Safety Update Report

P1.0023

TABLE OF CONTENTS

	PAGE
List of Tables	3
List of Figures	6
1. Overview	7
1.1 Organization of the Document	9
2. Update of Serious Clinical Adverse Experiences—All Body Systems	9
2.1 Update of Serious Clinical Adverse Experiences in Osteoarthritis Extension Studies	13
2.1.1 Long-Term Exposure OA Protocols 029, 034, 035	14
2.1.2 Elderly OA Protocol 058	25
2.2 Update of Serious Clinical Adverse Experiences in Studies Not Previously Submitted	31
2.2.1 Alzheimer's Disease—Protocol 091	31
2.2.1.1 Design	31
2.2.1.2 Extent of Exposure	32
2.2.1.3 Fatal and Nonfatal Serious Adverse Experiences	33
2.2.2 Alzheimer's Disease—Protocol 078	42
2.2.2.1 Design	42
2.2.2.2 Extent of Exposure	42
2.2.2.3 Fatal and Nonfatal Serious Adverse Experiences	43
2.2.3 Alzheimer's Disease—Protocol 126	50
2.2.3.1 Design	50
2.2.3.2 Extent of Exposure	50
2.2.3.3 Fatal and Nonfatal Serious Adverse Experiences	51
2.2.4 Protocols 078, 091, and 126 Combined	55
2.2.5 Bone Mineral Density—Protocol 083	57
2.2.5.1 Design	57
2.2.5.2 Extent of Exposure	58
2.2.5.3 Fatal and Nonfatal Serious Adverse Experiences	59
2.2.6 Chronic Prostatitis—Protocol 118	61
2.2.6.1 Design	61
2.2.6.2 Extent of Exposure	62
2.2.6.3 Fatal and Nonfatal Serious Adverse Experiences	62
2.2.7 Chronic Low Back Pain—Protocols 120 and 121	63
2.2.7.1 Design	63
2.2.7.2 Extent of Exposure	64
2.2.7.3 Fatal and Nonfatal Serious Adverse Experiences	65
2.2.8 Naproxen Comparison—Protocol 901	67
2.2.8.1 Design	67
2.2.8.2 Extent of Exposure	69
2.2.8.3 Fatal and Nonfatal Serious Adverse Experiences	69
2.2.9 ARTHROTEC™ Comparison—Protocol 902	71
2.2.9.1 Design	71

TABLE OF CONTENTS (CONT.)

	PAGE
2.2.9.2 Extent of Exposure	72
2.2.9.3 Fatal and Nonfatal Serious Adverse Experiences	72
2.2.10 Summary	73
3. Update of Thrombotic Cardiovascular Serious Adverse Experiences	74
3.1 Outline of Studies Included	75
3.1.1 Statistical Methods	76
3.1.2 Classifications of Events	77
3.2 New Information from Placebo-Controlled Protocols	77
3.2.1 Alzheimer's Disease Studies—APTC, Confirmed, and Investigator Reported	77
3.2.2 Prostatitis Study	85
3.3 New Information from Protocols Versus Non-Naproxen NSAIDs	85
3.3.1. Update on Phase IIb/III Osteoarthritis Studies—Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences and APTC Endpoints	85
3.4 Updated Meta-Analysis of Cardiovascular Events	89
3.4.1 Meta-Analysis of APTC Endpoint	90
3.5 Summary	99
4. Discussion	99
4.1 Adverse Experiences Associated with NSAIDs	100
4.2 Serious Cardiovascular Thromboembolic Adverse Experiences	102
4.3 Summary	105
5. Conclusions	105
References	--

LIST OF TABLES

		PAGE
Table 1	Summary of Studies Included in Update of Serious Clinical Adverse Experiences	10
Table 2	Number of Patients on Treatment by Dose—All Studies Included in Update of Serious Clinical Adverse Experiences	12
Table 3	Number of Patients on Study Drug by Dose and Actual Duration of Treatment Long-Term Exposure Osteoarthritis Studies Cumulative Data	15
Table 4	Number (%) of Patients With Serious Clinical Adverse Experiences by Body System (Incidence ≥0.5% in One or More Cumulative Treatment Groups)—Long-Term Exposure Osteoarthritis Studies	17
Table 5	Number (%) of Patients With Serious Clinical Adverse Experiences by Body System (Incidence ≥0.5% in One or More Cumulative Treatment Groups)—Long-Term Exposure Osteoarthritis Studies Including First 6 Months of Treatment—(Comprehensive Data)	21
Table 6	Listing of Deaths in Protocols 029, 034, 035	24
Table 7	Number of Patients on Study Drug by Dose and Actual Duration of Treatment Elderly OA Study Cumulative Data	26
Table 8	Number (%) of Patients With Serious Clinical Adverse Experiences by Body System (≥2 Patients in Any Treatment Group) Elderly Osteoarthritis Study—Cumulative Data	28
Table 9	Listing of Deaths in Elderly Osteoarthritis Study (Protocol 058)	30
Table 10	Baseline Demographics by Treatment Group—Protocol 091	32
Table 11	Number of Days on Therapy by Treatment—Protocol 091	32
Table 12	Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.5% in One or More Treatment Groups) by Body System—Protocol 091	34
Table 13	Listing of Deaths by Treatment Group—Protocol 091	37
Table 14	Number of Days on Therapy by Treatment—Protocol 078	42
Table 15	Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.5% in One or More Treatment Groups) by Body System—Protocol 078	44
Table 16	Listing of Deaths by Treatment Group—Protocol 078	47
Table 17	Number of Days on Therapy by Treatment—Protocol 126	50
Table 18	Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.5% in One or More Treatment Groups) by Body System—Protocol 126	52
Table 19	Listing of Deaths by Treatment Group—Protocol 126	54

LIST OF TABLES (CONT.)

		PAGE
Table 20	Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.3% in One or More Treatment Groups) by Body System—Protocols 078, 091, and 126	55
Table 21	Baseline Demographics by Treatment Group—Protocol 083	58
Table 22	Number of Patients on Study Drug—Protocol 083	58
Table 23	Numbers (%) of Patients With Fatal and Nonfatal Clinical Serious Adverse Experiences—Protocol 083	59
Table 24	Baseline Demographics by Treatment Group—Protocol 118	61
Table 25	Number of Days on Therapy by Treatment—Protocol 118	62
Table 26	Number (%) of Patients With Serious Clinical Adverse Experiences—Protocol 118	62
Table 27	Baseline Patient Characteristics—Chronic Low Back Pain Studies (Protocols 120 and 121—Treatment Groups in Each Protocol Combined)	64
Table 28	Number of Days on Treatment—Chronic Low Back Pain Studies (Protocols 120 and 121 Combined)	64
Table 29	Listing of Patients With Serious Clinical Adverse Experiences Chronic Low Back Pain Studies (Protocols 120 and 121 Combined)	66
Table 30	Baseline Demographics by Treatment Group—Protocol 901	68
Table 31	Number of Days on Therapy by Treatment—Protocol 901	69
Table 32	Number (%) of Patients With Serious Clinical Adverse Experiences by Body System—Protocol 901	70
Table 33	Baseline Demographics by Treatment Group—Protocol 902	71
Table 34	Number of Days on Therapy by Treatment—Protocol 902	72
Table 35	Numbers and Percentages of Patients With Fatal and Nonfatal Serious Clinical Adverse Experiences for Each Treatment Group—Protocol 902	73
Table 36	Studies Included in this Cardiovascular Safety Analysis	76
Table 37	APTC Endpoint Rofecoxib Versus Placebo in Alzheimer's Disease Protocols Updated Results Using Adjudicated Data	79
Table 38	Summary of APTC Events by Type of Event Adjudicated Data—Alzheimer's Disease Protocols)	80
Table 39	Confirmed Thrombotic Cardiovascular Serious Adverse Experiences Rofecoxib Versus Placebo in Alzheimer's Disease Protocols Updated Results	81
Table 40	Summary of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences by Type of Event—Alzheimer's Disease Protocols	82

LIST OF TABLES (CONT.)

		PAGE
Table 41	Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences Rofecoxib Versus Placebo in Alzheimer's Disease Protocols Updated Results	83
Table 42	Summary of Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences by Type of Event—Alzheimer's Disease Protocols	84
Table 43	APTC Endpoint in OA-069 Rofecoxib Versus Non-Naproxen NSAIDs Updated Results	86
Table 44	Summary of APTC Events in OA-069	87
Table 45	Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences in OA-069 Rofecoxib Versus Non-Naproxen NSAIDs Updated Results	88
Table 46	Summary of Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences in OA-069	89
Table 47	Meta-Analysis of APTC Endpoint Rofecoxib Versus Non-Naproxen NSAIDs Updated Results	91
Table 48	Summary of APTC Endpoints by Type of Event Rofecoxib Versus Non-Naproxen NSAIDs	92
Table 49	Meta-Analysis of APTC Endpoint Rofecoxib Versus Non-Naproxen NSAIDs by Individual Comparator Updated Results	93
Table 50	Meta-Analysis of APTC Endpoint Rofecoxib Versus Placebo—Updated Results	95
Table 51	Summary of APTC Endpoints by Type of Event Rofecoxib Versus Placebo	96
Table 52	Meta-Analysis of APTC Endpoint Rofecoxib Versus Non-Naproxen NSAIDs Original Meta-Analysis (Submitted Jan-2001)	97
Table 53	Meta-Analysis of APTC Endpoint Rofecoxib Versus Placebo Original Meta-Analysis (Submitted Jan-2001)	98

LIST OF FIGURES

PAGE

There are no figures in this document.

1. Overview

Rofecoxib (MK-0966) is a cyclooxygenase-2 (COX-2) selective inhibitor (C-2SI) that is approved for the relief of the signs and symptoms of osteoarthritis (at chronic doses of 12.5 to 25 mg daily) and for the treatment of acute pain and dysmenorrhea (at a dose of 50 mg daily in studies up to 5 days). This Safety Update Report (SUR), with a data cutoff of 16-Mar-2001, summarizes the additional safety data accrued since the Original Marketing Application and the first SUR (data cutoff of 04-Sep-1998). The Original Marketing Application (hereafter referred to as the Original Application) demonstrated a generally favorable safety profile for rofecoxib. The aggregate of data in the Original Application was consistent with rofecoxib having an overall safety profile similar to nonsteroidal anti-inflammatory drugs (NSAIDs) but a gastrointestinal (GI) safety profile superior to NSAIDs, confirming a specific hypothesis of the rofecoxib program. The results of the VIOXX™[1] Gastrointestinal Outcomes Research (VIGOR) study confirmed that rofecoxib has a GI safety profile superior to naproxen, a nonselective NSAID. The safety profile for the 50-mg dose of rofecoxib (twice the maximum recommended chronic dose) demonstrated in VIGOR was similar to that in the Original Application and consistent with the current labeling. In the VIGOR study, however, the rate of confirmed thrombotic cardiovascular serious adverse experiences was lower with naproxen than with rofecoxib (0.70 per 100 patient-years compared to 1.67 per 100 patient-years). In order to further evaluate whether rofecoxib is associated with an increased risk of cardiovascular events, a meta-analysis of the available cardiovascular safety data was conducted and submitted to the U.S. Food and Drug Administration (FDA) in Jan-2001. This interim meta-analysis did not reveal a significant difference in the incidence of thrombotic cardiovascular events between rofecoxib and placebo or non-naproxen NSAIDs.

The present SUR has been prepared in response to the approvable letter dated 06-Apr-2001. FDA requested additional data before final action is taken on the VIGOR supplemental New Drug Application (sNDA). The focus of this SUR is 2-fold:

- Summarize the serious clinical adverse experiences with rofecoxib in clinical studies which have accrued since the SUR for the Original Application. Data from recently completed extensions of 4 previously reported Phase IIb/III OA trials and 9 new trials are presented. Complete data from the VIGOR, Assessment of Differences Between VIOXX™ and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness (ADVANTAGE), and the 2 Nabumetone Comparator Studies were previously submitted and are therefore not re-summarized in this SUR. Also, this SUR does not contain data from the Rheumatoid Arthritis Studies that were summarized in a separate Marketing Application and SUR for that application. This SUR, in addition to the VIGOR sNDA, the ADVANTAGE Clinical Study Report, and the Rheumatoid Arthritis sNDA and SUR, summarizes safety data on completed rofecoxib studies of more than 4 weeks in duration. As agreed upon by the FDA, the only exceptions to this are Clinical Pharmacology Studies and 3 relatively short-term studies (4 to

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

1. Overview (Cont.)

- 6 weeks) in which the efficacy of rofecoxib and celecoxib were compared (Protocols 106, 112, 116). Their exclusion from this SUR represents less than a 3% reduction of the database (as measured by patient-years of exposure) that was used in the preparation of this SUR.

- Update the cardiovascular safety profile of rofecoxib. The cardiovascular safety of rofecoxib was specifically addressed in the Original Application, VIGOR submission, the first VIGOR SUR, interim cardiovascular meta-analysis, and ADVANTAGE study report. This SUR summarizes the cardiovascular safety data obtained from clinical trials other than VIGOR and ADVANTAGE during the SUR period (05-Sep-1998 through 16-Mar-2001). An updated meta-analysis based on data from the Application through 16-Mar-2001 is also presented and focuses on the comparison of rofecoxib to placebo and to non-naproxen NSAIDs. This updated meta-analysis does not include new events in naproxen-controlled studies since the only new events come from extensions to the ongoing Phase IIb/III RA Studies. The number of additional events (5) and patient-years was quite small compared to the original meta-analysis which included VIGOR, ADVANTAGE, and events in the RA program at the time of the RA sNDA. The analyses comparing rofecoxib to placebo and to non-naproxen NSAIDs now include data from 23 clinical trials of rofecoxib, including the 13 studies with new safety data discussed in this SUR, with over 14,000 patients and 7000 patient-years on study medication (safety data from the other 10 studies were previously submitted).

Key findings of note in this report are as follows:

- The cumulative safety data available through 16-Mar-2001 are consistent with the originally reported safety profile and that reported in the VIGOR submission.

- The Long-Term Exposure Osteoarthritis (OA) Studies (Protocols 029, 034, and 035) report the additional serious adverse experience data accrued during the SUR period. There were no meaningful changes to the safety profile during the SUR period for this group of patients, whom, in many cases, had exposure to rofecoxib for more than 2 years (estimated 1800 patient-years on rofecoxib).

- Additional safety data accrued during the SUR period are also presented from the Elderly OA Study (Protocol 058) submitted in the Original Application. The Elderly OA safety data reveal no new safety concerns in this population of patients age 80 and older. The safety profile in this elderly cohort is generally similar to the overall OA rofecoxib group.

- The 3 placebo-controlled studies in Alzheimer's Disease and Mild Cognitive Impairment (MCI) (Protocols 078, 091, and 126) document that the profile of serious clinical adverse experiences with rofecoxib is generally similar to that of placebo in a large cohort of patients, most of whom were older than 65 years of age. The safety profile of rofecoxib was also similar to that of placebo in two 4-week studies of patients with chronic low back pain.

1. Overview (Cont.)

- The cardiovascular safety data from individual studies as well as the updated cardiovascular meta-analysis confirms the excellent cardiovascular safety profile of rofecoxib. The updated meta-analysis shows that the risk of thrombotic cardiovascular serious adverse experiences with rofecoxib is similar to that with placebo or non-naproxen NSAIDs.

1.1 Organization of the Document

This SUR is divided into 2 main sections. The first section summarizes serious fatal and nonfatal clinical adverse experiences in 13 clinical trials. All serious clinical adverse experiences that began within 14 days of the last dose of study medication, including events the investigators considered not drug related, are included in the counts tables. For extensions of studies previously submitted, the data accrued during both the first SUR and this SUR period (04-Sep-1998 through 16-Mar-2001) are summarized and the Comprehensive Data are also presented (encompassing the Original Application, first SUR, and present SUR periods). Deaths that occurred during the SUR period are discussed. For the studies not previously submitted, the adverse experience data available as of 16-Mar-2001 (for ongoing studies) are summarized and a listing of deaths is provided. Discontinuations due to nonserious adverse experiences are not presented as the focus of this report is on serious clinical adverse experiences.

The second section presents a summary of thrombotic cardiovascular serious adverse experiences reported in new clinical trials and extensions of previous studies of rofecoxib. This is followed by an update of the previously submitted cardiovascular meta-analysis.

The beginning of each section contains a list of the clinical studies that were included in that section's analysis. The overall extent of exposure to rofecoxib in those studies is tabulated.

2. Update of Serious Clinical Adverse Experiences—All Body Systems

This SUR summarizes serious clinical adverse experience data on completed or ongoing rofecoxib studies of at least 4 weeks duration, with the exception of the previously reported VIGOR, ADVANTAGE, Nabumetone Comparison Studies, and Rheumatoid Arthritis Studies. Shorter duration studies are clinical pharmacology or analgesic studies and are not included in this SUR since they have few serious adverse experiences. Per agreement with the FDA, three 6-week studies (Protocols 106, 112, and 116) comparing rofecoxib to celecoxib are also not included in this SUR.

Table 1 summarizes the 13 clinical studies included in the update of Serious Clinical Adverse Experiences. The number of patients evaluable for safety is presented. In the extension studies, the number shown is for the cumulative analysis, which is larger than the number of patients that have continued in the extension during this SUR period.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 1

Summary of Studies Included in Update of Serious Clinical Adverse Experiences

Study Type/ Protocol Numbers	Total Duration	Total Daily Rofecoxib Dose	Patients Treated		
			Rofecoxib	Placebo	Active Control
Extensions of Osteoarthritis Studies Previously Submitted					
Long-Term Exposure— 029, 034, 035	>2 years	12.5 to 50 mg 12.5 mg 25 mg 50 mg	923 415 475 78	0	409 (Diclofenac)
Elderly— 058	Up to 2 years	12.5 to 25 mg 12.5 mg 25 mg	70 46 25	0	36 (Nabumetone)
Completed Studies Not Included in First SUR					
Bone Density—083	Up to 65 weeks	25 mg	136	100	148 (Ibuprofen)
Alzheimer's Disease—091	Up to 479 days	25 mg	346	346	0
Chronic Prostatitis—118	6 weeks	25 to 50 mg 25 mg 50 mg	102 53 49	59	0

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 1 (Cont.)

Summary of Studies Included in Update of Serious Clinical Adverse Experiences

Study Type/ Protocol Numbers	Total Duration	Total Daily Rofecoxib Dose	Patients Treated		
			Rofecoxib	Placebo	Active Control
Completed Studies Not Included in First SUR (Cont.)					
Chronic Low Back Pain—120 and 121	4 weeks	25 to 50 mg 25 mg 50 mg	465 232 233	228	0
Osteoarthritis Versus Naproxen—901	6 weeks	12.5 mg	471	0	473 (Naproxen)
Osteoarthritis Versus ARTHROTEC™—902	6 weeks	12.5 mg	453	0	456 (Diclofenac-misoprostol)
Ongoing Studies Not Included in First SUR					
Alzheimer's Disease—078[†]	Up to 1052 days	25 mg	721	729	0
Alzheimer's Disease—126	Up to 430 days	25 mg	381	376	0

ARTHROTEC™ (diclofenac/misoprostol combination, G.D. Searle & Co.).
[†]Treatment is ongoing.

[1; 2; 3; 4; 5; 6; 7; 8]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Overall Exposure to Rofecoxib and Comparators

Table 2 presents the number of patients exposed to rofecoxib and comparators by the dose actually taken in the 13 clinical trials included in the Update of Serious Clinical Adverse Experiences. A total of 4068 patients received one or more dosages of rofecoxib, including 3075 patients who were not in the Original Application or first SUR. The doses with the most exposure are 25 mg and 12.5 mg. Including the primary study periods and extensions, a total of 205 patients have taken rofecoxib 12.5 mg for at least 2 years, and over 210 patients have taken rofecoxib 25 mg for at least 2 years [1].

Table 2

Number of Patients on Treatment by Dose—All Studies Included in Update of Serious Clinical Adverse Experiences

	Number of Patients
Rofecoxib—Any dose	**4068**
<12.5 mg	10
12.5 mg	1385
17.5 mg	1
25 mg	2369
50 mg	362
>50 mg	1
Diclofenac—Any dose	**409**
50 mg	188
100 mg	168
150 mg	409
Diclofenac/Misoprostol	**456**
Nabumetone—Any dose	**36**
500 mg	5
1000 mg	4
1500 mg	36
Ibuprofen 2400 mg	**148**
Naproxen 1000 mg	**473**
Placebo	**1838**

[1; 2; 3; 4; 5; 6; 7; 8]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Format of the Data Presentation

The format of the data presentation for a particular study group is dependent on the status of the study and the amount of new information received during the SUR period. For the OA extension studies, the serious adverse experience tables summarize by body system, the Cumulative Data from the first SUR (6 months to 86 weeks) and the Cumulative Data for the present SUR (6 months to 172 weeks). A table that includes data from the first 6 months is also presented (Comprehensive Data). Specific adverse experiences that occurred in ≥0.5% of any treatment group are presented in the tables. The data received during this SUR period are provided in a reference. For completed studies (Bone Mineral Density [Protocol 083] and Chronic Prostatitis [Protocol 118], the tables summarize the serious adverse experiences by body system for each entire study or provide a listing for the serious adverse experiences (Chronic Low Back Pain Studies [Protocols 120 and 121]). For the large Alzheimer's Disease Studies (Protocols 078, 091, and 126), the serious adverse experiences are summarized by body system, and specific serious adverse experiences that occurred in ≥0.5% of any treatment group are presented for each study and the 3 studies combined.

Data were derived from Case Report Forms for all protocols except 2 Alzheimer's protocols (078 and 126). The clinical databases for those 2 trials have not yet been frozen. Serious adverse experience information for Protocols 078 and 126 was derived from the Worldwide Adverse Experience System (WAES) using the cutoff date of 16-Mar-2001.

2.1 Update of Serious Clinical Adverse Experiences in Osteoarthritis Extension Studies

The Long-Term Exposure OA Studies consist of patient data from the extensions to the 3 OA Studies (Phase IIb/III OA Dose Ranging Study [Protocol 029], Phase III OA Diclofenac Comparison Studies [034, and 035]). The group is presented as a combined analysis to be consistent with the Application and first SUR. (In the Original Application, they were called the 6-Month-to-86-Week Studies). The Cumulative Data encompass:

- Protocols 034 and 035—the second 6 months plus all extension data from both studies. Data from the first 6 months is excluded to be consistent with the prior SUR.
- Protocol 029—the 3 extensions (029-20, 029-30, 029-40). Data from the first 6 months (029 base and 029-10) is excluded to be consistent with the prior SUR.

Comprehensive data including the first 6 months of Protocols 034 and 035 as well as the 6-week to 6-month data for Protocol 029-10, (per-protocol, patients who initially received placebo were re-randomized to active treatments at 6 weeks and therefore the first 6 weeks are excluded) is presented after the summary of the Cumulative Data.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

As was done in the Original Application and first SUR, the safety data for the Elderly Study (Protocol 058) are presented separately. This permits a direct evaluation of the safety profile in this older population. As this is a single study, the number of patients per group is small.

2.1.1 Long-Term Exposure OA Protocols 029, 034, 035

In the Long-Term Exposure OA Studies, the mean age at entry was 61.8 years, with a range of 39 to 85 years. The percent of males and females were 26.0% and 74.0%, respectively. Racial composition was primarily White (82.2%), Hispanic American (10.2%), and Black (5.8%). There were fewer Hispanic Americans in the 50-mg rofecoxib group as this dose was used in a single study (Protocol 029) that was conducted only in the United States. Otherwise, there were no clinically important demographic differences between groups[1]. The 3 most frequent secondary conditions in each group were hypertension, drug allergy, and hypercholesterolemia. The 3 most commonly used therapeutic classes of concomitant medications were vitamins, sex hormone and modulator of the genital system, and analgesics. Overall distribution of secondary conditions and concomitant therapies was similar among study groups [1].

