

APPENDIX R

POST-WITHDRAWAL ANALYSES AND REPORTING OF CARDIOVASCULAR DATA ARISING FROM THE APPROVe TRIAL.

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APPENDIX R

POST-WITHDRAWAL ANALYSES AND REPORTING OF CARDIOVASCULAR DATA ARISING FROM THE APPROVe TRIAL.

As discussed in Appendix Q, Merck voluntarily withdrew Vioxx from the worldwide market on September 30, 2004 on the basis of cardiovascular data from the prematurely terminated APPROVe Trial. Given the potential public health implications of those data, MRL scientists and external consultants conducted numerous post-hoc analyses both before and after withdrawal in an effort to understand the data to the extent possible. Based on the results of some of those analyses, Merck stated in its press release announcing the withdrawal:

In [the APPROVe Trial], there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX, and in this respect, are similar to the results of two placebo-controlled studies described in the current U.S. labeling for VIOXX.¹

In the months following withdrawal of the drug, MRL scientists, together with external members of the APPROVe Trial Administrative Committee and a member of the APPROVe Trial External Safety Monitoring Board, co-authored an article on the APPROVe Trial that was published in the New England Journal of Medicine in February 2005 (the “APPROVe article”). In June 2005, MRL scientists submitted the results of the

¹ 9/30/04 Merck press release, “Merck Announces Voluntary Worldwide Withdrawal of Vioxx®,” MRK-AFJ0008607, at 07.

APPROVe Trial to the FDA.² In addition, Merck undertook a follow-up study to determine whether APPROVe Trial patients who had taken Vioxx continued to experience increased rates of thrombotic events, relative to patients who had taken placebo, after stopping use of the drug.

In May 2006, Merck issued press releases (i) describing the results of the follow-up study and (ii) announcing that it had discovered that the APPROVe article and the APPROVe Trial abbreviated Clinical Study Report submitted to the FDA contained an error (described more fully below). Over the course of the next month, MRL scientists and external co-authors of the APPROVe article engaged in a dialogue with editors of the New England Journal of Medicine about the import of the error and of the follow-up data.

This Appendix discusses: (i) the data and post-hoc analyses from which MRL scientists concluded that the risk of cardiovascular events among patients in the Vioxx arm of the APPROVe Trial increased relative to that of patients on placebo after 18 months of continuous use and the Company's public statements regarding this apparent 18-month inflection point; (ii) the public presentation of the APPROVe Trial cardiovascular results in the APPROVe article and abbreviated Clinical Study Report, including the origin and import of the error discovered in May 2006; (iii) the follow-up study that Merck conducted and preliminary data from that study, which were submitted to the FDA in May 2006; and (iv) communications among the APPROVe article

² In May 2006, MRL scientists discovered that the FDA submission and the APPROVe article contained an error, as discussed in Section B of this Appendix.

co-authors and the New England Journal of Medicine editors regarding the error and the results of the follow-up study.

A. Merck's Statements Regarding the Time-Course of Cardiovascular Risk and Relevant Post-Hoc Analyses of the APPROVe Trial Cardiovascular Data.

As described above, Merck's September 30, 2004 press release announcing Merck's voluntary withdrawal of Vioxx from the worldwide market noted that there was an increased relative risk in the APPROVe Trial for confirmed cardiovascular events on Vioxx "beginning after 18 months of treatment" and that "results for the first 18 months of the [Trial] did not show any increased risk of confirmed cardiovascular events on VIOXX."³ The following section describes Merck's public statements regarding the time-course of cardiovascular risk on Vioxx and the data relevant to these statements.

1. 18-Month Statements.

Merck's public communications since September 30, 2004 concerning the APPROVe Trial cardiovascular results – in press releases,⁴ submissions to the FDA,⁵

³ 9/30/04 Merck press release, "Merck Announces Voluntary Worldwide Withdrawal of Vioxx®," MRK-AFJ0008607, at 07.

⁴ 9/30/04 Merck press release, "Merck Announces Voluntary Worldwide Withdrawal of Vioxx®," MRK-AFJ0008607, at 07; 1/10/06 Merck press release, "VIOXX® Trial Update: Statement on VIOXX® Product Liability Trial Scheduled in Starr County, Texas," MRK-AFV0496926, at 26; 2/17/06 Merck press release, "Merck Wins Federal VIOXX® Product Liability Case," MRK-AAD0521988, at 88; 5/11/06 Merck press release, "Merck Announces Preliminary Analyses of Off-Drug Extension of APPROVe Study," MRK-ARG0002290, at 91; 5/30/06 Merck press release, "Merck Corrects Description of a Statistical Method Used in APPROVe Study," MRK-ARQ0006011, at 11-12; 6/26/06 Merck press release, "Merck Stands Behind Original APPROVe Study Results," MRK-ASW0005632, at 32-33.

⁵ MRL Background Package for 2/16/05 – 2/18/05 Joint Meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, MRK-AAD0408404, at 439; 3/15/05 APPROVe Trial abbreviated Clinical Study Report, Synopsis and Cardiovascular Safety Report, MRK-I8940100731, at 0740, 0742, MRK-I8940100962, at 0969, 1020.

public statements before Congress and the FDA Advisory Committee,⁶ the APPROVe article,⁷ an Open Letter to the scientific community,⁸ and the Vioxx Information Center on Merck's website⁹ – have repeated, in generally similar formulations, the claim that the increased relative risk was not apparent until after 18 months of treatment. For example:

- The APPROVe article published in February 2005 stated: “In a post hoc analysis, the difference between the two groups in the incidence of thrombotic events was evident in the second 18 months of the study, whereas the event rates were similar for the first 18 months.”¹⁰
- The APPROVe abbreviated Clinical Study Report submitted on June 6, 2005 stated: “There is a significantly increased risk for confirmed thrombotic cardiovascular events with rofecoxib 25 mg daily compared with placebo, beginning only after 18 months of continuous treatment.”¹¹
- Merck's May 11, 2006 press release repeated the formulation used in the September 30, 2004 press release, stating: “As previously reported, in the

⁶ Transcript of 2/16/05 Joint Meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, MRK-AIU0185869, at 032-036; 11/18/04 Prepared testimony of Raymond V. Gilmartin before the United States Senate Committee on Finance, MRK-ABG0003548-52.

⁷ Bresalier* RS, Sandler* RS, Quan H, *et al.* Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial. *N Engl J Med.* 2005;352:1092-1102, MRK-ARQ0000659. The APPROVe article included 12 authors, 9 of whom were not employed by Merck, including the lead author, Dr. Robert Bresalier*. According to Dr. Bresalier*, the non-Merck authors had the final decision-making authority on the wording of the APPROVe article.

⁸ 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152, at 152-53; “APPROVe: Assessment,” MRK-AFO0300154, at 154-56 (attached to 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152).

