

e. Additional communications.

On May 30, 2006, in connection with the issuance of the press release, Dr. Kim, Mr. Frazier, and Dr. Bain held a teleconference for pharmaceutical analysts and journalists regarding the APPROVe Trial and the announcement of the error.³¹⁸ On the same day, Dr. Robert Silverman, MRL's regulatory liaison with the FDA, notified the FDA about the correction,³¹⁹ and Mr. Bolognese and Dr. Oxenius notified the New England Journal of Medicine about the need for a correction to the published article.³²⁰ Communications between and among authors of the article and editors of the New England Journal of Medicine about the correction are discussed in Section D of this Appendix.

C. Collection and Analysis of APPROVe Off-Drug Data.

1. Introduction.

The APPROVe Trial Protocol specified, as was standard in Merck trials, that data would be collected on serious adverse events, including cardiovascular events, that

³¹⁸ 5/30/06 Merck media advisory: Conference Call and Audio Web Cast, MRK-AFS0040985; APPROVe Media Call Speaker Notes, MRK-AFS0040987-88.

³¹⁹ 5/30/06 letter from P. Huang to B. Rappaport*, MRK-S0420112190 (“[A] telephone conversation between Dr. Robert Silverman of MRL, and Lisa Malandro of FDA . . . occurred on . . . May 30, 2006, in which notification was provided that MRL was correcting its prior description of one of the statistical methods used to analyze certain data in the APPROVe study published in 2005. MRL recently discovered the need for this correction while reviewing the preliminary analysis of the off-drug extension data for the APPROVe study. MRL believes that this correction does not change the results of the APPROVe study, which found an increased relative risk for confirmed thrombotic cardiovascular events for VIOXX™ compared to placebo beginning after 18 months of treatment.”).

³²⁰ 5/30/06 letter from J. Bolognese and B. Oxenius to the editor of the New England Journal of Medicine, MRK-AQU0000001.

occurred while patients were on treatment or within 14 days after discontinuation of treatment.³²¹ When Vioxx was withdrawn from the market on September 30, 2004 on the basis of cardiovascular data from the APPROVe Trial, MRL scientists and members of the APPROVe Trial Administrative Committee recognized that an important open question remained: whether patients who took Vioxx in the APPROVe Trial would continue to experience increased rates of thrombotic events compared to placebo more than 14 days after stopping use of the drug.

To answer those questions, MRL scientists, in consultation with members of the APPROVe Trial Administrative Committee and the FDA, amended the APPROVe Trial protocol to collect and analyze “off-drug” follow-up data on the incidence of cardiovascular events among patients who had participated in the trial, whether or not they had completed their intended course of treatment. On May 11, 2006, Merck reported preliminary analyses of these data to the FDA and issued a press release that summarized certain results.

The following subsections describe (i) MRL’s collection of this follow-up data, (ii) certain results of the analyses of these data, and (iii) Merck’s public presentation of those results and MRL scientists’ views of what the data show.

³²¹ 10/29/99 APPROVe Trial Protocol 122-00, MRK-I2220000130, at 173. If a patient discontinued the trial early, the investigator was to conduct a final visit 14 days after the date of discontinuation. Id. at 167. Fourteen days was the standard post-discontinuation follow-up period for all Merck clinical drug trials. See Merck Medical Affairs Procedures and Policies, Procedure 2, MRK-AGE0001483, at 1570.

2. Collection of Off-Drug Cardiovascular Data.

a. Collection of off-drug cardiovascular data
during the APPROVe Trial base study.

During the course of the APPROVe Trial, as described above, data on adverse events occurring more than 14 days after discontinuation of treatment were reported on an ad hoc basis but not systematically collected. For example, if a patient “brought to the attention of the investigator” a serious adverse event that occurred more than 14 days after discontinuation of treatment, the investigator was required to report that event only if the investigator deemed it to be possibly related to the study therapy.³²² Investigators were not required to take any affirmative steps to discover such events.

Dr. Quan, in his role as the unblinded Merck statistician tasked with analyzing data for the APPROVe Trial External Safety Monitoring Board, included certain off-drug cardiovascular events in his reports to the External Safety Monitoring Board beginning in

³²² 1/17/02 APPROVe Trial Protocol 122-02, MRK-AFL0000979, at 1033. This procedure was implemented in a protocol amendment in January 2002. The amendment also provided patients who discontinued early the option of returning for follow-up colonoscopies (at one and three years after they began study therapy). At these optional visits (and during an interim telephone call at year two), investigators were to inquire about serious adverse events and report any they deemed to be possibly related to the study therapy. Thus, pursuant to the amended protocol, adverse events occurring more than 14 days after discontinuation could get reported on a somewhat ad hoc basis, but there was still no systematic procedure for collecting data on such events. See *id.* at 1026; “Guidelines for conducting and reporting follow-up visits/phone contacts in patients who are off study drug but continuing in the APPROVe study for ITT analysis (‘ITT patients’),” MRK-AFN0036831.

In May 2004, at the request of the APPROVe Trial External Safety Monitoring Board, Merck amended the APPROVe Trial Protocol to require investigators to follow-up with all patients to obtain mortality data three years after they originally began study treatment, regardless of when or whether they had discontinued participation in the trial. 5/6/04 APPROVe Trial Protocol 122-04, MRK-AKS0003576, at 579; 5/20/04 letter from D. Louie to R. Justice, MRK-AAF0016119 at 119.

May 2003.³²³ Dr. Quan's final report to the External Safety Monitoring Board, dated September 13, 2004 and based on data reported as of August 16, 2004, reported 17 investigator-reported thrombotic cardiovascular events or deaths due to any cause that occurred more than 14 days after discontinuation of treatment (placebo and Vioxx, together), 16 of which had been adjudicated and 7 of which had been confirmed as thrombotic events.³²⁴ These data did not provide an adequate basis for meaningful analysis because they were not systematically collected, and, accordingly, Dr. Quan did not include these events in any of the graphical analyses of data, such as the "Kaplan-Meier" time to event plots, in his report.³²⁵

b. Creation of the APPROVe one-year off-drug extension.

On June 27, 2003, Merck submitted to the FDA a protocol amendment creating a one-year off-drug extension to the APPROVe Trial, termed Protocol 122-10, to assess whether patients who had completed all three years of the APPROVe Trial would experience any "rebound" effect in the recurrence of colon polyps within the year after they stopped treatment.³²⁶ As with any clinical trial, investigators were required to

³²³ 5/8/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AFK0202981, at 3007, 3041-42.

³²⁴ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 17, 32.

³²⁵ Dr. Quan did include in an appendix to his report a combined tabulation and analysis of data including both on-drug events as well as events that occurred more than 14 days after discontinuation. No graphical analyses of this combined data set, however, were included. 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 566-69.

³²⁶ 6/11/03 APPROVe Trial Protocol 122-10, MRK-I2220004382, at 86 (attached to 6/27/03 letter from D. Louie to R. Justice, MRK-I2220004378). Patients would undergo a colonoscopy one year after

collect and report any serious adverse events that patients experienced during this one-year off-drug extension, but patient participation was voluntary and there was no plan in place for adjudication and analysis of cardiovascular events so reported.³²⁷ In addition, patients who had discontinued their participation in the APPROVe Trial prior to its termination and before completing the full three years of treatment were not eligible for the extension study. As a result, this extension was neither a reliable nor a complete source of off-drug cardiovascular data.

c. The August 2005 amendments.