Table 3 summarizes the exposure to rofecoxib and diclofenac during the Long-Term Exposure OA Studies. For an individual patient, the days on treatment reported in this table concern only those days from 6 months and beyond, i.e., the primary study treatment duration was not added to the duration of the Long-Term Exposure OA Studies. Thus, the patients in the column of <1 week have actually been on treatment for a total of 26 weeks plus <1 week from allocation. An individual patient was counted only one time in the top row labeled "Any dose." A patient who received a variety of doses during a study is reported in each specific dosage row for the duration that the dose was taken. In Protocol 029-40, per the protocol, patients on rofecoxib 50 mg had their dose reduced to 25 mg.

Exposure to rofecoxib was substantially greater than to diclofenac (estimated 1164 patient-years versus 484 patient-years). A total of 923 patients with OA were treated with rofecoxib in the Long-Term Exposure OA Studies. The mean number of days on rofecoxib was 457. There were 314 patients who received rofecoxib for ≥2 years, and 196 who received rofecoxib for ≥1 to <2 years. There were 409 patients treated with diclofenac, with 120 patients receiving 150 mg for ≥2 years. The mean number of days on diclofenac was 439.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 3

Number of Patients on Study Drug by Dose and Actual Duration of Treatment
Long-Term Exposure Osteoarthritis Studies
Cumulative Data

	Treatment Intervals*							Total Number of Patients
	≤1 Week	≥1 Week to <2 Weeks	≥2 Weeks to <2 Months	≥2 Months to <6 Months	≥6 Months to <1 Year	≥1 Year to <2 Years	≥2 Years	
Rofecoxib								
Any dose	7	3	45	79	279	196	314	923
<12.5 mg	10	0	0	0	0	0	0	10
12.5 mg	5	2	17	30	135	83	143	415
17.5 mg	1	0	0	0	0	0	0	1
25 mg	6	1	25	42	158	107	136	475
50 mg	2	1	5	10	11	49	0	78
>50 mg	1	0	0	0	0	0	0	1
Diclofenac								
Any dose	1	0	25	44	120	97	122	409
50 mg	165	8	10	5	0	0	0	188
100 mg	118	17	28	5	0	0	0	168
150 mg	1	2	25	46	117	98	120	409
200 mg	0	0	0	0	0	0	0	0
250 mg	1	0	0	0	0	0	0	1

* Protocols include 029-20/30/40, 034, and 035 (the second 6 months of the initial 1-year study plus 034-10 and 035-10). Intervals are during Extension Treatment (i.e., those days from 6 months and beyond of a study).
Although some patients may have taken 2 or more different dosages, they have been counted only one time each, on the "Any dose" row.

[1]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

The serious clinical adverse experience by body system profiles of the first SUR Cumulative and present SUR Cumulative Long-Term Exposure OA data are summarized in Table 4. As previously described, data from the first 6 months of each study are not included. Both nonfatal and fatal events are included. Adverse experiences with an incidence ≥0.5% in any treatment group for the new Cumulative analysis are presented. The overall incidence of serious clinical adverse experiences was higher in the diclofenac group than the rofecoxib groups in the new Cumulative analysis. This was due to an increase in musculoskeletal events. The profiles by body system are otherwise similar for the rofecoxib and diclofenac groups. The safety profile of rofecoxib in the new Cumulative analysis was similar to that in the previous SUR Cumulative analysis. Tables providing counts for all serious clinical adverse experiences (incidence >0%) that occurred during this SUR period and the new Cumulative Data are in [1]. A listing of all serious clinical adverse experiences that occurred during this SUR period is in [1].

Most patients with serious clinical adverse experiences did not have the study medication discontinued because of the adverse experience. The proportion of patients who discontinued treatment with a serious adverse experience was low in each group (rofecoxib 12.5 mg, 2.9%; rofecoxib 25 mg, 1.3%; rofecoxib 50 mg, 4.0%; diclofenac 150 mg, 3.4%).

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 4

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System (Incidence ≥0.5% in One or More Cumulative Treatment Groups)—Long-Term Exposure Osteoarthritis Studies

	First SUR Cumulative Data[†]				New Cumulative Data			
	Rofecoxib			Diclofenac	Rofecoxib			Diclofenac
	12.5 mg (N=415)	25 mg (N=439)	50 mg (N=75)	150 mg (N=409)	12.5 mg (N=415)	25 mg (N=472)	50 mg (N=75)	150 mg (N=409)
Patients with one or more adverse experiences	37 (8.9)	42 (9.6)	9 (12.0	50 (12.2)	60 (14.5)	67 (14.2)	9 (12.0)	74 (18.1)
Patients with no adverse experience	378 (91.1)	397 (90.4)	66 (88.0)	359 (87.8)	355 (85.5)	405 (85.8)	66 (88.0)	335 (81.9)
Body as Whole/Site Unspecified	**4 (1.0)**	**5 (1.1)**	**0 (0.0)**	**9 (2.2)**	**10 (2.4)**	**8 (1.7)**	**0 (0.0)**	**12 (2.9)**
Chest pain	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.7)	3 (0.7)	1 (0.2)	0 (0.0)	3 (0.7)
Inguinal hernia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)
Malignant neoplasm	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
Cardiovascular System	**12 (2.9)**	**5 (1.1)**	**1 (1.3)**	**6 (1.5)**	**19 (4.6)**	**12 (2.5)**	**1 (1.3)**	**10 (2.4)**
Angina pectoris	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)
Arterial fibrillation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.2)	1 (0.2)	0 (0.0)	0 (0.0)
Cerebrovascular accident	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)
Congestive heart failure	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.5)
Deep venous thrombosis	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.4)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.2)
Transient ischemic attack	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 4 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System (Incidence ≥0.5% in One or More Cumulative Treatment Groups)—Long-Term Exposure Osteoarthritis Studies

	First SUR Cumulative Data†				New Cumulative Data			
	Rofecoxib			Diclofenac	Rofecoxib			Diclofenac
	12.5 mg (N=415)	25 mg (N=439)	50 mg (N=75)	150 mg (N=409)	12.5 mg (N=415)	25 mg (N=472)	50 mg (N=75)	150 mg (N=409)
Digestive System	**2 (0.5)**	**7 (1.6)**	**1 (1.3)**	**8 (2.0)**	**6 (1.4)**	**9 (1.9)**	**1 (1.3)**	**10 (2.4)**
Colonic malignant neoplasm	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Gastric ulcer	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.5)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Infectious gastroenteritis	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)
Pancreatitis	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.2)	0 (0.0)	1 (0.2)
Endocrine System	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**
Hemic/Lymphatic System	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**3 (0.7)**
Anemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Hepatobiliary System	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.5)**
Cholecystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Metabolism and Nutrition	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 4 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System (Incidence ≥0.5% in One or More Cumulative Treatment Groups)—Long-Term Exposure Osteoarthritis Studies

	First SUR Cumulative Data†				New Cumulative Data			
	Rofecoxib			Diclofenac	Rofecoxib			Diclofenac
	12.5 mg (N=415)	25 mg (N=439)	50 mg (N=75)	150 mg (N=409)	12.5 mg (N=415)	25 mg (N=472)	50 mg (N=75)	150 mg (N=409)
Musculoskeletal System	**12 (2.9)**	**15 (3.4)**	**3 (4.0)**	**17 (4.2)**	**14 (3.4)**	**22 (4.7)**	**3 (4.0)**	**28 (6.8)**
Arthralgia	3 (0.7)	8 (1.8)	0 (0.0)	8 (2.0)	4 (1.0)	10 (2.1)	0 (0.0)	9 (2.2)
Back pain	0 (0.0)	1 (0.2)	0 (0.0)	4 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)	4 (1.0)
Femoral fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Hip pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)
Knee pain	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.2)	1 (0.2)	1 (0.2)	1 (1.3)	5 (1.2)
Osteoarthritis	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)
Spinal stenosis	1 (0.2)	1 (0.2)	1 (1.3)	0 (0.0)	1 (0.2)	2 (0.4)	1 (1.3)	0 (0.0)
Nervous System	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**	**2 (0.5)**	**1 (0.2)**	**0 (0.0)**	**1 (0.2)**
Psychiatric disorder	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	0 (0.0)	0 (0.0)
Depression	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 4 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System (Incidence ≥0.5% in One or More Cumulative Treatment Groups)—Long-Term Exposure Osteoarthritis Studies

	First SUR Cumulative Data[†]				New Cumulative Data			
	Rofecoxib			Diclofenac	Rofecoxib			Diclofenac
	12.5 mg (N=415)	25 mg (N=439)	50 mg (N=75)	150 mg (N=409)	12.5 mg (N=415)	25 mg (N=472)	50 mg (N=75)	150 mg (N=409)
Respiratory System	**2 (0.5)**	**2 (0.5)**	**1 (1.3)**	**4 (1.0)**	**5 (1.2)**	**2 (0.4)**	**1 (1.3)**	**4 (1.0)**
Dyspnea	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Pneumonia	1 (0.2)	1 (0.2)	1 (1.3)	1 (0.2)	3 (0.7)	1 (0.2)	1 (1.3)	1 (0.2)
Skin and Skin Appendages	**4 (1.0)**	**6 (1.4)**	**1 (1.3)**	**4 (1.0)**	**5 (1.2)**	**9 (1.9)**	**1 (1.3)**	**7 (1.7)**
Basal cell carcinoma	3 (0.7)	4 (0.9)	0 (0.0)	3 (0.7)	4 (1.0)	6 (1.3)	0 (0.0)	6 (1.5)
Skin malignant neoplasm	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.7)	2 (0.4)	0 (0.0)	1 (0.2)
Urogenital System	**3 (0.7)**	**5 (1.1)**	**3 (4.0)**	**4 (1.0)**	**6 (1.4)**	**11 (2.3)**	**3 (4.0)**	**7 (1.7)**
Breast malignant neoplasm	0 (0.0)	1 (0.2)	1 (1.3)	1 (0.2)	0 (0.0)	3 (0.6)	1 (1.3)	3 (0.7)
Ovarian cyst	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)
Urolithiasis	0 (0.0)	2 (0.5)	1 (1.3)	1 (0.2)	0 (0.0)	2 (0.4)	1 (1.3)	2 (0.5)

[†] Fatal and nonfatal serious adverse experiences were presented separately in first SUR but are both included in this table.

[1]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Comprehensive data for Protocols 029, 034, and 035 is presented in Table 5. In contrast to Table 4, Table 5 summarizes the serious clinical adverse experiences by body system for the Long-Term Exposure OA studies including the first 6 months of treatment for Protocols 034 and 035 as well the 6-week to 6-month data for Protocol 029 (placebo patients were re-randomized to active treatment at 6 weeks.) This dataset represents approximately 1698 patient-years on rofecoxib and 733 patient-years on diclofenac [1]. Both nonfatal and fatal serious clinical adverse experiences are included. Adverse experiences with an incidence ≥0.5% in any treatment group are presented. The overall incidence of serious clinical adverse experiences was slightly higher in the diclofenac group than the rofecoxib groups when the first 6-months is included in the analysis. This was primarily due to a small increase in musculoskeletal events. The profiles by body system are otherwise similar for the rofecoxib and diclofenac groups.

Table 5

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System (Incidence ≥0.5% in One or More Cumulative Treatment Groups)—Long-Term Exposure Osteoarthritis Studies Including First 6 Months of Treatment†—(Comprehensive Data)

	Rofecoxib 12.5 mg (N=594)	Rofecoxib 25 mg (N=674)	Rofecoxib 50 mg (N=123)	Diclofenac 150 mg (N=590)
Patients with one or more adverse experiences	89 (15.0)	95 (14.1)	11 (8.9)	106 (18.0)
Patients with no adverse experience	505 (85.0)	579 (85.9)	112 (91.1)	484 (82.0)
Body as Whole/Site Unspecified	**18 (3.0)**	**12 (1.8)**	**1 (0.8)**	**16 (2.7)**
Chest pain	5 (0.8)	3 (0.4)	1 (0.8)	4 (0.7)
Inguinal hernia	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)
Cardiovascular System	**26 (4.4)**	**20 (3.0)**	**3 (2.4)**	**20 (3.4)**
Angina pectoris	1 (0.2)	2 (0.3)	0 (0.0)	3 (0.5)
Atrial fibrillation	6 (1.0)	3 (0.4)	0 (0.0)	0 (0.0)
Congestive heart failure	2 (0.3)	0 (0.0)	2 (1.6)	1 (0.2)
Coronary artery disease	1 (0.2)	2 (0.3)	0 (0.0)	3 (0.5)
Coronary artery occlusion	1 (0.2)	0 (0.0)	1 (0.8)	1 (0.2)
Myocardial infarction	2 (0.3)	2 (0.3)	1 (0.8)	3 (0.5)
Digestive System	**13 (2.2)**	**10 (1.5)**	**1 (0.8)**	**13 (2.2)**
Colonic malignant neoplasm	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal bleeding	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Endocrine System	**1 (0.2)**	**1 (0.1)**	**0 (0.0)**	**1 (0.2)**
Hemic and Lymphatic System	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**3 (0.5)**

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 5 (Cont.)

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System (Incidence ≥0.5% in One or More Cumulative Treatment Groups)—Long-Term Exposure Osteoarthritis Studies Including First 6 Months of Treatment†—(Comprehensive Data)

	Rofecoxib 12.5 mg (N=594)	Rofecoxib 25 mg (N=674)	Rofecoxib 50 mg (N=123)	Diclofenac 150 mg (N=590)
Hepatobiliary System	**2 (0.3)**	**0 (0.0)**	**0 (0.0)**	**4 (0.7)**
Cholelithiasis	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.5)
Metabolism and Nutrition	**0 (0.0)**	**1 (0.1)**	**1 (0.8)**	**1 (0.2)**
Weight gain	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Musculoskeletal System	**19 (3.2)**	**26 (3.9)**	**3 (2.4)**	**34 (5.8)**
Arthralgia	6 (1.0)	13 (1.9)	0 (0.0)	10 (1.7)
Back pain	0 (0.0)	2 (0.3)	0 (0.0)	4 (0.7)
Bursitis	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Hip pain	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.5)
Knee pain	1 (0.2)	1 (0.1)	1 (0.8)	5 (0.8)
Spinal stenosis	1 (0.2)	2 (0.3)	1 (0.8)	0 (0.0)
Nervous System	**3 (0.5)**	**2 (0.3)**	**0 (0.0)**	**2 (0.3)**
Psychiatric Disorder	**2 (0.3)**	**3 (0.4)**	**0 (0.0)**	**1 (0.2)**
Respiratory System	**6 (1.0)**	**5 (0.7)**	**1 (0.8)**	**8 (1.4)**
Pneumonia	4 (0.7)	2 (0.3)	1 (0.8)	4 (0.7)
Skin and Skin Appendages	**7 (1.2)**	**13 (1.9)**	**1 (0.8)**	**10 (1.7)**
Basal cell carcinoma	6 (1.0)	9 (1.3)	0 (0.0)	8 (1.4)
Cellulitis	0 (0.0)	0 (0.0)	1 (0.8)	2 (0.3)
Skin malignant neoplasm	3 (0.5)	3 (0.4)	0 (0.0)	1 (0.2)
Urogenital System	**8 (1.3)**	**16 (2.4)**	**3 (2.4)**	**9 (1.5)**
Breast malignant neoplasm	1 (0.2)	3 (0.4)	1 (0.8)	3 (0.5)
Prostatic malignant neoplasm	1 (0.2)	2 (0.3)	1 (0.8)	3 (0.5)
Urolithiasis	0 (0.0)	2 (0.3)	1 (0.8)	2 (0.3)

†Excludes first 6 weeks of Protocol 029.

[1]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Deaths

Two patients died during the SUR period. One had received diclofenac and 1 had received rofecoxib 12.5 mg. Both deaths occurred after study medication was discontinued, and both were considered not related to study medication [9].

- Protocol 034, Allocation Number (AN) 5568: 75-year-old woman received diclofenac 150 mg for 719 days. Medication was discontinued prior to total hip replacement. Postoperatively, she developed hypovolemic shock due to iliac artery rupture and died.
- Protocol 035, AN 8353: 64-year-old man received rofecoxib 12.5 mg for 607 days. Medication was discontinued prior to coronary artery bypass surgery for severe triple vessel disease. Postoperatively, he had a sternal wound infection (within 14 days of discontinuing study medication) requiring surgery then developed respiratory distress with ventricular tachycardia and died.

There were 8 deaths that occurred prior to this SUR period and were reported in the Original Application. Seven of the deaths occurred in the diclofenac group, and one occurred in the rofecoxib 12.5-mg group. Table 6 is a listing of all deaths in Protocols 029, 034, and 035 [1]. From study inception through the final extension, there were more deaths in the diclofenac group than the rofecoxib group (8 versus 2), even though the exposure to rofecoxib was over 2-fold greater than diclofenac.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 6

Listing of Deaths in Protocols 029, 034, 035

AN	Study Number	Gender	Race	Age	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relationship	Action Taken	Outcome
Included In Original Application											
Assigned Therapy: Rofecoxib 12.5 mg											
7588	035016	F	White	79	52	Unknown cause of death	1.00 day	Severe	Definitely not	Discontinued PRx	Not recovered
Assigned Therapy: Diclofenac 150 mg											
5599	034001	F	White	79	22	Myocardial infarction	1.00 day	Severe	Probably not	PRx continued[1]	Not recovered
5068	034012	F	White	55	106	Suicide attempt	1.00 day	Severe	Definitely not	Discontinued PRx	Not recovered
5320	034015	F	Hispanic	78	56	Cerebrovascular accident	2.00 days	Severe	Definitely not	Discontinued PR	Not recovered
7517	035011	F	White	70	85	Cardiac arrest	1.00 day	Severe	Possibly	Discontinued PRx	Not recovered
2395	029050	M	White	72	88	Coronary artery occlusion, multiple organ failure	25.00 days	Severe	Definitely not	Discontinued PRx	Not recovered
5761	034033	F	White	75	225	Postoperative complication	1.15 months	Severe	Definitely not	PRx continued	Not recovered
7922	035044	M	White	75	175	Atherosclerosis	1.00 day	Severe	Probably not	Discontinued PRx	Not recovered
Included In Previous SUR											
None											
Occurring During This SUR Period											
Assigned Therapy: Rofecoxib 12.5 mg											
8353	035073	M	White	64	639	Respiratory distress	23.00 days	Severe	Definitely not	PRx continued	Not recovered
					661	Ventricular arrhythmia	1.00 day	Severe	Definitely not	PRx continued	Not recovered
Assigned Therapy: Diclofenac 150 mg											
5568	034022	F	Hispanic	75	720	Hypovolemic shock	2.00 hours	Severe	Definitely not	Discontinued PRx	Not recovered

[1] No action taken with regard to study medication. Death occurred after patient discontinued study medication. Per data handling guidelines "PRx continued" used to record action taken.
PRx = Prime therapy (study drug).

[1]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.1.2 Elderly OA Protocol 058

In the Elderly Study, the mean age was 82.6 years at entry, with a range of 79 to 94 years. The percent of men and women were 34.2% and 65.8%, respectively. Most patients were White (95.4%). The 3 most common secondary conditions were hypertension, cataract/cataract surgery, and hysterectomy. The 3 most frequently used therapeutic classes were vitamins, antacids, and analgesics. There were no clinically important differences between groups with regard to demographics, secondary conditions, or concomitant therapies [1].

Table 7 summarizes the exposure to rofecoxib and nabumetone in the Elderly OA Study. At the conclusion of the 6-week, placebo-controlled study, patients could choose to enroll in a long-term extension study. During the first 6 weeks, patients in the placebo group were re-randomized to the 3 active-treatment groups in the extension. For an individual patient, the days on treatment reported in Table 7 concern only those days from 6 weeks and beyond, i.e., the initial placebo-controlled study period was not added to the duration calculated in the table. A total of 70 patients received rofecoxib in the study, with 24 taking 12.5 mg or 25 mg for ≥1 year to <2 years. The mean number of days on rofecoxib was 248. A total of 36 received nabumetone, with 17 receiving 1500 mg for ≥1 year to <2 years. The mean number of days on nabumetone was 266. Estimated exposure to rofecoxib was slightly greater than to nabumetone (46 versus 30 patient-years).

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 7

Number of Patients on Study Drug by Dose and Actual Duration of Treatment
Elderly OA Study
Cumulative Data

	Treatment Intervals[†]							
	≤1 Week	≥1 Week to <2 Weeks	≥2 Weeks to <2 Months	≥2 Months to <6 Months	≥6 Months to <1 Year	≥1 Year to <2 Years	≥2 Years	Total Number of Patients
Rofecoxib								
Any dose	0	1	7	10	28	24	0	70
12.5 mg	0	1	3	7	20	15	0	46
25 mg	1	0	4	3	8	9	0	25
50 mg	0	0	0	0	0	0	0	0
Nabumetone								
Any dose	0	1	3	3	10	19	0	36
500 mg	3	0	2	0	0	0	0	5
1000 mg	3	1	0	0	0	0	0	4
1500 mg	0	1	3	3	12	17	0	36

[†] Not including first 6 weeks of treatment.
Although some patients may have taken 2 or more different dosages, they have been counted only one time each, on the "Any dose" row.

[1]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

The serious clinical adverse experience by body system profiles of the first SUR Cumulative and present SUR Cumulative Data are summarized in Table 8. Events (nonfatal and fatal) occurring in 2 or more patients in any treatment group in the new Cumulative analysis are shown. The profiles of serious clinical adverse experiences by body system in the new Cumulative Data are generally similar for the rofecoxib and nabumetone groups except for the musculoskeletal system: 4 patients on rofecoxib 12.5 mg had a serious musculoskeletal adverse experience (arthralgia, back injury, and 2 with femoral fracture), but none were considered drug related. The profile for rofecoxib was similar in the previous and new Cumulative Data. The new Cumulative Data show that few patients in any treatment group discontinued treatment because of a serious adverse experience (rofecoxib 12.5 mg, 7.4%; rofecoxib 25 mg, 8.0%; nabumetone 1500 mg, 3.3%). Tables providing counts for all serious clinical adverse experiences (incidence >0%) during the present SUR period and new Cumulative Data are in [1]. A complete listing of all serious clinical adverse experiences that occurred during the SUR period is in [1] and narratives for these patients are in [9].

