	1196	Cardiac failure NOS, Illeus paralytic, Pancreatitis NOS, Renal failure NOS	Other event	No	No	Yes	Yes
551	334	Rofecoxib25 mg	03NOV99	480	480	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
487	335	Placebo	15DEC99	259	262	Cerebrovascular accident; Carotid occlusion	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
563	352	Rofecoxib25 mg	30JUL99	323	322	Hemorrhagic duodenal ulcer	Other event	No	No	Yes	No
570	359	Rofecoxib25 mg	24NOV98	624	624	Atherosclerosis, hypertension	Sudden cardiac death	Yes	Yes	Yes	No
160	360	Placebo	21OCT98	444	356	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
377	360	Placebo	21OCT98	444	444	Myocardial infarction, Ventricular tachycardia	Acute myocardial infarction	No	Yes[‡]	Yes[‡]	Yes[‡]
776	362	Rofecoxib25 mg	19SEP98	574	1236	Coronary artery diseease NOS	Sudden cardiac death	No	Yes[†]	Yes[†]	Yes[†]
800	365	Placebo	19MAR99	1455	1123	Angina pectoris	Other event	No	No	No	Yes

Table 89 (Cont.)

Listing of Cardiovascular Events Intention-to-Treat Population

Case ID	AN	Treatment	Random Date	Last Day on Treatment	Event Day	Investigator Reported Term	Adjudication Term	Throm. Card. Mort.	Conf. Throm. Events	APTC	Invt. Rpt. Throm.
609	376	Rofecoxib 25 mg	05MAY99	1284	609	Ventricular tachycardia	Other event	No	No	No	Yes
764	376	Rofecoxib 25 mg	05MAY99	1284	931	Angina, unstable	Unstable angina pectoris	No	Yes	No	Yes[‡]
893	376	Rofecoxib 25 mg	05MAY99	1284	1284	Myocardial infarction	Acute myocardial infarction	No	Yes[‡]	Yes	Yes[‡]
608	377	Rofecoxib 25 mg	07AUG99	977	575	Coronary artery disease NOS	Unstable angina pectoris	No	Yes	No	Yes
133	378	Placebo	06AUG99	1225	29	Transient ischaemic attack	Transient ischemic attack	No	Yes	No	Yes
427	398	Placebo	23SEP98	611	656	Transient ischaemic attack	Other event	No	No	No	Yes[†]
365	412	Rofecoxib 25 mg	08JUL98	618	618	Coronary artery disease NOS	Other event	No	No	No	Yes
95	423	Rofecoxib 25 mg	24APR99	187	54	Transient ischaemic attack	Transient ischemic attack	No	Yes	No	Yes
321	451	Rofecoxib 25 mg	12NOV98	466	449	Coronary artery disease NOS	Other event	No	No	No	Yes
647	470	Placebo	27FEB99	822	822	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
925	470	Placebo	27FEB99	822	836	Coronary artery disease NOS	Other event	No	No	No	Yes[‡]
1	481	Placebo	23JUN98	205	56	Transient ischaemic attack	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
471	500	Rofecoxib 25 mg	01JUL99	45	457	Cardiac Arrest	Fatal acute myocardial infarction	No	Yes[†]	Yes[†]	Yes[†]
636	502	Rofecoxib 25 mg	29JUN99	760	683	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
699	536	Rofecoxib 25 mg	03NOV98	850	954	Ovarian malignant neoplasm	Other event	No	No	No	No
753	538	Placebo	24OCT98	1076	1076	Myocardial infarction	Unstable angina pectoris	No	Yes	No	Yes
561	539	Placebo	23OCT98	242	243	Hypertension	Other event	No	No	No	No
562	583	Rofecoxib 25 mg	02SEP98	312	324	Hypercoagulation, Hypoxia, Pancreatic malignant neoplasm, Pulmonary embolism	Other event	No	No	No	Yes
2	585	Rofecoxib 25 mg	20AUG98	48	29	Transient ischaemic attack	Transient ischemic attack	No	Yes	No	Yes
623	600	Placebo	08FEB00	617	383	Transient ischaemic attack	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
746	607	Rofecoxib 25 mg	01OCT98	1277	1150	Myocardial infarction, Coronary artery disease NOS	Acute myocardial infarction	No	Yes	Yes	Yes
711	621	Placebo	15OCT99	692	692	Acute myocardial infarction	Sudden cardiac death	Yes	Yes	Yes	Yes
707	626	Rofecoxib 25 mg	02JUN99	490	787	Malignant neoplasm of unknown primary; Cholelithiasis	Other event	No	No	No	No
564	639	Rofecoxib 25 mg	08AUG98	426	482	Acute myocardial infarction	Sudden cardiac death	No	Yes[†]	Yes[†]	Yes[†]
179	670	Placebo	30SEP99	1	2	Transient ischaemic attack	Other event	No	No	No	Yes

Table 89 (Cont.)