⁹ <http://www.merck.com/newsroom/vioxx>.

¹⁰ Bresalier* RS, Sandler* RS, Quan H, *et al.* Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial. *N Engl J Med.* 2005;352:1092-1102, at 1097, MRK-ARQ0000659.

¹¹ 3/15/05 APPROVe Trial abbreviated Clinical Study Report, Cardiovascular Safety Report, MRK-I8940100731, at 0742 (submitted with 6/06/05 letter from P. Huang to B. Harvey* (FDA), MRK-S0420050996).

base study, there was an increased relative risk for confirmed thrombotic cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo.”¹²

- Merck’s May 30, 2006 and June 26, 2006 press releases modified this formulation slightly, noting that the increased cardiovascular risk on Vioxx was “observed beginning after 18 months.”¹³

Some of Merck’s statements regarding the time-course of potential cardiovascular risk on Vioxx have also asserted that there was no evidence of a pre-18-month cardiovascular effect in Merck’s pre-APPROVe clinical trials of Vioxx. For instance, Merck’s September 30, 2004 press release stated: “The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX, and in this respect, are similar to the results of two placebo-controlled studies described in the current U.S. labeling for VIOXX.”¹⁴ Similarly, Merck’s Background Package for the February 16 to 18, 2005 FDA Advisory Committee Meeting stated: “Data from the APPROVe study confirm the findings in our other clinical trial databases that there is no evidence for an increase in the relative risk of sustaining a thrombotic CV

¹² 5/11/06 Merck press release, “Merck Announces Preliminary Analyses of Off-Drug Extension of APPROVe Study,” MRK-ARQ0002290, at 91.

¹³ 5/30/06 Merck press release, “Merck Corrects Description of a Statistical Method Used in APPROVe Study,” MRK-ARQ0006011, at 11; 6/26/06 Merck press release, “Merck Stands Behind Original APPROVe Study Results,” MRK-ASW0005632, at 32.

¹⁴ 9/30/04 Merck press release, “Merck Announces Voluntary Worldwide Withdrawal of Vioxx®,” MRK-AFJ0008607, at 07.

event for the rofecoxib group versus placebo over the first 18 months of treatment.”¹⁵

Many of these statements appeared in voluminous documents that provided the data and analyses on which the statements were based.

2. Data Relevant to the 18-Month Claim.

Merck’s statements regarding the time-course of cardiovascular risk in the APPROVe Trial were based on various analyses of the APPROVe Trial cardiovascular data, including “Kaplan-Meier” time-to-event plots, statistical tests of the proportionality of the hazard rates on Vioxx versus placebo (*i.e.*, whether the relative risk of cardiovascular events on Vioxx versus placebo remained constant over time), and analyses of the relative risk for cardiovascular events on Vioxx versus placebo broken down into 6-month intervals. These analyses were initially performed in September 2004 by Dr. Hui Quan, unblinded statistician for the APPROVe Trial, on behalf of the APPROVe Trial External Safety Monitoring Board, using preliminary data. The analyses were repeated when the final APPROVe Trial data became available. The results of these analyses, based both on the preliminary data (available when the decision to withdraw Vioxx from the market and the initial public statements regarding the results of the APPROVe Trial were made) and the final data, are summarized below.

To the extent that Merck’s statements went beyond the APPROVe Trial data to assert a broader evidentiary basis for the absence of an increased risk for Vioxx during

¹⁵ MRL Background Package for 2/16/05 – 2/18/05 Joint Meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, MRK-AAD0408404, at 439.

the first 18 months of continuous treatment, data relevant to these assertions, from Merck's other clinical trials and from the ever-growing body of epidemiological studies on Vioxx, are also summarized below.

- a. Analyses of preliminary APPROVe data:
Dr. Quan's September 13, 2004 report to the
APPROVe Trial External Safety Monitoring Board.

On September 13, 2004, Dr. Quan sent a preliminary analysis of APPROVe Trial data to the trial's External Safety Monitoring Board in advance of the Board's September 17, 2004 meeting.¹⁶ This analysis was based on data that Dr. Quan had received as of August 16, 2004 and provided the basis on which the APPROVe Trial External Safety Monitoring Board recommended terminating the APPROVe Trial.¹⁷ The data and analyses in Dr. Quan's September 13 report also informed MRL scientists' initial conclusions regarding the meaning of the APPROVe Trial data (including the time-course of the cardiovascular risk) and decision to recommend that Vioxx be withdrawn from the market.¹⁸

Dr. Quan's report analyzed the data in terms of two composite cardiovascular endpoints: (i) the Antiplatelet Trialists' Collaboration ("APTCL") composite cardiovascular endpoint; and (ii) Merck's internally created "confirmed thrombotic"

¹⁶ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517-69.

¹⁷ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 517. The termination of the APPROVe Trial is discussed in detail in Appendix Q.

¹⁸ As discussed in Appendix Q, during that time frame (late September 2004), Merck statisticians also performed additional analyses on the preliminary data, and MRL scientists and consultants considered data from the entire Vioxx clinical program before recommending the withdrawal of Vioxx.

endpoint.¹⁹ As demonstrated in Table 1, below, the composition of the two confirmed event endpoints overlapped, but the endpoints differed in that (i) the confirmed thrombotic event endpoint included certain peripheral vascular events, such as pulmonary embolism, that the APTC composite cardiovascular endpoint did not include; and (ii) the APTC composite cardiovascular endpoint included three hemorrhagic adverse events, such as hemorrhagic cerebrovascular stroke, that the confirmed thrombotic endpoint did not include.²⁰

¹⁹ Events falling under both composite endpoint definitions were reviewed and “confirmed” by a blinded expert adjudication committee pursuant to MRL’s Cardiovascular Adjudication SOP.

²⁰ For more information regarding the two composite endpoints, see Appendix F.

Table 1

Events Included in the Confirmed Thrombotic and APTC Composite Cardiovascular Endpoints²¹

	Confirmed Thrombotic Endpoint	APTC Composite Cardiovascular Endpoint
<i>Thrombotic Events</i>		
Cardiac Events		
Acute MI	✓	✓
Fatal: Acute MI	✓	✓
Unstable Angina Pectoris	✓	
Sudden and/or Unexplained Death	✓	✓
Resuscitated Cardiac Arrest	✓	✓
Cardiac Thrombus	✓	
Peripheral Vascular Events		
Pulmonary Embolism	✓	
Fatal: Pulmonary Embolism	✓	
Peripheral Arterial Thrombosis	✓	
Fatal: Peripheral Arterial Thrombosis	✓	✓
Peripheral Venous Thrombosis	✓	
Cerebrovascular Events		
Ischemic Cerebrovascular Stroke	✓	✓
Fatal: Ischemic Cerebrovascular Stroke	✓	✓
Cerebrovascular Venous Thrombosis	✓	
Fatal: Cerebrovascular Venous Thrombosis	✓	✓
Transient Ischemic Attack	✓	
Hemorrhagic Events		
Hemorrhagic Cerebrovascular Stroke		✓
Fatal: Hemorrhagic Cerebrovascular Stroke		✓
Fatal: Hemorrhagic deaths of any cause		✓