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 8

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System (≥2 Patients in Any Treatment Group)
Elderly Osteoarthritis Study—Cumulative Data

	Cumulative Data Through 04-Sep-1998[†]			New Cumulative Data		
	Rofecoxib		Nabumetone	Rofecoxib		Nabumetone
	12.5 mg (N=95)	25 mg (N=50)	1500 mg (N=92)	12.5 mg (N=95)	25 mg (N=50)	1500 mg (N=92)
Patients with one or more adverse experiences	13 (13.7)	5 (10.0)	7 (7.6)	21 (22.1)	10 (20.0)	12 (13.0)
Patients with no adverse experience	82 (86.3)	45 (90.0)	85 (92.4)	74 (77.9)	40 (80.0)	80 (87.0)
Body as Whole/Site Unspecified	**4 (4.2)**	**0 (0.0)**	**1 (1.1)**	**5 (5.3)**	**1 (2.0)**	**3 (3.3)**
Chest pain	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	2 (2.2)
Cardiovascular System	**4 (4.2)**	**2 (4.0)**	**3 (3.3)**	**5 (5.3)**	**3 (6.0)**	**5 (5.4)**
Angina pectoris	1 (1.1)	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)
Atrial fibrillation	2 (2.1)	0 (0.0)	1 (1.1)	2 (2.1)	0 (0.0)	1 (1.1)
Congestive heart failure	0 (0.0)	1 (2.0)	3 (3.3)	0 (0.0)	1 (2.0)	3 (3.3)
Digestive System	**2 (2.1)**	**1 (2.0)**	**1 (1.1)**	**3 (3.2)**	**2 (4.0)**	**1 (1.1)**
Anorectal hemorrhage	1 (1.1)	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)
Musculoskeletal System	**2 (2.1)**	**1 (2.0)**	**1 (1.1)**	**6 (6.3)**	**2 (4.0)**	**2 (2.2)**
Femoral fracture	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)	1 (1.1)
Nervous System	**1 (1.1)**	**1 (2.0)**	**0 (0.0)**	**1 (1.1)**	**2 (4.0)**	**0 (0.0)**
Respiratory System	**1 (1.1)**	**0 (0.0)**	**0 (0.0)**	**2 (2.1)**	**1 (2.0)**	**0 (0.0)**
Skin and Skin Appendages	**1 (1.1)**	**0 (0.0)**	**2 (2.2)**	**1 (1.1)**	**0 (0.0)**	**2 (2.2)**
Basal cell carcinoma	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)	0 (0.0)	2 (2.2)
Urogenital System	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (2.1)**	**1 (2.0)**	**0 (0.0)**

[†] Excluding first 6 weeks of treatment.

[1]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Deaths

There were no deaths in Protocol 058 during this SUR period. Two deaths occurred during the earlier extension and were reported in the first SUR. Both occurred in the 12.5-mg rofecoxib group (AN 1283, cardiac arrest, and AN 1502, bacterial sepsis and multiple organ failure). Both deaths were considered not related to study medication. A listing of the deaths is in Table 9.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 9

Listing of Deaths in Elderly Osteoarthritis Study (Protocol 058)

AN	Study Number	Gender	Race	Age	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation	Action Taken	Outcome
Included in Previous SUR											
Rofecoxib 12.5 mg											
1283	058020	F	White	86	179	Cardiac arrest	1.00 day	Severe	Definitely not	Discontinued PRx	Not recovered
1502	058044	F	White	87	165	Bacterial sepsis	10.00 days	Severe	Probably not	Discontinued PRx	Not recovered
					173	Multiple organ failure	2.00 days	Severe	Probably not	PRx continued	Not recovered
Occurring During This SUR Period											
None											

PRx = Prime therapy (study drug).

[1]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2 Update of Serious Clinical Adverse Experiences in Studies Not Previously Submitted

2.2.1 Alzheimer's Disease—Protocol 091

2.2.1.1 Design

This was a placebo-controlled, parallel-group, multicenter, 15-month double-blind study to evaluate the efficacy and safety of rofecoxib 25 mg to slow the progression of symptoms of Alzheimer's Disease. Patients of either gender who were ≥50 years of age with possible or probable Alzheimer's Disease were eligible to participate. Patients using NSAIDs for ≥7 days/month for the 2 months immediately prior to entry were not eligible. Patients were excluded if they were living in a nursing home or skilled nursing facility. They were also excluded if they had a history of angina or congestive heart failure with symptoms at rest, uncontrolled hypertension, or cerebrovascular disease (e.g., major stroke or transient ischemic attacks). Eligible patients were randomized to rofecoxib 25 mg or placebo for 12 months. This was followed by an additional 3-month treatment phase in which 90% of the patients initially assigned to rofecoxib were treated with placebo while the other patients remained on their initial treatment. Safety and tolerability were assessed at each visit (screening, Months 1, 3, 6, 9, 12, 13.5, and 15). A complete description of the study design is in the protocol synopsis [10].

Table 10 shows the baseline demographics of the patients studied. There were no clinically important differences between treatment groups with regard to demographics, concomitant conditions, or concomitant therapies. The most common secondary diagnoses were hypertension, osteoarthritis, depression, hearing loss, and cataract. The most common concomitant therapies were vitamins, analgesics, and psychoanaleptic drugs (primarily donepezil hydrochloride). After enrollment was completed, the protocol was amended to allow concomitant use of low-dose aspirin (<100 mg/day) for cardioprotection. Approximately 7% of the patients took aspirin while taking study medication [3].

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 10

Baseline Demographics by Treatment Group—Protocol 091

	Rofecoxib 25 mg/ Rofecoxib 25 mg	Rofecoxib 25 mg/ Placebo	Placebo/ Placebo	Total
Total N	35	311	346	692
Gender—n (%)				
Male	20 (57.1)	139 (44.7)	165 (47.7)	324 (46.8)
Female	15 (42.9)	172 (55.3)	181 (52.3)	368 (53.2)
Race—n (%)				
White	33 (94.3)	296 (95.2)	325 (93.9)	654 (94.5)
Black	0 (0.0)	7 (2.3)	7 (2.0)	14 (2.0)
Hispanic	2 (5.7)	5 (1.6)	9 (2.6)	16 (2.3)
Asian	0 (0.0)	3 (1.0)	3 (0.9)	6 (0.9)
European	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.3)
Age (years)				
50 and Under	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
51 to 64	4 (11.4)	36 (11.6)	44 (12.7)	84 (12.1)
65 to 74	11 (31.4)	78 (25.1)	98 (28.3)	187 (27.0)
Over 74	20 (57.1)	197 (63.3)	203 (58.7)	420 (60.7)
Mean	74.8	75.7	75.0	75.3
SD	7.68	8.42	8.81	8.58
Median	76.0	77.0	76.0	77.0
Range	58 to 85	52 to 92	49 to 92	49 to 92

[3]

2.2.1.2 Extent of Exposure

This study is completed, all data have been reviewed, and the database has been frozen. Table 11 shows the extent of exposure to study medication. Thirty-five patients received rofecoxib 25 mg for 15 months, and 311 patients received rofecoxib 25 mg for 12 months then placebo for 3 months.

Table 11

Number of Days on Therapy by Treatment—Protocol 091

	Treatment		
	Rofecoxib 25 mg/ Rofecoxib 25 mg	Rofecoxib 25 mg/ Placebo	Placebo/ Placebo
N	35	311	346
Mean	355.7	340.8	365.7
Range (min to max)	461 (2 to 463)	479 (1 to 480)	475 (1 to 476)

[3]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.1.3 Fatal and Nonfatal Serious Adverse Experiences

Table 12 provides the numbers and percentages of patients with fatal and nonfatal serious clinical adverse experiences. Specific clinical adverse experiences that occurred in ≥0.5% of any treatment group are displayed. A table displaying all serious clinical adverse experiences by treatment group is in [3]. A listing of patients with serious clinical adverse experiences is in [3], and narratives for those patients are in [11].

The proportion of patients with one or more serious clinical adverse experiences was similar in the 3 treatment groups (21.2% to 22.9%). The proportion of patients who discontinued treatment because of a serious adverse experience was also similar in the three treatment groups (rofecoxib/rofecoxib, 5.7%; rofecoxib/placebo, 7.7%; placebo/placebo, 6.4%). The proportion of patients with serious clinical adverse experiences in the body as a whole, digestive, respiratory, and urogenital body systems was slightly higher in the rofecoxib/placebo group than in the placebo/placebo group. The proportion of patients with serious clinical adverse experiences classified as cardiovascular, musculoskeletal, nervous, or psychiatric was slightly higher in the placebo group than the rofecoxib group. Review of specific adverse experiences does not reveal any previously unexpected association with rofecoxib.

Body as a Whole

The 2 groups were similar except that 2 patients in the rofecoxib/placebo group had abdominal pain while receiving rofecoxib (ANs 447 and 614) and 2 had hernias while receiving rofecoxib (ANs 614 and 938).

Digestive

Four patients in the rofecoxib/placebo group had a gastric ulcer (ANs 383, 669) or gastrointestinal bleeding (AN 779, gastritis, MalloryWeiss tear; AN 969, intestinal diverticulum, AN 383, gastric ulcer) while 1 in the placebo/placebo group had a hemorrhagic gastric ulcer (AN 22). The 2 groups were otherwise similar.

Respiratory

Two patients in the rofecoxib/placebo group had malignant lung neoplasms (ANs 165, 382) and 2 had asthma (ANs 231, 401). The incidence of pneumonia was comparable in the 2 groups (8 patients on rofecoxib and 7 on placebo). The remaining respiratory adverse experiences were equally infrequent in the 2 groups.

Urogenital

Two patients in the rofecoxib/placebo group had acute renal failure that was considered not related to study medication. AN 376 ingested a caustic substance that caused esophageal burns. While hospitalized, he developed bacteremia, fungemia, acute renal failure, and died. AN 542 had study medication discontinued after being hospitalized for hypercalcemia and altered mental status. After discharge to a nursing home, she had an acute myocardial infarction complicated by acute renal failure and died.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 12

Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.5% in One or More Treatment Groups) by Body System—Protocol 091

	Rofecoxib 25 mg/ Rofecoxib 25 mg (N=35)		Rofecoxib 25 mg/ Placebo (N=311)		Placebo/Placebo (N=346)	
	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	8	(22.9)	66	(21.2)	72	(20.8)
Patients with no adverse experience	27	(77.1)	245	(78.8)	274	(79.2)
Body as a Whole/Site Unspecified	**0**	**(0.0)**	**18**	**(5.8)**	**15**	**(4.3)**
Abdominal pain	0	(0.0)	2	(0.6)	0	(0.0)
Bacterial sepsis	0	(0.0)	0	(0.0)	2	(0.6)
Dehydration	0	(0.0)	5	(1.6)	4	(1.2)
Hernia	0	(0.0)	2	(0.6)	0	(0.0)
Syncope	0	(0.0)	5	(1.6)	6	(1.7)
Cardiovascular System	**3**	**(8.6)**	**18**	**(5.8)**	**27**	**(7.8)**
Aortic valve regurgitation	1	(2.9)	0	(0.0)	0	(0.0)
Atrial fibrillation	1	(2.9)	2	(0.6)	2	(0.6)
Bradycardia	0	(0.0)	1	(0.3)	3	(0.9)
Cardiac arrest	0	(0.0)	2	(0.6)	2	(0.6)
Carotid artery obstruction	0	(0.0)	1	(0.3)	2	(0.6)
Cerebrovascular accident	1	(2.9)	3	(1.0)	3	(0.9)
Congestive heart failure	2	(5.7)	2	(0.6)	3	(0.9)
Hypertension	1	(2.9)	0	(0.0)	0	(0.0)
Mitral valve regurgitation	1	(2.9)	0	(0.0)	0	(0.0)
Multifocal atrial tachycardia	1	(2.)	0	(0.0)	0	(0.0)
Myocardial infarction	1	(2.9)	2	(0.6)	4	(1.2)
Supraventricular tachycardia	1	(2.9	00	(0.0)	1	(0.3)
Ventricular fibrillation	0	(0.0)	2	(0.6)	0	(0.0)
Digestive System	**1**	**(2.9)**	**14**	**(4.5)**	**8**	**(2.3)**
Gastric ulcer	0	(0.0)	2	(0.6)	0	(0.0)
Gastrointestinal bleeding	0	(0.0)	3	(1.0)	0	(0.0)
Intestinal diverticulum	1	(2.9)	2	(0.6)	1	(0.3)
Lower gastrointestinal hemorrhage	1	(2.9)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	1	(0.3)	2	(0.6)
Endocrine System	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.3)**
Eyes, Ears, Nose, and Throat	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**
Hemic and Lymphatic System	**0**	**(0.0)**	**1**	**(0.3)**	**2**	**(0.6)**
Hepatobiliary System	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**
Metabolism and Nutrition	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**
Musculoskeletal System	**2**	**(5.7)**	**8**	**(2.6)**	**11**	**(3.2)**
Hip fracture	1	(2.9)	2	(0.6)	2	(0.6)
Muscular weakness	0	(0.0)	4	(1.3)	1	(0.3)
Musculoskeletal chest pain	1	(2.9)	0	(0.0)	0	(0.0)

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 12 (Cont.)

Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.5% in One or More Treatment Groups) by Body System—Protocol 091

	Rofecoxib 25 mg/ Rofecoxib 25 mg (N=35)		Rofecoxib 25 mg/ Placebo (N=311)		Placebo/Placebo (N=346)	
	n	(%)	n	(%)	n	(%)
Nervous System	2	(5.7)	4	(1.3)	6	(1.7)
Encephalopathy	1	(2.9)	0	(0.0)	0	(0.0)
Gait abnormality	0	(0.0)	0	(0.0)	2	(0.6)
Parkinsonism	1	(2.9)	0	(0.0)	0	(0.0)
Psychiatric Disorder	2	(5.7)	6	(1.9)	8	(2.3)
Agitation	1	(2.9)	0	(0.0)	3	(0.9)
Confusion	1	(2.9)	1	(0.3)	0	(0.0)
Delusion	1	(2.9)	0	(0.0)	1	(0.3)
Depression	0	(0.0)	2	(0.6)	1	(0.3)
Mental status change	0	(0.0)	2	(0.6)	0	(0.0)
Respiratory System	2	(5.7)	14	(4.5)	10	(2.9)
Asthma	0	(0.0)	2	(0.6)	0	(0.0)
Lung malignant neoplasm	0	(0.0)	2	(0.6)	0	(0.0)
Pneumonia	1	(2.9)	8	(2.6)	7	(2.0)
Respiratory distress	0	(0.0)	0	(0.0)	2	(0.6)
Respiratory failure	1	(2.9)	1	(0.3)	0	(0.0)
Skin and Skin Appendages	0	(0.0)	6	(1.9)	4	(1.2)
Basal cell carcinoma	0	(0.0)	3	(1.0)	2	(0.6)
Cellulitis	0	(0.0)	2	(0.6)	1	(0.3)
Skin malignant neoplasm	0	(0.0)	2	(0.6)	1	(0.3)
Urogenital System	1	(2.9)	10	(3.2)	6	(1.7)
Acute renal failure	0	(0.0)	2	(0.6)	0	(0.0)
Breast malignant neoplasm	1	(2.9)	0	(0.0)	2	(0.6)
Prostatic malignant neoplasm	0	(0.0)	2	(0.6)	0	(0.0)
Urinary tract infection	0	(0.0)	2	(0.6)	2	(0.6)

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.

[3]

Deaths

There were 22 deaths in the study population. This includes patients who developed serious adverse experiences within 14 days of the last dose of study medication and then died more than 14 days after the last dose of study medication. (The Clinical Study Report will include a summary of all deaths that occurred during follow-up, including patients who developed fatal serious adverse experiences more than 14 days after the last dose of study medication.) Fourteen patients in the rofecoxib/placebo group and 8 in the

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

placebo/placebo group died; there were no deaths in the rofecoxib/rofecoxib group. All of the deaths in the rofecoxib/placebo group occurred before patients began treatment with placebo. Table 13 is a listing of deaths by treatment group. Narratives for these patients are in [11]. All of the deaths were considered by the investigators to be definitely not or probably not related to study medication. The deaths usually occurred after a prolonged period on drug. There was no apparent pattern suggesting a risk with rofecoxib. All deaths in the Alzheimer's Disease Studies were sent for adjudication per recent update to the Standard Operating Procedure for Adjudication. The number of patients adjudicated as having confirmed thromboembolic events as the cause of death were 3 (ANs 332, 601, 831) and 2 (ANs 784, 827) for rofecoxib and placebo, respectively [12]. Three patients (ANs 282, 382, 691) died of a neoplasm (carcinoma or leukemia) in the rofecoxib group compared with 2 (ANs 394, 830) in the placebo group. Four patients (ANs 3, 42, 835, 915) died of pneumonia in the rofecoxib group compared with 2 (ANs 613, 832) in the placebo group. Two (ANs 42, 835) of the 4 patients who died of pneumonia in the rofecoxib group had an underlying or complicating condition (interstitial lung disease, suspected endocarditis). The overall incidence of pneumonia (including nonfatal cases) was similar in the rofecoxib and placebo groups (see Table 12).

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 13

Listing of Deaths by Treatment Group—Protocol 091

AN	Gender	Race	Age	Phase of AE	Therapy	Rel. Day of AE Onset	Adverse Experience	Duration of Adverse Experience	Rel. Day of Discontin-uance	Drug Relation-ship	Action Taken	Rel. Day of Death	Phase of Death	Date of Death
Rofecoxib 25 mg/Placebo Group														
3	F	Black	91	Treatment on drug	On drug	260	Pneumonia	4.00 day	260	Def not	Discontinued PRx	263	Treatment on drug	13-Nov-1999
42	M	White	83	Treatment on drug	Off drug 2 days	303	Endocarditis	3.00 day	301	Def not	No action with test drug	305	Treatment on drug	04-Jun-2000
				Treatment on drug	Off drug 2 days	303	Pneumonia	3.00 day	301	Def not	Discontinued PRx	305	Treatment on drug	04-Jun-2000
282	F	White	71	Treatment on drug	Off drug 2 days	165	Lung malignant neoplasm	26.00 day	171	Def not	Discontinued PRx	190	Treatment off drug	05-Nov-1999
332	M	White	78	Treatment on drug	Off drug 1 day	328	Cardiac arrest† (Fatal myocardial infarction)	0.33 hr	327	Prob not	Discontinued PRx	328	Treatment on drug	20-Jul-2000
				Treatment on drug	Off drug 1 day	328	Ventricular fibrillation	0.33 hr	327	Prob not	Discontinued PRx	328	Treatment on drug	20-Jul-2000
376‡	M	White	62	Treatment on drug	On drug	172	Burn	1.61 mo	172	Def not	Discontinued PRx	220	Treatment off drug	01-Nov-1999
				Treatment off drug	Off drug 31 days	203	Fungemia	18.00 day	172	Def not	No action with test drug	220	Treatment off drug	01-Nov-1999
				Treatment off drug	Off drug 34 days	206	Anuria	15.00 day	172	Def not	No action with test drug	220	Treatment off drug	01-Nov-1999

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 13 (Cont.)

Listing of Deaths by Treatment Group—Protocol 091

AN	Gender	Race	Age	Phase of AE	Therapy	Rel. Day of AE Onset	Adverse Experience	Duration of Adverse Experience	Rel. Day of Discontin-uance	Drug Relation-ship	Action Taken	Rel. Day of Death	Phase of Death	Date of Death
Rofecoxib 25 mg/Placebo Group (Cont.)														
382	F	White	77	Treatment on drug	Off drug 4 days	123	Brain malignant neoplasm	1.38 mo	119	Prob not	No action with test drug	164	Treatment off drug	16-Sep-1999
				Treatment on drug	Off drug 4 days	123	Lung malignant neoplasm	1.38 mo	119	Prob not	No action with test drug	164	Treatment off drug	16-Sep-1999
542	F	White	82	Treatment on Drug	Off drug 7 days	188	Hypercalcemia, Acute renal failure	2.00 day	181	Prob not	Discontinued PRx	189	Treatment on drug	22-Feb-2000
601	M	White	75	Treatment on Drug	Off drug 1 day	228	Ventricular fibrillation† (Sudden and/or unexplained death)	1.00 day	227	Prob not	Discontinued PRx	228	Treatment on drug	09-Oct-1999
691	M	White	86	Treatment on drug	Rofecoxib	323	Esophageal malignant neoplasm	6.60 mo	348	Def not	Discontinued PRx	523	Randomized withdrawal off drug	27-Aug-2000
				Randomized withdrawal off drug	Off drug 42 days	390	Pneumonia	4.40 mo	348	Def not	No action with test drug	523	Randomized withdrawal off drug	27-Aug-2000
831	M	White	85	Treatment on drug	Rofecoxib	296	Cerebrovascular accident†	8.00 day	296	Prob not	Discontinued PRx	303	Treatment on drug	12-May-2000

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 13 (Cont.)

Listing of Deaths by Treatment Group—Protocol 091

AN	Gender	Race	Age	Phase of AE	Therapy	Rel. Day of AE Onset	Adverse Experience	Duration of Adverse Experience	Rel. Day of Discontin-uance	Drug Relation-ship	Action Taken	Rel. Day of Death	Phase of Death	Date of Death
Rofecoxib 25 mg/Placebo Group (Cont.)														
835	M	White	82	Treatment on drug	Rofecoxib	269	Interstitial lung disease	1.00 day	269	Def not	No action with test drug	269	Treatment on drug	15-Apr-2000
				Treatment on drug	Rofecoxib	269	Pneumonia	1.00 day	269	Def not	No action with test drug	269	Treatment on drug	15-Apr-2000
				Treatment on drug	Rofecoxib	269	Cardiac arrest (secondary to pneumonia)	1.00 day	269	Prob not	Discontinued PRx	269	Treatment on drug	15-Apr-2000
891	F	White	88	Treatment on drug	On drug	76	Fever	13.00 day	76	Prob not	Discontinued PRx	269	Treatment on drug	06-Nov-1999
				Treatment on drug	Off drug 12 days	88	Unknown cause of death (Insufficient data)	1.00 day	76	Prob not	Discontinued PRx	88	Treatment on drug	06-Nov-1999
915	F	White	79	Treatment on drug	Off drug 1 day	260	Pneumonia	5.00 day	259	Def not	Discontinued PRx	264	Treatment on drug	21-May-2000
964‡	F	White	86	Treatment on drug	Rofecoxib	29	Dizziness, nausea	30.00 day	29	Prob not	Discontinued PRx	58	Treatment off drug	10-Sep-1999
				Treatment off drug	Off drug 29 days	58	Cerebrovascular accident (Insufficient data)	0.10 hr	29	Def not	No action with test drug	58	Treatment off drug	10-Sep-1999
				Treatment off drug	Off drug 29 days	58	Respiratory failure	0.07 hr	29	Def not	No action with test drug	58	Treatment off drug	10-Sep-1999

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 13 (Cont.)

Listing of Deaths by Treatment Group—Protocol 091

AN	Gender	Race	Age	Phase of AE	Therapy	Rel. Day of AE Onset	Adverse Experience	Duration of Adverse Experience	Rel. Day of Discontin-uance	Drug Relation-ship	Action Taken	Rel. Day of Death	Phase of Death	Date of Death
Placebo/Placebo Group														
394	M	White	68	Randomized withdrawal on drug	Off drug 1 day	452	Metastatic neoplasm of unknown primary	1.22 mo	451	Def not	Discontinued PRx	488	Randomized withdrawal off drug	09-Dec-2000
613	M	White	88	Treatment on drug	Off drug 11 days	109	Chronic obstructive pulmonary disease	23.00 day	98	Prob not	Discontinued PRx	131	Treatment off drug	05-Sep-1999
				Treatment off drug	Off drug 33 days	131	Aspiration pneumonia	1.00 day	98	Prob not	No action with test drug	131	Treatment off drug	05-Sep-1999
664	M	White	84	Randomized withdrawal on drug	Off drug 1 day	417	Alzheimer's disease, Pneumonia	1.00 day	416	Def not	Discontinued PRx	417	Randomized withdrawal on drug	12-May-2000
784	F	White	70	Randomized withdrawal on drug	Placebo	458	Myocardial infarction†, Cardiac arrest (Sudden and/or unexplained death)	10.00 hr	458	Prob not	Discontinued PRx	458	Randomized withdrawal on drug	04-Sep-2000
827	M	White	74	Treatment on drug	Placebo	70	Intracranial hemorrhage†	1.00 day	70	Def not	Discontinued PRx	70	Treatment on drug	27-Aug-1999

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 13 (Cont.)