Listing of Cardiovascular Events Intention-to-Treat Population

Case ID	AN	Treatment	Random Date	Last Day on Treatment	Event Day	Investigator Reported Term	Adjudication Term	Throm. Card. Mort.	Conf. Throm. Events	APTC	Invt. Rpt. Throm.
417	682	Placebo	02JUL98	1183	114	Angina pectoris	Other event	No	No	No	Yes
14	737	Rofecoxib 25 mg	16JUL98	185	185	Cardiac arrest	Sudden cardiac death	Yes	Yes	Yes	Yes
389	759	Placebo	18SEP98	812	617	Acute myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
390	760	Rofecoxib 25 mg	10SEP98	1464	615	Transient ischaemic attack	Transient ischemic attack	No	Yes	No	Yes
630	762	Rofecoxib 25 mg	20AUG98	760	707	Renal failure; Prostatic malignant neoplasm	Other event	No	No	No	No
35	770	Placebo	10SEP98	199	199	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
772	796	Rofecoxib 25 mg	30OCT99	17	726	Subarachnoid haemorrhage NOS; Myocardial infarction	Acute myocardial infarction	No	Yes[†]	Yes[‡]	Yes[†]
747	796	Rofecoxib 25 mg	30OCT99	17	727	Subarachnoid haemorrhage NOS	Other event	No	No	Yes[†‡]	Yes[†‡]
455	799	Rofecoxib 25 mg	23SEP99	308	312	Cardiac arrest	Sudden cardiac death	Yes	Yes	Yes	Yes
782	801	Placebo	07JUL98	1499	1316	Vertebrobasilar insufficiency	Other event	No	No	No	Yes
113	805	Placebo	11FEB99	196	128	Carotid artery stenosis	Other event	No	No	No	Yes
158	811	Placebo	09SEP98	1434	381	Carotid artery stenosis	Other event	No	No	No	Yes
671	812	Rofecoxib 25 mg	28AUG98	1057	1054	Cerebrovascular Accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
869	814	Rofecoxib 25 mg	02JUN99	4	4	Cardiac fibrillation NOS	Other event	No	No	No	Yes
676	815	Rofecoxib 25 mg	30JUN99	753	753	Ventricular fibrillation	Sudden cardiac death	Yes	Yes	Yes	Yes
690	819	Rofecoxib 25 mg	21JUL99	747	709	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
574	821	Rofecoxib 25 mg	05NOV99	271	271	Head trauma	Other event	No	No	No	No
675	823	Rofecoxib 25 mg	07JAN00	547	547	Cardio-respiratory arrest; Pneumonia NOS	Other event	No	No	No	Yes
838	826	Rofecoxib 25 mg	25JAN00	1014	910	Cerebrovascular accident	Other event	No	No	No	Yes
927	826	Rofecoxib 25 mg	25JAN00	1014	1010	Transient ischaemic attack	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes[‡]
928	826	Rofecoxib 25 mg	25JAN00	1014	1015	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes[‡]	Yes[‡]	Yes[‡]
633	835	Rofecoxib 25 mg	29SEP98	827	777	Transient ischaemic attack	Other event	No	No	No	Yes
715	839	Rofecoxib 25 mg	19AUG98	1462	957	Angina pectoris; Coronary artery disease NOS	Unstable angina pectoris	No	Yes	No	Yes
319	854	Placebo	13NOV98	1433	111	Carotid artery stenosis	Other event	No	No	No	Yes
737	881	Rofecoxib 25 mg	07MAY99	733	696	Pulmonary embolism	Other event	No	No	No	Yes

Table 89 (Cont.)

Listing of Cardiovascular Events Intention-to-Treat Population

Case ID	AN	Treatment	Random Date	Last Day on Treatment	Event Day	Investigator Reported Term	Adjudication Term	Throm. Card. Mort.	Conf. Throm. Events	APTC	Invt. Rpt. Throm.
924	881	Rofecoxib 25 mg	07MAY99	733	747	Angina pectoris	Other event	No	No	No	Yes‡
163	882	Placebo	30APR99	777	159	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
538	882	Placebo	30APR99	777	634	Angina pectoris, Coronary artery disease NOS, Angina unstable	Unstable angina pectoris	No	Yes‡	No	Yes‡
665	882	Placebo	30APR99	777	644	Angina pectoris	Other event	No	No	No	Yes‡
687	882	Placebo	30APR99	777	684	Carotid artery obstruction	Other event	No	No	No	Yes‡
655	882	Placebo	30APR99	777	712	Cerebrovascular accident	Other event	No	No	No	Yes‡
918	882	Placebo	30APR99	777	723	Subararachnoid haemorrhage NOS, subdural haematoma	Other event	No	No	No	Yes‡
710	882	Placebo	30APR99	777	759	Angina unstable	Unstable angina pectoris	No	Yes‡	No	Yes‡
643	882	Placebo	30APR99	777	774	Angina pectoris	Unstable angina pectoris	No	Yes‡	No	Yes‡
610	889	Rofecoxib 25 mg	09JUN99	256	654	Myocardial infarction; Coronary artery disease	Fatal acute myocardial infarction	No	Yes†	Yes†	Yes†
318	920	Rofecoxib 25 mg	12OCT99	133	101	Cerebrovascular accident	Hemorrhagic stroke	No	No	Yes	Yes
645	925	Rofecoxib 25 mg	17APR99	666	656	Transient ischaemic attack	Transient ischemic attack	No	Yes	No	Yes
632	925	Rofecoxib 25 mg	17APR99	666	663	Coronary artery disease NOS	Unstable angina pectoris	No	Yes‡	No	Yes‡
892	926	Placebo	14APR99	1276	1311	Completed suicide	Other event	No	No	No	No
826	928	Rofecoxib 25 mg	18MAR99	1187	1187	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
604	934	Rofecoxib 25 mg	21JAN99	770	771	Coronary artery disease NOS	Other event	No	No	No	Yes
577	935	Rofecoxib 25 mg	24DEC98	94	106	Trauma	Other event	No	No	No	No
578	1021	Placebo	03DEC99	265	417	Hepatic carcinoma	Other event	No	No	No	No
923	1025	Rofecoxib 25 mg	03OCT98	128	119	Coronary artery disease NOS	Other event	No	No	No	Yes
291	1025	Rofecoxib 25 mg	03OCT98	128	125	Unstable angina	Unstable angina pectoris	No	Yes	No	Yes‡
27	1025	Rofecoxib 25 mg	03OCT98	128	138	Acute myocardial infarction	Fatal acute myocardial infarction	Yes	Yes‡	Yes	Yes‡
540	1037	Rofecoxib 25 mg	15JUN99	1347	593	Acute myocardial infarction	Other event	No	No	No	Yes
428	1041	Rofecoxib 25 mg	17JUN99	1357	363	Coronary artery disease	Other event	No	No	No	Yes
603	1041	Rofecoxib 25 mg	17JUN99	1357	628	Coronary artery stenosis	Other event	No	No	No	Yes‡
18	1058	Placebo	10SEP98	677	123	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes

Table 89 (Cont.)