The two endpoints were alternative means of measuring cardiovascular risk that MRL scientists used somewhat interchangeably. For instance, Dr. Quan's September 13, 2004 safety report to the APPROVe Trial External Safety Monitoring Board stated: "To be consistent with the current approaches for [cardiovascular] combined analysis, APTC is the primary event, the [confirmed thrombotic] event is the

²¹ 3/15/05 APPROVe Trial abbreviated Clinical Study Report, Cardiovascular Safety Report, MRK-I8940100962, at 975.

secondary event.”²² And MRL used the APTC composite cardiovascular event endpoint as the primary endpoint in its four pooled analyses of cardiovascular events in all of its Vioxx trials (discussed in Appendices F, I, J, and O). On the other hand, the Statistical Data Analysis Plan for Protocol 203 (discussed in Appendices M and Q), a combined analysis of cardiovascular data from three placebo controlled trials including the APPROVe Trial, pre-specified the confirmed thrombotic event endpoint as the “primary endpoint.”²³ In addition, MRL had used the confirmed thrombotic endpoint in analyzing cardiovascular data from the VIGOR Trial (discussed in Appendices E, F, and I) and the APPROVe Trial.

Dr. Quan’s September 13 report noted that (i) 33 patients on Vioxx experienced an APTC composite cardiovascular endpoint event²⁴ on treatment or within 14 days of discontinuation compared to 16 patients on placebo, translating to a relative risk of 2.25 (95% confidence interval, 1.24 to 4.08),²⁵ and (ii) 45 patients on Vioxx experienced a confirmed thrombotic event²⁶ on treatment or within 14 days of discontinuation compared to 25 patients in the placebo arm, for a relative risk of 1.96 (95% confidence

²² 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 517.

²³ Protocol 203 Statistical Data Analysis Plan, MRK-AAB0083231, at 242.

²⁴ As discussed in Appendix F, the APTC composite cardiovascular endpoint consisted of cardiovascular death, myocardial infarction, stroke (both ischemic and hemorrhagic), and death due to unknown cause or due to bleeding.

²⁵ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 521, 533.

²⁶ The “confirmed thrombotic” composite endpoint consisted of events confirmed as serious cardiovascular thrombotic events by external adjudicators pursuant to Merck’s cardiovascular adjudication SOP.

interval, 1.20 to 3.19).²⁷ These data reflected an overall statistically significantly higher rate for both endpoints for Vioxx compared to placebo. The analyses of these data aimed at assessing the time-course of cardiovascular risk are discussed below.

i. Kaplan-Meier plots.

Dr. Quan's September 13 report included Kaplan-Meier plots for both the confirmed thrombotic endpoint and the APTC composite cardiovascular endpoint. As discussed in Appendix Q, Kaplan-Meier plots graphically depict the cumulative incidence of events in treatment groups over time. They provide visual evidence regarding the shapes of the hazard curves but do not, standing alone, provide a basis for any definitive conclusions regarding the time-course of risk or whether the hazard rates for Vioxx and placebo remain proportional over time. As indicated in the figures below taken from Dr. Quan's September 13 report, for both endpoints (confirmed thrombotic events and APTC composite cardiovascular endpoint events), the Kaplan-Meier curves for placebo (Treatment A) and Vioxx (Treatment B) appeared to substantially overlap until approximately 540 days (18 months) of continuous treatment and appeared to separate at around the 18-month point.²⁸

²⁷ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 521, 533.

²⁸ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 536-37. These plots reflect events that occurred on treatment or within 14 days of discontinuation of treatment.

Figure 1

APPROVe Trial – Kaplan-Meier Plot for Confirmed Thrombotic Events
(August 2004 Data)

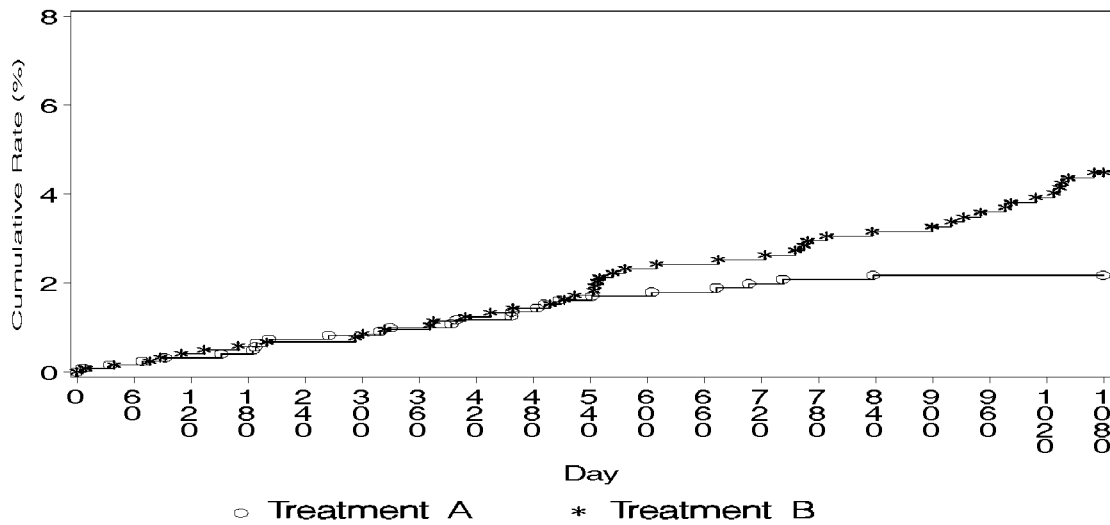
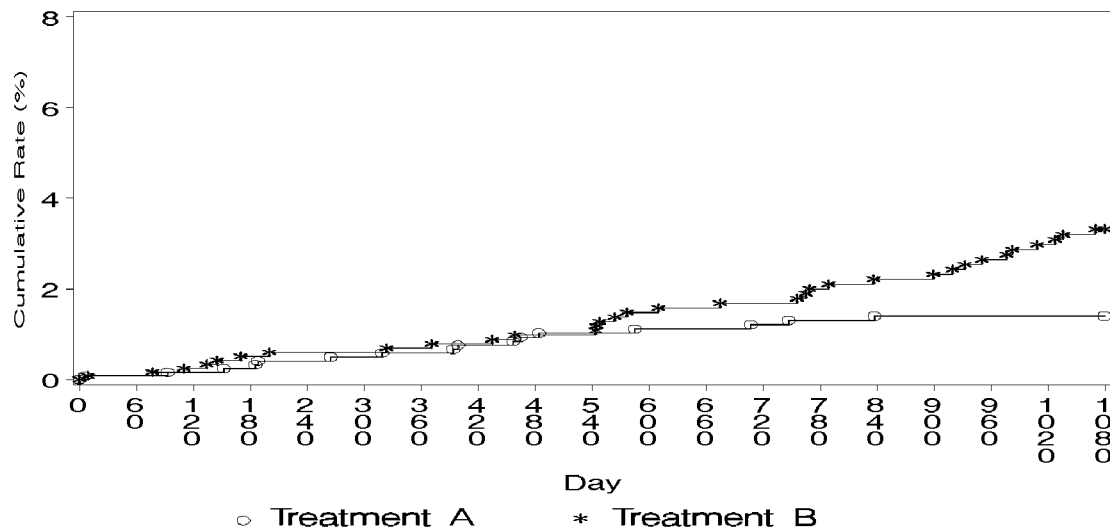