Listing of Deaths by Treatment Group—Protocol 091

AN	Gender	Race	Age	Phase of AE	Therapy	Rel. Day of AE Onset	Adverse Experience	Duration of Adverse Experience	Rel. Day of Discontin-uance	Drug Relation-ship	Action Taken	Rel. Day of Death	Phase of Death	Date of Death
Placebo/Placebo Group (Cont.)														
830	F	White	79	Treatment on drug	Placebo	99	Acute myelogenous leukemia	1.05 mo	99	Prob not	Discontinued PRx	130	Treatment off drug	08-Nov-1999
832‡	M	White	82	Randomized withdrawal off drug	Off drug 9 days	470	Pneumonia	10.00 day	461	Prob not	No action with test drug	479	Randomized withdrawal off drug	10-Nov-2000
				Randomized withdrawal off drug	Off drug 18 days	479	Cardiac arrest (Adjudication committee considered death secondary to aspiration pneumonia and sepsis)	1.00 day	461	Def not	No action with test drug	479	Randomized withdrawal off drug	10-Nov-2000
956	M	White	81	Treatment on drug	Placebo	16	Ruptured aortic aneurysm	1.00 day	16	Def not	Discontinued PRx	16	Treatment on drug	16-Sep-1999

† Adjudicated as confirmed thromboembolic event. Adjudicated terms that differ from reported term are shown in parentheses.
‡ Nonfatal serious adverse experience occurred within 14 days of last dose of study medication. Investigators reported that fatal serious adverse experiences occurred more than 14 days after last dose of study medication.

[11; 3]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.2 Alzheimer's Disease—Protocol 078

2.2.2.1 Design

This is a placebo-controlled, parallel-group, double-blind, multicenter study to evaluate the effects of rofecoxib 25 mg on the prevention of Alzheimer's Disease and cognitive decline in patients ≥65 years of age with mild cognitive impairment. Complete information about study design is in the protocol synopsis [13]. Only patients who were not anticipated to need chronic NSAID or estrogen replacement during the trial were eligible. Patients with a history of angina or congestive heart failure with symptoms at rest, uncontrolled hypertension, or cerebrovascular disease (e.g., major stroke, transient ischemic events) were excluded. Eligible patients were randomized to receive rofecoxib 25 mg or placebo for 2 years or until 220 cases of clinically diagnosed probable or possible Alzheimer's Disease are observed, whichever comes later. Safety and tolerability were to be assessed at all visits (Baseline, Months 1, 4, 8, 12, 16, 20, 24, and endpoint confirmation visits). After enrollment was complete, the protocol was amended to allow concomitant use of low-dose aspirin (<100 mg/day) for cardioprotection.

This study is still ongoing and therefore has not achieved frozen file by the cutoff date for this SUR. Consequently, demographics, secondary diagnoses, and concomitant therapies by treatment group are not available.

2.2.2.2 Extent of Exposure

Table 14 presents the estimated extent of exposure to study medication as of the cutoff date. Most of the patients have been on study medication for >1 year.

Table 14

Number of Days on Therapy by Treatment—Protocol 078

	Treatment	
	Rofecoxib 25 mg	Placebo
N	721	729
Mean (SD)	500.16 (276.60)	549.50 (271.06)
Range (min to max)	1052 (0 to 1052)	1039 (0 to 1039)

[6]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.2.3 Fatal and Nonfatal Serious Adverse Experiences

Table 15 provides the numbers and percentages of patients with fatal and nonfatal serious clinical adverse experiences. These data were obtained from the Worldwide Adverse Experience System (WAES) database rather than the Clinical Trial System database, which has not been frozen, and is still blinded. The WAES database is more current than the Clinical Trial System database for this ongoing study. Specific clinical adverse experiences that occurred in ≥0.5% of any treatment group are displayed. A table displaying all serious clinical adverse experiences by treatment group is in [3]. Narratives for patients with serious clinical adverse experiences are in [11], but treatment groups are not identified in order to maintain the blind at the individual patient level for this ongoing study.

The proportion of patients with one or more serious clinical adverse experiences was similar in the 2 treatment groups. The proportion of patients known to have discontinued due to a serious adverse experience was also similar in the 2 groups (rofecoxib, 4.0%; placebo, 4.3%) [14]. The proportion of patients with serious clinical adverse experiences in the Body as a Whole, Digestive, Musculoskeletal, and Respiratory systems was slightly higher in the rofecoxib group than the placebo group. The proportion of patients with serious clinical adverse experiences in the Cardiovascular, Skin, and Urogenital systems was slightly higher in the placebo than the rofecoxib group. Specific adverse experiences other than basal cell carcinoma and hemorrhagic gastric ulcers had a similar incidence in both treatment groups. There were 4 patients in the rofecoxib group and 0 in the placebo group with a hemorrhagic gastric ulcer (ANs 425, 690, 1025, 1221). One of the patients (AN 425) was also on aspirin, and another patient (AN 1025) received aspirin then heparin and enoxaparin after coronary artery bypass surgery [11].

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 15

Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.5% in One or More Treatment Groups) by Body System—Protocol 078

	Treatment Group			
	Rofecoxib 25 mg (N=721)		Placebo (N=729)	
	n	(%)	n	(%)
With one or more serious adverse experiences	164	(22.7)	161	(22.1)
With no serious adverse experience	557	(77.3)	568	(77.9)
Body as a Whole/Site Unspecified	**41**	**(5.7)**	**31**	**(4.3)**
Chest pain	11	(1.5)	8	(1.1)
Malignant neoplasm	2	(0.3)	4	(0.5)
Syncope	6	(0.8)	6	(0.8)
Cardiovascular System	**46**	**(6.4)**	**52**	**(7.1)**
Angina pectoris	0	(0.0)	4	(0.5)
Atrial fibrillation	5	(0.7)	6	(0.8)
Carotid artery obstruction	0	(0.0)	7	(1.0)
Cerebrovascular accident	4	(0.6)	6	(0.8)
Congestive heart failure	3	(0.4)	4	(0.5)
Coronary artery disease	11	(1.5)	8	(1.1)
Myocardial infarction	5	(0.7)	7	(1.0)
Transient ischemic attack	6	(0.8)	7	(1.0)
Digestive System	**26**	**(3.6)**	**20**	**(2.7)**
Hemorrhagic gastric ulcer	4	(0.6)	0	(0.0)
Intestinal diverticulitis	1	(0.1)	4	(0.5)
Vomiting	4	(0.6)	1	(0.1)
Endocrine System	**1**	**(0.1)**	**0**	**(0.0)**
Eyes, Ears, Nose, and Throat	**1**	**(0.1)**	**3**	**(0.4)**
Hemic and Lymphatic System	**5**	**(0.7)**	**3**	**(0.4)**
Hepatobiliary System	**1**	**(0.1)**	**3**	**(0.4)**
Immune System	**1**	**(0.1)**	**0**	**(0.0)**
Metabolism and Nutrition	**1**	**(0.1)**	**1**	**(0.1)**
Musculoskeletal System	**22**	**(3.1)**	**15**	**(2.1)**
Hip fracture	7	(1.0)	3	(0.4)
Nervous System	**9**	**(1.2)**	**10**	**(1.4)**
Psychiatric Disorder	**5**	**(0.7)**	**3**	**(0.4)**

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 15 (Cont.)

Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.5% in One or More Treatment Groups) by Body System—Protocol 078

	Treatment Group			
	Rofecoxib 25 mg (N=721)		Placebo (N=729)	
	n	(%)	n	(%)
Respiratory System	**19**	**(2.6)**	**13**	**(1.8)**
Pneumonia	7	(1.0)	8	(1.1)
Skin and Skin Appendages	**14**	**(1.9)**	**32**	**(4.4)**
Basal cell carcinoma	9	(1.2)	21	(2.9)
Skin malignant neoplasm	2	(0.3)	8	(1.1)
Urogenital System	**25**	**(3.5)**	**32**	**(4.4)**
Bladder malignant neoplasm	1	(0.1)	4	(0.5)
Breast malignant neoplasm	4	(0.6)	2	(0.3)
Prostatic malignant neoplasm	10	(1.4)	13	(1.8)

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.

[3]

Deaths

There were 24 deaths in the study population prior to the data cutoff: 15 patients in the rofecoxib group and 9 in the placebo group. This includes patients who had a serious adverse experience that began within 14 days after the last dose of study medication but who died more than 14 days after the last dose of study medication. (The Clinical Study Report will include a summary of all deaths that occurred during follow-up, including patients who developed fatal serious adverse experiences more than 14 days after the last dose of study medication.) Table 16 is a listing of deaths by treatment group. Narratives for these patients are in [11]. None of the deaths was considered related to study medication. There was no apparent pattern suggesting a risk with rofecoxib. There were 5 patients in the rofecoxib group adjudicated as having sudden, unexplained death (4 cases, ANs 248, 359, 737, 799) or confirmed fatal thromboembolic events (AN 1025 with acute myocardial infarction) compared to 2 with sudden, unexplained death in the placebo group. However, the total number of confirmed thromboembolic cases (fatal and nonfatal) was not larger in the rofecoxib group than the placebo group (see Section 2.4.2). Three patients in the rofecoxib group died of a neoplasm

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

(carcinoma/leukemia) compared with 6 in the placebo group. A fifth patient in the rofecoxib group had a history of non-small cell lung carcinoma but died of a hemorrhagic duodenal ulcer. Another difference between the groups was the number of deaths related to trauma. There were 5 patients in the rofecoxib group (versus 0 on placebo) who died from head or chest trauma, hip fracture, or electrical shock. In contrast to Protocol 091, there were no patients in whom pneumonia was considered the primary cause of death.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 16

Listing of Deaths by Treatment Group—Protocol 078

AN	WAES No.	Gender	Age	Therapy	Rel. Day of Onset	Adverse Experience	Drug Relationship	Onset Date	Date of Death
264	99121965	M	76	Placebo	430	Colonic malignant neoplasm	No	11/26/1999	02/20/2001
294	00041761	M	77	Placebo	556	Malignant melanoma	No	02/28/2000	04/27/2000
308	01012577	M	85	Placebo	407	Myelogenous leukemia, acute renal failure, pneumonia	No	11/17/2000	11/26/2000
539	99061595	M	72	Placebo	243	Hypertension (insufficient data)	No	06/22/1999	06/22/1999
1144	00062812	F	94	Placebo	496	Pancreatic malignant neoplasm	No	03/01/2000	05/04/2000
1256	00111838	F	82	Placebo	674	Cardiac arrest (sudden death†)	No	11/16/2000	11/16/2000
1350	00110087	F	79	Placebo	708	Bladder malignant neoplasm	No	10/12/2000	10/22/2000
1378	99111806	M	74	Placebo	392	Acute myocardial infarction (sudden death†)	No	11/04/1999	11/04/1999
1547	00050406	M	82	Placebo	96	Metastatic neoplasm of unknown primary	No	05/01/2000	07/07/2000
158	00011935	M	82	Rofecoxib	430	Myocardial infarction (insufficient data)	No	01/15/2000	01/15/2000

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 16 (Cont.)

Listing of Deaths by Treatment Group—Protocol 078

AN	WAES No.	Gender	Age	Therapy	Rel. Day of Onset	Adverse Experience	Drug Relationship	Onset Date	Date of Death
205	00040385	M	85	Rofecoxib	496	Postoperative complication, hip fracture, pulmonary embolism	No	04/02/2000	04/03/2000
248	00112454	F	71	Rofecoxib	747	Unknown cause of death (sudden death†)	No	11/28/2000	11/28/2000
352	99091191	M	67	Rofecoxib	322	Hemorrhagic duodenal ulcer, non-small cell lung carcinoma	No	06/15/2000	06/16/2000
359	00091551	M	68	Rofecoxib	624	Atherosclerosis, hypertension (sudden death†)	No	08/08/2000	08/08/2000
583	99081659	M	70	Rofecoxib	357	Pulmonary embolism, pancreatic malignant neoplasm coagulation disorder	No	7/22/1999	08/26/1999
737	99011060	M	84	Rofecoxib	185	Cardiac arrest (sudden death†)	No	01/16/1999	01/16/1999
762	00080158	M	87	Rofecoxib	707	Metastatic prostate cancer renal failure	No	07/26/2000	10/07/2000
799	00080993	M	85	Rofecoxib	312	Cardiac arrest (sudden death†)	No	07/30/2000	07/30/2000

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 16 (Cont.)

Listing of Deaths by Treatment Group—Protocol 078

AN	WAES No.	Gender	Age	Therapy	Rel. Day of Onset	Adverse Experience	Drug Relationship	Onset Date	Date of Death
821	00080437	M	85	Rofecoxib	271	Head trauma	No	08/01/2000	08/01/2000
935	99040946	M	75	Rofecoxib	106	Trauma	No	04/08/1999	04/08/1999
1025	99020820	M	83	Rofecoxib	138	Acute myocardial infarction†	No	02/17/1999	02/17/1999
1097	99061411	M	69	Rofecoxib	248	Electrical shock	No	06/18/1999	06/18/1999
1423	01020692	M	83	Rofecoxib	611	Chest trauma	No	01/27/2001	01/27/2001
1453	99061591	M	80	Rofecoxib	53	Bacterial sepsis, acute myelogenous leukemia	No	6/15/1999	07/05/1999

† Adjudicated as sudden/unexplained death or confirmed thromboembolic event. Adjudicated terms that differ from reported term are shown in parentheses.

[3]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.3 Alzheimer's Disease—Protocol 126

2.2.3.1 Design

This study has a design which is similar to Protocol 091. It is a placebo-controlled, parallel-group, multicenter, 15-month, double-blind study to evaluate the efficacy and safety of rofecoxib 25 mg to slow the progression of symptoms of Alzheimer's Disease. Patients of either gender who were ≥50 years of age with probable Alzheimer's Disease were eligible to participate. Patients using NSAIDs for ≥7 days/month for the 2 months immediately prior to entry were not eligible. Patients were excluded if they were living in a nursing home or skilled nursing facility. They were also excluded if they had a history of angina or congestive heart failure with symptoms at rest, uncontrolled hypertension, or cerebrovascular disease (e.g., major stroke or transient ischemic attacks). Eligible patients were randomized to rofecoxib 25 mg or placebo for 12 months. This was to be followed by an additional 3-month treatment phase in which 90% of the patients initially assigned to rofecoxib were treated with placebo while the other patients remained on their initial treatment. Safety and tolerability were assessed at each visit (Screening, Months 1, 3, 6, 9, 12, 13.5, and 15). The protocol synopsis contains complete information about study design [10]. The trial was still enrolling patients when it was prematurely terminated in Mar-2001 because Protocol 091 showed that rofecoxib 25 mg was not more effective than placebo in slowing the progression of symptoms of Alzheimer's Disease. Frozen file was not achieved by the cutoff date for this SUR. Consequently, demographics, secondary diagnoses, and concomitant therapies by treatment group are not available.

2.2.3.2 Extent of Exposure

A total of 757 patients have been randomized and are evaluable for safety. The estimated duration of treatment is shown in Table 17. Only 1 patient was treated for longer than 12 months.

Table 17

Number of Days on Therapy by Treatment—Protocol 126

	Treatment	
	Rofecoxib 25 mg	Placebo
N	381	376
Mean (SD)	155.96 (94.90)	161.84 (95.68)
Range (min to max)	349 (1 to 350)	429 (1 to 430)

[6]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.3.3 Fatal and Nonfatal Serious Adverse Experiences

Table 18 provides the numbers and percentages of patients with fatal and nonfatal serious clinical adverse experiences. This data was obtained from the WAES database rather than the Clinical Trial System database, which has not been frozen and is still blinded. Specific clinical adverse experiences that occurred in ≥0.5% of any treatment group are displayed. The overall number of serious adverse experiences reported in each treatment group were similar and low. The proportion of patients known to have discontinued treatment because of a serious clinical adverse experience was lower with rofecoxib (1.3%) than with placebo (2.1%) [14]. There were no reports of gastrointestinal bleeding or gastric ulcers in the rofecoxib group, but there was a report of hemorrhagic gastric ulcer in the placebo group. A table displaying all serious clinical adverse experiences by treatment group is in [3]. Narratives for patients with serious clinical adverse experiences are in [11], but the treatment groups are not identified in order to maintain the blind at the individual patient level until the data has been completely reviewed and frozen file achieved.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 18

Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.5% in One or More Treatment Groups) by Body System—Protocol 126

	Treatment Group			
	Rofecoxib 25 mg (N=381)		Placebo (N=376)	
	n	(%)	n	(%)
With one or more serious adverse experiences	34	(8.9)	29	(7.7)
With no serious adverse experience	347	(91.1)	347	(92.3)
Body as a Whole/Site Unspecified	**13**	**(3.4)**	**9**	**(2.4)**
Chest pain	3	(0.8)	1	(0.3)
Dizziness	2	(0.5)	0	(0.0)
Malignant neoplasm	0	(0.0)	2	(0.5)
Syncope	3	(0.8)	2	(0.5)
Cardiovascular System	**13**	**(3.4)**	**6**	**(1.6)**
Cerebrovascular accident	3	(0.8)	1	(0.3)
Congestive heart failure	3	(0.8)	0	(0.0)
Coronary artery occlusion	2	(0.5)	1	(0.3)
Myocardial infarction	0	(0.0)	2	(0.5)
Transient ischemic attack	2	(0.5)	1	(0.3)
Digestive System	**2**	**(0.5)**	**5**	**(1.3)**
Pancreatitis	0	(0.0)	2	(0.5)
Hemic and Lymphatic System	**0**	**(0.0)**	**3**	**(0.8)**
lymphoma	0	(0.0)	2	(0.5)
Musculoskeletal System	**7**	**(1.8)**	**3**	**(0.8)**
Hip fracture	2	(0.5)	0	(0.0)
Muscular weakness	3	(0.8)	0	(0.0)
Nervous System	**3**	**(0.8)**	**3**	**(0.8)**
Seizure	2	(0.5)	1	(0.3)
Psychiatric Disorder	**3**	**(0.8)**	**1**	**(0.3)**
Respiratory System	**3**	**(0.8)**	**1**	**(0.3)**
Skin and Skin Appendages	**1**	**(0.3)**	**6**	**(1.6)**
Basal cell carcinoma	1	(0.3)	6	(1.6)
Urogenital System	**2**	**(0.5)**	**2**	**(0.5)**

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.

[5]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Deaths

There were 7 deaths in the study population: 4 patients in the rofecoxib group and 3 in the placebo group. (The Clinical Study Report will include a summary of all deaths that occurred during follow-up, including patients who developed fatal serious adverse experiences more than 14 days after the last dose of study medication.) Table 19 is a listing of deaths by treatment group. Narratives for these patients are in [11]. All but 1 of the deaths (AN 125) were considered not related to study medication. There was no apparent pattern suggesting a risk with rofecoxib. Two patients on rofecoxib (ANs 532 and 743) and one on placebo (AN 661) had a confirmed thromboembolic event. The 2 rofecoxib patients were both taking aspirin and had intracranial hemorrhagic events.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 19

Listing of Deaths by Treatment Group—Protocol 126

AN	WAES No.	Gender	Age	Therapy	Relative Day of Onset	Adverse Experience	Drug Relationship	Onset Date	Date of Death
257	00100108	M	79	Placebo	82	Trauma	No	09/25/2001	09/25/2000
635	00120930	F	78	Placebo	216	Bacterial sepsis gastrointestinal bleeding lymphoma	No	12/7/2000	12/14/2000
661	00112101	M	77	Placebo	236	Myocardial infarction†, meningitis	No	11/29/2000	11/29/2000
125	01021457	F	86	Rofecoxib	214	Unknown cause of death, gastrointestinal perforation - large intestine	Yes	02/16/2001	02/16/2001
466	00110088	M	86	Rofecoxib	190	Hip fracture, dyspnea	No	11/17/2000	11/18/2000
532	00092449	M	80	Rofecoxib	48	Cerebrovascular accident (hemorrhagic CVA†)	No	09/20/2000	09/20/2000
743	01010909	F	76	Rofecoxib	82	Intracranial hemorrhage (hemorrhagic CVA†) cerebral atherosclerosis	No	12/27/2000	01/04/2001

† Adjudicated as confirmed thromboembolic event. Adjudicated term is in parentheses.

[11; 5]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.4 Protocols 078, 091, and 126 Combined

Protocols 078, 091, and 126 each evaluated an older population with cognitive impairment. Table 20 summarizes the serious clinical adverse experiences by body system for the 3 protocols combined [15]. Events with an incidence ≥0.3% in any treatment group are shown. For this analysis, patients in Protocol 091 randomized to receive rofecoxib for the first 12 months then placebo for 3 months are only included in the rofecoxib group; data from the subsequent placebo period are not included. While the numbers of patients exposed to rofecoxib and placebo are similar, the extent of exposure was slightly less for rofecoxib than placebo since 199 of the patients initially randomized to rofecoxib in Protocol 091 were reassigned to placebo after 12 months as per the study design [3]. Overall, the proportion of patients with 1 or more serious adverse experiences was similar during exposures to rofecoxib and placebo. The type and frequency of events were generally similar in the 2 treatment groups. The proportion of patients with serious adverse experiences in the Body as a Whole, Digestive, and Respiratory systems was slightly higher in the rofecoxib than the placebo group. The incidence of specific adverse experiences within the respiratory system (e.g., pneumonia) was similar in the 2 treatment groups. The placebo group had a slightly higher incidence than the rofecoxib group in the Skin and Skin Appendage system, primarily due to a larger number of patients with skin cancers. Both NSAIDs and COX-2 inhibitors are associated with reductions in glomerular filtration rate and reductions in the renal excretion of sodium with the potential for fluid retention, edema, and hypertension. In both the rofecoxib and placebo groups, the number of patients with serious adverse experiences such as edema (1 versus 0), congestive heart failure (10 versus 7), hypertension (3 versus 1) or renal failure (3 versus 2) were low and similar.

Table 20

Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.3% in One or More Treatment Groups) by Body System—Protocols 078, 091, and 126

	Rofecoxib 25 mg (N=1448) n (%)	Placebo (N=1451) n (%)
With one or more serious adverse experiences	261 (18.0)	260 (17.9)
With no serious adverse experience	1187 (82.0)	1191 (82.1)
Body as a Whole/Site Unspecified	**70 (4.83)**	**55 (3.79)**
Chest pain	14 (0.97)	10 (0.69)
Dehydration	6 (0.41)	4 (0.28)
Malignant neoplasm	2 (0.14)	6 (0.41)
Syncope	14 (0.97)	14 (0.96)
Cardiovascular System	**77 (5.32)**	**82 (5.65)**
Angina pectoris	2 (0.14)	5 (0.34)

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 20 (Cont.)

Number (%) of Patients With Fatal or Nonfatal Serious Clinical Adverse Experiences (Incidence ≥0.3% in One or More Treatment Groups) by Body System—Protocols 078, 091, and 126

	Rofecoxib 25 mg (N=1448) n (%)	Placebo (N=1451) n (%)
Atrial fibrillation	8 (0.55)	7 (0.48)
Carotid artery obstruction	2 (0.14)	8 (0.55)
Cerebrovascular accident	10 (0.69)	10 (0.69)
Congestive heart failure	10 (0.69)	7 (0.48)
Coronary artery disease	11 (0.76)	9 (0.62)
Myocardial infarction	7 (0.48)	12 (0.83)
Transient ischemic attack	9 (0.62)	8 (0.55)
Digestive System	**40 (2.76)**	**32 (2.21)**
Gastrointestinal bleeding	5 (0.35)	1 (0.07)
Vomiting	5 (0.35)	3 (0.21)
Endocrine System	**2 (0.14)**	**1 (0.07)**
Eyes, Ears, Nose, and Throat	**1 (0.07)**	**4 (0.28)**
Hemic and Lymphatic System	**6 (0.41)**	**8 (0.55)**
Hepatobiliary System	**1 (0.07)**	**4 (0.28)**
Immune System	**1 (0.07)**	**0 (0.00)**
Metabolism and Nutrition	**3 (0.21)**	**3 (0.21)**
Musculoskeletal System	**37 (2.56)**	**29 (2.00)**
Hip fracture	10 (0.69)	5 (0.34)
Muscular weakness	8 (0.55)	3 (0.21)
Nervous System	**17 (1.17)**	**19 (1.31)**
Psychiatric Disorder	**12 (0.83)**	**11 (0.76)**
Respiratory System	**34 (2.35)**	**23 (1.59)**
Pneumonia	14 (0.97)	15 (1.03)
Skin and Skin Appendages	**20 (1.38)**	**42 (2.89)**
Basal cell carcinoma	13 (0.90)	29 (2.00)
Cellulitis	5 (0.35)	2 (0.14)
Skin malignant neoplasm	3 (0.21)	10 (0.69)
Urogenital System	**35 (2.42)**	**39 (2.69)**
Breast malignant neoplasm	6 (0.41)	4 (0.28)
Prostatic malignant neoplasm	12 (0.83)	14 (0.96)

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.