Listing of Cardiovascular Events Intention-to-Treat Population

Case ID	AN	Treatment	Random Date	Last Day on Treatment	Event Day	Investigator Reported Term	Adjudication Term	Throm. Card. Mort.	Conf. Throm. Events	APTC	Invt. Rpt. Throm.
72	1058	Placebo	10SEP98	677	131	Angina pectoris	Unstable angina pectoris	No	Yes‡	No	Yes‡
36	1058	Placebo	10SEP98	677	187	Unstable angina	Unstable angina pectoris	No	Yes‡	No	Yes‡
669	1060	Placebo	24SEP98	1456	723	Coronary artery disease	Other event	No	No	No	Yes
444	1061	Placebo	17SEP98	1342	706	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
908	1068	Rofecoxib25 mg	09JUL98	378	506	Transient ischemic attack	Other event	No	No	No	Yes†
762	1068	Rofecoxib25 mg	09JUL98	378	1265	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes†	Yes†	Yes†‡
831	1068	Rofecoxib25 mg	09JUL98	378	1330	Cerebrovascular accident	Fatal hemorrhagic stroke	No	No	Yes†‡	Yes†‡
475	1092	Placebo	15DEC98	677	678	Myocardial infarction	Other event	No	No	No	Yes
466	1096	Rofecoxib25 mg	21OCT98	717	717	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
576	1097	Rofecoxib25 mg	14OCT98	247	248	Electrical shock	Other event	No	No	No	No
341	1111	Rofecoxib25 mg	01DEC99	710	37	Coronary artery disease	Other event	No	No	No	Yes
573	1113	Rofecoxib25 mg	06NOV99	40	102	Acute lymphocytic leukemia	Other event	No	No	No	No
913	1133	Placebo	13OCT98	217	216	Phlebitis NOS	Peripheral venous thrombosis	No	Yes	No	Yes
22	1137	Placebo	13JAN99	5	5	Transient ischemic attack	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
848	1143	Rofecoxib25 mg	23OCT98	1448	1285	Angina pectoris	Other event	No	No	No	Yes
569	1144	Placebo	23OCT98	120	510	Pancreatic malignant neoplasm	Other event	No	No	No	No
458	1151	Rofecoxib25 mg	06APR99	510	511	Acute myocardial infarction, Coronary artery disease	Acute myocardial infarction	No	Yes	Yes	Yes
700	1153	Rofecoxib25 mg	01JUL98	684	684	Intracranial hemorrhage	Other event	No	No	No	Yes
48	1163	Rofecoxib25 mg	21JUL98	1470	249	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
839	1169	Placebo	16JUN99	1184	1151	Transient ischemic attack	Transient ischemic attack	No	Yes	No	Yes
937	1169	Placebo	16JUN99	1184	1153	Transient ischemic attack	Transient ischemic attack	No	Yes‡	No	Yes‡
216	1170	Rofecoxib25 mg	15MAY99	1330	105	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
488	1172	Placebo	06MAY99	1343	570	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
758	1174	Placebo	17APR99	964	964	Cerebrovascular accident	Other event	No	No	No	Yes
462	1201	Placebo	12AUG99	425	429	Coronary artery disease NOS	Other event	No	No	No	Yes

Table 89 (Cont.)

Listing of Cardiovascular Events Intention-to-Treat Population

Case ID	AN	Treatment	Random Date	Last Day on Treatment	Event Day	Investigator Reported Term	Adjudication Term	Throm. Card. Mort.	Conf. Throm. Events	APTC	Invt. Rpt. Throm.
148	1202	Rofecoxib 25 mg	17JUL99	51	68	Cerebrovascular accident	Fatal hemorrhagic stroke	No	No	Yes†	Yes†
96	1217	Rofecoxib 25 mg	22AUG98	216	219	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
7	1218	Placebo	04SEP98	122	48	Unstable angina; Coronary artery disease	Unstable angina pectoris	No	Yes	No	Yes
934	1224	Rofecoxib 25 mg	17NOV98	1245	1114	Myocardial ischaemia	Other event	No	No	No	Yes
19	1227	Placebo	29DEC98	1470	15	Deep venous thrombosis	Other event	No	No	No	Yes
500	1227	Placebo	29DEC98	1470	581	Coronary artery disease	Other event	No	No	No	Yes‡
666	1227	Placebo	29DEC98	1470	907	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes‡
541	1240	Placebo	11JUN99	515	516	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
766	1245	Placebo	05MAR00	744	663	Coronary artery disease	Other event	No	No	No	Yes
813	1248	Rofecoxib 25 mg	18FEB00	800	801	Cardiac arrest, Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
483	1256	Placebo	13JAN99	674	674	Cardio-respiratory arrest	Sudden cardiac death	Yes	Yes	Yes	Yes
147	1260	Rofecoxib 25 mg	24SEP98	1212	295	Transient ischemic attack	Other event	No	No	No	Yes
777	1271	Rofecoxib 25 mg	24APR99	33	32	Coronary artery disease, Angina pectoris	Other event	No	No	No	Yes
855	1280	Rofecoxib 25 mg	23NOV99	1170	1060	Myocardial infarction, Coronary artery disease Nos	Acute myocardial infarction	No	Yes	Yes	Yes
349	1321	Rofecoxib 25 mg	08MAY99	339	338	Transient ischemic attack	Transient ischemic attack	No	Yes	No	Yes
670	1326	Rofecoxib 25 mg	18MAR99	373	816	Cerebrovascular accident, Deep venous thrombosis	Other event	No	No	Yes†	Yes†
366	1339	Placebo	30NOV99	136	141	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
367	1339	Placebo	30NOV99	136	141	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes‡	Yes‡	Yes‡
472	1345	Rofecoxib 25 mg	20OCT98	777	670	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
575	1350	Placebo	05NOV98	707	708	Bladder malignant neoplasm	Other event	No	No	No	No
662	1360	Rofecoxib 25 mg	22DEC98	134	897	Myocardial infarction	Sudden cardiac death	No	Yes†	Yes†	Yes†
201	1362	Placebo	10DEC98	1398	357	Myocardial infarction	Acute myocardial infarction	No	Yes	Yes	Yes
380	1363	Placebo	21JAN99	490	490	Cerebellar haemorrhage	Hemorrhagic stroke	No	No	Yes	Yes
900	1365	Rofecoxib 25 mg	05FEB99	1450	1450	Acute myocardial infarction	Sudden cardiac death	Yes	Yes	Yes	Yes
152	1370	Placebo	11JUN99	706	71	Carotid artery stenosis	Other event	No	No	No	Yes