Figure 2

APPROVe Trial – Kaplan-Meier Plot for APTC Events
(August 2004 Data)



ii. Test of the proportionality of hazards.

In his September 13, 2004 report to the APPROVe Trial External Safety Monitoring Board, Dr. Quan performed a statistical test of the proportionality of the hazard rates using a Cox proportional hazards model to determine whether the hazard ratio (or relative risk) between Vioxx and placebo remained constant over time.²⁹ Statistical tests of the proportionality of the hazard rates are the most formal means of testing whether the between-treatment hazard ratio changes during the course of a clinical trial. Such tests may confirm a visual impression from a Kaplan-Meier plot that the hazard ratio is different at the end of a trial than at the beginning, but, as conducted by MRL, they did not identify when any change in hazard ratio occurred.

The result of a hazard rate proportionality test is presented as a “proportionality p-value,” which can range from 0 to 1. Generally, a p-value of 0.05 or less contradicts the assumption built into the Cox proportional-hazards model that the hazard ratio is constant over time. Because the test of proportionality of hazard rates has low statistical power, however, many biostatisticians may consider a p-value of 0.10 or less, in conjunction with graphical analysis, sufficient to reject the assumption that the hazard ratio is constant. Dr. Quan reported that the proportionality p-values for the confirmed

²⁹ There are a variety of ways to perform this test, and biostatisticians commonly perform it by analyzing the interaction between the assigned treatment and either the logarithm of time or linear time in the Cox proportional-hazards model. Dr. Quan’s report did not specify which method he had used for the test. As discussed in more detail below, in Section B of this Appendix, MRL scientists were under the impression that reported results were from the Cox proportional-hazards model using the “logarithm of time” covariate, whereas, in fact, Dr. Quan’s report provided the result of the Cox proportional-hazards model using the “linear time” covariate.

thrombotic and the APTC event endpoints were 0.0056 and 0.0235, respectively.³⁰ Both p-values were low, suggesting that the hazard ratio for cardiovascular events changed over time.

iii. Event rates and ratios in 6-month intervals.

Dr. Quan's September 13 report also included tables of the cardiovascular event rates and hazard ratios for confirmed thrombotic and APTC events for the Vioxx and placebo arms of the APPROVe Trial broken out into 6-month intervals (the sixth and last of which for some patients was not yet complete). This analysis was an attempt to examine how and when the hazard ratio changed over time, which neither the overall relative risk for the entire study period nor the test of the proportionality of hazards could illuminate. These tables are reproduced below (again with Treatment A representing placebo and Treatment B representing Vioxx).³¹

Table 2
APPROVe Trial (August 2004 Data)
Confirmed Thrombotic Events in 6-Month Intervals

Re/day	Treatment A		Treatment B		Hazard Ratio
	Number of Events	Hazard (SE)	Number of Events	Hazard (SE)	
0 - 180	5	0.0040(0.0018)	7	0.0058(0.0022)	1.4459
181 - 360	7	0.0060(0.0023)	4	0.0037(0.0018)	0.6147
361 - 540	7	0.0063(0.0024)	8	0.0078(0.0028)	1.2490
541 - 720	4	0.0038(0.0019)	8	0.0083(0.0029)	2.2000
721 - 900	2	0.0020(0.0014)	7	0.0076(0.0029)	3.8938
> 900	0	0(0)	11	0.0245(0.0074)	.

³⁰ 9/13/04 report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 536, 537.

³¹ 9/13/04 report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 536, 537. These tables reflect events that occurred on treatment or within 14 days of discontinuation of treatment.

Table 3

APPROVe Trial (August 2004 Data)
APTC Events in 6-Month Intervals

Relday	Treatment A		Treatment B		Hazard Ratio
	Number of Events	Hazard (SE)	Number of Events	Hazard (SE)	
0 - 180	3	0.0024(0.0014)	6	0.0050(0.0020)	2.0672
181 - 360	4	0.0034(0.0017)	2	0.0018(0.0013)	0.5385
361 - 540	5	0.0045(0.0020)	3	0.0029(0.0017)	0.6553
541 - 720	2	0.0019(0.0013)	7	0.0072(0.0027)	3.8372
721 - 900	2	0.0020(0.0014)	6	0.0065(0.0026)	3.3241
> 900	0	0(0)	9	0.0199(0.0066)	.

As reflected in the tables, there was a higher incidence of confirmed thrombotic and APTC events on Vioxx than on placebo in the first, fourth, fifth, and sixth intervals, and in the third interval as well for confirmed thrombotic events. However, the hazard ratios for the fourth, fifth, and sixth³² intervals were noticeably higher than those for the preceding intervals for both confirmed thrombotic and APTC events.

b. Analyses of final APPROVe Trial cardiovascular data.

MRL scientists obtained final data for the APPROVe Trial in December 2004. These data showed that 46 patients on Vioxx experienced confirmed thrombotic events on treatment or within 14 days of discontinuation compared to 26 patients on placebo – a statistically significantly higher rate on Vioxx than on placebo, reflected in a relative risk

³² The hazard ratio for the sixth 6-month interval could not be calculated because there had been 11 versus 0 and 9 versus 0 confirmed thrombotic and APTC events, respectively, in the Vioxx and placebo arms, but the difference in the numbers of events between the two groups was greater than for any of the preceding 6-month intervals.

of 1.92 (95% confidence interval, 1.19 to 3.11).³³ Thirty-four patients on Vioxx experienced confirmed APTC events on treatment or within 14 days of discontinuation compared to 18 patients on placebo – again a statistically significantly higher rate on Vioxx as reflected in the relative risk of 2.06 (95% confidence interval, 1.16 to 3.64).³⁴ Once the final data became available, MRL scientists re-ran many of the analyses relevant to the time-course of cardiovascular risk that had been performed on the preliminary data and included the updated analyses in the APPROVe Trial abbreviated Clinical Study Report and the APPROVe article. The results of analyses of the final data are summarized below.

i. Kaplan-Meier plots.