On October 4, and October 7, 2004, within one week of the termination of the APPROVe Trial and the withdrawal of Vioxx, MRL scientists proposed to the APPROVe Trial Administrative Committee and to the FDA, amending the protocol of the ongoing one-year off-drug extension to facilitate the collection of off-drug cardiovascular data.³²⁸ Specifically, MRL proposed (i) making optional the previously required colonoscopy at the end of the one-year extension in the hope of increasing patient participation, and (ii) mandating that all eligible cardiovascular events reported during the extension be

completing the trial and discontinuing treatment. They would also attend two interim clinic visits with the investigator during the one-year off-drug period. Id. at 404.

³²⁷ 6/11/03 APPROVe Trial Protocol 122-10, MRK-I2220004382, at 414-15; see also 4/22/03 memorandum from Z. Wang to Distribution, "Vioxx Product Development Team Meeting Summary and Assignments from Meeting on 04/22/2003," MRK-AAD0271628, at 628. Merck's Cardiovascular Adjudication SOP required adjudication of thrombotic events occurring within 14 days of stopping treatment. It allowed adjudication of later events, but only if specified in an individual trial's protocol. Revised Cardiovascular Adjudication SOP, MRK-AAC0142324, at 327 (attached to 1/16/04 email from D. Ramey to A. Altmeyer and T. Malloy, MRK-AAC0142323).

³²⁸ Minutes of 10/4/04 APPROVe Administrative Committee meeting, MRK-AFN0054807, at 807-08; Minutes of 10/11/04 APPROVe Administrative Committee meeting, MRK-AGO0025741, at 742; 10/7/04 email from D. Louie to N. Braunstein, et al., MRK-AAF0017620, at 620-21.

adjudicated pursuant to the Cardiovascular Adjudication SOP.³²⁹ At the same time, Dr. John Baron*, a professor of medicine at Dartmouth Medical School and chair of the APPROVe Trial Administrative Committee, suggested that the APPROVe Trial investigators should also try retrospectively to obtain data on off-drug cardiovascular events from patients who had discontinued the trial early (and were therefore not eligible to participate in the extension).³³⁰

Over the next several months, MRL scientists, in consultation with the APPROVe Trial Administrative Committee and the FDA, drafted protocol amendments that essentially mirrored the initial proposals discussed in early October 2004.

On August 29, 2005, Merck submitted to the FDA two amendments to the APPROVe Trial Protocol, labeled Protocols 122-11 and 122-20.³³¹

i. Protocol 122-11: amendment to ongoing extension.

The first amendment, Protocol 122-11, amended the ongoing one-year off-drug extension to (i) make clear that investigators were required to collect and report data, including adjudication packages, on thrombotic cardiovascular events occurring during the one-year off-drug period, (ii) require that all such events as well as all deaths experienced by patients in the extension be sent for external adjudication pursuant to the

³²⁹ Minutes of 10/4/04 APPROVe Administrative Committee meeting, MRK-AFN0054807, at 807-08; Minutes of 10/11/04 APPROVe Administrative Committee meeting, MRK-AGO0025741, at 742; 10/7/04 email from D. Louie to N. Braunstein, et al., MRK-AAF0017620, at 620-21.

³³⁰ Minutes of 10/4/04 APPROVe Administrative Committee meeting, MRK-AFN0054807, at 808.

³³¹ 8/29/05 letter from P. Huang to B. Harvey*, MRK-I2220005686; 8/29/05 letter from P. Huang to B. Harvey*, MRK-I2220005784.

Cardiovascular Adjudication SOP, and (iii) mitigate disincentives for patients to participate in the one-year off-drug extension study by making the colonoscopy at the end of the one-year off-drug period discretionary rather than mandatory.³³² Although Protocol 122-11 was not finalized until August 2005, investigators were informed in October 2004 of the pending changes in procedures, and data on thrombotic events experienced by patients enrolled in the extension were being collected and adjudicated throughout 2005.³³³

ii. Protocol 122-20: amendment creating new “extension.”

Unlike the first amendment, Protocol 122-11, which only modified procedures in the ongoing one-year extension study, the second amendment, Protocol 122-20, created a new “extension,” the purpose of which was to “assess thrombotic cardiovascular outcomes including death in all patients randomized in the APPROVe study . . . until every patient has been off treatment for at least a year, in October 2005.”³³⁴ Under this Protocol, investigators were required to contact all patients who were originally enrolled and randomized into the APPROVe Trial, regardless of when they discontinued from the trial and regardless of whether they had enrolled in the extension, to collect data on any

³³² 8/9/05 APPROVe Trial Protocol 122-11, MRK-I2220005737, at 739; see also Minutes of 10/11/04 APPROVe Administrative Committee meeting, MRK-AGO0025741, at 742.

³³³ 10/14/04 – 10/15/04 presentation “APPROVe Study Investigator Teleconference,” MRK-AHC0010447, at 454; 11/3/04 memorandum from Vioxx Product Development Team to LDRC, “Close-Out of Rofecoxib Development Program,” MRK-AHC0001590, at 1594; 3/1/05 email from S. Loftus to J. Bolognese, K. Horgan, and H. Quan, MRK-AGO0101171, at 171.

³³⁴ 8/9/05 APPROVe Trial Protocol 122-20, MRK-I2220005789, at 790. A small number of patients who were originally randomized to receive 50 mg of Vioxx, a dosage that was eliminated from the trial within months of its start, were not included. Id. at 800.

serious thrombotic cardiovascular events (including death due to any cause) that these patients had experienced any time after they discontinued treatment in the base trial.³³⁵

These contacts were to take place between August and October 2005. The Protocol specified that the data so collected would be sent for external adjudication pursuant to the Cardiovascular Adjudication SOP.³³⁶ A new Statistical Data Analysis Plan submitted to the FDA in February 2006 set forth analyses to be conducted on the follow-up cardiovascular data that was being collected pursuant to Protocols 122-11 and 122-20, as discussed more fully below.³³⁷

d. Collection of off-drug cardiovascular data
pursuant to the August 2005 protocol amendments.

After submission to the FDA, the August 2005 protocol amendments were sent to the sites at which patients had been enrolled in the APPROVe Trial for approval by those sites' Institutional Review Boards.³³⁸ According to Dr. Bettina Oxenius, clinical monitor for the APPROVe Trial, obtaining Institutional Review Board approval for some sites took longer than anticipated, which delayed the process of investigators contacting all of

³³⁵ 8/9/05 APPROVe Trial Protocol 122-20, MRK-I2220005789, at 793-94, 800-01.

³³⁶ 8/9/05 APPROVe Trial Protocol 122-20, MRK-I2220005789, at 801.

³³⁷ Protocol 122-20 Statistical Analysis Plan, MRK-I2220005957, at 961 (attached to 2/10/06 letter from P. Huang to B. Harvey*, MRK-I2220005952).

³³⁸ An Institutional Review Board, or "IRB," is a "committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. All clinical trials in the U.S. must be approved by an IRB before they begin." <http://www.clinicaltrials.gov/ct/info/glossary>.

their patients to inquire about cardiovascular events.³³⁹ As of May 11, 2006, follow-up data on cardiovascular events from one investigator site, responsible for 17 patients, were still outstanding.³⁴⁰

As of March 15, 2006, investigators had succeeded in contacting 2178 (84%) of the 2587 patients originally randomized into the APPROVe base study³⁴¹ to determine whether they had experienced any thrombotic cardiovascular events more than 14 days after stopping study therapy.³⁴² The 84% follow-up rate was the same for patients who had been assigned to the Vioxx arm of the APPROVe base study as for those assigned to the placebo arm.³⁴³ The follow-up rate was higher (93%) among the 1857 patients who completed the original three-year base study than among patients who discontinued the base study prematurely.³⁴⁴

Based on these collection efforts, investigators identified (with confirmation by external adjudicators) 58 patients who had experienced confirmed thrombotic

³³⁹ Draft minutes of 1/13/06 APPROVe Administrative Committee meeting, MRK-ARQ0008008, at 009; Draft minutes of 4/25/06 APPROVe Administrative Committee meeting, MRK-ARQ0002839, at 839.