Table 89 (Cont.)

Listing of Cardiovascular Events Intention-to-Treat Population

Case ID	AN	Treatment	Random Date	Last Day on Treatment	Event Day	Investigator Reported Term	Adjudication Term	Throm. Card. Mort.	Conf. Throm. Events	APTC	Invt. Rpt. Throm.
279	1378	Placebo	09OCT98	391	392	Acute myocardial infarction	Sudden cardiac death	Yes	Yes	Yes	Yes
778	1417	Rofecoxib 25 mg	17MAR99	1444	1016	Transient Ischemic Attack	Other event	No	No	No	Yes
199	1419	Rofecoxib 25 mg	03MAR99	688	261	Coronary artery occlusion	Other event	No	No	No	Yes
580	1419	Rofecoxib 25 mg	03MAR99	688	676	Chronic lymphocytic leukemia	Other event	No	No	No	No
572	1423	Rofecoxib 25 mg	28MAY99	611	611	Chest trauma	Other event	No	No	No	No
678	1445	Placebo	20FEB99	884	884	Intracranial hemorrhage	Fatal hemorrhagic stroke	No	No	Yes	Yes
560	1453	Rofecoxib 25 mg	11MAY99	36	36	Bacterial sepsis, Acute myelogenous leukemia	Other event	No	No	No	No
516	1458	Placebo	25JUN99	824	519	Angina pectoris	Unstable angina pectoris	No	Yes	No	Yes
660	1472	Placebo	11AUG99	607	591	Metastatic neoplasm of unknown primary	Other event	No	No	No	No
790	1475	Placebo	31MAR99	918	1069	Therapeutic agent poisoning, Renal impairment NOS	Other event	No	No	No	No
929	1478	Rofecoxib 25 mg	15DEC98	1184	1185	Angina pectoris	Unstable angina pectoris	No	Yes	No	Yes
822	1481	Rofecoxib 25 mg	16JUN99	1346	1091	Coronary artery disease NOS	Other event	No	No	No	Yes
895	1506	Rofecoxib 25 mg	07MAR00	1029	1030	Pancreatic neoplasm NOS	Other event	No	No	No	No
894	1525	Placebo	30MAR00	819	758	Coronary artery disease NOS	Other event	No	No	No	Yes
854	1530	Rofecoxib 25 mg	01DEC99	33	1017	Myocardial infarction	Fatal acute myocardial infarction	No	Yes[†]	Yes[†]	Yes[†]
798	1535	Placebo	03MAR00	782	783	Coronary artery disease NOS	Other event	No	No	No	Yes
886	1543	Placebo	01APR00	954	967	Acute respiratory failure	Other event	No	No	Yes	Yes
320	1547	Placebo	27JAN00	84	36	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
568	1547	Placebo	27JAN00	84	93	Adenocarcinoma of unknown primary	Other event	No	No	No	No
539	1559	Placebo	01DEC99	470	428	Coronary artery occlusion	Other event	No	No	No	Yes
353	1573	Rofecoxib 25 mg	11MAR00	24	24	Thrombosis	Other event	No	No	No	Yes
789	1577	Rofecoxib 25 mg	16MAR00	707	707	Myocardial infarction	Sudden cardiac death	Yes	Yes	Yes	Yes
440	1588	Placebo	03FEB00	1097	189	Coronary artery disease NOS	Unstable angina pectoris	No	Yes	No	Yes
364	1592	Rofecoxib 25 mg	09DEC99	126	126	Coronary artery disease	Other event	No	No	No	Yes
503	1613	Placebo	24FEB00	519	306	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes

Table 89 (Cont.)