The APPROVe Trial abbreviated Clinical Study Report, submitted to the FDA on June 6, 2005, contained Kaplan-Meier plots for both confirmed thrombotic events and APTC events. As with the Kaplan-Meier plots based on preliminary data, the Kaplan-Meier curves for placebo and Vioxx, for both endpoints, appeared to be similar until approximately 540 days (18 months) of continuous treatment and appeared to separate around the 18-month point. The plots are reproduced below.³⁵

³³ 3/15/05 APPROVe Trial abbreviated Clinical Study Report, Cardiovascular Safety Report, MRK-I8940100962, at 0985-986.

³⁴ 3/15/05 APPROVe Trial abbreviated Clinical Study Report, Cardiovascular Safety Report, MRK-I8940100962, at 0992.

³⁵ 3/15/05 APPROVe Trial abbreviated Clinical Study Report, Cardiovascular Safety Report, MRK-I8940100962, at 0986, 0993. These plots reflect events that occurred on treatment or within 14 days of discontinuation of treatment.

Figure 3

APPROVe Trial – Kaplan-Meier Plot for Confirmed Thrombotic Events
(Final Data)

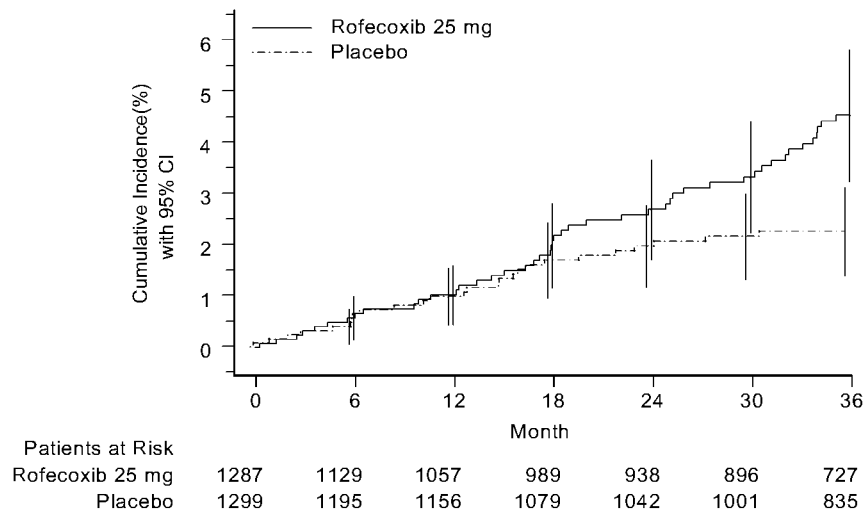
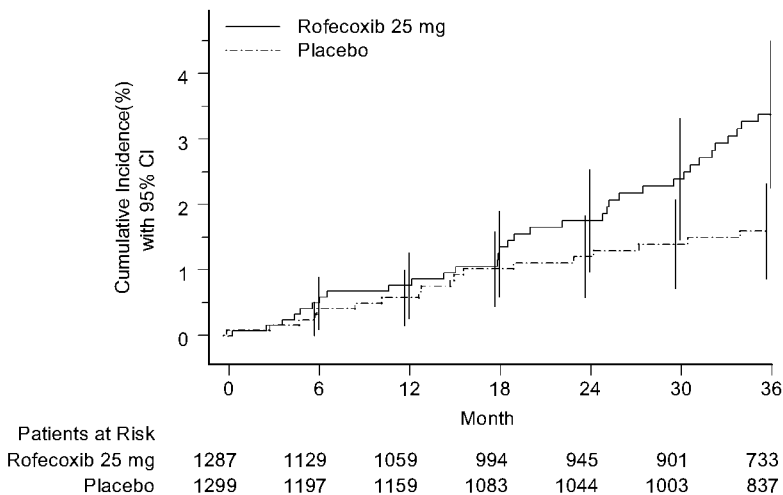


Figure 4

APPROVe Trial – Kaplan-Meier Plot for APTC Events
(Final Data)



ii. Test of the proportionality of hazards.

MRL scientists also performed a test of the proportionality of hazards on the final data using the same statistical model Dr. Quan had used to prepare his September 13, 2004 report.³⁶ Final data yielded proportionality p-values of 0.014 and 0.119 for the confirmed thrombotic and APTC event endpoints, respectively.³⁷ While the p-value of 0.014 for the confirmed thrombotic endpoint was low enough to contradict the assumption that the hazard ratio was constant through the trial, the p-value of 0.119 for APTC events was slightly above the threshold for rejecting the constant hazards assumption.

iii. Event rates and ratios in 6- and 18-month intervals.

The APPROVe Trial abbreviated Clinical Study Report included tables of the cardiovascular event rates and hazard ratios for confirmed thrombotic and APTC events for the Vioxx and placebo arms of the APPROVe Trial broken out into both 6-month and 18-month intervals. These tables are presented below.³⁸

³⁶ “APPROVe: Assessment,” MRK-AFO0300154, at 54-55 (attached to 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152). The discovery of which statistical model was used in Dr. Quan’s report and in the abbreviated Clinical Study Report is discussed in detail in Section B.6.b of this Appendix.

³⁷ 3/15/05 APPROVe Trial abbreviated Clinical Study Report, Cardiovascular Safety Report, MRK-I8940100962, at 0986, 0994.

³⁸ 3/15/05 APPROVe Trial abbreviated Clinical Study Report, Cardiovascular Safety Report, MRK-I8940100962, at 0988, 0995. These tables reflect events that occurred on treatment or within 14 days of discontinuation of treatment.

Table 4

**APPROVe Trial (Final Data)
Confirmed Thrombotic Events in 6-Month Intervals**

Time Interval	Rofecoxib 25 mg (N=1287)			Placebo (N=1299)			Relative Risk(95% CI)
	Number At Risk	Events/Patient-years	Rate (95% CI) [†]	Number At Risk	Events/Patient-years	Rate (95% CI) [†]	
0 - 6 Months	1287	7/602	1.16(0.47, 2.40)	1299	5/622	0.80(0.26, 1.88)	1.45 (0.40, 5.78)
6 - 12 Months	1129	5/544	0.92(0.30, 2.14)	1195	7/586	1.20(0.48, 2.46)	0.77 (0.19, 2.81)
12 - 18 Months	1057	10/510	1.96(0.94, 3.61)	1156	8/558	1.43(0.62, 2.82)	1.37 (0.49, 3.99)
18 - 24 Months	989	7/481	1.46(0.59, 3.00)	1079	3/531	0.57(0.12, 1.65)	2.58 (0.59, 15.43)
24 - 30 Months	938	6/456	1.32(0.48, 2.86)	1042	2/510	0.39(0.05, 1.42)	3.35 (0.60, 33.97)
> 30 Months	896	11/466	2.36(1.18, 4.23)	1001	1/521	0.19(0.00, 1.07)	12.30 (1.79, 529.46)