³⁴⁰ 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 93.

³⁴¹ The APPROVe base study refers to the 3-year APPROVe Trial, without the extensions.

³⁴² 5/11/06 APPROVe Extension Statistical Package, MRK-S0420112022, at 023.

³⁴³ 5/11/06 APPROVe Extension Statistical Package, MRK-S0420112022, at 023.

³⁴⁴ Of the 2587 patients originally randomized into the APPROVe Trial, 1857 completed all three years of the base study and off-drug cardiovascular data were available for 93% of those patients. 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 95.

cardiovascular events more than 14 days after discontinuing study treatment.³⁴⁵ Of these 58 patients, 44 experienced such events within 210 weeks (4 years) of the patients' entry into the study and the remaining 14 experienced events more than 210 weeks after entering the study.³⁴⁶

3. Development of Statistical Data Analysis Plan for Protocol 122-20.

While the data collection effort was underway, MRL statisticians began drafting a Statistical Data Analysis Plan for Protocol 122-20 to pre-specify the analyses to be conducted. Merck's initial draft plan pre-specified analyses of the newly collected off-drug data (i.e., data from the period beginning 15 days after discontinuation of study therapy) for three different populations:

- All patients who completed the three-year base study;
- All patients who received study therapy for at least 18 months; and
- All patients who took at least one dose of study therapy.³⁴⁷

The first of these populations was the narrowest, and the second and third progressively expanded from that base.³⁴⁸ Mr. Cook, one of the authors of the Statistical Data Analysis Plan, stated that these analyses were designed to address the question that motivated Merck to collect off-drug data on cardiovascular events during the extension period:

³⁴⁵ 5/11/06 APPROVe Extension Statistical Package, MRK-S0420112022, at 088.

³⁴⁶ 5/11/06 APPROVe Extension Statistical Package, MRK-S0420112022, at 038, 088.

³⁴⁷ 11/22/05 draft Protocol 122-20 Statistical Analysis Plan, MRK-ARQ0000343, at 55.

³⁴⁸ 11/22/05 draft Protocol 122-20 Statistical Analysis Plan, MRK-ARQ0000343, at 55.

whether any increased risk associated with Vioxx therapy persisted more than 14 days after the discontinuation of treatment.³⁴⁹

Mr. Cook presented a draft of the Statistical Data Analysis Plan to the APPROVe Trial Administrative Committee on December 12, 2005, explaining the analyses set forth above.³⁵⁰ At the meeting, the Committee agreed with the proposed plan,³⁵¹ but Dr. Baron, the Chair of the Committee, inquired as to whether there would be a combined analysis of both the cardiovascular data from the base study and the newly collected off-drug data, which he termed a “combined ITT analysis.”³⁵² Mr. Cook indicated that MRL scientists were discussing whether to include such an analysis.³⁵³

In the most general sense, the term “ITT” or “intention-to-treat” refers to a standard analytical approach under which all patients who are randomized into a clinical trial are included in the analyses performed on data from the trial, regardless of whether they discontinue treatment early or otherwise violate the study protocol. Although the term “intention-to-treat analysis” does not imply any particular length of patient follow-

³⁴⁹ Although Mr. Cook stated that the scientific question motivating the collection of additional cardiovascular follow-up data was whether Vioxx posed an increased cardiovascular risk after termination of treatment, none of the analyses in the original Statistical Data Analysis Plan examined all post-termination data. The newly specified analyses excluded data from the first two weeks after the cessation of treatment. As described below, none of the analyses in the final Statistical Data Analysis Plan examined exclusively all of the data from the entire off-drug period.

³⁵⁰ Minutes of 12/12/05 meeting of APPROVe Administrative Committee, MRK-AFN0190925, at 25.

³⁵¹ Minutes of 12/12/05 meeting of APPROVe Administrative Committee, MRK-AFN0190925, at 25.

³⁵² Minutes of 12/12/05 meeting of APPROVe Administrative Committee, MRK-AFN0190925, at 26.

³⁵³ Minutes of 12/12/05 meeting of APPROVe Administrative Committee, MRK-AFN0190925, at 26.

up time, clinical investigators frequently use the term to describe analyses that follow all patients who discontinue treatment (for any reason) through the end of the planned study period, thereby capturing any events of interest that occur during the study period among all patients initially randomized to treatment. In many situations, the study period corresponds to, or extends only slightly beyond, the prescribed course of study treatment. As a result, intention-to-treat analyses typically follow the majority of patients who complete the study for a short time after they cease treatment and follow the minority who discontinue early for longer periods after discontinuation of treatment, depending on how early they cease treatment. This type of analysis is common and widely accepted in clinical trials, as is the use of a 14-day post-discontinuation follow-up period that Merck typically uses. The main advantage to using an intention-to-treat approach in appropriate circumstances is that it continues to follow patients even after they stop treatment, which can give an unbiased assessment of the comparison between treatment groups. As explained more fully in the next subsection, increasing the post-treatment follow-up time for such patients may capture potentially drug-related adverse events that occur after discontinuation of treatment, which may otherwise go unnoticed.

According to Mr. Bolognese, after the December 2005 APPROVe Trial Administrative Committee meeting, the MRL clinicians working on Protocol 122-20 organized a meeting to discuss the Statistical Data Analysis Plan and, specifically, Dr. Baron's suggestion that the Company perform an intention-to-treat analysis that included both the on-drug and off-drug data. Mr. Bolognese could not recall who attended this meeting, but stated that Dr. Alise Reicin, Dr. Bettina Oxenius, Dr. Janet van Adelsberg,

and Dr. Ned Braunstein were all invited.³⁵⁴ At the time of the meeting, Mr. Cook, the author of the Statistical Data Analysis Plan, was on vacation and did not attend.

Mr. Bolognese stated that the consensus among those who participated in the meeting was that there was no clearly identifiable scientific reason to conduct the intention-to-treat analysis proposed by Dr. Baron. The analysis Dr. Baron had proposed would not only follow all patients through the intended three-year period of the base study, but also include at least a full year of off-drug follow-up data on all patients enrolled in the study. While Merck had conducted intention-to-treat analyses in the past, Mr. Bolognese said, he could not recall any prior Merck-sponsored intention-to-treat analysis in which the study period exceeded the end of the planned course of treatment by more than one month. As described more fully below, although the advantage to intention-to-treat analyses is their ability to detect potentially drug-related adverse events after the discontinuation of treatment, MRL scientists emphasized that, in their view, an analysis that follows patients for too long a period after discontinuation of treatment (i.e., beyond the point at which any harmful effect of the study treatment persists) could actually dilute a safety signal. According to Mr. Bolognese, the consensus among those at the meeting was that the analysis Dr. Baron requested, due to the long post-discontinuation follow-up time it entailed, would indeed likely dilute the cardiovascular safety signal observed in the APPROVe base study.³⁵⁵ Nonetheless, because it appeared

³⁵⁴ Dr. Braunstein confirmed that he did attend the meeting.