Listing of Cardiovascular Events Intention-to-Treat Population

Case ID	AN	Treatment	Random Date	Last Day on Treatment	Event Day	Investigator Reported Term	Adjudication Term	Throm. Card. Mort.	Conf. Throm. Events	APTC	Invt. Rpt. Throm.
342	1651	Placebo	21JAN00	474	64	Transient ischemic attack	Transient ischemic attack	No	Yes	No	Yes
422	1664	Placebo	18MAR00	1025	117	Coronary arery disease NOS	Other event	No	No	No	Yes
695	1666	Placebo	16FEB00	554	555	Cerebrovascular accident	Ischemic cerebrovascular stroke	No	Yes	Yes	Yes
504	1695	Placebo	28MAR00	1071	237	Transient ischemic attack	Other event	No	No	No	Yes

† Was excluded from counts and analyses because event occurred greater than 14 days after the last dose of study medication.
‡ Was excluded from the analysis due to multiple events.
AN = Allocation number
Throm. Card. Mort. = Thrombotic Cardiovascular Mortality
Conf. Thromb. Events = Confirmed Thrombotic Events
APTC = Antiplatelet Trialists' Collaboration
Invt. Rpt. Throm. = Investigator -Reported Thrombotic Events

Data Source: [4.2;4.7]

Table 90

Listing of GI Clinical Events and Adjudicated Results
Intention-to-Treat Population

Patient Baseline Number	Allocation Number	PI Reported Event	Adjudicated Result
Rofecoxib 25 mg On-Drug Events			
001059	0667	Gastric ulcer	Gastric ulcer unconfirmed, uncomplicated
033010	1025	Bleeding gastric ulcer	Gastric ulcer confirmed (criteria - endoscopy, autopsy), complicated (criteria - confirmed UGIB 1) Upper GI-hemorrhage confirmed (criteria - witnessed hematemesis; source - gastric ulcer), complicated (criteria - sig. blood loss)
009056	0287	Stool black	Gastric ulcer confirmed (criteria - endoscopy), complicated (criteria - confirmed UGIB 2) Upper GI-hemorrhage confirmed (criteria - witnessed melena; source - gastric ulcer), uncomplicated
012030	0366	Duodenal ulcer Bleeding duodenal ulcer	Duodenal ulcer confirmed (criteria - endoscopy), uncomplicated Upper GI-hemorrhage confirmed (criteria - heme-pos. stool + UGI lesion, patient hematemesis/ melena + UGI lesion; source - duodenal ulcer), complicated (criteria - sig. blood loss)
013047	0394	Upper GI hemorrhage	Upper GI-hemorrhage confirmed (criteria - documented melena; source - unknown), uncomplicated
014017	0425	Bleeding gastric ulcer	Gastric ulcer confirmed (criteria - endoscopy), complicated (criteria - confirmed UGIB 1) Upper GI-hemorrhage confirmed (criteria - heme-pos. stool + UGI lesion; source - gastric ulcer), complicated (criteria - sig. blood loss)
014025	0352	Bleeding duodenal ulcer	Duodenal ulcer confirmed (criteria - endoscopy), complicated (criteria - confirmed UGIB 2, confirmed UGIB 3) Upper GI-hemorrhage confirmed (criteria - witnessed melena, documented active bleed, heme-pos stool + UGI lesion, patient hematemesis/ melena + UGI lesion; source - duodenal ulcer), complicated (criteria - sig. blood loss)
023024	0681	Mallory-Weiss tear	Upper GI-hemorrhage confirmed (criteria - documented hematemesis), uncomplicated
023080	0690	Pyloric ulcer GI bleeding	Duodenal ulcer confirmed (criteria - endoscopy), uncomplicated Upper GI-hemorrhage confirmed (criteria - patient hematemesis/ melena + UGI lesion; source - duodenal ulcer), complicated (criteria - sig. blood loss)

Table 90 (Cont.)

Listing of GI Clinical Events and Adjudicated Results
Intention-to-Treat Population

Patient Baseline Number	Allocation Number	PI Reported Event	Adjudicated Result
024079	1311	Fecal occult blood positive	Upper GI-hemorrhage unconfirmed, complicated (criteria - sig. blood loss)
025106	0826	Duodenal ulcer	Duodenal ulcer confirmed (criteria - endoscopy), uncomplicated
027025	0851	Duodenal ulcer Fecal occult blood positive	Duodenal ulcer confirmed (criteria - endoscopy), uncomplicated Upper GI-hemorrhage confirmed (criteria - heme-pos stool + UGI lesion; source - duodenal ulcer), complicated (criteria - sig. blood loss)
035040	1650	Gastric ulcer Fecal occult blood positive	Gastric ulcer confirmed (criteria - endoscopy), uncomplicated Upper GI-hemorrhage confirmed (criteria - heme-pos stool + UGI lesion; source - gastric ulcer), complicated (criteria - sig. blood loss)
037002	1153	Hematemesis	Upper GI-hemorrhage confirmed (criteria - witnessed hematemesis), uncomplicated
039022	1221	Gastric ulcer Upper GI hemorrhage	gastric ulcer confirmed (criteria - endoscopy), complicated (criteria - confirmed UGIB 1) Upper GI-hemorrhage confirmed (criteria - witnessed hematemesis, patient hematemesis/ melena + UGI lesion; source - gastric ulcer), complicated (criteria - sig. blood loss)
043028	1360	Esophageal ulcer/ Melena	Upper GI-hemorrhage confirmed (criteria - witnessed melena, heme-pos stool + UGI lesion, patient hematemesis/ melena + UGI lesion; source - esophageal ulcer), complicated (criteria - sig. blood loss)
Rofecoxib 25 mg Off-Drug Events			
004056	0112	Gastric erosions /Gastric ulcer	Gastric ulcer confirmed (criteria - endoscopy), uncomplicated
023103	0478	GI bleeding	Upper GI-hemorrhage confirmed (criteria - heme-pos stool + UGI lesion; source - angiodysplasia), complicated (criteria - sig. blood loss)
027025	0851	GI bleeding	Upper GI-hemorrhage confirmed (criteria - witnessed melena, heme-pos stool + UGI lesion, patient hematemesis/ melena + UGI lesion), complicated (criteria - sig. blood loss)
034101	1087	Esophagitis ulcerative/ Melena	Upper GI-hemorrhage confirmed (criteria - heme-pos stool + UGI lesion, patient hematemesis/ melena + UGI lesion; source - erosive esophagitis), complicated (criteria - sig. blood loss)

Table 90 (Cont.)