[15]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Deaths

There were 53 deaths in Protocols 078, 091, and 126 (in patients with a fatal or nonfatal serious adverse experience on drug or within 14 days of last dose). The deaths were attributed to a variety of causes. As would be expected in an elderly population with cognitive impairment, the most common causes of death were thromboembolic cardiovascular events, neoplasms, various forms of trauma, and pneumonia. All but 1 of the deaths (Protocol 126, AN 125) were considered by the investigator to be not related to study medication. There were more deaths in the rofecoxib group (33) than the placebo group (20). Review of the individual deaths shows the rofecoxib and placebo groups had similar numbers of deaths due to neoplasms (6 versus 9) and pneumonia (4 versus 2). Compared with the placebo group, the rofecoxib group had 6 more deaths due to trauma (e.g., falls, burns). Compared with the placebo group, the rofecoxib group had 5 more deaths adjudicated as due to thromboembolic cardiovascular events (10 versus 5). Review of the thromboembolic events shows a variety of events, including 2 patients in the rofecoxib group who were also taking aspirin and had intracranial bleeding (Protocol 126 ANs 532, 743). The proportion of patients with a serious cardiovascular adverse experience (fatal or nonfatal) was similar in the 2 groups (rofecoxib, 5.3%; placebo, 5.7%), suggesting the difference in deaths was not due to a pharmacologic effect. This is supported by the analysis of confirmed thromboembolic events in the Alzheimer Studies (Section 3.2.1) and the cardiovascular meta-analysis of data from 23 clinical trials (Section 3.4). Overall, review of the deaths does not identify a clear a pattern or likely relationship to rofecoxib.

2.2.5 Bone Mineral Density—Protocol 083

2.2.5.1 Design

This was a multicenter, randomized, active comparator- and partially placebo-controlled, parallel-group, 15-month, double-blind study to assess the effects of rofecoxib versus ibuprofen on markers of bone turnover and bone density in patients with osteoarthritis. The protocol contains complete information about study design [16]. Osteoarthritis (OA) was diagnosed individually by clinical criteria. Two types of patients were studied: (1) patients with a history of chronic, extensive NSAID use (i.e., >20 days per month) for the treatment of OA; and (2) patients without a history of chronic, extensive NSAID use (i.e., ≤20 days per month; regular use of acetaminophen allowed) for the treatment of OA. There was a 12-week, double-blind, active-comparator- and placebo-controlled treatment period. This was followed by a double-blind, active-comparator treatment period for a total study duration of 15 months. At allocation, 305 patients who met entry criteria were randomized to one of the following treatment sequences (Weeks 1 to 12/Weeks 12 to 65): placebo/rofecoxib 25 mg daily (n=51), placebo/ibuprofen 800 mg three times daily (n=49), rofecoxib 25 mg daily/rofecoxib 25 mg daily (n=98), and ibuprofen 800 mg three times daily/ibuprofen 800 mg three times daily (n=107) [16]. Concomitant use of low-dose aspirin was prohibited.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 21 shows the demographics of the patients studied. There were no clinically important differences between treatment groups.

Table 21

Baseline Demographics by Treatment Group—Protocol 083

Total N	Placebo/ Rofecoxib 51	Placebo/ Ibuprofen 49	Rofecoxib/ Rofecoxib 98	Ibuprofen/ Ibuprofen 107	Total 305
Gender—n (%)					
Male	22 (43.1)	21 (42.9)	49 (50.0)	49 (45.8)	141 (46.2)
Female	29 (56.9)	28 (57.1)	49 (50.0)	58 (54.2)	164 (53.8)
Race—n (%)					
White	45 (88.2)	43 (87.8)	83 (84.7)	94 (87.9)	265 (86.9)
Black	2 (3.9)	3 (6.1)	6 (6.1)	6 (5.6)	17 (5.6)
Hispanic	4 (7.8)	2 (4.1)	6 (6.1)	5 (4.7)	17 (5.6)
Other	0 (0.0)	1 (2.0)	3 (3.0)	2 (1.9)	6 (2.0)
Age (years)					
Mean	62.63	65.04	62.46	61.92	62.71
SD	8.31	7.77	8.94	8.11	8.39
Range	(49, 78)	(49, 83)	(48, 88)	(49, 80)	(48, 88)

[2]

2.2.5.2 Extent of Exposure

Table 22 shows the extent of exposure to study drug.

Table 22

Number of Patients on Study Drug—Protocol 083

Treatment	Total Patients	Days on Drug	
		Range	Mean
Population I (Weeks 1 to 12)			
Placebo	100	1 to 98	72.7
Rofecoxib	98	3 to 100	74.5
Ibuprofen	107	4 to 98	73.7
Population II (Weeks 1 to 65)			
Rofecoxib	136	3 to 479	305.8
Ibuprofen	148	1 to 494	291.8

[2]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.5.3 Fatal and Nonfatal Serious Adverse Experiences

Table 23 provides the numbers and percentages of patients with fatal and nonfatal clinical serious adverse experiences according to the treatment period in which they occurred. A slightly higher percentage of patients in the ibuprofen group experienced serious events compared to the rofecoxib group (10.8% versus 8.8%). Importantly, 8 patients (5.4%) in the ibuprofen group (ANs 015, 063, 252, 254, 690, 702, 788, 848) experienced serious cardiovascular events compared with 1 patient (0.7%) in the rofecoxib group (AN 130). There were no other clinically important differences between the treatment groups. Few patients in any group discontinued treatment because of a serious adverse experience (placebo—0, rofecoxib—1, ibuprofen—3).

Table 23

Numbers (%) of Patients With Fatal and Nonfatal Clinical Serious Adverse Experiences—Protocol 083

	Placebo (N=100)		Rofecoxib 25 mg (N=136)		Ibuprofen 2400 mg (N=148)	
	n	(%)	n	(%)	n	(%)
Patients with one or more clinical serious adverse experiences	1	(1.0)	12	(8.8)	16	(10.8)
Patients with no clinical serious adverse experience	99	(99.0)	124	(91.2)	132	(89.2)
Body as a Whole/Site Unspecified	**0**	**(0.0)**	**2**	**(1.5)**	**3**	**(2.0)**
Chest pain	0	(0.0)	1	(0.7)	1	(0.7)
Inguinal hernia	0	(0.0)	1	(0.7)	0	(0.0)
Syncope	0	(0.0)	0	(0.0)	1	(0.7)
Wound infection	0	(0.0)	0	(0.0)	1	(0.7)
Cardiovascular System	**1**	**(1.0)**	**1**	**(0.7)**	**8**	**(5.4)**
Angina pectoris	0	(0.0)	0	(0.0)	1	(0.7)
Atrial fibrillation	0	(0.0)	0	(0.0)	1	(0.7)
Cardiac arrest	0	(0.0)	0	(0.0)	1	(0.7)
Cardiac tamponade	0	(0.0)	0	(0.0)	1	(0.7)
Cardiomyopathy	0	(0.0)	1	(0.7)	0	(0.0)
Coronary artery disease	0	(0.0)	0	(0.0)	1	(0.7)
Deep venous thrombosis	1	(1.0)	0	(0.0)	0	(0.0)
Hypertension	0	(0.0)	0	(0.0)	2	(1.4)
Myocardial infarction	0	(0.0)	0	(0.0)	1	(0.7)
Pulmonary edema	0	(0.0)	0	(0.0)	1	(0.7)
Unstable angina	0	(0.0)	0	(0.0)	2	(1.4)
Ventricular fibrillation	0	(0.0)	0	(0.0)	1	(0.7)
Digestive System	**0**	**(0.0)**	**2**	**(1.5)**	**0**	**(0.0)**
Intestinal obstruction	0	(0.0)	1	(0.7)	0	(0.0)
Lower gastrointestinal hemorrhage	0	(0.0)	1	(0.7)	0	(0.0)
Hemic and Lymphatic	**0**	**(0.0)**	**1**	**(0.7)**	**0**	**(0.0)**
Hodgkin's lymphoma	0	(0.0)	1	(0.7)	0	(0.0)

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 23 (Cont.)

Numbers (%) of Patients With Fatal and Nonfatal Clinical Serious Adverse Experiences—Protocol 083

	Placebo (N=100)		Rofecoxib 25 mg (N=136)		Ibuprofen 2400 mg (N=148)	
	n	(%)	n	(%)	n	(%)
Hepatobiliary System	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.7)**
Cholecystitis	0	(0.0)	0	(0.0)	1	(0.7)
Musculoskeletal System	**1**	**(1.0)**	**3**	**(2.2)**	**2**	**(1.4)**
Hip osteoarthritis	0	(0.0)	1	(0.7)	0	(0.0)
Intervertebral disc displacement	0	(0.0)	1	(0.7)	1	(0.7)
Osteoarthritis	1	(1.0)	1	(0.7)	0	(0.0)
Traumatic arthropathy	0	(0.0)	0	(0.0)	1	(0.7)
Psychiatric Disorder	**0**	**(0.0)**	**2**	**(0.7)**	**0**	**(0.0)**
Depression	0	(0.0)	1	(0.7)	0	(0.0)
Refractory depression†	0	(0.0)	1	(0.7)	0	(0.0)
Skin and Skin Appendages	**0**	**(0.0)**	**1**	**(0.7)**	**2**	**(1.4)**
Basal cell carcinoma	0	(0.0)	1	(0.7)	2	(1.4)
Urogenital System	**0**	**(0.0)**	**1**	**(0.7)**	**2**	**(1.4)**
Breast malignant neoplasm	0	(0.0)	0	(0.0)	1	(0.7)
Prostatic malignant neoplasm	0	(0.0)	0	(0.0)	1	(0.7)
Urinary tract obstruction	0	(0.0)	1	(0.7)	0	(0.0)

†Incorrectly noted in supporting reference as refraction disorder

[2]

Deaths

One death occurred in the trial in Population II: a 60-year-old white woman (Study No. 023, AN 0063, WAES 99020977) with a history of hypertension and obesity was randomized to ibuprofen 800 mg three times daily on 11-Sept-1998. The patient's family reported that the patient had experienced a cardiac arrest and died in her sleep during the night of 10-Feb-1999. Concomitant therapy included acetaminophen 325 mg for treatment of OA, hydrochlorothiazide, and lisinopril. The reporting physician considered the event to be probably not related to study therapy [17].

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.6 Chronic Prostatitis—Protocol 118

2.2.6.1 Design

This placebo-controlled, parallel-group, double-blind, multicenter trial examined the effects of rofecoxib for 6 weeks on pain associated with chronic prostatitis/chronic pelvic pain syndrome. Men older than 18 years old with chronic pelvic pain for at least 3 months were eligible for inclusion. Men with signs or symptoms of urinary tract infection or sexually transmitted disease were excluded as were patients who had undergone any from of prostate surgery. Additional exclusions were angina or congestive heart failure with symptoms at rest, or history of coronary artery angioplasty or bypass grafting, uncontrolled hypertension, stroke within 2 years, transient ischemic event, or neoplastic disease. Following a 1-week placebo run-in period, eligible patients were randomized to placebo, rofecoxib 25 mg/day, or rofecoxib 50 mg/day for 6 weeks. Clinical safety was assessed at each on-drug visit (Weeks 1, 3, and 6). The protocol provides complete details regarding study design [18].

Table 24 shows the baseline demographics of the patients studied. In each treatment group the most common secondary diagnoses were drug allergy, headache, and previous surgical procedures (appendectomy, herniorrhaphy, tonsillectomy). In each treatment group, the most commonly used concomitant medications were vitamins, antacids, and analgesics (aspirin was prohibited). There were no clinically important differences between treatment groups with regard to demographics, secondary conditions, or concomitant medications.

Table 24

Baseline Demographics by Treatment Group—Protocol 118

Statistic/Category		Rofecoxib		
	Placebo	25 mg	50 mg	Total
Total N	59	53	49	161
Age (years)				
Mean (SD)	45.8 (12.0)	44.1 (12.0)	48.0 (13.3)	45.9 (12.4)
Median	45.0	43.0	48.0	44.0
Range	19 to 76	20 to 75	26 to 80	19 to 80
Race—n (%)				
White	47 (79.7)	47 (88.7)	42 (85.7)	136 (84.5)
Black	8 (13.6)	4 (7.5)	3 (6.1)	15 (9.3)
Hispanic	3 (5.1)	2 (3.8)	2 (4.1)	7 (4.3)
Asian	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.6)
Multiracial	0 (0.0)	0 (0.0)	2 (4.1)	2 (1.2)

[4]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.6.2 Extent of Exposure

A total of 49 patients received rofecoxib 50 mg, 53 received rofecoxib 25 mg, and 59 received placebo for up to 6 weeks in this completed study.

Table 25

Number of Days on Therapy by Treatment—Protocol 118

	Treatment		
	Rofecoxib 50 mg	Rofecoxib 25 mg	Placebo
N	51	53	58
Mean	37.2	36.4	38.4
Range (min to max)	48 (1 to 49)	50 (1 to 51)	46 (4 to 50)

[4]

2.2.6.3 Fatal and Nonfatal Serious Adverse Experiences

Four patients had a serious adverse experience—2 patients who received rofecoxib 50 mg and 2 patients who received placebo (see Table 26). There were no deaths reported. A listing of patients with serious clinical adverse experiences is in [4], and narratives for the patients are in [19].

Table 26

Number (%) of Patients With Serious Clinical Adverse Experiences—Protocol 118

	Placebo (N=59)	Rofecoxib 25 mg (N=53)	Rofecoxib 50 mg (N=49)
	n (%)	n (%)	n (%)
Patients with one or more adverse experiences	2 (3.4)	0 (0.0)	2 (4.1)
Patients with no adverse experience	57 (96.6)	53 (100.0)	47 (95.9)
Body as whole/site unspecified	**1 (1.7)**	**0 (0.0)**	**1 (2.0)**
Chest pain	1 (1.7)	0 (0.0)	1 (2.0)
Cardiovascular system	**1 (1.7)**	**0 (0.0)**	**0 (0.0)**
Atrial flutter	1 (1.7)	0 (0.0)	0 (0.0)
Musculoskeletal system	**0 (0.0)**	**0 (0.0)**	**1 (2.0)**
Musculoskeletal chest pain	0 (0.0)	0 (0.0)	1 (2.0)

[4]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.7 Chronic Low Back Pain—Protocols 120 and 121

2.2.7.1 Design

Protocols 120 and 121 were identical multicenter, randomized, placebo-controlled, parallel group, 4-week, double-blind studies conducted to evaluate the efficacy and safety of rofecoxib with that of placebo in the treatment of chronic low back pain. The protocols contain complete information about study design [20]. Inclusion criteria were: back pain present for at least 3 months prior to study entry and for the majority of days in the month preceding study entry, and regular use of NSAIDs, acetaminophen, codeine, or propoxyphene. After the prestudy analgesic washout, patients were randomized to rofecoxib 50 mg, rofecoxib 25 mg, or placebo for 4 weeks (approximately 100 to 120 patients per group).

Table 27 shows the demographics of the patients in Protocols 120 and 121. The populations in the 2 trials were similar, and within each trial there were no clinically important differences between treatment groups with regard to demographics, secondary diagnoses, or concomitant therapies. The most common secondary diagnoses in both protocols were drug allergy (33 to 45%), hypertension (23 to 30%), OA (25 to 31%), and being status post-hysterectomy. The most frequently used concomitant medications in both trials were anti-inflammatory and antirheumatic drugs, analgesics other than rescue acetaminophen, vitamins, and sex hormones (aspirin was prohibited) [8]. Given the identical protocols and similar populations, the safety data from the 2 protocols are presented together.

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 27

Baseline Patient Characteristics—Chronic Low Back Pain Studies
(Protocols 120 and 121—Treatment Groups in Each Protocol Combined)

	Protocol 120		Protocol 121		Total	
	n	(%)	n	(%)	n	(%)
Age (years)						
Mean	52.5		54.5		53.4	
SD	13.1		12.6		12.9	
Gender						
Female	240	(63.2)	190	(61.3)	430	(62.3)
Male	140	(36.8)	120	(38.7)	260	(37.7)
Race						
White	341	(89.7)	275	(88.7)	616	(89.3)
Black	28	(7.4)	19	(6.1)	47	(6.8)
Hispanic	6	(1.6)	10	(3.2)	16	(2.3)
Asian	1	(0.3)	2	(0.6)	3	(0.4)
Native American	2	(0.5)	1	(0.3)	3	(0.4)
Multiracial	1	(0.3)	2	(0.6)	3	(0.4)
Indian	1	(0.3)	1	(0.3)	2	(0.3)

[8]

2.2.7.2 Extent of Exposure

Table 28 shows the extent of exposure to study medication in Protocols 120 and 121. The mean duration of treatment was approximately 26 days.

Table 28

Number of Days on Treatment—Chronic Low Back Pain Studies
(Protocols 120 and 121 Combined)

	Treatment		
	Rofecoxib 25 mg	Rofecoxib 50 mg	Placebo
N	233	232	228
Mean	26.1	25.9	25.2
Range (min to max)	34 (2 to 36)	34 (1 to 35)	37 (1 to 38)

[8]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.7.3 Fatal and Nonfatal Serious Adverse Experiences

The number and incidence of nonfatal serious adverse experiences (within 14 days of study medication) were 1 (0.4%), 4 (1.7%), and 3 (1.3%) for the placebo and 25- and 50-mg rofecoxib groups, respectively. None of these adverse experiences was considered by the investigators to be drug related. Two of the patients in the 25-mg group and 1 in the 50-mg group discontinued treatment because of a serious adverse experience. There were no deaths reported. Table 29 provides a listing of patients with serious adverse experiences in the 2 protocols. Narratives for these patients are in [21].

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 29

Listing of Patients With Serious Clinical Adverse Experiences
Chronic Low Back Pain Studies (Protocols 120 and 121 Combined)

Study Number	AN	Gender	Race	Age	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontinuation	Intensity	Drug Relationship	Action Taken	Outcome
Placebo												
120-041	1372	M	White	72	7	Syncope	2.00 days	13	Severe	Definitely not	No action with test drug	Recovered
Rofecoxib 25 mg												
120-022	1273	F	White	75	8	Atrial fibrillation	20.00 days	19	Severe	Definitely not	Discontinued PRx	Recovered
121-017	2158†	F	Black	59	4	Pneumonia	1.08 months	36	Moderate	Definitely not	Interrupted PRx	Recovered
121-029	2082‡	M	White	69	23	Skin malignant neoplasm	15.00 days	16	Mild	Definitely not	No action with test drug	Recovered
121-039	2214	M	White	55	24	Appendicitis	23.59 hours	24	Severe	Probably not	Discontinued PRx	Recovered
Rofecoxib 50 mg												
120-001	1154	F	white	51	4	Acute myocardial infarction	7.00 days	4	Severe	Probably not	Discontinued PRx	Recovered
120-006	1336	F	white	65	24	Presyncope	4.00 days	28	Moderate	Probably not	No action with test drug	Recovered
121-037	2196	F	white	31	14	Ovarian cyst	6.00 days	29	Severe	Definitely not	Interrupted PRx	Recovered

PRx = Prime therapy (study drug).
† This patient was off study medication 1 day prior to the onset of the serious adverse experience.
‡ This patient was off study medication 7 days prior to the onset of the serious adverse experience.

[8]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.8 Naproxen Comparison—Protocol 901

2.2.8.1 Design

This parallel group, double-blind study compared the efficacy, tolerability, and safety of rofecoxib 12.5 mg versus naproxen 1000 mg/day in the treatment of OA. Patients were randomized to receive rofecoxib or naproxen for 6 weeks. Low-dose aspirin (<100 mg) could be used concomitantly. The protocol synopsis is in [22]. The study was conducted at multiple centers in Europe (901-OC) and Asia (901-OF). The baseline demographics for the populations enrolled in Europe and Asia are shown in Table 30. The most commonly used concomitant medications were analgesics, antihypertensive agents, and sex hormones, and the most common secondary conditions were hypertension and history of surgical procedures (appendectomy, cholecystectomy, hysterectomy, tonsillectomy). Within each geographic area, there were no meaningful differences between treatment groups with regard to demographics, secondary diagnoses, or concomitant therapies [7].

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 30

Baseline Demographics by Treatment Group—Protocol 901

	901—OF		901—OC	
	Rofecoxib 12.5 mg (N=229)	Naproxen (N=233)	Rofecoxib 12.5 mg (N=242)	Naproxen (N=240)
Total	n (%)	n (%)	n (%)	n (%)
Gender—n (%)				
Male	39 (17.0)	44 (18.9)	54 (22.3)	67 (27.9)
Female	190 (83.0)	189 (81.1)	188 (77.7)	173 (72.1)
Race—n (%)				
White	0 (0.0)	0 (0.0)	231 (95.5)	232 (96.7)
Black	0 (0.0)	0 (0.0)	3 (1.2)	6 (2.5)
African	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	229 (100.0)	233 (100.0)	0 (0.0)	0 (0.0)
Hispanic American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multi-Racial	0 (0.0)	0 (0.0)	7 (2.9)	2 (0.8)
Indian	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Age (years)				
20 and under				
21 to 30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
31 to 40	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
41 to 50	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.8)
51 to 60	35 (15.3)	33 (14.2)	22 (9.1)	28 (11.7)
61 to 70	81 (35.4)	84 (36.1)	64 (26.4)	60 (25.0)
71 to 80	71 (31.0)	80 (34.3)	102 (42.1)	102 (42.5)
81 to 90	40 (17.5)	33 (14.2)	46 (19.0)	46 (19.2)
Over 90	1 (0.4)	2 (0.9)	6 (2.5)	1 (0.4)
Mean	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
SD	60.6	60.1	63.2	62.5
Median	9.34	9.17	9.08	9.39
Range	60.0	60.0	64.0	63.0
	40 to 84	40 to 86	38 to 85	37 to 91

[7]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.8.2 Extent of Exposure

A total of 471 patients received rofecoxib 12.5 mg and 473 received naproxen 1000 mg for approximately 6 weeks [7]. The mean duration of therapy by treatment for the populations enrolled in Europe (901-OC) and Asia (901-OF) are shown in Table 31.