³⁵⁵ Although Mr. Bolognese stated that the analysis would likely dilute the safety signal, he and Dr. Braunstein both acknowledged an advantage of the intention-to-treat analysis relative to the

that there would be scientific interest in the analysis, Mr. Bolognese said, the Company decided to amend the Statistical Data Analysis Plan in order to include it.³⁵⁶

As Dr. Baron had requested, the intention-to-treat analysis pre-specified as primary in the final Statistical Data Analysis Plan was to follow patients through the intended three-year study period plus a fourth follow-up year in which no treatment would be administered.³⁵⁷ The secondary analysis set forth in the revised Statistical Data Analysis Plan would examine off-drug cardiovascular events occurring from 15 days after discontinuation of study treatment through at least the end of the fourth year of follow-up among all patients for whom off-drug data was available. This analysis was essentially identical to the third analysis that the Company had put forth in its initial draft Statistical Data Analysis Plan. The first and second analyses proposed in the initial draft of the Statistical Data Analysis Plan (the analyses of off-drug cardiovascular events among those patients who finished the three-year base study and among those patients who remained in the base study for more than 18 months) were not included in the

previously planned off-drug analyses. According to both Mr. Bolognese and Dr. Braunstein, the former would preserve randomization, whereas the off-drug analyses did not because off-drug data had not been collected for all patients originally randomized in the base study. Thus, the off-drug analysis was potentially subject to a bias not present in the intention-to-treat analysis.

³⁵⁶ 1/20/06 email from J. Bolognese to R. Bain et al., MRK-ARQ0000370-71 (summarizing agreed upon changes to Statistical Data Analysis Plan). Although the Statistical Data Analysis Plan did not designate the intention-to-treat analysis as “primary,” it did list this analysis first. *Id.* The Company later described this analysis as the “primary” analysis and the analysis including only the off-drug data as the “secondary” analysis. See 5/11/06 APPROVe Off-Drug Extension: Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-S0420112129, at 29.

³⁵⁷ Technically, this analysis differed from the standard understanding of an intention-to-treat analysis because the analysis did not include the full range of post-discontinuation follow-up data for all of the patients randomized. Protocol 122-20 Statistical Data Analysis Plan, MRK-I2220005957, at 72.

revised Statistical Data Analysis Plan, although the Company performed those analyses as post-hoc analyses.³⁵⁸

The Company submitted the Statistical Data Analysis Plan in its revised form to the FDA on February 10, 2006.³⁵⁹

4. Overview of Benefits and Limitations
of Long Post-Discontinuation Follow-Up Times.

As mentioned above, the intention-to-treat analysis specified in the Statistical Data Analysis Plan for Protocol 122-20 followed all patients for at least four years after their first dose of study treatment. In effect, this analysis extended each patient's follow-up time after discontinuation of treatment from 14 days (the amount of post-discontinuation follow-up in the base study) to a minimum of one year for patients who completed the three-year base study and longer for those who dropped out of the base study prematurely. For some patients who discontinued treatment very early in the base study, the post-discontinuation follow-up time was almost four years.

The optimal amount of post-treatment follow-up time in a clinical trial varies depending primarily on the way in which the relative risk of the relevant endpoint – in this case, cardiovascular events – changes after discontinuation of treatment.³⁶⁰ In a safety analysis, if the study treatment is associated with an elevated relative risk that

³⁵⁸ See 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 95-96.

³⁵⁹ 2/10/06 letter from P. Huang to B. Harvey*, MRK-I2220005952-53.

³⁶⁰ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 114.

dissipates very quickly after the end of treatment, then a relatively short post-discontinuation follow-up time (or an “on-drug analysis”) – like the 14-day period used in the APPROVe base study – may be appropriate. In this case, analyses of the data would capture all relevant events. Furthermore, the analysis would avoid potential sources of bias that could affect the analysis if it were to follow patients for a longer off-treatment period. For example, if patients who discontinued the study treatment were to begin taking a substitute treatment, then an analysis that followed them for a longer period could be skewed by any effects of the substitute treatment.³⁶¹ Also, if the excess risk associated with a study drug dissipates shortly after discontinuation, following patients for more than a short period after they discontinue treatment could mask or dilute the safety effect.³⁶² This is because in the absence of a lingering treatment effect, the hazard rate of a given event in the off-drug period should be roughly equal in both the treatment and comparator arms of a study. If the hazard rate is roughly equal between both arms in the off-drug period, then the inclusion of off-drug data in the analysis will tend to reduce any elevation in the hazard rate that would otherwise be seen in treatment arms versus comparator arms due to events in the on-drug period.

Alternatively, if the increased risk associated with the study treatment in a safety analysis persists for a significant period after discontinuation of treatment, then a longer

³⁶¹ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 113.

³⁶² Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 113.

follow-up time may be appropriate. In such a situation, a 14-day post-treatment follow-up period would not capture events occurring after the cut-off date that would still be attributable to the study treatment. This problem would be most pronounced if numerous patients in the active treatment arm of a study discontinued treatment due to drug-related symptoms, as in the APPROVe base study, but remained at an elevated risk for a subsequent adverse event of interest more than 14 days after discontinuation.³⁶³

Following patients throughout the intended study period would eliminate any bias resulting from the cut-off date and ensure accurate accounting of both types of events in the study population.

When, as in the APPROVe base study, an on-drug analysis reveals a safety signal and the mechanism and duration of the harmful effect is not well understood, performing an intention-to-treat analysis with extended follow-up time, like the one Dr. Baron suggested, may be advisable in order to correct any bias that may have existed in the on-drug analysis. Because such an intention-to-treat analysis followed all patients throughout the entire study period, it would capture any events occurring beyond the cut-off period in the on-drug analysis among patients who discontinued treatment early.

³⁶³ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 114. In the APPROVe base study, 410 patients randomized to the Vioxx treatment arm discontinued treatment prematurely, as compared to 319 patients randomized to the placebo arm. Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, Figure 1 at 1094, MRK-ARQ0000659, at 661.

5. Results from Preliminary Analyses of Follow-Up Data.

The results of preliminary analyses of cardiovascular data from Protocol 122-20 (the extension of the APPROVe Trial to assess cardiovascular outcomes with reference to off-drug follow-up data for patients enrolled in the base study) became available in May 2006. This subsection describes the analyses performed and their results.

a. Results of pre-specified analyses.

As described above, the final Statistical Data Analysis Plan for Protocol 122-20 specified two analyses: (i) an analysis of cardiovascular events occurring at any time during at least a four-year period since the beginning of study therapy among all patients who took at least one dose of study treatment (the “Intention-to-Treat Analysis”); and (ii) an analysis of cardiovascular events occurring 15 days after discontinuation of treatment or later during this same period among all patients for whom the Company had collected data beyond 15 days after discontinuation (the “Off-Drug Analysis”) (collectively, the “APPROVe Extension Analyses”).³⁶⁴ The specified primary and secondary endpoints for both analyses were, respectively, confirmed thrombotic events and the APTC composite cardiovascular endpoint, the same cardiovascular endpoints analyzed following termination of the APPROVe base study. The Statistical Data Analysis Plan stated that the following analyses would be conducted for both endpoints in both study populations:

³⁶⁴ The Statistical Data Analysis Plan actually specified two data-censoring dates – 210 weeks and October 31, 2005. Protocol 122-20 Statistical Analysis Plan, MRK-12220005957, at 71-72. For the purposes of this subsection, we report the results using the 210-week censoring date, which included roughly four years of patient follow-up.