Listing of GI Clinical Events and Adjudicated Results
Intention-to-Treat Population

Patient Baseline Number	Allocation Number	PI Reported Event	Adjudicated Result
Placebo On-Drug Events			
004044	0117	Bloody diarrhea	Upper GI-hemorrhage not a UGI event
007062	1547	Gastric ulcer Upper GI hemorrhage	Gastric ulcer confirmed (criteria - endoscopy), complicated (criteria - confirmed UGIB 1, confirmed UGIB 2) Upper GI-hemorrhage confirmed (criteria - witnessed hematemesis, witnessed melena, heme-pos stool + UGI lesion; source - gastric ulcer), complicated (criteria - sig. blood loss)
008095	1689	Hematemesis	Upper GI-hemorrhage unconfirmed, uncomplicated
012009	0360	Duodenal ulcer perforation Duodenal ulcer perforation	Duodenal ulcer confirmed (criteria - surgery), uncomplicated Gastric or duodenal perforation confirmed (criteria - surgery, radiology), complicated
013059	0411	Gastric ulcer Bleeding gastric ulcer/ esophageal ulcer hemorrhage	Gastric ulcer confirmed (criteria - endoscopy), uncomplicated Upper GI-hemorrhage confirmed (criteria - heme-pos stool + UGI lesion; source - esophageal ulcer, gastric ulcer), complicated (criteria - sig. blood loss)
019034	0600	Upper GI hemorrhage	Upper GI-hemorrhage unconfirmed, uncomplicated
026061	1245	Gastric ulcer /Gastric erosions	Gastric ulcer confirmed (criteria - endoscopy), uncomplicated
Placebo Off-Drug Events			
008017	0232	Gastric ulcer	Gastric ulcer confirmed (criteria - endoscopy), uncomplicated
014013	0426	Mallory-Weiss tear	Upper GI-hemorrhage confirmed (criteria - witnessed hematemesis, patient hematemesis/ melena + UGI lesion; source - Mallory-Weiss tear), uncomplicated
025095	0832	Duodenal ulcer	Duodenal ulcer confirmed (criteria - endoscopy), uncomplicated
047009	1475	Duodenal ulcer GI bleeding	duodenal ulcer confirmed (criteria - endoscopy), uncomplicated Upper GI-hemorrhage not a UGI event-certain or highly probable lower GI bleeding
013236	1599	GI bleeding	Upper GI-hemorrhage unconfirmed, complicated (criteria - sig. blood loss)

Data Source: [4.2;4.7]

Table 91

Listing of Patients With Osteoporosis and Osteopenia
On-Drug†

Study Number	Allo-cation	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontin-uance	Intensity	Serious	Drug Relationship	Action Taken	Outcome
Treatment Group: Rofecoxib 25mg															
078004	118	M	White	83	MK-0966	25.00 mg	496	Osteoporosis	CONT	1099	Mod	N	Def. not	No action with test drug	Not recovered
078004	1015	M	White	82	MK-0966	25.00 mg	99	Osteoporosis	CONT	395	Mild	N	Prob not	No action with test drug	Not recovered
078006	178	F	White	77	MK-0966	25.00 mg	684	Osteoporosis	CONT	1462	Mod	N	Def not	No action with test drug	Not recovered
078007	886	F	White	83	MK-0966	25.00 mg	525	Osteoporosis	CONT	881	Mild	N	Prob not	No action with test drug	Not recovered
078007	887	F	White	76	MK-0966	25.00 mg	133	Osteoporosis	CONT	1327	Mod	N	Def not	No action with test drug	Not recovered
078008	1531	F	White	83	MK-0966	25.00 mg	466	Osteoporosis	CONT	1194	Mild	N	Def not	No action with test drug	Not recovered
078010	299	F	White	75	MK-0966	25.00 mg	94	Osteoporosis	CONT	288	Mod	N	Prob not	No action with test drug	Not recovered
078013	414	M	White	70	MK-0966	25.00 mg	855	Osteopenia	CONT	1307	Mild	N	Def not	no action With test drug	Not recovered

Table 91 (Cont.)

Listing of Patients With Osteoporosis and Osteopenia
On-Drug†

Study Number	Allo-cation	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontin-uance	Intensity	Serious	Drug Relationship	Action Taken	Outcome
078021	619	M	White	77	MK-0966	25.00 mg	97	Osteoporosis	CONT	371	Mod	N	Def not	No action with test drug	Not recovered
078021	622	F	White	80	MK-0966	25.00 mg	15	Osteoporosis	CONT	263	Mod	N	Def not	No action with test drug	Not recovered
078021	624	F	White	78	MK-0966	25.00 mg	188	Osteoporosis	CONT	1322	Mod	N	Def not	No action with test drug	Not recovered
078023	702	M	White	76	MK-0966	25.00 mg	499	Osteoporosis	CONT	1080	Mild	N	Def not	No action with test drug	Not recovered
078025	831	F	White	86	MK-0966	25.00 mg	974	Osteoporosis	CONT	1115	Mild	N	Def not	No action with test drug	Not recovered
078026	1199	F	White	77	MK-0966	25.00 mg	16	Osteoporosis	CONT	554	Mod	N	Def not	No action with test drug	Not recovered
078032	1003	F	White	69	MK-0966	25.00 mg	534	Osteoporosis	CONT	1484	Mod	N	Prob not	No action with test drug	Not recovered
078035	1587	M	White	71	MK-0966	25.00 mg	171	Osteoporosis	CONT	1094	Mild	N	Prob not	No action with test drug	Not recovered
078039	1224	M	White	84	MK-0966	25.00 mg	738	Osteoporosis	CONT	1245	Mild	N	Def not	No action with test drug	Not recovered

Table 91 (Cont.)