[†] Events per 100 Patient-Years (PY)

Data Source: [4.4.1]

Table 5

**APPROVe Trial (Final Data)
Confirmed Thrombotic Events in 18-Month Intervals**

Time Interval	Rofecoxib 25 mg (N=1287)			Placebo (N=1299)			Comparison	
	Number At Risk	Events/Patient-years	Rate (95% CI) [†]	Number At Risk	Events/Patient-years	Rate (95% CI) [†]	Difference(95% CI)	Relative Risk(95% CI)
Months 0 - 18	1287	22/1656	1.33(0.83, 2.01)	1299	20/1765	1.13(0.69, 1.75)	0.20 (-0.55, 0.94)	1.18 (0.64, 2.15)
Months 19 - 36	989	24/1403	1.71(1.10, 2.55)	1079	6/1561	0.38(0.14, 0.84)	1.33 (0.58, 2.08)	4.45 (1.77, 13.32)
Ratio			1.32 (0.74, 2.35)			0.34 (0.11, 0.88)		

[†] Events per 100 Patient-Years (PY)

Data Source: [4.4.1]

Table 6

**APPROVe Trial (Final Data)
APTC Events in 6-Month Intervals**

Time Interval	Rofecoxib 25 mg (N=1287)			Placebo (N=1299)			Relative Risk(95% CI)
	Number At Risk	Events/Patient-years	Rate (95% CI) [†]	Number At Risk	Events/Patient-years	Rate (95% CI) [†]	
0 - 6 Months	1287	6/602	1.00(0.37, 2.17)	1299	3/622	0.48(0.10, 1.41)	2.07 (0.44, 12.78)
6 - 12 Months	1129	3/545	0.55(0.11, 1.61)	1197	4/587	0.68(0.19, 1.75)	0.81 (0.12, 4.78)
12 - 18 Months	1059	5/512	0.98(0.32, 2.28)	1159	5/560	0.89(0.29, 2.08)	1.09 (0.25, 4.75)
18 - 24 Months	994	5/484	1.05(0.34, 2.41)	1083	2/532	0.38(0.05, 1.36)	2.75 (0.45, 28.87)
24 - 30 Months	945	6/459	1.31(0.48, 2.85)	1044	2/511	0.39(0.05, 1.41)	3.34 (0.60, 33.82)
> 30 Months	901	9/469	1.92(0.88, 3.65)	1003	2/522	0.38(0.05, 1.39)	5.01 (1.04, 47.63)

[†] Events per 100 Patient-Years (PY)

Data Source: [4.4.1]

Table 7

APPROVe Trial (Final Data)
APTC Events in 18-Month Intervals

Time Interval	Rofecoxib 25 mg (N=1287)			Placebo (N=1299)			Comparison	
	Number At Risk	Events/Patient-years	Rate (95% CI) [†]	Number At Risk	Events/Patient-years	Rate (95% CI) [†]	Difference(95% CI)	Relative Risk(95% CI)
Months 0 - 18	1287	14/1658	0.84(0.46, 1.42)	1299	12/1769	0.68(0.35, 1.18)	0.17 (-0.42, 0.75)	1.25 (0.58, 2.69)
Months 19 - 36	994	20/1412	1.42(0.87, 2.19)	1083	6/1565	0.38(0.14, 0.83)	1.03 (0.34, 1.73)	3.69 (1.43, 11.24)
Ratio			1.72 (0.87, 3.41)	.		0.57 (0.17, 1.63)		

[†] Events per 100 Patient-Years (PY)

Data Source: [4.4.1]

Similar to the 6-month interval analysis provided in Dr. Quan’s September 13 report based on preliminary data, the final data reflected: (i) a higher incidence of confirmed thrombotic events and APTC events on Vioxx than on placebo in all but the second 6-month interval, and (ii) a notably higher relative risk for Vioxx versus placebo in the fourth, fifth, and sixth 6-month intervals as compared to the first three 6-month intervals, which would be consistent with an increase in the relative cardiovascular risk of Vioxx compared to placebo at approximately the 18-month point of the trial.

The 18-month interval analysis showed that, in the first 18 months, there were just two more events among patients on Vioxx compared to patients on placebo for either endpoint. However, in the second 18 months, there were statistically significantly more events among patients on Vioxx compared to patients on placebo for both endpoints.

c. Data from other Merck clinical trials of Vioxx.

As discussed above, some of Merck’s public statements concerning the APPROVe Trial results noted that the Company’s previous placebo-controlled trials did not show an increased cardiovascular risk on Vioxx during the first 18 months of treatment. The September 30, 2004 press release specifically mentioned “two

placebo-controlled studies described in the current U.S. labeling for VIOXX,³⁹ a reference to the two Alzheimer's Trials, Protocols 078 and 091, in which the overall relative risk for confirmed thrombotic events for Vioxx 25 mg versus placebo in the two trials combined was 1.01 (95% confidence interval, 0.67 to 1.53).⁴⁰ In addition, there was a lower rate of confirmed thrombotic events and APTC events on Vioxx versus placebo during the first 18 months of the Alzheimer's trials, as shown in Tables 8 and 9⁴¹ and Figures 5 and 6⁴² below. However, in these trials, patients on Vioxx experienced a statistically significant increase in overall mortality (relative risk 2.23; 95% confidence interval, 1.33 to 3.73) and a numerical but not statistically significant increase in thrombotic cardiovascular-related mortality (relative risk 2.56; 95% confidence interval, 0.89 to 7.35) compared to patients on placebo.⁴³

³⁹ 9/30/04 Merck press release, "Merck Announces Voluntary Worldwide Withdrawal of Vioxx®," MRK-AFJ0008607, at 07.

⁴⁰ 12/12/03 Alzheimer's Disease Combined Safety Analysis, MRK-AFL0059959, at 964, 018. The relative risk, Vioxx versus placebo, for APTC events in the two Alzheimer's Trials combined was 0.96 (95% confidence interval 0.60 to 1.52). Id. at 022. The final results of the Alzheimer's Trials are discussed in Appendix Q.

⁴¹ 12/12/03 Alzheimer's Disease Combined Safety Analysis, MRK-AFL0059959, at 020, 024. These figures reflect events that occurred on treatment or within 14 days of discontinuation of treatment.

⁴² 12/12/03 Alzheimer's Disease Combined Safety Analysis, MRK-AFL0059959, at 021, 025. These tables reflect events that occurred on treatment or within 14 days of discontinuation of treatment.

⁴³ 12/12/03 Alzheimer's Disease Combined Safety Analysis, MRK-AFL0059959, at 000, 028. There were 41 deaths due to any cause among patients taking Vioxx compared to 23 among patients taking placebo. There were 11 thrombotic cardiovascular deaths among patients taking Vioxx compared to 5 among patients taking placebo. Figures are for deaths that occurred (or were related to adverse experiences that occurred) while patients were on treatment or within 14 days of discontinuation of treatment. Id.