- calculation of the overall relative risk and 95% confidence intervals;
- a plot of the Kaplan-Meier time-to-event curves; and
- an assessment of the constancy of hazards over time, including plots of hazard rates as functions of time and tests of the proportional hazards assumption.³⁶⁵

The results of these analyses are discussed below.

i. Relative risk.

Table 16, below, summarizes the overall relative risk and 95% confidence intervals for both the APPROVe base study (which included three years of data) and the Intention-to-Treat and Off-Drug Analyses (which included four years of data):

³⁶⁵ Protocol 122-20 Statistical Analysis Plan, MRK-I2220005957, at 73. The particular model specified for these tests was the Cox proportional hazards model using two covariates, treatment and treatment*log(time (month) + 1). Id. As described below, however, the tests performed used covariates for treatment, and either treatment*time or treatment*log(time). According to Mr. Cook, using these tests was a deviation from the Statistical Analysis Plan that will be disclosed to the FDA in the Company's final report on these analyses. The reason for the deviation, according to Mr. Cook, was to use the same tests that had been employed to assess the constancy of hazards in the base study data set. He also stated that the Company had not performed the test using the covariates listed in the Statistical Data Analysis Plan.

Table 16

APPROVe Trial & APPROVe Extension Analyses
Overall Relative Risk – Confirmed Thrombotic Events & APTC Events

	Endpoint	Events/Patient-Years in Vioxx Arm	Events/Patient-Years in Placebo Arm	Relative Risk (95% CI)
APPROVe Base Study	Confirmed Thrombotic - Events	46/3059	26/3327	1.92 (1.19, 3.11)
	APTC Events	34/3070	18/3334	2.06 (1.16, 3.64)
Intention-to-Treat Analysis	Confirmed Thrombotic Events ³⁶⁶	71/4557	42/4697	1.74 (1.19, 2.55)
	APTC Events ³⁶⁷	54/4581	30/4722	1.86 (1.19, 2.90)
Off-Drug Analysis	Confirmed Thrombotic Events ³⁶⁸	28/1535	16/1402	1.64 (0.89, 3.04)
	APTC Events ³⁶⁹	21/1538	12/1406	1.64 (0.81, 3.35)

As discussed in Exhibit 3, the confidence interval reported in parentheses next to the relative risk point estimate indicates whether a given result reaches statistical significance. If the entire confidence interval is above 1.0 (as in the results for the APPROVe base study and Intention-to-Treat Analysis), then the result is statistically significant. If the confidence interval crosses 1.0 (as in the Off-Drug Analysis), then the result is not statistically significant. In either case, the confidence interval defines the range of possible outcomes. Thus, although the results set forth in Table 16 for the Off-Drug Analysis are not statistically significant, one cannot exclude any result within

³⁶⁶ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 217.

³⁶⁷ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 228.

³⁶⁸ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 223.

³⁶⁹ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 233.

the confidence interval, including a slightly decreased relative risk on Vioxx, no difference between the two treatments (if the relative risk is equal to 1.0), and up to a three-fold increased risk on Vioxx.

As Table 16 indicates, in the Intention-to-Treat Analysis, there were 71 patients in the Vioxx treatment arm and 42 patients in the placebo arm who experienced confirmed thrombotic events through the 210 week censoring date.³⁷⁰ The relative risk of experiencing a confirmed thrombotic event among patients in the Vioxx arm versus patients in the placebo arm was 1.74 (95% confidence interval, 1.19 to 2.55).³⁷¹ With regard to the secondary APTC composite cardiovascular endpoint, there were 54 such events among patients randomized to the Vioxx arm of the study and 30 among those randomized to the placebo arm.³⁷² Again, the difference reached statistical significance (relative risk 1.86; 95% confidence interval, 1.19 to 2.90).³⁷³

As indicated in Table 16 above, the overall relative risk in the Intention-to-Treat Analysis for both the confirmed thrombotic events endpoint (relative risk 1.74; 95% confidence interval, 1.19 to 2.55) and APTC composite cardiovascular endpoint (relative risk 1.86; 95% confidence interval, 1.19 to 2.55) was numerically lower in the Intention-to-Treat Analysis than in the APPROVe base study (confirmed thrombotic events:

³⁷⁰ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 217.

³⁷¹ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 217.

³⁷² 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 228.

³⁷³ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 228.

relative risk 1.92; 95% confidence interval, 1.19 to 3.11; APTC events: relative risk 2.06; 95% confidence interval, 1.16 to 3.64). However, because the confidence intervals for these results overlapped substantially with the confidence intervals in the base study results, it is not possible to conclude that the results of the Intention-to-Treat Analysis were different from the results of the APPROVe base study.

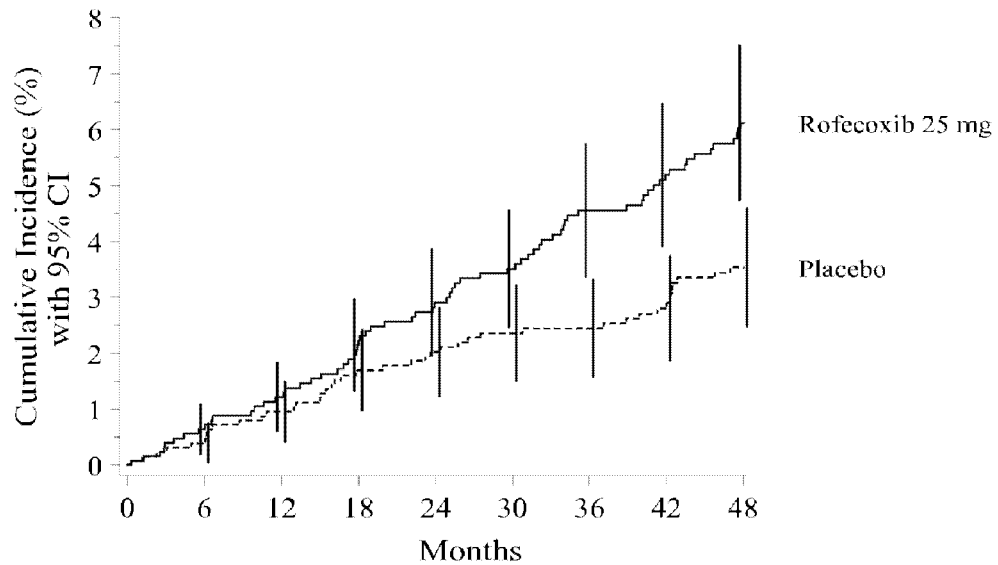
In the Off-Drug Analysis, which included only those events occurring at least 15 days after discontinuation of treatment, there were numerically more events on Vioxx than placebo for both endpoints – 28 versus 16 for confirmed thrombotic events and 21 versus 12 for APTC events – but the difference was not statistically significant. The Company did not perform a similar analysis of all off-drug cardiovascular events occurring from the time of discontinuation of treatment forward.

ii. Kaplan-Meier plots.