Listing of Patients With Osteoporosis and Osteopenia
On-Drug†

Study Number	Allo-cation	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontin-uance	Intensity	Serious	Drug Relationship	Action Taken	Outcome
078045	881	M	White	75	MK-0966	25.00 mg	429	Osteoporosis	CONT	733	Mod	N	Def not	No action with test drug	Not recovered
078045	1413	F	White	72	MK-0966	25.00 mg	718	Osteoporosis	CONT	915	Mod	N	Def not	No action with test drug	Not recovered
078046	1441	F	White	86	MK-0966	25.00 mg	116	Osteoporosis	CONT	116	Severe	N	Def not	No action with test drug	Not recovered
078046	1451	F	White	75	MK-0966	25.00 mg	148	Osteoporosis	CONT	1213	Mild	N	Def not	No action with test drug	Not recovered
Treatment Group: Placebo															
078002	55	F	White	80	Placebo	0.00 mg	707	Osteoporosis	CONT	742	Mild	N	Def not	No action with test drug	Not recovered
078006	910	M	White	87	Placebo	0.00 mg	99	Osteoporosis	CONT	99	Severe	N	Def not	No action with test drug	Not recovered
078013	432	F	White	65	Placebo	0.00 mg	164	Osteoporosis	CONT	683	Mild	N	Def not	No action with test drug	Not recovered
078017	514	F	White	70	Placebo	0.00 mg	301	Osteoporosis	CONT	674	Mild	N	Prob not	No action with test drug	Not recovered

Table 91 (Cont.)

Listing of Patients With Osteoporosis and Osteopenia
On-Drug[†]

Study Number	Allo-cation	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontin-uance	Intensity	Serious	Drug Relationship	Action Taken	Outcome
078021	1586	F	White	82	Placebo	0.00 mg	78	Osteoporosis	CONT	547	Mild	N	Def not	No action with test drug	Not recovered
078021	1684	F	White	69	Placebo	0.00 mg	133	Osteoporosis	CONT	1107	Mild	N	Def not	No action with test drug	Not recovered
078025	749	F	White	82	Placebo	0.00 mg	824	Osteoporosis	CONT	1453	Mild	N	Def not	No action with test drug	Not recovered
078036	1130	F	White	71	Placebo	0.00 mg	596	Osteoporosis	CONT	771	Mild	N	Def not	No action With test drug	Not recovered
078037	1159	F	White	75	Off Drug 1 day		889	Osteoporosis	CONT	1472	Mild	N	Def not	No action with test drug	Not recovered
078040	1215	F	White	84	Placebo	0.00 mg	943	Osteopenia	CONT	1198	Mod	N	Prob not	No action with test drug	Not recovered
078046	1447	M	White	74	Placebo	0.00 mg	950	Osteopenia	CONT	1427	Mild	N	Def not	No action with test drug	Not recovered

[†] On drug includes the period through 14 days after discontinuation of study drug.
CONT = Continuing
N = Not serious
Def Not = Definitely not
Prob not = Probably not

Data Source: [4.2]

Table 92

Patients Exceeding the Predefined Limits of Change
(Neuropharmacology Division Criteria)
On Drug[†]

Laboratory Test	Predefined Limit of Change[‡]	Treatment	Number[§] / Total[‖] (%)
WBC count (10[3]/microL)	Value ≤0.642 * LLN	Rofecoxib 25 mg	5/722 (0.7)
		Placebo	1/728 (0.1)
	Value ≥1.49 * ULN	Rofecoxib 25 mg	7/722 (1.0)
		Placebo	4/728 (0.5)
Eosinophil count (10[3]/microL)	Value ≥1.47 * ULN	Rofecoxib 25 mg	13/722 (1.8)
		Placebo	19/728 (2.6)
Hematocrit (%) F	Value ≤0.941 * LLN	Rofecoxib 25 mg	6/247 (2.4)
		Placebo	6/225 (2.7)
Hematocrit (%) M	Value ≤0.949 * LLN	Rofecoxib 25 mg	37/475 (7.8)
		Placebo	29/503 (5.8)
Hemoglobin (gm/dL) F	Value ≤0.819 * LLN	Rofecoxib 25 mg	2/247 (0.8)
		Placebo	2/225 (0.9)
Hemoglobin (gm/dL) M	Value ≤0.905 * LLN	Rofecoxib 25 mg	14/475 (2.9)
		Placebo	11/503 (2.2)
Neutrophil count (10[3]/microL)	Value ≤0.37 * LLN	Rofecoxib 25 mg	2/722 (0.3)
		Placebo	0/728 (0.0)
Platelet count (10[3]/microL)	Value ≤0.577 * LLN	Rofecoxib 25 mg	7/722 (1.0)
		Placebo	6/728 (0.8)
	Value ≥1.777 * ULN	Rofecoxib 25 mg	1/722 (0.1)
		Placebo	0/728 (0.0)
Serum alanine aminotransferase (IU[aminotransferase]/L)	Value ≥3 * ULN	Rofecoxib 25 mg	7/723 (1.0)
		Placebo	1/728 (0.1)
Serum alkaline phosphatase (IU[alk phos]/L)	Value ≥3 * ULN	Rofecoxib 25 mg	1/723 (0.1)
		Placebo	0/728 (0.0)
Serum aspartate aminotransferase (IU[aminotransferase]/L)	Value ≥3 * ULN	Rofecoxib 25 mg	3/723 (0.4)
		Placebo	0/728 (0.0)
Serum creatinine (mg/dL)	Value ≥1.429 * ULN	Rofecoxib 25 mg	17/723 (2.4)
		Placebo	0/728 (0.0)

Table 92 (Cont.)