Table 31

Number of Days on Therapy by Treatment—Protocol 901

	901—F		901—C	
	Rofecoxib 12.5 mg	Naproxen	Rofecoxib 12.5 mg	Naproxen
N	229	233	241	240
Mean	41.0	39.3	40.0	40.6
Range (min to max)	53 (1 to 54)	54 (1 to 55)	73 (1 to 74)	53 (6 to 59)

[7]

2.2.8.3 Fatal and Nonfatal Serious Adverse Experiences

Table 32 provides the numbers and percentages of patients with fatal and nonfatal serious clinical adverse experiences for each treatment group. The proportion of patients with serious adverse experiences was low and similar in the rofecoxib (1.5%) and naproxen (2.3%) groups. The table indicates that there were 6 patients with drug overdoses in the study. These 6 patients (ANs 3227, 3230, 3243, 3247, 3261, 3124) took more medication than the instructions stated and were coded as drug overdoses but in fact had no serious clinical adverse experience. A listing of all patients with adverse experiences coded as serious is in [7] and narratives for the cases are in [23].

There was 1 death (AN 2301). A 55-year-old woman with a history of chest pain and palpitations was found dead in bed 4 days after taking rofecoxib 12.5 mg for 4 days. Autopsy revealed coronary artery disease [23].

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 32

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System—Protocol 901

	Rofecoxib 12.5 mg (N=471)		Naproxen 1000 mg (N=473)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	7	(1.5)	11	(2.3)
Patients with no adverse experience	464	(98.5)	462	(97.7)
Body as a Whole/Site Unspecified	**2**	**(0.4)**	**4**	**(0.8)**
Drug overdose	2	(0.4)	4	(0.8)
Cardiovascular System	**3**	**(0.6)**	**2**	**(0.4)**
Angina pectoris	1	(0.2)	0	(0.0)
Cardiac arrest	1	(0.2)	0	(0.0)
Congestive heart failure	1	(0.2)	1	(0.2)
Unstable angina	0	(0.0)	1	(0.2)
Digestive System	**0**	**(0.0)**	**3**	**(0.6)**
Duodenal ulcer	0	(0.0)	1	(0.2)
Gastric ulcer	0	(0.0)	1	(0.2)
Hemorrhagic gastric ulcer	0	(0.0)	1	(0.2)
Hepatobiliary System	**1**	**(0.2)**	**1**	**(0.2)**
Acute cholecystitis	0	(0.0)	1	(0.2)
Choledocholithiasis	1	(0.2)	0	(0.0)
Nervous System	**0**	**(0.0)**	**1**	**(0.2)**
Stupor	0	(0.0)	1	(0.2)
Urogenital System	**1**	**(0.2)**	**0**	(0.0)
Uterine fibroid	1	(0.2)	0	(0.0)

[7]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.9 ARTHROTEC™ Comparison—Protocol 902

2.2.9.1 Design

This parallel group, randomized, double-blind protocol evaluated the tolerability profile of rofecoxib 12.5 mg versus ARTHROTEC™ (diclofenac 50 mg/misoprostol 200 mcg) in patients with osteoarthritis. Patients received treatment for 6 weeks. Concomitant low-dose aspirin (<100 mg/day) was allowed. The protocol synopsis is provided in [24]. The study was conducted at multiple centers in Europe (Protocol 902-OD) and in South and Central America (Protocol 902-OA). The baseline demographics for the populations enrolled in Europe and the Americas are shown in Table 33. The most commonly used concomitant medications were vitamins, sex hormones, and analgesics, and the most common secondary conditions were hysterectomy, tonsillectomy, osteoporosis, and obesity. Within each geographic area, there were no meaningful differences between treatment groups with regard to demographics, secondary diagnoses, or concomitant therapies [7].

Table 33

Baseline Demographics by Treatment Group—Protocol 902

	902—D		902—OA	
	Rofecoxib 12.5 mg (N=211)	ARTHROTEC™ (N=215)	Rofecoxib 12.5 mg (N=242)	ARTHROTEC™ (N=241)
Total	n (%)	n (%)	n (%)	n (%)
Gender—n (%)				
Male	61 (28.9)	48 (22.3)	50 (20.7)	45 (18.7)
Female	150 (71.1)	167 (77.7)	192 (79.3)	196 (81.3)
Race—n (%)				
White	203 (96.2)	207 (96.3)	101 (41.7)	103 (42.7)
Black	4 (1.9)	5 (2.3)	2 (0.8)	0 (0.0)
African	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	3 (1.4)	1 (0.5)	2 (0.8)	4 (1.7)
Hispanic American	0 (0.0)	0 (0.0)	40 (16.5)	40 (16.6)
Multi-Racial	0 (0.0)	2 (0.9)	97 (40.1)	94 (39.0
Age (years)				
20 and under	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
21 to 30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
31 to 40	2 (0.9)	0 (0.0)	1 (0.4)	1 (0.4)
41 to 50	30 (14.2)	23 (10.7)	28 (11.6)	22 (9.1)
51 to 60	84 (39.8)	83 (38.6)	78 (32.2)	74 (30.7)
61 to 70	61 (28.9)	75 (34.9)	87 (36.0)	97 (40.2)
71 to 80	31 (14.7)	31 (14.4)	46 (19.0)	43 (17.8)
81 to 90	2 (0.9)	3 (1.4)	2 (0.8)	4 (1.7)
Over 90	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Mean	60.1	61.2	61.8	62.4
SD	9.76	8.80	9.28	8.65
Median	59.0	61.0	62.0	63.0
Range	34 to 94	42 to 89	39 to 85	40 to 82

[7]

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

2.2.9.2 Extent of Exposure

A total of 453 patients received rofecoxib and 456 received ARTHROTEC™ for approximately 6 weeks [7]. The mean duration of therapy by treatment group for the populations enrolled in Europe (902-OD) and South and Central America (902-OA) are shown in Table 34.

Table 34

Number of Days on Therapy by Treatment—Protocol 902

	902—OD		902—OA	
	Rofecoxib 12.5 mg	ARTHROTEC™	Rofecoxib 12.5 mg	ARTHROTEC™
N	211	215	242	241
Mean	39.1	38.1	40.9	39.8
Range (min to max)	61 (1 to 62)	62 (1 to 63)	50 (1 to 51)	48 (2 to 50)

[7]

2.2.9.3 Fatal and Nonfatal Serious Adverse Experiences

Table 35 provides the numbers and percentages of patients with fatal and nonfatal serious clinical adverse experiences for each treatment group. The proportion of patients with serious adverse experiences was low and identical in the rofecoxib (1.1%) and ARTHROTEC™ (1.1%) groups. One patient on rofecoxib had a gastrointestinal perforation, AN 616, a 69-year-old man with a history of diverticulosis, was hospitalized with diverticulitis and intestinal perforation 13 days after completing the study. A listing of all patients with adverse experiences coded as serious is in [7] and narratives for the cases are in [23].

There was one death. A 94-year-old man (AN 1659) on rofecoxib 12.5 mg for 15 days committed suicide by putting a plastic bag over his head. The investigator stated the cause of death (asphyxiation) was not related to study medication [23].

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

Table 35

Numbers and Percentages of Patients With Fatal and Nonfatal Serious Clinical Adverse Experiences for Each Treatment Group—Protocol 902

	Rofecoxib 12.5 mg (N=453)		ARTHROTEC™ (N=456)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	5	(1.1)	5	(1.1)
Patients with no adverse experience	448	(98.9)	451	(98.9)
Body as a Whole/Site Unspecified	**1**	**(0.2)**	**0**	**(0.0)**
Upper respiratory infection	1	(0.2)	0	(0.0)
Digestive System	**1**	**(0.2)**	**0**	(0.0)
Gastrointestinal perforation	1	(0.2)	0	(0.0)
Metabolism and Nutrition	**0**	**(0.0)**	**1**	**(0.2)**
Hypoglycemia	0	(0.0)	1	(0.2)
Musculoskeletal System	**1**	**(0.2)**	**1**	**(0.2)**
Knee pain	1	(0.2)	0	(0.0)
Polymyalgia rheumatica	0	(0.0)	1	(0.2)
Respiratory System	**2**	**(0.4)**	**0**	**(0.0)**
Asphyxiation	1	(0.2)	0	(0.0)
Lobar pneumonia	1	(0.2)	0	
Skin and Skin Appendages	**0**	**(0.0)**	**1**	**(0.2)**
Cellulitis	0	(0.0)	1	(0.2)
Urogenital System	**0**	**(0.0)**	**2**	**(0.4)**
Cervix malignant neoplasm	0	(0.0)	1	(0.2)
Hypermenorrhea	0	(0.0)	1	(0.2)

[7]

2.2.10 Summary

The Serious Adverse Experience data accrued since the previous SUR are consistent with the data previously submitted to the FDA. Rofecoxib has a favorable safety profile in the OA population, including patients aged 80 and older. There are no findings on new clinically important adverse experiences with the longer durations of exposures accrued

2. Update of Serious Clinical Adverse Experiences—All Body Systems (Cont.)

since the first SUR. There was no evidence of an increased incidence of serious clinical adverse experiences compared to comparator NSAIDS or to placebo. The incidence of serious cardiovascular adverse experiences with rofecoxib was generally similar to that with diclofenac, nabumetone, and placebo. The incidence of congestive heart failure, hypertension, and renal failure was low and similar among the treatment groups. The causes of death were multifactorial and did not indicate a specific drug-related cause.

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences

In Jan-2001, a cardiovascular meta-analysis was submitted to the FDA that included studies completed by Sep-2000, with the exception of studies in Alzheimer's patients (Protocols 078 and 091) which were ongoing. The meta-analysis included analyses that compared rofecoxib with naproxen, placebo, and non-naproxen NSAIDs. This report is an update to the information provided in the meta-analysis prepared in Jan-2001 with a focus on studies which compared rofecoxib to non-naproxen NSAIDs and to placebo. The only new cardiovascular safety information from naproxen controlled studies comes from extensions to the RA Phase III studies. Few events occurred in those extensions which are the focus of a separate RA SUR.

Section 3.1 provides an outline of the studies and information included in this update. Section 3.2 summarizes updated cardiovascular safety information from the placebo-controlled Alzheimer's Disease Studies (Protocols 078, 091, 126) and a newly completed Prostatitis Study (Protocol 118). Section 3.3 summarizes updated cardiovascular safety information from the Phase IIb/III OA Studies (Protocols 029, 033, 034, 035, 040, 044, 045, 058, collectively referred to 069 in the previous meta-analysis). Section 3.4 provides an update of the meta-analysis of endpoints that meet the definitions of the Antiplatelet Trialists' Collaboration (APTC) [25] comparing rofecoxib with non-naproxen NSAIDs and placebo. This endpoint measures the incidence of fatal and irreversible morbid cardiovascular events: cardiovascular, hemorrhagic, and unknown death; myocardial infarction; and cerebrovascular accident (APTC combined endpoint).

As explained in the previous meta-analysis, after the Phase IIb/III OA studies but before VIGOR, Merck Research Laboratories (MRL) implemented a Cardiovascular Adjudication Standard Operating Procedure (SOP) to collect data in a uniform manner and to evaluate further whether there were any differences in the incidence of thrombotic cardiovascular serious adverse experiences during chronic therapy with rofecoxib versus comparator agents. Wherever possible, adjudicated data were used in the preparation of this meta-analysis. In some cases (i.e., in studies that were completed prior to implementation of the Cardiovascular Adjudication SOP), investigator-reported data were utilized.

In this report, as in the previous meta-analysis, it should be noted that the comparator (non-naproxen NSAID or placebo) is the reference group (denominator) for all comparisons for relative risk assessments.

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

3.1 Outline of Studies Included

Studies included in this updated analysis are shown in Table 36. All studies that were 4 weeks or more in duration, that included a placebo or non-naproxen NSAID comparator, and had a complete and frozen database by 16-Mar-2001 were included. The exception to this are the ongoing (Protocol 078) or recently ended (Protocol 126) Alzheimer's Disease Studies for which thrombotic cardiovascular serious adverse experiences reported to Merck & Co., Inc. by 16-Mar-2001 were included in the Investigator Reported Cardiovascular Event analyses. Data adjudicated by 15-May-2001 from Protocols 078, 091, and 126 were included in the APTC and Confirmed Cardiovascular Event analyses. A new study in patients with prostatitis (Protocol 118) is included in this update but was not included in the prior meta-analysis. Data from Alzheimer's Disease Protocol 126 also were not included in the prior meta-analysis. Information about studies for which newly accrued data has been included is in Table 36. Protocols 120 and 121 (Chronic Low Back Pain Studies), 083 (Bone Density Study), and 902 (ARTHROTEC™ Comparison Study) which were presented in Part I of this SUR, were previously included in the cardiovascular meta-analysis sent to the FDA in Jan-2001.

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 36

Studies Included in this Cardiovascular Safety Analysis

Indication for Therapy	Protocol No.	Short Study Title	Comparator	Updated Information (Versus Original Meta-Analysis)
Rheumatoid Arthritis	068	Phase IIb dose finding	Placebo	No additional data
	096	Phase III pivotal U.S.	Placebo	No additional data
	097	Phase III pivotal Int'l	Placebo	No additional data
	098+103	Phase III endoscopy	Placebo	No additional data
Osteoarthritis	029[†]	Ph IIb dose ranging study	Diclofenac, Placebo	Additional data from extension patients
	033[†]	Ph III U.S.	Ibuprofen, Placebo	No additional data
	034[†]	Ph III pivotal Int'l	Diclofenac	Additional data from extension patients
	035[†]	Ph III pivotal U.S.	Diclofenac	Additional data from extension patients
	040[†]	Ph III Int'l	Ibuprofen, Placebo	No additional data
	044[†]	Ph III endoscopy U.S.	Ibuprofen, Placebo	No additional data
	045[†]	Ph III endoscopy Int'l	Ibuprofen, Placebo	No additional data
	058[†]	Elderly	Nabumetone, Placebo	Additional data from extension patients
	083	Bone mineral density study	Ibuprofen, Placebo	No additional data
	085	Nabumetone study #1	Nabumetone, Placebo	No additional data
	090	Nabumetone study #1	Nabumetone, Placebo	No additional data
	902	ARTHROTEC™ study	Diclofenac	No additional data
	078	Alzheimer's prevention	Placebo	Additional data from ongoing study
	091	Alzheimer's slowing progr'n	Placebo	Additional data from completed study
	118	Prostatitis	Placebo	Newly-completed study
	120	Ph III chronic low back pain	Placebo	No additional data
	121	Ph III chronic low back pain	Placebo	No additional data
	126	Alzheimer's slowing progr'n	Placebo	New study, not yet complete

[†] The Phase IIb/III osteoarthritis studies were designated collectively as 069 in previous meta-analysis.

3.1.1 Statistical Methods

Since individual patient data were not available for all studies (clinical trial database for Protocols 078 and 126 not yet frozen), evaluation could not use statistical survival techniques such as the Cox proportional hazards model, Kaplan-Meier plots, tests of

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

proportionality, and tests of homogeneity using the Cox model. Instead, cases, patient-years, rates per 100 patient-years, and ratios of rates with 95% confidence intervals [26] were provided. Homogeneity among the individual studies for each comparison was examined using Zelen's exact test [27; 28; 29]. Patient-years were calculated as time to event or until discontinuation plus 14 days for those without events.

3.1.2 Classifications of Events

Three types of endpoints are addressed in this report:

APTC endpoints: The APTC endpoint includes fatal and irreversible morbid cardiovascular events: cardiovascular, hemorrhagic, and unknown death; myocardial infarction; and cerebrovascular accident (APTC combined endpoint). Adjudicated data were utilized for all studies except the Phase IIb/III OA Studies (Protocols 029, 033, 034, 035, 040, 044, 045, 058) and the Phase IIb/III RA Dose Ranging Study (Protocol 068), since these studies were complete or ongoing at the time the Cardiovascular SOP was initiated.

Confirmed thrombotic cardiovascular serious adverse experiences: This category includes both arterial and venous thromboembolic events confirmed by the adjudication committee as myocardial infarction, unstable angina, transient ischemic attack, cerebrovascular accident, arterial thrombosis, deep venous thrombosis, pulmonary embolism, or sudden death/unexplained death. Hemorrhagic strokes confirmed by the adjudication committee were considered an APTC event but not a confirmed thrombotic cardiovascular event for this analysis.

Investigator-reported events: This category incorporates a larger group of terms, as reported by investigators. See [31] for details.

3.2 New Information from Placebo-Controlled Protocols

3.2.1 Alzheimer's Disease Studies—APTC, Confirmed, and Investigator Reported

Data from the Alzheimer's Disease Studies (Protocols 091, 078, and 126) are in Tables 37 through 42. Table 37 provides data for the APTC endpoint for these studies. Table 39 provides data for confirmed thrombotic cardiovascular serious adverse experiences from these studies. Most of the cases in the Alzheimer's population reported by the serious adverse experience cutoff date (16-Mar-2001) were adjudicated; 9 cases were not adjudicated by the cutoff for this SUR (15-May-2001), however the impact of this on the analysis is considered to be insignificant. Of these 9 cases, 5 were cerebrovascular accidents (3 on rofecoxib, 2 on placebo); of the other 4 events (thrombosis, myocardial infarction, coronary artery disease, tachycardia), 3 were on rofecoxib and 1 was on placebo. All of the deaths were sent for adjudication; 4 patients (3 on rofecoxib [Protocol 078, AN 158; Protocol 091, ANs 891, 964], 1 on placebo [Protocol 078, AN 539]) had insufficient data to confirm a cause of death and therefore

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

were not included as an endpoint (sudden/unexplained death). Table 41 shows investigator-reported cardiovascular thrombotic cardiovascular serious adverse experiences in these studies. Serious adverse experiences reported to the Merck & Co., Inc. WAES as of 16-Mar-2001 were included in the analyses.

Data adjudicated by 15-May-2001 were included in the analyses presented in Table 37 and Table 38. As shown in Table 37, there were 22 rofecoxib patients with APTC endpoints during 1461 patient-years for a rate of 1.51 events per 100 patient-years. In the placebo group, there were 30 patients with events during 1634 patient-years for a rate of 1.84. The ratio (95% CI) of rofecoxib to placebo among the subset of Alzheimer's patients was 0.82 (0.45, 1.47). Even if the deaths with insufficient information were included as sudden death, the number of events would still be higher in the placebo group than the rofecoxib group.

Table 38 provides counts of confirmed APTC events in this population, by type of event (class-of-term). Results from the individual studies are in [31].

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 37

APTC Endpoint
Rofecoxib Versus Placebo in Alzheimer's Disease Protocols
Updated Results Using Adjudicated Data

Indication for Treatment	Study Group	Rofecoxib N	Rofecoxib Cases/PYR[†] (Rate[‡])	Placebo N	Placebo Cases/PYR[†] (Rate[‡])	Relative Risk (95% CI)[§]
Rofecoxib Vs. Placebo						
Alzheimer's	Protocol 078	721	13/996 (1.31)	729	17/1098 (1.55)	0.84 (0.38, 1.84)
	Protocol 091	346	4/301 (1.33)	346	10/366 (2.73)	0.49 (0.11, 1.69)
	Protocol 126	381	5/165 (3.03)	376	3/169 (1.77)	1.71 (0.33, 11.02)
Total	**All**	**1448**	**22/1461 (1.51)**	**1451**	**30/1634 (1.84)**	**0.82 (0.45, 1.47)**

[†]Patient-years at risk.
[‡]Per 100 PYR.
[§]Relative risk of rofecoxib with respect to comparator is calculated from ratio of rates.

[30]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 38

Summary of APTC Events by Type of Event Adjudicated Data—
Alzheimer's Disease Protocols)

	Rofecoxib N=1448		Placebo N=1451	
	n	(%)	n	(%)
Patients with one or more adverse experiences	22	1.52	30	2.07
Patients with no adverse experience	1426	98.48	1421	97.93
Cardiac Events	**14**	**0.97**	**16**	**1.10**
Acute myocardial infarction	9	0.62	13	0.90
Fatal acute myocardial infarction	2	0.14	1	0.07
Sudden/unexplained death	5	0.35	3	0.21
Cerebrovascular Events	**8**	**0.55**	**15**	**1.03**
Hemorrhagic stroke	3	0.21	2	0.14
Fatal hemorrhagic stroke	2	0.14	1	0.07
Ischemic cerebrovascular stroke	5	0.35	13	0.90
Fatal ischemic cerebrovascular stroke	1	0.07	0	0
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted once within a category. The same patient may appear in different categories.				

[31]

As shown in Table 39, there were 25 rofecoxib patients with confirmed thrombotic cardiovascular serious adverse experience endpoints during 1461 patient-years for a rate of 1.71 events per 100 patient-years. In the placebo group, there were 39 patients with events during 1634 patient-years for a rate of 2.39. The ratio (95% CI) of rofecoxib to placebo among the subset of Alzheimer's patients was 0.72 (0.42, 1.21).

Table 40 provides counts of confirmed thrombotic cardiovascular serious adverse experiences in this population, by type of event. Both fatal and nonfatal events are included. Results from the individual studies are in [31].

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 39

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Rofecoxib Versus Placebo in Alzheimer's Disease Protocols
Updated Results

Indication for Treatment	Study Group	Rofecoxib N	Rofecoxib Cases/PYR[†] (Rate[‡])	Placebo N	Placebo Cases/PYR[†] (Rate[‡])	Relative Risk (95% CI)[§]
Rofecoxib Vs. Placebo						
Alzheimer's	Protocol 078	721	17/996 (1.71)	729	23/1098 (2.09)	0.82 (0.41, 1.59)
	Protocol 091	346	4/301 (1.33)	346	12/366 (3.28)	0.41 (0.10, 1.34)
	Protocol 126	381	4/165 (2.43)	376	4/169 (2.36)	1.03 (0.19, 5.51)
Total	**All**	**1448**	**25/1461 (1.71)**	**1451**	**39/1634 (2.39)**	**0.72 (0.42, 1.21)**

[†]Patient-years at risk.
[‡]Per 100 PYR.
[§]Relative risk of rofecoxib with respect to comparator is calculated from ratio of rates.

[30]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 40

Summary of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences by Type of Event—Alzheimer's Disease Protocols

	Rofecoxib N=1448		Placebo N=1451	
	n	(%)	n	(%)
Patients with one or more adverse experiences	25	1.73	39	2.69
Patients with no adverse experience	1423	98.27	1412	97.31
Cardiac Events	**14**	**0.97**	**21**	**1.45**
Acute myocardial infarction	9	0.62	13	0.90
Sudden/unexplained death	5	0.35	3	0.21
Unstable angina pectoris	1	0.07	8	0.55
Cerebrovascular Events	**11**	**0.76**	**16**	**1.10**
Ischemic cerebrovascular stroke	5	0.35	13	0.90
Transient ischemic attack	6	0.41	3	0.21
Peripheral Events	**0**	**0**	**3**	**0.21**
Peripheral arterial thrombosis	0	0	1	0.07
Peripheral venous thrombosis	0	0	2	0.14

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

[31]

As shown in Table 41, there were 52 rofecoxib patients with investigator-reported thrombotic cardiovascular serious adverse experiences during 1450 patient-years for a rate of 3.59 events per 100 patient-years. In the placebo group, there were 62 patients with events during 1615 patient-years for a rate of 3.84. The ratio (95% CI) of rofecoxib to placebo among the subset of Alzheimer's patients was 0.93 (0.63, 1.37).

Table 42 provides counts of investigator-reported thrombotic cardiovascular serious adverse experiences in this population, by type of event. Results from the individual studies are in [31].

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 41

Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences
Rofecoxib Versus Placebo in Alzheimer's Disease Protocols
Updated Results

Indication for Treatment	Study Group	Rofecoxib N	Rofecoxib Cases/PYR† (Rate‡)	Placebo N	Placebo Cases/PYR† (Rate‡)	Relative Risk (95% CI)§
Rofecoxib Vs. Placebo						
Alzheimer's	Protocol 078	721	32/987 (3.24)	729	42/1080 (3.89)	0.83 (0.51, 1.35)
	Protocol 091	346	12/298 (4.02)	346	15/366 (4.10)	0.98 (0.42, 2.25)
	Protocol 126	381	8/164 (4.86)	376	5/169 (2.95)	1.65 (0.47, 6.40)
Total	**All**	**1448**	**52/1450 (3.59)**	**1451**	**62/1615 (3.84)**	**0.93 (0.63, 1.37)**

†Patient-years at risk.
‡Per 100 PYR.
§Relative risk of rofecoxib with respect to comparator is calculated from ratio of rates.