The Statistical Data Analysis Plan also required Kaplan-Meier plots for both the Intention-to-Treat and Off-Drug Analyses. As discussed above, Kaplan-Meier plots represent graphically the cumulative incidence of events over time in each arm of a study. They may provide some evidence as to whether the hazard ratio is constant over time, but, standing alone, do not provide a sufficient basis for reaching a conclusion regarding the proportionality of hazards. The Kaplan-Meier plots for the Intention-to-Treat Analysis and Off-Drug Analysis for both endpoints are reproduced below in Figures 8 through 11:

Figure 8

APPROVe Extension – Intention-to-Treat Analysis
Kaplan-Meier Plot – Confirmed Thrombotic Events³⁷⁴

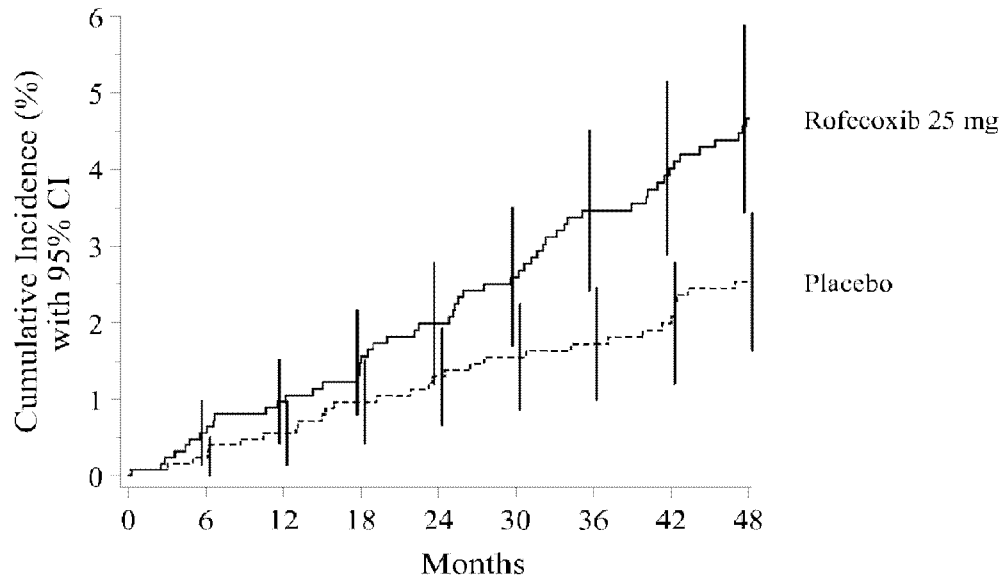


Patients at Risk	
Rofecoxib 25 mg	1287 1221 1187 1152 1131 1117 1092 1032 989
Placebo	1300 1247 1224 1189 1173 1157 1133 1071 1027

³⁷⁴ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 219.

Figure 9

APPROVe Extension – Intention-to-Treat Analysis
Kaplan-Meier Plot – APTC Events³⁷⁵

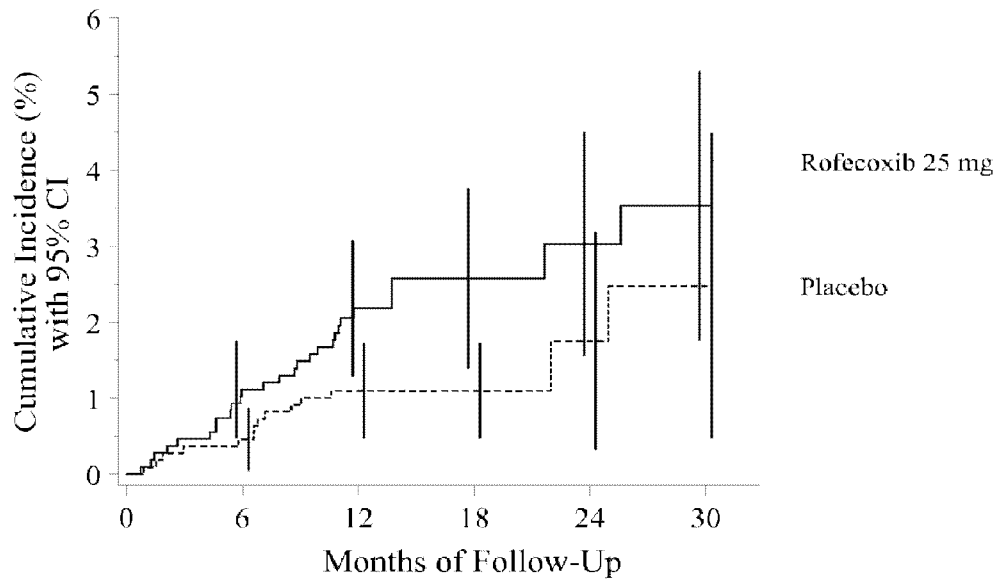


Patients at Risk									
Rofecoxib 25 mg	1287	1220	1188	1158	1140	1125	1102	1042	1002
Placebo	1300	1249	1228	1196	1181	1165	1140	1079	1036

³⁷⁵5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 230.

Figure 10

APPROVe Extension – Off-Drug Analysis
Kaplan-Meier Plot – Confirmed Thrombotic Events³⁷⁶

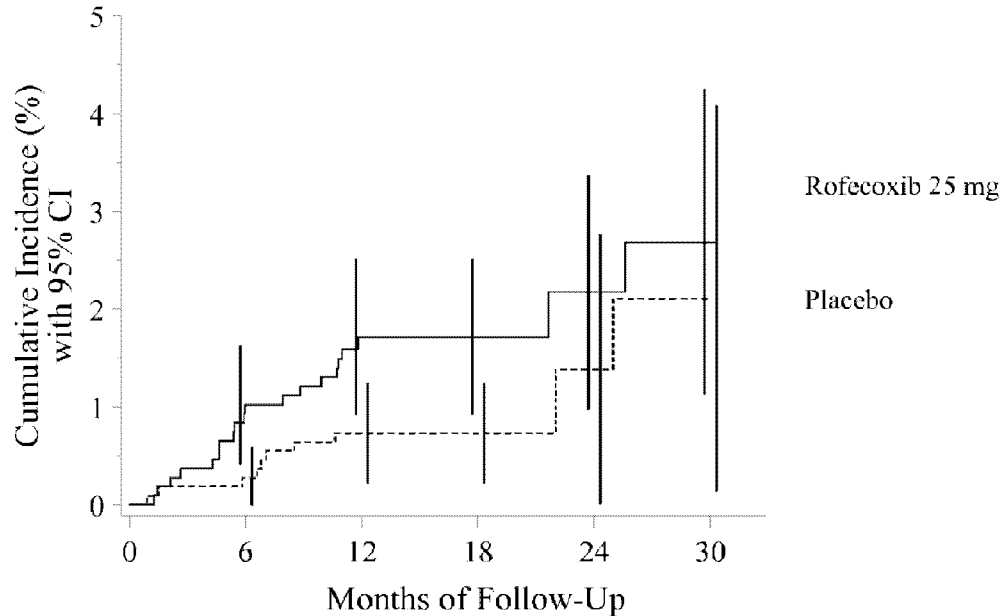


Patients at Risk	0	6	12	18	24	30
Rofecoxib 25 mg	1081	1063	498	226	199	167
Placebo	1097	1091	488	165	139	114

³⁷⁶ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 225.

Figure 11

APPROVe Extension – Off-Drug Analysis
Kaplan-Meier Plot – APTC Events³⁷⁷



Patients at Risk						
Rofecoxib 25 mg	1080	1063	500	228	200	167
Placebo	1097	1093	492	166	140	115

iii. Assessments of proportionality of hazards over time.

In addition to the two analyses above, the Statistical Data Analysis Plan for Protocol 122-20 specified an assessment of the proportionality of hazards over time. The plan required two different statistical methods for this assessment. The first method was to plot the hazard rates for the Vioxx and placebo treatment arms as a function of time.³⁷⁸ These plots, reproduced in Figures 12 through 15 at the end of this section, displayed graphically the estimated percentage of the patients in each treatment group that

³⁷⁷ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 234.