Table 8

**Combined Alzheimer's Trials
Confirmed Thrombotic Events in 6-Month Intervals**

Time Interval	Rofecoxib			Placebo			Relative Risk [‡] (95% CI)
	Number At Risk	Cases/PYR (Rate [†])	95% CI	Number At Risk	Cases/PYR (Rate [†])	95% CI	
0 to 6 Month	1069	6/481 (1.25)	(0.56, 2.78)	1074	12/500 (2.40)	(1.36, 4.23)	0.520 (0.195, 1.385)
6 to 12 Month	878	8/398 (2.01)	(1.01, 4.02)	939	15/433 (3.46)	(2.09, 5.75)	0.580 (0.246, 1.369)
12 to 18 Month	707	2/242 (0.83)	(0.21, 3.30)	797	5/319 (1.57)	(0.65, 3.77)	0.527 (0.102, 2.718)
18 to 24 Month	415	10/184 (5.43)	(2.92, 10.10)	463	7/214 (3.27)	(1.56, 6.86)	1.661 (0.632, 4.365)
24 to 30 Month	318	6/130 (4.62)	(2.07, 10.27)	385	4/157 (2.55)	(0.96, 6.79)	1.812 (0.511, 6.420)
30 to 36 Month	226	6/103 (5.83)	(2.62, 12.97)	283	2/132 (1.52)	(0.38, 6.06)	3.845 (0.776, 19.049)
>36 Month	185	4/121 (3.31)	(1.24, 8.81)	243	3/162 (1.85)	(0.60, 5.74)	1.785 (0.400, 7.976)

PYR = Patient-years at risk.
[†] Per 100 PYR.
[‡] Relative Risk = Ratio of rates.

Table 9

**Combined Alzheimer's Trials
APTC Events in 6-Month Intervals**

Time Interval	Rofecoxib 25 mg			Placebo			Relative Risk [‡] (95% CI)
	Number At Risk	Cases/PYR (Rate [†])	95% CI	Number At Risk	Cases/PYR (Rate [†])	95% CI	
0 to 6 Month	1069	4/482 (0.83)	(0.31, 2.21)	1074	10/501 (2.00)	(1.07, 3.71)	0.416 (0.130, 1.326)
6 to 12 Month	880	8/399 (2.01)	(1.00, 4.01)	941	11/435 (2.53)	(1.40, 4.57)	0.793 (0.319, 1.971)
12 to 18 Month	708	2/243 (0.82)	(0.21, 3.29)	802	5/320 (1.56)	(0.65, 3.75)	0.527 (0.102, 2.715)
18 to 24 Month	416	7/185 (3.78)	(1.80, 7.94)	466	6/216 (2.78)	(1.25, 6.18)	1.362 (0.458, 4.053)
24 to 30 Month	320	5/131 (3.82)	(1.59, 9.17)	389	4/159 (2.52)	(0.94, 6.70)	1.517 (0.407, 5.650)
30 to 36 Month	228	3/105 (2.86)	(0.92, 8.86)	287	1/134 (0.75)	(0.11, 5.30)	3.829 (0.398, 36.808)
>36 Month	188	4/124 (3.23)	(1.21, 8.60)	247	3/164 (1.83)	(0.59, 5.67)	1.763 (0.395, 7.879)

PYR = Patient-years at risk.
[†] Per 100 PYR.
[‡] Relative Risk = Ratio of rates.

Figure 5

Combined Alzheimer's Trials
Kaplan-Meier Plot for Confirmed Thrombotic Events

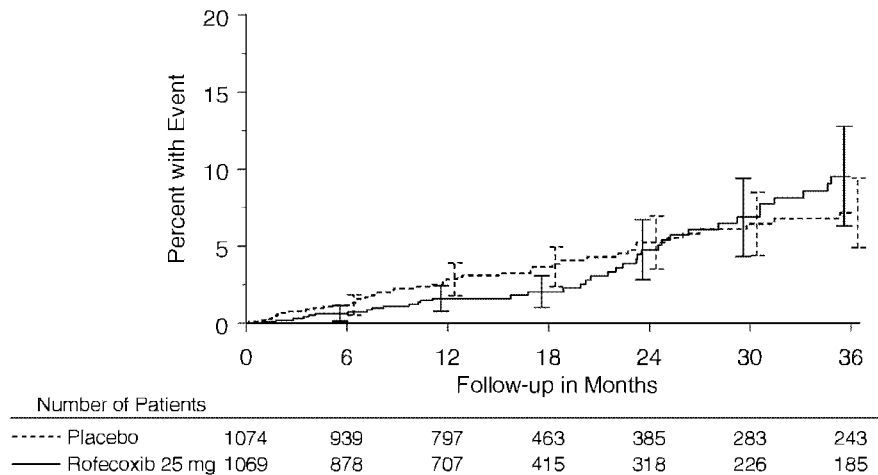
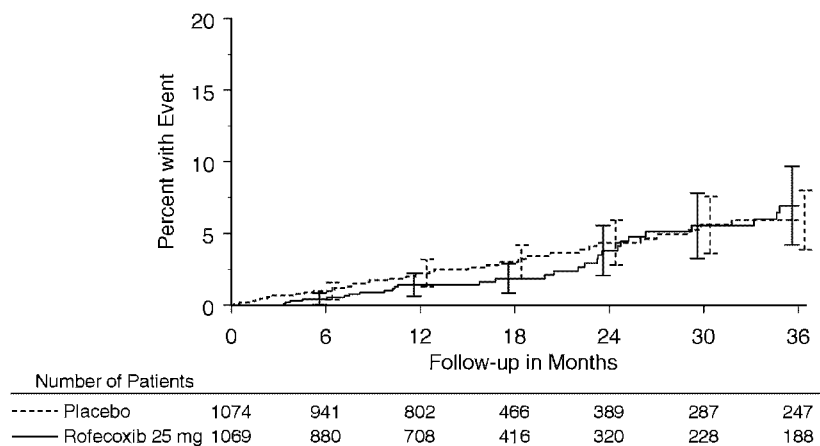


Figure 6

Combined Alzheimer's Trials
Kaplan-Meier Plot for APTC Events



The Alzheimer's Trials were the longest placebo-controlled trials of Vioxx other than the APPROVe Trial, but Merck had also conducted several short-term placebo-controlled trials of Vioxx. Merck's pooled analyses, discussed in more detail

above in Appendices F, J, and O, included data on the relative risk for cardiovascular events for Vioxx compared to placebo over all of Merck's clinical trials of Vioxx. The last of these pooled analyses, sent to the FDA in March 2004 and based on data from trials completed and unblinded as of June 2003, showed no statistically significant difference between Vioxx and placebo in the rate of confirmed thrombotic events or APTC events. The relative risk of Vioxx compared to placebo in the pooled analysis sent to the FDA in 2004 was 1.26 (95% confidence interval, 0.89 to 1.78) for confirmed thrombotic events and 1.14 (95% confidence interval, 0.77 to 1.68) for APTC events.⁴⁴ This pooled analysis also analyzed APTC events based on duration of treatment, as summarized in the table below:⁴⁵

Table 10

Relative Risk of Vioxx Versus Comparators by Duration of Treatment
As Reported in Merck's 2004 Pooled Analysis

Duration of Treatment	Relative Risk of Vioxx Versus Comparator (95% confidence interval)
Placebo Controlled Data	
≤ 3 months	1.28 (0.61, 2.67)
3 – 12 months	0.80 (0.40, 1.57)
> 12 months	1.37 (0.74, 2.55)

d. Data from epidemiological studies.