Patients Exceeding the Predefined Limits of Change
(Neuropharmacology Division Criteria)
On Drug[†]

Laboratory Test	Predefined Limit of Change[‡]	Treatment	Number[§] / Total[‖] (%)
Serum potassium (mEq[K]/L)	Value ≤0.882 * LLN	Rofecoxib 25 mg	0/723 (0.0)
		Placebo	1/728 (0.1)
Serum potassium (mEq[K]/L)	Value ≥1.111 * ULN	Rofecoxib 25 mg	13/723 (1.8)
		Placebo	6/728 (0.8)
Serum sodium (mEq[Na]/L)	Value ≤0.947 * LLN	Rofecoxib 25 mg	2/723 (0.3)
		Placebo	1/728 (0.1)
	Value ≥1.054 * ULN	Rofecoxib 25 mg	0/723 (0.0)
		Placebo	2/728 (0.3)
Total serum bilirubin (mg/dL)	Value ≥1.667 * ULN	Rofecoxib 25 mg	6/723 (0.8)
		Placebo	2/728 (0.3)

ULN = Upper limit of normal range. LLN = Lower limit of normal range.
† On drug includes the period through 14 days after discontinuation of study drug.
‡ Increases and decreases are compared with baseline, which is defined as the last laboratory test value prior to the first randomized dose.
§ Number of patients meeting the predefined limit criteria.
‖ Total number of patients with valid values of the laboratory test for the given treatment group.

Data Source: [3.4; 4.2]

Table 93

Patients Exceeding the Predefined Limits of Change
(Neuropharmacology Division Criteria)
Intention-to-Treat

Laboratory Test	Predefined Limit of Change[†]	Treatment	Number[‡]/ Total[§] (%)
WBC count (10[3]/microL)	Value ≤0.642 * LLN	Rofecoxib 25 mg	5/722 (0.7)
		Placebo	3/728 (0.4)
	Value ≥1.49 * ULN	Rofecoxib 25 mg	8/722 (1.1)
		Placebo	5/728 (0.7)
Eosinophil count (10[3]/microL)	Value ≥1.47 * ULN	Rofecoxib 25 mg	16/722 (2.2)
		Placebo	20/728 (2.7)
Hematocrit (%) F	Value ≤0.941 * LLN	Rofecoxib 25 mg	10/247 (4.0)
		Placebo	7/225 (3.1)
Hematocrit (%) M	Value ≤0.949 * LLN	Rofecoxib 25 mg	43/475 (9.1)
		Placebo	41/503 (8.2)
Hemoglobin (gm/dL) F	Value ≤0.819 * LLN	Rofecoxib 25 mg	3/247 (1.2)
		Placebo	3/225 (1.3)
Hemoglobin (gm/dL) M	Value ≤0.905 * LLN	Rofecoxib 25 mg	21/475 (4.4)
		Placebo	16/503 (3.2)
Neutrophil count (10[3]/microL)	Value ≤0.37 * LLN	Rofecoxib 25 mg	4/722 (0.6)
		Placebo	0/728 (0.0)
Platelet count (10[3]/microL)	Value ≤0.577 * LLN	Rofecoxib 25 mg	7/722 (1.0)
		Placebo	6/728 (0.8)
	Value ≥1.777 * ULN	Rofecoxib 25 mg	1/722 (0.1)
		Placebo	0/728 (0.0)
Serum alanine aminotransferase (IU[aminotransferase]/L)	Value ≥3 * ULN	Rofecoxib 25 mg	7/723 (1.0)
		Placebo	2/728 (0.3)
Serum alkaline phosphatase (IU[alk phos]/L)	Value ≥3 * ULN	Rofecoxib 25 mg	1/723 (0.1)
		Placebo	0/728 (0.0)
Serum aspartate aminotransferase (IU[aminotransferase]/L)	Value ≥3 * ULN	Rofecoxib 25 mg	3/723 (0.4)
		Placebo	0/728 (0.0)
Serum creatinine (mg/dL)	Value ≥1.429 * ULN	Rofecoxib 25 mg	19/723 (2.6)
		Placebo	2/728 (0.3)

Table 93 (Cont.)

Patients Exceeding the Predefined Limits of Change
(Neuropharmacology Division Criteria)
Intention-to-Treat

Laboratory Test	Predefined Limit of Change†	Treatment	Number‡/ Total§ (%)
Serum potassium (mEq[K]/L)	Value ≤0.882 * LLN	Rofecoxib 25 mg	0/723 (0.0)
		Placebo	1/728 (0.1)
Serum potassium (mEq[K])/L)	Value ≥1.111 * ULN	Rofecoxib 25 mg	14/723 (1.9)
		Placebo	8/728 (1.1)
Serum sodium (mEq[Na]/L)	Value ≤0.947 * LLN	Rofecoxib 25 mg	2/723 (0.3)
		Placebo	1/728 (0.1)
	Value ≥1.054 * ULN	Rofecoxib 25 mg	0/723 (0.0)
		Placebo	2/728 (0.3)
Total serum bilirubin (mg/dL)	Value ≥1.667 * ULN	Rofecoxib 25 mg	6/723 (0.8)
		Placebo	2/728 (0.3)

ULN = Upper limit of normal range. LLN = Lower limit of normal range.
† Increases and decreases are compared with baseline, which is defined as the last laboratory test value prior to the first randomized dose.
‡ Number of patients meeting the predefined limit criteria.
§ Total number of patients with valid values of the laboratory test for the given treatment group.

Data Source: [3.4; 4.2]

12. LIST OF APPENDICES

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* Refer to Case Report Tabulations

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