³⁷⁸ Protocol 122-20 Statistical Analysis Plan, MRK-I2220005957, at 73.

experienced an endpoint event at every point in time covered by the analysis. Visual inspection of the relative positions of these curves may provide evidence as to whether the hazard ratio changes over time.

The second method – and the most formal means of evaluating whether the hazard ratio was constant over time – was to test the proportional hazards assumption using the Cox proportional hazards model. Merck applied two such tests for both endpoints in both analyses – the Linear Time Test and Logarithm of Time Test, both of which are described in Section B of this Appendix. As discussed above, the relevant output from both tests are p-values that indicate whether sufficient evidence exists to reject the model's assumption of the model that the hazard ratio is constant over time. Although there was no pre-specified level of statistical significance in the Statistical Data Analysis Plan, as discussed above, because the test of proportionality of hazard rates has low statistical power, many biostatisticians may consider a p-value of 0.10 or less, in conjunction with graphical analysis, sufficient to reject the model's assumption that the hazard ratio is constant over time. The p-values calculated in the APPROVe Extension Analyses are reported in Table 17 below:

Table 17

APPROVe Extension Analyses – Proportionality P-values

	Endpoint	Linear Time Test	Logarithm of Time Test
Intention-to-Treat Analysis	Confirmed Thrombotic Events ³⁷⁹	0.345	0.306
	APTC Events ³⁸⁰	0.748	0.687
Off-Drug Analysis	Confirmed Thrombotic Events ³⁸¹	0.255	0.597
	APTC Events ³⁸²	0.069	0.256

All but one of the proportionality p-values resulting from these tests were greater than 0.10, indicating that there was insufficient evidence to reject the assumption that the hazard ratio was constant over time. The p-values for the Intention-to-Treat Analysis of both endpoints did not approach statistical significance. Thus, in contrast to the proportionality p-values calculated in the APPROVe base study, they provide no evidence that the hazard ratio changes over time. This, together with a significantly increased relative risk on Vioxx compared to placebo, raises the question of whether the increase in risk for both endpoints emerged immediately.

With respect to the Off-Drug Analysis, the p-value for the confirmed thrombotic events endpoint provided no evidence of non-proportional hazards. However, the p-value for the APTC endpoint in the Off-Drug Analysis – p=0.069 – might indicate a change in the hazard ratio over time.

³⁷⁹ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 221.

³⁸⁰ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 231.

³⁸¹ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 226.

³⁸² 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 235.

This p-value, when considered together with the corresponding hazard plot (see Figure 15 below), provides some evidence that an excess risk of APTC events associated with Vioxx may have persisted for some period of time after discontinuation of Vioxx therapy in the APPROVe Trial, but there is insufficient data to reach any conclusion concerning the magnitude of the increased risk or how long the increased risk lasted. A post-hoc analysis of the relative risk of APTC events in 6-month time intervals over the course of the Off-Drug Analysis likewise provided some evidence of an increased hazard of APTC events after discontinuation of therapy with Vioxx. This analysis showed that during the first 6 months post-discontinuation, there was a statistically significant increased risk for APTC events among patients who had previously taken Vioxx relative to patients who had previously taken placebo (relative risk 3.74; 95% confidence interval, 1.04 to 13.42).³⁸³ This 6-month interval analysis did not provide evidence of a persistent risk of APTC events post-discontinuation for any other portion of the Off-Drug Analysis, nor did it provide any evidence of an increased risk of confirmed thrombotic events during any portion of the Off-Drug analysis.

b. Results of additional subgroup analyses.

In addition to performing the analyses specified in the Statistical Data Analysis Plan, MRL scientists also performed post-hoc subgroup analyses that explored the relative risk of Vioxx versus placebo among patient populations other than the ones in the Intention-to-Treat Analysis and Off-Drug Analysis, within particular time intervals, and

³⁸³ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 259.

for particular types of cardiovascular events that were part of the two composite

endpoints. Three notable subgroup analyses are reported here:

- an analysis of Year 4 off-drug data from those patients who completed the three-year APPROVe base study;
- an analysis of hazard ratios for the confirmed thrombotic events endpoint across different time intervals in the Intention-to-Treat Analysis; and
- analyses of the incidence of myocardial infarction in the Intention-to-Treat Analysis and Off-Drug Analysis.
 - i. Analyses of off-drug data for patients who completed the APPROVe base study.

Among those patients who had completed the APPROVe base study and for whom year-four follow-up data had been collected, 15 patients who had previously taken Vioxx experienced confirmed thrombotic events, and 9 patients who had previously taken placebo experienced confirmed thrombotic events.³⁸⁴ As indicated by Table 18, the difference was not statistically significant.³⁸⁵

³⁸⁴ 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 95.

³⁸⁵ 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 95.

Table 18

APPROVe Extension – Year-Four Population
Overall Relative Risk – Confirmed Thrombotic Events³⁸⁶

	Events/Patient-Years in Vioxx Arm	Events/Patient-Years in Placebo Arm	Relative Risk (95% CI)
Confirmed thrombotic events	15/802	9/885	1.85 (0.81, 4.22)

ii. Hazard ratios pre- and post-18 months since the beginning of treatment.

MRL scientists also conducted post-hoc analyses of hazard ratios pre- and post-18 months in order to compare the results to similar analyses from the APPROVe base study. The comparison was not completely parallel because the Intention-to-Treat Analysis included a longer post-18-month period than the base study did (18 months versus 30 months, respectively). In addition, there was no evidence of non-proportional hazard rates in the Intention-to-Treat Analysis dataset. In the Intention-to-Treat Analysis, the risk of confirmed thrombotic events on Vioxx relative to placebo appeared to be different before and after the 18-month mark. Results using the APTC endpoint also appeared to reflect a difference, but of a lesser magnitude, before and after the 18-month mark. The table below summarizes the data relevant to these conclusions:

³⁸⁶ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 296.

Table 19

APPROVe Extension – Intention-to-Treat Analysis
Relative Risk by Time Interval – Confirmed Thrombotic Events & APTC Events

Endpoint	Time Interval	Events/Patient-Years for Vioxx Arm	Events/Patient-Years for Placebo Arm	Relative Risk (95% Confidence Interval)
Confirmed Thrombotic Events ³⁸⁷	0 – 18 months	26/1813	21/1855	1.27 (0.71, 2.25)
	> 18 months	45/2744	21/2842	2.22 (1.32, 3.73)
APTC Events ³⁸⁸	0 – 18 months	18/1815	12/1860	1.54 (0.74, 3.19)
	> 18 months	36/2766	18/2862	2.07 (1.18, 3.65)

As indicated by the relative risks and confidence intervals in Table 19, based on the data available, there was no statistically significant difference between Vioxx and placebo during the first 18 months after the beginning of treatment with respect to the incidence of confirmed thrombotic events (relative risk 1.27; 95% confidence interval, 0.71 to 2.25) or APTC events (relative risk 1.54; 95% confidence interval, 0.74 to 3.19), but the data could not rule out the possibility of an increased risk associated with Vioxx during this period. After the first 18 months of treatment, however, there was a statistically significant increased risk of confirmed thrombotic events on Vioxx relative to placebo (relative risk 2.22; 95% confidence interval, 1.32 to 3.73) and APTC events (relative risk 2.07; 95% confidence interval, 1.18 to 3.65).

³⁸⁷ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 218. These data were censored at 210 Weeks.

³⁸⁸ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 229.