[30]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 42

Summary of Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences by Type of Event—Alzheimer's Disease Protocols

	Rofecoxib N=1448		Placebo N=1451	
	n	(%)	n	(%)
Patients with one or more adverse experiences	52	3.59	62	4.27
Patients with no adverse experience	1396	96.41	1389	95.73
Cardiac Events	**28**	**1.93**	**32**	**2.21**
Acute myocardial infarction	3	0.21	3	0.21
Angina pectoris	2	0.14	5	0.34
Cardiac arrest	4	0.28	2	0.14
Coronary artery disease	11	0.76	9	0.62
Coronary artery occlusion	2	0.14	3	0.21
Coronary artery stenosis	0	0	1	0.07
Myocardial infarction	7	0.48	12	0.83
Non-Q-wave myocardial infarction	1	0.07	1	0.07
Unstable angina	3	0.21	3	0.21
Ventricular fibrillation	2	0.14	0	0
Ventricular tachycardia	0	0	4	0.28
Cerebrovascular Events	**21**	**1.45**	**29**	**2.00**
Carotid artery obstruction	2	0.14	8	0.55
Cerebellar hemorrhage	0	0	1	0.07
Cerebral atherosclerosis	1	0.07	0	0
Cerebral infarction	1	0.07	0	0
Cerebrovascular accident	10	0.69	10	0.69
Intracranial hemorrhage	1	0.07	1	0.07
Lacunar infarction	0	0	1	0.07
Transient ischemic attack	9	0.62	8	0.55
Peripheral Events	**3**	**0.21**	**4**	**0.28**
Deep venous thrombosis	0	0	3	0.21
Femoral artery occlusion	0	0	1	0.07
Pulmonary embolism	2	0.14	0	0
Thrombosis	1	0.07	0	0
Vascular graft occlusion	0	0	1	0.07

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.

[31]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

3.2.2 Prostatitis Study

This was a placebo-controlled, parallel-group, double-blind, multicenter trial to examine the effects of rofecoxib for 6 weeks on pain associated with chronic prostatitis/chronic pelvic pain syndrome (Protocol 118). No cardiovascular events were reported in this trial.

3.3 New Information from Protocols Versus Non-Naproxen NSAIDs

3.3.1. Update on Phase IIb/III Osteoarthritis Studies—Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences and APTC Endpoints

There were 8 Phase IIb/III OA studies (OA-069) that were included as a part of the Original Application. The primary phases of these studies were completed prior to the implementation of the Cardiovascular Adjudication SOP, therefore, the events from these studies were not adjudicated. Cardiovascular events from these studies at the time of cutoff for the Original Application were reported as part of the original VIGOR sNDA, submitted to the agency 29-Jun-2000. At the time of the Original Application, Protocols 033, 040, 044, and 045 were completed. Studies 029, 034, 035, and 058 had ongoing comparator-controlled extensions (diclofenac in 029, 034, 035; nabumetone in 058). These extension studies have recently completed, and the data are included in this section. The mean duration of treatment with rofecoxib in the 4 protocols with extensions was 458 days.

Table 43 shows a comparison of rofecoxib versus non-naproxen NSAIDs in the OA-069 OA population for the APTC endpoint. As noted above, these cases were not adjudicated. In these trials, there were 24 rofecoxib patients with events during 2372 years of follow-up for a rate of 1.01 events per 100 patient-years. In the non-naproxen NSAIDs group, there were 13 patients with events during 1026 patient-years for a rate of 1.27. The ratio of rates (95% CI) of rofecoxib to non-naproxen NSAIDs was 0.80 (0.39, 1.71).

3. **Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)**

Table 43

APTC Endpoint in OA-069
Rofecoxib Versus Non-Naproxen NSAIDs
Updated Results

Indication for Treatment	Study Group	Rofecoxib N	Rofecoxib Cases/PYR[†] (Rate[‡])	Non-Naproxen NSAIDs N	Non-Naproxen NSAIDs Cases/PYR[†] (Rate[‡])	Relative Risk (95% CI)[§]
Rofecoxib Vs. Non-Naproxen NSAIDs[¶]						
OA	Protocol 029	479	8/523 (1.53)	92	1/136 (0.74)	2.08 (0.28, 92.21)
	Protocol 033	446	0/66 (0.00)	221	1/32 (3.09)	0.00 (0.00, 19.19)
	Protocol 034	463	5/631 (0.79)	230	3/307 (0.98)	0.81 (0.16, 5.21)
	Protocol 035	516	4/640 (0.62)	268	7/313 (2.24)	0.28 (0.06, 1.10)
	Protocol 040	486	1/72 (1.38)	249	0/37 (0.00)	-
	Protocol 044	381	3/154 (1.95)	184	0/60 (0.00)	-
	Protocol 045	388	0/157 (0.00)	193	0/64 (0.00)	-
	Protocol 058	19	3/128 (2.34)	128	1/78 (1.28)	1.83 (0.15, 95.87)
Total	**All**	**3358**	**24/2372 (1.01)**	**1565**	**13/1026 (1.27)**	**0.80 (0.39, 1.71)**

[†]Patient-years at risk.
[‡]Per 100 PYR.
[§]Relative risk of rofecoxib with respect to comparator is calculated from ratio of rates.
[¶]Comparators: Protocols 029, 034, 035: diclofenac; Protocols 033, 040, 044, 045: ibuprofen; Protocol 058: nabumetone.

[30]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 44 provides counts for the APTC endpoint in the OA-069 OA population. (The classification by Type-of-Event differs from Table 38 because the cases were not adjudicated.)

Table 44

Summary of APTC Events in OA-069

	Rofecoxib N=3358		Non-Naproxen NSAIDs N=1565	
	n	(%)	n	(%)
Patients with one or more adverse experiences	24	0.71	13	0.83
Patients with no adverse experience	3334	99.29	1552	99.17
Cardiac Events	**12**	**0.36**	**8**	**0.51**
Acute myocardial infarction	3	0.09	1	0.06
Cardiac arrest	0	0	2	0.13
Coronary artery occlusion	2	0.06	1	0.06
Myocardial infarction	7	0.21	3	0.19
Sudden cardiac death	0	0	1	0.06
Cerebrovascular Events	**10**	**0.30**	**4**	**0.26**
Carotid artery obstruction	1	0.03	0	0
Cerebrovascular accident	9	0.27	4	0.26
Other Events	**2**	**0.06**	**1**	**0.06**
Hemorrhagic shock	0	0	1	0.06
Sudden/unknown cause of death	2	0.06	0	0

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

[32]

Table 45 shows a comparison of investigator-reported thrombotic cardiovascular serious adverse experiences for rofecoxib versus non-naproxen NSAIDs in the OA-069 OA population. There were 49 rofecoxib patients with events during 2372 years of follow-up for a rate of 2.07 events per 100 patient-years. In the non-naproxen NSAIDs group, there were 21 patients with events during 1026 patient-years for a rate of 2.05. The ratio of rates (95% CI) of rofecoxib to non-naproxen NSAIDs was 1.01 (0.59, 1.77).

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 45

Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences in OA-069
Rofecoxib Versus Non-Naproxen NSAIDs
Updated Results

Indication for Treatment	Study Group	Rofecoxib N	Rofecoxib Cases/PYR[†] (Rate[‡])	Non-Naproxen NSAIDs N	Non-Naproxen NSAIDs Cases/PYR[†] (Rate[‡])	Relative Risk (95% CI)[§]
Rofecoxib Vs. Non-Naproxen NSAIDs[¶]						
OA	Protocol 029	479	11/523 (2.10)	92	2/136 (1.47)	1.43 (0.31, 13.26)
	Protocol 033	446	2/66 (3.04)	221	1/32 (3.09)	0.99 (0.05, 58.12)
	Protocol 034	463	11/631 (1.74)	230	4/307 (1.30)	1.34 (0.40, 5.75)
	Protocol 035	516	12/640 (1.87)	268	11/313 (3.52)	0.53 (0.22, 1.33)
	Protocol 040	486	1/72 (1.38)	249	0/37 (0.00)	-
	Protocol 044	381	4/154 (2.60)	184	0/60 (0.00)	-
	Protocol 045	388	3/157 (1.91)	193	1/64 (1.57)	1.22 (0.10, 63.80)
	Protocol 058	199	5/128 (3.90)	128	2/78 (2.57)	1.52 (0.25, 15.98)
Total	**All**	**3358**	**49/2372 (2.07)**	**1565**	**21/1026 (2.05)**	**1.01 (0.59, 1.77)**

[†]Patient-years at risk.
[‡]Per 100 PYR.
[§]Relative risk of rofecoxib with respect to comparator is calculated from ratio of rates.
[¶]Comparators: Protocols 029, 034, 035: diclofenac; Protocols 033, 040, 044, 045: ibuprofen; Protocol 058: nabumetone

[30]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 46 provides counts of investigator-reported thrombotic cardiovascular serious adverse experiences in OA-069 OA population.

Table 46

Summary of Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences in OA-069

	Rofecoxib N=3358		Non-Naproxen NSAIDs N=1565	
	n	(%)	N	(%)
Patients with one or more adverse experiences	49	1.46	21	1.34
Patients with no adverse experience	3309	98.54	1544	98.66
Cardiac Events	**28**	**0.83**	**14**	**0.89**
Acute myocardial infarction	3	0.09	1	0.06
Angina pectoris	5	0.15	4	0.26
Cardiac arrest	1	0.03	2	0.13
Coronary artery disease	6	0.18	3	0.19
Coronary artery occlusion	2	0.06	1	0.06
Coronary vasospasm	1	0.03	0	0
Myocardial infarction	7	0.21	3	0.19
Unstable angina	4	0.12	0	0
Cerebrovascular Events	**15**	**0.45**	**5**	**0.32**
Carotid artery obstruction	1	0.03	0	0
Cerebrovascular accident	9	0.27	4	0.26
Transient ischemic attack	6	0.18	1	0.06
Peripheral Events	**7**	**0.21**	**2**	**0.13**
Arterial occlusion	1	0.03	0	0
Deep venous thrombosis	5	0.15	0	0
Peripheral vascular disorder	0	0	1	0.06
Vascular insufficiency	1	0.03	1	0.06

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

[32]

3.4 Updated Meta-Analysis of Cardiovascular Events

This meta-analysis focuses on the ratio of risk of APTC endpoint events in patients taking rofecoxib as compared to placebo and to non-naproxen NSAIDs. This report is an update of the meta-analysis prepared in Jan-2001.

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

3.4.1 Meta-Analysis of APTC Endpoint

As with the prior meta-analysis, the endpoint used in this SUR is the combined endpoint defined by the APTC. As was the case in the previous meta-analysis, adjudicated data were used when the study had undergone adjudication, otherwise investigator-reported data were used. All studies except Protocol 068 (RA Dose Ranging Study) and the Phase IIb/III OA studies (029, 033, 034, 035, 040, 044, 045, 058, which had been initiated prior to implementation of the Cardiovascular Adjudication SOP) had adjudicated data. As noted previously, 9 cases in the Alzheimer's Disease population have not yet been adjudicated, however, the impact of this on the analysis is considered to be insignificant. The p-values for the test for homogeneity for the non-naproxen NSAID and the placebo comparisons were 0.100 and 0.110, respectively, showing no evidence of heterogeneity and no reason why these trials could not be combined.

Table 47 shows a comparison of rofecoxib to non-naproxen NSAIDs for the APTC endpoint. In this table, Protocols 029, 034, 035, and 058 have updated data while information for the other protocols was unchanged from the original meta-analysis. Among the non-naproxen NSAID comparative studies there were 29 rofecoxib patients with APTC endpoint events during 2648 patient-years for a rate of 1.10 events per 100 patient-years in the rofecoxib group. In the non-naproxen NSAIDs group, there were 17 patients with events during 1303 patient-years for a rate of 1.30. The ratio of rates (95% CI) was 0.84 (0.45, 1.63).

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 47

Meta-Analysis of APTC Endpoint
Rofecoxib Versus Non-Naproxen NSAIDs
Updated Results

Indication for Treatment	Study Group/ Protocol	N	Rofecoxib Cases/PYR* (Rate‡)	N	Non-Naproxen NSAIDs Cases/PYR* (Rate‡)	Relative Risk (95% CI)†
Rofecoxib vs Non-Naproxen NSAIDs¶						
RA	All	0	-	0	-	-
OA	All	4550	29/2648 (1.10)	2756	17/1303 (1.30)	0.84 (0.45, 1.63)
	Protocol 029	479	8/523 (1.53)	92	1/136 (0.74)	2.08 (0.28, 92.21)
	Protocol 033	446	0/66 (0.00)	221	1/32 (3.09)	0.00 (0.00, 19.19)
	Protocol 034	463	5/631 (0.79)	230	3/307 (0.98)	0.81 (0.16, 5.21)
	Protocol 035	516	4/640 (0.62)	268	7/313 (2.24)	0.28 (0.06, 1.10)
	Protocol 040	486	1/72 (1.38)	249	0/37 (0.00)	-
	Protocol 044	381	3/154 (1.95)	184	0/60 (0.00)	-
	Protocol 045	388	0/157 (0.00)	193	0/64 (0.00)	-
	Protocol 058	199	3/128 (2.34)	128	1/78 (1.28)	1.83 (0.15, 95.87)
	Protocol 083	136	0/121 (0.00)	148	3/127 (2.37)	0.00 (0.00, 2.54)
	Protocol 085	424	1/61 (1.63)	410	0/59 (0.00)	-
	Protocol 090	390	4/56 (7.11)	392	1/57 (1.77)	4.02 (0.40, 198.1)
	Protocol 902	242	0/37 (0.00)	241	0/36 (0.00)	-
Alz/LBP	All	0	-	0	-	-
Total	**All**	**4550**	**29/2648 (1.10)**	**2756**	**17/1303 (1.30)**	**0.84 (0.45, 1.63)**

*Patient-years at risk.
‡Per 100 PYR.
†Relative risk of rofecoxib with respect to comparator is calculated from ratio of rates.
¶Comparators: Protocols 029, 034, 035: diclofenac; Protocols 033, 040, 044, 045: ibuprofen; Protocol 058: nabumetone.

[30]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 48 provides counts of APTC events, by class-of-term.

Table 48

Summary of APTC Endpoints by Type of Event
Rofecoxib Versus Non-Naproxen NSAIDs

	Rofecoxib N=4550		Non-Naproxen NSAIDs N=2756	
	n	(%)	n	(%)
Patients with one or more adverse experiences	29	0.64	17	0.62
Patients with no adverse experience	4521	99.36	2739	99.38
Cardiac Events	**16**	**0.35**	**12**	**0.44**
Acute myocardial infarction	7	0.15	4	0.15
Cardiac arrest	0	0	2	0.07
Coronary artery occlusion	2	0.04	1	0.04
Myocardial infarction	7	0.15	3	0.11
Sudden cardiac death	0	0	2	0.07
Cerebrovascular Events	**11**	**0.24**	**4**	**0.15**
Carotid artery obstruction	1	0.02	0	0
Cerebrovascular accident	9	0.20	4	0.15
Ischemic cerebrovascular stroke	1	0.02	0	0
Other Events	**2**	**0.04**	**1**	**0.04**
Hemorrhagic shock	0	0	1	0.04
Sudden/unknown cause of death	2	0.04	0	0
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted once within a category. The same patient may appear in different categories.				

[32]

Table 49 shows a comparison of rofecoxib versus individual non-naproxen NSAID comparators for the APTC endpoint. The ratio of rates (95% CI) for diclofenac, ibuprofen, and nabumetone were 0.65 (0.29, 1.54), 0.56 (0.10, 3.00), and 3.15 (0.63, 30.40), respectively.

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 49

Meta-Analysis of APTC Endpoint
Rofecoxib Versus Non-Naproxen NSAIDs by Individual Comparator
Updated Results

Indication for Treatment	Study Group	Rofecoxib		Non-Naproxen NSAIDs		Relative Risk (95% CI)[‡]
		N	Cases/PYR[†] (Rate[‡])	N	Cases/PYR[†] (Rate[‡])	
Rofecoxib Vs. Diclofenac						
OA	All	1700	17/1795 (0.95)	831	11/755 (1.46)	0.65 (0.29, 1.54)
	Protocol 029	479	8/523 (1.53)	92	1/136 (0.74)	2.08 (0.28, 92.21)
	Protocol 034	463	5/631 (0.79)	230	3/307 (0.98)	0.81 (0.16, 5.21)
	Protocol 035	516	4/640 (0.62)	268	7/313 (2.24)	0.28 (0.06, 1.10)
	Protocol 902	242	0/37 (0.00)	241	0/36 (0.00)	-
Rofecoxib Vs. Ibuprofen						
OA	All	1837	4/570 (0.70)	995	4/319 (1.25)	0.56 (0.10, 3.00)
	Protocol 033	446	0/66 (0.00)	221	1/32 (3.09)	0.00 (0.00, 19.19)
	Protocol 040	486	1/72 (1.38)	249	0/37 (0.00)	-
	Protocol 044	381	3/154 (1.95)	184	0/60 (0.00)	-
	Protocol 045	388	0/157 (0.00)	193	0/64 (0.00)	-
	Protocol 083	136	0/121 (0.00)	148	3/127 (2.37)	0.00 (0.00, 2.54)
Rofecoxib Vs. Nabumetone						
OA	All	1013	8/246 (3.26)	930	2/193 (1.04)	3.15 (0.63, 30.40)
	Protocol 058	199	3/128 (2.34)	128	1/78 (1.28)	1.83 (0.15, 95.87)
	Protocol 085	424	1/61 (1.63)	410	0/59 (0.00)	-
	Protocol 090	390	4/56 (7.11)	392	1/57 (1.77)	4.02 (0.40, 198.1)
Total	**All**	**4550**	**29/2648 (1.10)**	**2756**	**17/1303 (1.30)**	**0.84 (0.45, 1.63)**

[†]Patient-years at risk.
[‡]Per 100 PYR.
[‡]Relative risk of rofecoxib with respect to comparator is calculated from ratio of rates.

[30]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 50 shows a comparison of rofecoxib versus placebo for the APTC endpoint. In this table, Protocols 118 (Prostatitis) and 126 (Alzheimer's Disease) have been added, and Protocols 078 and 091 (Alzheimer's Disease) contain updated data (adjudicated), and all other studies were unchanged. Among these placebo comparative trials, there were 38 rofecoxib patients with events during 2518 years of follow-up for a rate of 1.51 events per 100 patient-years. In the placebo group, there were 34 patients with events during 2099 patient-years for a rate of 1.62. The ratio of rates (95% CI) was 0.93 (0.57, 1.53).

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 50

Meta-Analysis of APTC Endpoint Rofecoxib Versus Placebo—Updated Results

Indication for Treatment	Study Group	Rofecoxib N	Rofecoxib Cases/PYR* (Rate‡)	Placebo N	Placebo Cases/PYR* (Rate‡)	Relative risk (95% CI)¶
Rofecoxib Vs. Placebo						
RA	All	1622	3/337 (0.89)	989	1/201 (0.50)	1.78 (0.14, 93.70)
	Protocol 068	332	0/49 (0.00)	168	0/24 (0.00)	-
	Protocol 096	459	3/97 (3.10)	301	0/58 (0.00)	-
	Protocol 097	612	0/136 (0.00)	299	0/62 (0.00)	-
	Protocol 098+103	219	0/55 (0.00)	221	1/56 (1.78)	0.00 (0.00, 39.95)
OA	All	3165	12/655 (1.83)	1215	3/232 (1.30)	1.42 (0.38, 7.81)
	Protocol 029	378	2/45 (4.41)	145	0/16 (0.00)	-
	Protocol 033	446	0/66 (0.00)	69	1/9 (10.59)	0.00 (0.00, 5.60)
	Protocol 040	486	1/72 (1.38)	74	0/11 (0.00)	-
	Protocol 044	381	3/154 (1.95)	177	0/52 (0.00)	-
	Protocol 045	388	0/157 (0.00)	194	2/61 (3.28)	0.00 (0.00, 2.07)
	Protocol 058	174	1/21 (4.70)	52	0/6 (0.00)	-
	Protocol 083	98	0/21 (0.00)	100	0/21 (0.00)	-
	Protocol 085	424	1/61 (1.63)	208	0/28 (0.00)	-
	Protocol 090	390	4/56 (7.11)	196	0/27 (0.00)	-
Alz/LBP/Prostatitis	All	2012	23/1526 (1.51)	1737	30/1667 (1.80)	0.84 (0.46, 1.49)
	Protocol 078	721	13/996 (1.31)	729	17/1098 (1.55)	0.84 (0.38, 1.84)
	Protocol 091	346	4/301 (1.33)	346	10/366 (2.73)	0.49 (0.11, 1.69)
	Protocol 118	102	0/14 (0.00)	58	0/8 (0.00)	-
	Protocol 120	252	1/28 (3.61)	128	0/14 (0.00)	-
	Protocol 121	210	0/23 (0.00)	100	0/11 (0.00)	-
	Protocol 126	381	5/165 (3.03)	376	3/169 (1.77)	1.71 (0.33, 11.02)
Total	All	6799	38/2518 (1.51)	3941	34/2099 (1.62)	0.93 (0.57, 1.53)

*Patient-years at risk.
‡Per 100 PYR.
¶Relative risk of rofecoxib with respect to comparator is calculated from ratio of rates.

[30]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 51 provides counts of patients for rofecoxib versus placebo for the APTC endpoint.

Table 51

Summary of APTC Endpoints by Type of Event
Rofecoxib Versus Placebo

	Rofecoxib N=6799		Placebo N=3941	
	N	(%)	n	(%)
Patients with one or more adverse experiences	38	0.56	34	0.86
Patients with no adverse experience	6761	99.44	3907	99.14
Cardiac Events	**25**	**0.37**	**18**	**0.46**
Acute myocardial infarction	17	0.25	14	0.36
Fatal acute myocardial infarction	2	0.03	1	0.03
Myocardial infarction	3	0.04	1	0.03
Sudden cardiac death	5	0.07	3	0.08
Cerebrovascular Events	**13**	**0.19**	**17**	**0.43**
Cerebrovascular accident	4	0.06	1	0.03
Fatal hemorrhagic stroke	2	0.03	1	0.03
Fatal ischemic cerebrovascular stroke	1	0.01	0	0
Hemorrhagic stroke	3	0.04	2	0.05
Ischemic cerebrovascular stroke	6	0.09	14	0.36

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted once within a category. The same patient may appear in different categories.
[32]

Also presented for comparative purposes are the previous results for the comparison to non-naproxen NSAIDs (Table 52) and to placebo (Table 53) for the APTC endpoint that were previously provided to the FDA in the original (interim) meta-analysis in Jan-2001 (IND No. 46,894, 08-Jan-2001, Serial No. 847; NDA 21-042, 12-Jan-2001). In the original (interim) meta-analysis unadjudicated APTC endpoints were used for Protocols 078 and 091 since the majority of events had not yet been adjudicated. The relative risk (95% CI) for rofecoxib versus non-naproxen NSAIDs in the original meta-analysis was 0.79 (0.40, 1.55), and the relative risk (95% CI) for rofecoxib versus placebo was 0.84 (0.51, 1.38).