As discussed in Appendix P, numerous epidemiological studies have been conducted regarding the cardiovascular risks of Vioxx and other Cox-2 selective

⁴⁴ 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, Figure 1 at 57, Figure 5 at 71. The 2004 pooled analysis is discussed in Appendix O.

⁴⁵ For the underlying data, see 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, at 89.

inhibitors and NSAIDs,⁴⁶ and those studies have reached different and sometimes conflicting conclusions with regard to those risks.⁴⁷ Some of these studies included information on the duration of Vioxx use and a few specifically examined the relationship between duration and cardiovascular risk. Epidemiological studies bearing on the time-course of cardiovascular risk with Vioxx are discussed below.

i. Studies published, presented, or available to Merck prior to the withdrawal of Vioxx.

Prior to the withdrawal of Vioxx from the market and the public disclosure of the APPROVe Trial results, most of the epidemiological studies examining the cardiovascular risk of Vioxx did not focus primarily on a “time-course of risk” analysis. Some, however, included data on the observed risk of cardiovascular events among patients with specific durations of use of Vioxx.

One study, for example, found that use of Vioxx for less than one year was not associated with an elevated risk of myocardial infarction compared to non-use of any NSAID (adjusted rate ratio 1.0; 95% confidence interval, 0.6 to 1.7).⁴⁸ Another study found that use of Vioxx was associated with an elevated, but not statistically significant, risk of acute myocardial infarctions compared to no NSAID use (odds ratio 1.14; 95%

⁴⁶ The uses and limitations of epidemiological studies in general, as well as the results of 18 individual studies published, presented, or available as of the withdrawal of Vioxx, are discussed in Appendix P.

⁴⁷ For a summary of the results of 18 epidemiological studies published, presented or available as of the withdrawal of Vioxx, see Appendix P.

⁴⁸ Mamdani* M, Rohon* P, Juurlink* DN, et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. *Arch Intern Med.* 2003;163:481-486, MRK-ADM0165206. For a more complete discussion of this study, see Appendix P.

confidence interval, 1.00 to 1.31), and further found that the risk was higher during the first 90 days of Vioxx use than in longer durations of use.⁴⁹ A third study found that use of Vioxx was associated with a significantly elevated risk of certain cardiovascular events as compared to use of ibuprofen or diclofenac (adjusted rate ratio 1.35; 95% confidence interval, 1.09 to 1.68), but did not find a clear relationship between cardiovascular events and duration of use.⁵⁰

ii. Studies published, presented, or available
to Merck after the withdrawal of Vioxx.

After Vioxx was withdrawn from the market and the APPROVe Trial results became publicly known, scientific and medical journals published a number of epidemiological studies that used various methodologies to examine the cardiovascular risks of Vioxx. Some attempted to analyze the time-course of any cardiovascular risk associated with Vioxx, although the varying methodologies used in the studies make the results difficult to compare.

One study found that “long-term” (more than six months) use of Vioxx was associated with significantly elevated cardiovascular risk compared to long-term use of ibuprofen, but use of Vioxx for fewer than 6 months was not associated with any elevated

⁴⁹ Solomon* DH, Schneeweiss* S, Glynn* RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation. 2004;109:2068-2073, at 2071-72 and Table 2, MRK-ADY0006986. For a more complete discussion of this study, see Appendix P.

⁵⁰ 9/20/04 report by Priscilla Velentgas* et al., “Cardiovascular Risk of Cox-2 Inhibitors and Other NANSaIDs,” MRK-ABY0154716, at 31, 55. For a more complete discussion of this study, see Appendix P.

risk compared to ibuprofen.⁵¹ In contrast, another study found that use of Vioxx compared to no NSAID use was associated with elevated cardiovascular risk among patients having received only one prescription of Vioxx, but not among patients who received multiple prescriptions.⁵² Two studies found an elevated cardiovascular risk among Vioxx users compared with nonusers of any NSAID that did not appear to vary with time,⁵³ though only one of the studies contained data from more than 180 days of use.⁵⁴ Numerous other studies have assessed the cardiovascular risk of Vioxx without a particular focus on duration of treatment.⁵⁵

⁵¹ Motsko* SP, Rascati* KL, Busti* AJ, *et al.* Temporal relationship between use of NSAIDs, including selective COX-2 inhibitors, and cardiovascular risk. *Drug Saf.* 2006;29:621-32.

⁵² Levesque* LE, Brophy* JM, Zhang* B. Time variations in the risk of myocardial infarction among elderly users of COX-2 inhibitors. *CMAJ.* 2006;174:1563-69.

⁵³ Solomon* DH, Avorn* J, Sturmer* T, Glynn* RJ, Mogun* H, Schneeweiss* S. Cardiovascular outcomes in new users of coxibs and nonsteroidal antiinflammatory drugs: High-risk subgroups and time course of risk. *Arthritis Rheum.* 2006;54:1378-89; Helin-Salmivaara* A, Virtanen* A, Vesalainen* R, *et al.* NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. *Eur Heart J.* 2006;27:1657-63.

⁵⁴ Helin-Salmivaara* A, Virtanen* A, Vesalainen* R, *et al.* NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. *Eur Heart J.* 2006;27:1657-63.

⁵⁵ See, e.g., Kimmel* SE, Berlin* JA, Reilly* M, Jaskowiak* J, Kishel* L, Chittams* J, Strom* BL. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. *Ann Intern Med.* 2005;142:157-164 (for a more complete discussion of this study, see Appendix P); Hippisley-Cox* J, Coupland* C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ.* 2005;330:1366; Johnsen* SP, Larsson* H, Tarone* RE, *et al.* Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study. *Arch Intern Med.* 2005;165:978-84; Gislason* GH, Jacobsen* S, Rasmussen* JN, *et al.* Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation.* 2006;113:2906-13; Andersohn* F, Suissa* S, Garbe* E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs and risk of acute myocardial infarction. *Circulation.* 2006;113:1950-7.