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 52

Meta-Analysis of APTC Endpoint
Rofecoxib Versus Non-Naproxen NSAIDs
Original Meta-Analysis (Submitted Jan-2001)

Indication for Treatment	Study Group	Rofecoxib N	Rofecoxib Cases/PYR[†] (Rate[‡])	Non-Naproxen NSAIDs N	Non-Naproxen NSAIDs Cases/PYR[†] (Rate[‡])	Relative risk (95% CI)[¶]
Rofecoxib Vs. Non-Naproxen NSAIDs[¶]						
RA	All	0	-	0	-	-
OA	All	4549	21/1934 (1.09)	2755	14/984 (1.42)	0.79 (0.40, 1.55)
	Protocol 029	479	4/369 (1.09)	92	1/87 (1.15)	0.94 (0.09, 46.51)
	Protocol 033	446	0/66 (0.00)	221	1/32 (3.09)	0.00 (0.00, 19.19)
	Protocol 034	463	3/399 (0.75)	230	2/195 (1.02)	0.73 (0.08, 8.78)
	Protocol 035	516	4/396 (1.01)	268	6/202 (2.97)	0.34 (0.07, 1.43)
	Protocol 040	486	1/72 (1.38)	249	0/37 (0.00)	-
	Protocol 044	381	3/154 (1.95)	184	0/60 (0.00)	-
	Protocol 045	388	0/157 (0.00)	193	0/64 (0.00)	-
	Protocol 058	198	1/46 (2.18)	127	0/30 (0.00)	-
	Protocol 083	136	0/121 (0.00)	148	3/127 (2.37)	0.00 (0.00, 2.54)
	Protocol 085	424	1/61 (1.63)	410	0/59 (0.00)	-
	Protocol 090	390	4/56 (7.11)	392	1/57 (1.77)	4.02 (0.40, 198.1)
	Protocol 902	242	0/37 (0.00)	241	0/36 (0.00)	-
Alz/LBP	All	0	-	0	-	-
Total	All	4549	21/1934 (1.09)	2755	14/984 (1.42)	0.79 (0.40, 1.55)

† Patient-years at risk.
‡ Per 100 PYR.
¶ Relative risk of rofecoxib with respect to comparator from Cox model stratified by indication for subtotals and unstratified elsewhere when number of cases is at least 11, otherwise relative risk is ratio of rates.
¶ Comparators: Protocols 029, 034, 035: diclofenac; Protocols 033, 040, 044, 045: ibuprofen; Protocol 058: nabumetone

[30]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

Table 53

Meta-Analysis of APTC Endpoint Rofecoxib Versus Placebo
Original Meta-Analysis (Submitted Jan-2001)

Indication for Treatment	Study Group	Rofecoxib N	Rofecoxib Cases/PYR[†] (Rate[‡])	Placebo N	Placebo Cases/PYR[†] (Rate[‡])	Relative risk (95% CI)[¶]
Rofecoxib Vs. Placebo						
RA	All	1622	3/337 (0.89)	989	1/201 (0.50)	1.78 (0.14, 93.70)
	Protocol 068	332	0/49 (0.00)	168	0/24 (0.00)	-
	Protocol 096	459	3/97 (3.10)	301	0/58 (0.00)	-
	Protocol 097	612	0/136 (0.00)	299	0/62 (0.00)	-
	Protocol 098+103	219	0/55 (0.00)	221	1/56 (1.78)	0.00 (0.00, 39.95)
OA	All	3165	12/655 (1.83)	1215	3/232 (1.30)	1.53 (0.43, 5.44)
	Protocol 029	378	2/45 (4.41)	145	0/16 (0.00)	-
	Protocol 033	446	0/66 (0.00)	69	1/ 9 (10.59)	0.00 (0.00, 5.60)
	Protocol 040	486	1/72 (1.38)	74	0/11 (0.00)	-
	Protocol 044	381	3/154 (1.95)	177	0/52 (0.00)	-
	Protocol 045	388	0/157 (0.00)	194	2/61 (3.28)	0.00 (0.00, 2.07)
	Protocol 058	174	1/21 (4.70)	52	0/ 6 (0.00)	-
	Protocol 083	98	0/21 (0.00)	100	0/21 (0.00)	-
	Protocol 085	424	1/61 (1.63)	208	0/28 (0.00)	-
	Protocol 090	390	4/56 (7.11)	196	0/27 (0.00)	-
Alz/LBP	All	1503	18/1197 (1.50)	1278	28/1246 (2.25)	0.68 (0.37, 1.23)
	Protocol 078	700	10/856 (1.17)	707	17/913 (1.86)	0.63 (0.29, 1.38)
	Protocol 091	341	7/290 (2.42)	343	11/308 (3.57)	0.68 (0.26, 1.75)
	Protocol 120	252	1/28 (3.61)	128	0/14 (0.00)	-
	Protocol 121	210	0/23 (0.00)	100	0/11 (0.00)	-
Total	**All**	**6290**	**33/2189 (1.51)**	**3482**	**32/1678 (1.91)**	**0.84 (0.51, 1.38)**

[†] Patient-years at risk.
[‡] Per 100 PYR.
[¶] Relative risk of rofecoxib with respect to comparator from Cox model stratified by indication for subtotals and unstratified elsewhere when number of cases is at least 11, otherwise relative risk is ratio of rates.

[30]

3. Update of Thrombotic Cardiovascular Serious Adverse Experiences (Cont.)

3.5 Summary

The primary objective of this meta-analysis is to provide a global summation of the rates of cardiovascular events in the clinical development program for rofecoxib. The combination of all of these trials improves the likelihood of detecting differences in these cardiovascular events. This analysis which includes studies that compared rofecoxib to placebo and to non-naproxen NSAIDs provides information on more than 14,000 patients and over 7000 patient-years of treatment [33].

The principal findings of this analysis are 2-fold. First, a meta-analysis of all placebo-controlled trials with rofecoxib demonstrated comparable cardiovascular event rates for rofecoxib and placebo, whether these events were defined by the investigator or by the adjudication process. This observation is of special interest in that it includes a significant proportion of elderly patients at increased risk for cardiovascular disease. Furthermore, a meta-analysis comparing rofecoxib with non-naproxen NSAIDs also demonstrated comparability in the frequency of cardiovascular event rates. These results indicate that rofecoxib treatment is not associated with an increase in the risk of cardiovascular events across a broad population of patients compared with the NSAIDs that do not demonstrate potent and sustained anti-platelet effects. Finally, the results of this meta-analysis are consistent with those observed in the interim analysis submitted Jan-2001.

4. Discussion

The Original Application contained substantial data regarding safety of rofecoxib in OA patients and the Original Application summarized data from 1385 patients who received rofecoxib for 6 months or longer. Rofecoxib was generally well tolerated and had a safety profile that was favorable in comparison to nonselective NSAIDs. The 4 extension studies that contributed data to the first SUR have now been completed, with at least 415 patients having taken rofecoxib for longer than 2 years. The accrued data are consistent both qualitatively and quantitatively with the approved U.S. Product Circular for rofecoxib.

In the VIGOR study, rofecoxib 50 mg was compared with naproxen 1000 mg in patients with rheumatoid arthritis. Rofecoxib was associated with significantly fewer clinical upper GI events, complicated upper GI events, and GI bleeding than naproxen in this high-risk population. There was, however, a statistically significant difference in the incidence of thrombotic cardiovascular serious adverse experiences between the rofecoxib and naproxen groups, with fewer events occurring in the naproxen group. This difference in thrombotic events was mostly attributable to a difference in the incidence of myocardial infarction between the groups. Whether the difference in the incidence of thrombotic cardiovascular serious adverse experiences between the rofecoxib and naproxen groups in VIGOR represented a prothrombotic effect of rofecoxib, a cardioprotective effect due to inhibition of platelet function by naproxen, or a chance finding, could not be determined by the evaluation of the VIGOR results in isolation.

4. Discussion (Cont.)

Therefore, a meta-analysis of all rofecoxib studies was undertaken. Included in this latter analysis was preliminary data from 2 placebo-controlled studies in patients with Alzheimer's Disease or mild cognitive impairment. This meta-analysis demonstrated that the risk of thrombotic cardiovascular events in patients taking rofecoxib was similar in patients receiving placebo or other non-naproxen NSAIDs.

Since the submission of the VIGOR study, one Alzheimer's Disease study (Protocol 091) has been completed, a second study has been terminated but is not yet complete (Protocol 126), and a study in patients with mild cognitive impairment (Protocol 078) has completed enrollment. Together, these 3 placebo-controlled trials provide important safety data on 1448 elderly patients exposed to rofecoxib for up to 2.8 years. Within each trial, the proportion of patients with serious clinical adverse experiences in the rofecoxib group was similar to that in the placebo group. Combining the final data from Protocol 091 and preliminary data from Protocols 078 and 126 did not reveal any substantial difference between rofecoxib and placebo, including the cardiovascular body system. These substantial new data from the Alzheimer Studies, along with data from other placebo-controlled trials, indicate that the incidence of thrombotic cardiovascular serious adverse experiences is similar in patients taking rofecoxib and placebo and are consistent with a lack of prothrombotic effect of rofecoxib, even in high-risk, elderly patients.

4.1 Adverse Experiences Associated with NSAIDs

This SUR summarized serious clinical adverse experience data from recently completed extensions of 4 previously reported Phase IIb/III OA trials and 9 new trials. There were no meaningful changes to the safety profile of rofecoxib in the extensions or new trials. The 3 placebo-controlled studies in Alzheimer's Disease document that the profile of serious clinical adverse experiences with rofecoxib is generally similar to that of placebo in a large cohort of patients, most of whom were older than 65 years of age.

NSAIDs have been associated with gastric and renal toxicity. No meta-analysis of serious events related to these organs was planned or performed for this SUR. However, data from individual studies have been examined.

Adverse Experiences Related to Renal Function

Renal adverse experiences commonly associated with the use of NSAIDs include reductions in glomerular filtration and reductions in the renal excretion of sodium and potassium with the potential for fluid retention, edema, hypertension, and hyperkalemia. These adverse experiences are mechanism-based and dose related.

The accrued safety data do not suggest that serious renal function impairment is more common with rofecoxib than with NSAIDs. Neither edema nor hypertension were reported as serious adverse experiences in ≥0.5% of patients receiving rofecoxib or diclofenac in the Long-Term Exposure OA Studies. There were 2 patients who developed congestive heart failure on rofecoxib 12.5 mg but none on rofecoxib 25 or

4. Discussion (Cont.)

50 mg, or diclofenac. There was 1 case of congestive heart failure on rofecoxib and there were 3 on nabumetone in the Elderly Study (Protocol 058). The incidence of congestive heart failure with rofecoxib 25 mg and placebo was low and similar in the combined Alzheimer's Protocols 078, 091, and 126 (10 patients [0.69%] and 7 patients [0.48%], respectively). Acute renal failure was reported in 2 patients who received rofecoxib in Protocol 091 but in both cases the event was clearly not related to study medication.

Adverse Experiences Related to Digestive System

Previous analyses have shown that rofecoxib is associated with significantly fewer clinical upper GI events than nonselective NSAIDs. The data accrued since the VIGOR submission are consistent with that observation. Since the previous SUR, no gastric ulcers occurred in patients treated with rofecoxib in the Long-Term OA Exposure Studies, while 2 occurred in patients treated with diclofenac. In Protocol 901, there was 1 gastric ulcer and 1 duodenal ulcer on naproxen but none on rofecoxib. In the Alzheimer's Disease/Mild Cognitive Impairment Studies, there were more patients with gastric ulcers in the rofecoxib group than the placebo group, but the overall incidence of gastric ulcers with rofecoxib was still less than 0.5%. Assessment of causality in some of these cases is confounded since patients were allowed to take aspirin concomitantly.

Fatal Serious Adverse Experiences

None of the rofecoxib studies were designed to demonstrate differences in mortality. In the Long-Term OA Exposure Studies (Protocols 029, 034, and 035), in which there was substantially greater exposure to rofecoxib than to diclofenac, there were 8 deaths in the diclofenac group and 2 in the rofecoxib group. In the Elderly OA Study, there were 2 deaths among the 145 patients who received rofecoxib and none in the 92-patient nabumetone group. In the placebo-controlled Alzheimer's Disease Studies there were fewer deaths in the placebo group than the rofecoxib group (8 versus 14 in Protocol 091, 9 versus 15 in Protocol 078, and 3 versus 4 in Protocol 126). In the remaining studies (Protocols 083, 118, 120, 121, 901, 902), there were 2 deaths on rofecoxib and 1 on ibuprofen.

Careful review of the available information for each of the deaths does not reveal any pattern suggesting a risk with rofecoxib. Compared to the placebo group in Protocol 091, the rofecoxib group had 1 more cardiovascular death, 1 more death from a malignancy, and 2 more deaths from pneumonia. In Protocol 078, compared with the placebo group, the rofecoxib group had 3 more cardiovascular deaths and 5 more deaths due to trauma. The meta-analysis (discussed below) did not show any increased risk of fatal and nonfatal cardiovascular events, so it is unlikely that the small difference in the number of deaths reflects a prothrombotic effect. The overall incidence of pneumonia (nonfatal and fatal) with rofecoxib was similar to placebo in the Alzheimer's Studies (Protocols 078, 091, 126). The deaths due to trauma did not appear drug related. Therefore, review of the deaths does not identify a specific increased risk with rofecoxib.

4. Discussion (Cont.)

4.2 Serious Cardiovascular Thromboembolic Adverse Experiences

Despite the favorable results from the original OA program, and based on the pharmacodynamic effects of COX-2 inhibitors on the balance of prostanoid production, it was considered important to continue to characterize the effects of rofecoxib with regard to thrombotic cardiovascular serious adverse experiences. Studies of predominantly elderly patients with numerous investigators could have a low "signal-to-noise" ratio and mask a drug-related cardiovascular effect. Therefore, MRL implemented in the second quarter, 1998, a second initiative: a Cardiovascular Adjudication Standard Operating Procedure (Adjudication SOP) for the Post Phase III OA rofecoxib development program. The purpose of the Adjudication SOP was to collect data in a uniform manner and to evaluate further whether there were any differences in the incidence of thrombotic cardiovascular serious adverse experiences during chronic therapy with rofecoxib versus nonselective NSAIDs or placebo. All MRL clinical trials that were initiated in or after the second quarter, 1998, including VIGOR, were to have data on thrombotic cardiovascular serious adverse experiences collected as part of the Adjudication SOP.

The purpose of the Adjudication SOP was: (1) to improve accuracy in diagnosis across a heterogeneous group of study investigators in different nations and having different clinical specialties; and (2) to standardize the evaluation of thrombotic cardiovascular serious adverse experiences across ongoing clinical studies of rofecoxib. The analysis of cardiovascular outcomes in trials of rofecoxib as described in the SOP did not envision a separate analysis of individual trials. Instead, the SOP was designed to examine the combined incidence of cardiovascular outcomes across a broad range of patients in all post-Phase III OA trials of rofecoxib initiated by or after the second quarter 1998. Nevertheless, adjudicated events have been examined within individual studies.

APTC Events

The most widely used classification scheme for quantifying the impact of antithrombotic compounds in clinical trials is that defined by the Antiplatelet Trialists' Collaboration (APTC) [25]. This endpoint measures the incidence of fatal and irreversible morbid cardiovascular events: cardiovascular, hemorrhagic, and unknown cause of death; myocardial infarction; and cerebrovascular incidence (APTC combined endpoint). Both the VIGOR data and combined data from the OA program have previously been analyzed and presented using this classification. The updated data from the OA program and new studies in other populations have now been analyzed using the APTC classification.

In the Alzheimer's Studies (Protocols 091, 078, and 126) there were 22 cases in the rofecoxib group and 30 cases in the placebo group with an APTC event that was confirmed by the Adjudication committees. The ratio of rates was 0.82 with 95% CI of (0.45, 1.47). Within each of the individual studies the ratio of rates was also not significantly different than 1.0. The relative risk was also not increased in OA Protocols 029, 034, 035 (versus diclofenac) and Protocol 058 (versus nabumetone), although the number of events was quite small within each study. The relative risks (95% CI) for

4. Discussion (Cont.)

rofecoxib versus diclofenac were 2.08 (0.28, 92.21), 0.81 (0.16, 5.21) and 0.28 (0.06, 1.10) for Protocols 029, 034, and 035, respectively. The relative risk for rofecoxib versus nabumetone in Protocol 058 was 1.83 (0.15, 95.87). The Adjudication committees also evaluated thrombotic cardiovascular serious adverse experiences that did not meet the strict APTC criteria. The Adjudication committees confirmed that in the Alzheimer's Disease studies there were 25 rofecoxib patients with thrombotic cardiovascular serious adverse experiences during 1461 patient-years for a rate of 1.71 confirmed events per 100 patient-years. This is similar to the rate of 2.39 events per 100 patient-years with placebo (39 events/1634 patient-years). The relative risk is 0.72 with a 95% CI of (0.42, 1.21). In each of these 3 large studies, the rate for rofecoxib was statistically indistinguishable from that with placebo. There was no apparent difference when cardiac events or cerebrovascular events were examined separately.

Broadening the analysis to include potential thrombotic cardiovascular events reported by the investigators but not confirmed by adjudication does not change the overall result. In Protocols 078, 091, and 126, investigators reported 52 rofecoxib patients with thrombotic cardiovascular serious adverse experiences during 1450 patient-years for a rate of 3.59 events per 100 patient-years. This is similar to the rate of 3.84 events per 100 patient-years with placebo (62 events/1615 patient-years). In each of these 3 large studies, the rate for rofecoxib was similar to that with placebo. There was no apparent difference when cardiac events or cerebrovascular events were examined separately.

Re-examination of the newly available non-naproxen comparison data from the recently completed extensions revealed no evidence of an increased risk of a potential thrombotic cardiovascular serious adverse experience with rofecoxib compared with that with a non-naproxen NSAID (diclofenac or nabumetone) in Protocols 029, 034, 035, and 058. The relative risks (95% CI) for rofecoxib versus diclofenac were 1.43 (0.31, 13.26), 1.34 (0.40, 5.75), and 0.53 (0.22, 1.33) for Protocols 029, 034, and 035, respectively. The relative risk (95% CI) for rofecoxib versus nabumetone in Protocol 058 was 1.52 (0.25, 15.98).

Cardiovascular Meta-Analysis

As noted above, a combined analysis of thrombotic cardiovascular serious adverse experiences was to be performed based on a prespecified meta-analysis Data Analysis Plan. In addition to the VIGOR Study, Phase IIb/III OA, and Alzheimer's Disease clinical studies described above, the rofecoxib clinical program has included several smaller studies in diverse patient populations. All Phase IIb through Phase V rofecoxib clinical studies that were at least 4 weeks long and included either placebo and/or active-comparator nonselective NSAID controls are included in this meta-analysis. Three 6-week celecoxib studies were excluded because they did not provide comparisons of specific COX-2 inhibition to nonselective NSAIDs. Studies in healthy subjects were excluded because of the substantially different patient population (e.g., differences in underlying cardiovascular risk factors) and the generally very brief nature of these Phase-I trials.

4. Discussion (Cont.)

The comparisons of interest in this meta-analysis were rofecoxib versus non-naproxen NSAIDs and rofecoxib versus placebo. (The new data versus naproxen are limited compared with VIGOR, ADVANTAGE, and the original RA submission and are summarized in the Rheumatoid Arthritis SUR). These comparisons were assessed across all patient populations and within blocks of studies defined by indication for therapy and therefore contained unique patient populations. The blocks included: studies in rheumatoid arthritis (RA) patients (no new data in this report), studies in OA patients, and studies in patients without a primary diagnosis of arthritis (e.g., Alzheimer's Disease, low back pain, and prostatitis). Patient cohorts receiving rofecoxib doses 12.5, 25, or 50 mg were combined into the rofecoxib group because comparisons across doses could not be performed due to confounding of dose with protocol-type.

The primary endpoint being used in the meta-analysis is the combined endpoint defined by the APTC. The choice of the APTC endpoint was prespecified for this analysis for the following reasons: (1) as noted above, it is the most commonly accepted endpoint used in trials evaluating antithrombotic agents, and this was the endpoint suggested by a group of consultants after reviewing the initial VIGOR results; and (2) investigator-reported events were included from studies and patients that will not or have not yet completed the adjudication process. Since cardiovascular and unknown cause of death, myocardial infarction, and cerebrovascular accident are "hard endpoints"; the correlation is quite high between investigator-reported events and events confirmed by the Adjudication committee. Therefore, use of the APTC endpoint helped ensure consistency between trials that used adjudicated data and those which used investigator reported data.

Among the non-naproxen NSAID comparative studies there were 29 rofecoxib patients with confirmed APTC endpoint events (rate of 1.10 events per 100 patient-years). In the non-naproxen NSAID group, there were 17 patients with events (rate of 1.30 events per 100 patient-years). Thus, there was no evidence of any difference for rofecoxib versus non-naproxen NSAIDs in the risk of an APTC event. This is consistent with the results of the interim meta-analysis previously submitted. It is known that diclofenac, ibuprofen, and nabumetone do not provide sustained and nearly complete (>90%) inhibition of platelet function throughout the dosing interval. Therefore, it is not surprising that there is no meaningful difference between rofecoxib and non-naproxen NSAIDs with regard to risk of thrombotic events.

In the placebo-controlled trials, there were 38 rofecoxib patients with confirmed APTC events during 2518 years of follow-up for a rate of 1.51 events per 100 patient-years. There were 34 patients with events in the placebo group during 2099 years of follow-up for a rate of 1.62. The ratio of rates (95% CI) was 0.93 (0.57, 1.53). There is no evidence to suggest that rofecoxib has a clinically apparent prothrombotic effect

Hemorrhagic strokes are an APTC endpoint that may not reflect an underlying thrombotic event. Inclusion of bleeding events in the primary endpoint could reduce the sensitivity to detect a prothrombotic effect of COX-2 selective inhibitors. However,

4. Discussion (Cont.)

given that the primary endpoint reflects a traditional definition of a set of relevant events by a consensus of experts, it was chosen as primary for this analysis. Since the incidence of hemorrhagic strokes was quite low (3 hemorrhagic strokes on rofecoxib and 2 on placebo), exclusion of these events would not change the conclusions of the primary analysis.

4.3 Summary

This Safety Update Report has summarized serious clinical adverse experience data accrued since the last SUR. Data from recently completed extensions of 4 previously reported Phase IIb/III OA Studies and 9 new trials in different patient populations have been presented. There were no meaningful changes to the safety profile of rofecoxib with the extensive new data. A comprehensive analysis of the cardiovascular safety data from the individual studies as well as the updated cardiovascular meta-analysis confirms the excellent safety profile of rofecoxib. The meta-analysis clearly shows that the risk of thrombotic cardiovascular serious adverse experiences with rofecoxib is similar to that with placebo or non-naproxen NSAIDs.

5. Conclusions

Rofecoxib has an excellent safety profile with continuous use in excess of 2 years compared with either nonselective COX-1/COX-2 inhibitors or placebo. The conclusions reached in the Original Application and VIGOR remain valid. The safety data submitted with the RA sNDA (28-Feb-2001) and RA SUR (27-Jun-2001) further confirm those conclusions in the RA population. The data in this report demonstrate that rofecoxib:

1. Has a favorable safety profile in the OA population, including patients age 80 and older. The updated safety data are consistent with the previously reported data. There are no findings on new clinically important adverse experiences with the longer durations of exposures.
2. Has a cardiovascular safety profile comparable to that of placebo. The risk of sustaining a thrombotic cardiovascular event is similar in patients treated with rofecoxib, placebo, or non-naproxen non-selective NSAIDs that lack potent and sustained inhibition of platelet function.