The relative risk of Vioxx versus placebo after the first 18 months from the beginning of study therapy was numerically lower in the Intention-to-Treat Analysis than it was in the APPROVe base study (relative risk 4.45; 95% confidence interval, 1.77 to 13.32).³⁸⁹ This result likely reflects the difference in follow-up time in the APPROVe base study as compared to the Intention-to-Treat Analysis. As noted above, the former followed patients only through 14 days after they discontinued treatment, whereas the latter followed patients for a total of four years – a minimum of one year after discontinuation of treatment and, for patients who discontinued treatment early in the base study, as much as almost four years. If there were a reduction in the relative risk for confirmed thrombotic events after discontinuation of treatment, therefore, the relative risk for the post-18-month period would be reduced in the Intention-to-Treat Analysis versus the APPROVe base study.

iii. Incidence of myocardial infarction in
the Intention-to-Treat and Off-Drug Analyses.

The Company performed a subgroup analysis of myocardial infarctions – a component event of both cardiovascular endpoints – in both the Intention-to-Treat and Off-Drug Analyses. In the Intention-to-Treat Analysis, there were numerically more acute myocardial infarctions in the Vioxx treatment group than the placebo treatment group (31 versus 15, respectively).³⁹⁰ This difference was statistically significant

³⁸⁹ Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, Table 3 at 98.

³⁹⁰ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 217.

(relative risk 2.12; 95% confidence interval, 1.15 to 3.93).³⁹¹ Although there were also numerically more events on Vioxx versus placebo in the Off-Drug Analysis (10 versus 6, respectively), this difference was not statistically significant (relative risk 1.67; 95% confidence interval, 0.61 to 4.59).³⁹²

6. Reporting of Results.

a. Merck's report to the FDA.

On May 11, 2006, Merck provided the FDA with a 107-page report containing the data and preliminary analyses from the one-year off-drug extension study.³⁹³ Attached to the report was a four-page summary of the data and analyses that focused on the extension study's primary endpoint of confirmed thrombotic cardiovascular events.³⁹⁴

³⁹¹ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 217. These data were censored at 210 Weeks.

³⁹² 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 223. These data were censored at 210 Weeks.

³⁹³ Letter from P. Huang to B. Rappaport* attaching report of preliminary analysis of APPROVe off-drug extension study and press release, MRK-S0420112017, at 017. Merck noted in its cover letter that the final study report, which would include colonoscopy data and additional safety analyses, was expected to be completed in July. Id. However, completion of the report was delayed because of a new requirement established by European regulators to whom the report is also to be sent. Merck expects to submit the final abbreviated Clinical Study Report to the FDA and other regulators within the month. Merck also produced a copy of the preliminary analyses to plaintiffs pursuant to commitments it had made in pending litigation. See "Brief in Support of Merck's Motion for Reconsideration and Entry of Temporary Protective Order Regarding Interim APPROVe Follow-Up Study Data," In re Vioxx Litigation, N.J. Super. Ct., Case Code No. 619, 12/28/05, at 1 ("Merck expects to have finished collecting the data [from the APPROVe follow-up studies] by mid-2006 and is prepared to make an immediate production to plaintiffs at that time."); Transcript of 12/15/05 hearing, In re Vioxx Litigation, N.J. Super. Ct., Case Code No. 619, statement of Benjamin Barnett, counsel for Merck, at 25 ("If the data is final this is consistent with the agreement I have reached with your colleagues in the MDL is when we have final data we'll produce it.").

³⁹⁴ As noted above, the summary advised that "[f]ollow-up data remain outstanding from 1 investigator site that had 17 randomized patients." 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 93.

Merck's submission to the FDA also included a copy of the press release announcing the results of the preliminary analyses that it planned to issue later that day.³⁹⁵

The report consisted mostly of statistical information in the form of tables and charts listing the numbers and types of adverse cardiovascular events, mortality data, relative risks calculations, hazard rate plots and Kaplan-Meier curves.³⁹⁶ Merck later prepared an updated, expanded version of the report, which it sent to the FDA on May 30, 2006.³⁹⁷ The updated, 137-page report added a new section that presented tables and charts related to confirmed thrombotic cardiovascular events and APTC events in patients who did not experience such an event while on study therapy through 14 days after discontinuation. The updated report noted that these analyses were conducted to address what happened to patients off-drug who did not have an event while on study therapy.³⁹⁸

In the May 30 letter that accompanied the updated report, Merck also notified the FDA of the discovery of the statistical error regarding the proportionality testing done on the APPROVe base study and the need for a correction of its prior description of the

³⁹⁵ 5/06 draft Merck press release, "Merck Announces Preliminary Analysis of Off-Drug Extension of APPROVe," MRK-S0420112019 (attached to letter from P. Huang to B. Rappaport, MRK-S0420112017).

³⁹⁶ 5/11/06 APPROVe Extension Statistical Package, MRK-S0420112022, at 023-128.

³⁹⁷ 5/30/06 letter from P. Huang to B. Rappaport*, MRK-AFV0518069, at 69. The report was updated as of May 26, 2006. 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 195. Among other things, the updated report corrected an error in the original report's presentation of the hazard rate plot for confirmed thrombotic cardiovascular events. In the original version sent to the FDA on May 11, the plot set forth for that endpoint (at Figure B2) was actually the hazard rate plot for APTC events, which was set forth at Figure B6. See 5/11/06 APPROVe Extension Statistical Package, MRK-S0420112022, at 037, 046. In the updated report, Figure B2 contains the correct hazard rate plot. 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 220-21.

³⁹⁸ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 196.

method used. Merck stated that it “believes that this correction does not change the results of the APPROVe study, which found an increased relative risk for confirmed thrombotic cardiovascular events for VIOXX™ compared to placebo beginning after 18 months of treatment.”³⁹⁹

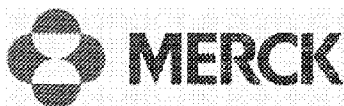
b. Merck’s May 11 press release.

i. Contents of the press release.

On May 11, 2006 , Merck issued a press release announcing the results of the preliminary analyses of the APPROVe off-drug extension study.⁴⁰⁰ The release, which is reproduced below, attached a copy of the four-page summary that Merck had sent to the FDA earlier that day.

³⁹⁹ 5/30/06 letter from P. Huang to B. Rappaport*, MRK-AFV0518069, at 69.

⁴⁰⁰ 5/11/06 Merck press release, “Merck Announces Preliminary Analyses of Off-Drug Extension of APPROVe Study, MRK-ARQ0002290.



Press Release

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Merck Announces Preliminary Analyses of Off-Drug Extension of APPROVe Study

WHITEHOUSE STATION, N.J., May 11, 2006 – In the off-drug follow-up period for patients in the APPROVe study, there was not a statistically significant difference in the risk of confirmed thrombotic cardiovascular events in patients who had previously taken VIOXX compared to those who had previously taken placebo, according to preliminary analyses announced today by the study sponsor, Merck & Co., Inc. This prespecified analysis included patients regardless of when they discontinued study therapy. Furthermore, in the one-year off-drug follow-up period for patients who completed approximately three years of therapy in the APPROVe study, there was not a statistically significant difference in the risk of confirmed thrombotic cardiovascular events in patients who had previously taken VIOXX compared to those who had previously taken placebo. In these analyses, the data were insufficient to conclude that there was an increased relative risk of confirmed thrombotic cardiovascular events following discontinuation of therapy. In the prespecified primary analysis of each patient's four-year data (that combined data from the on-drug period and the off-drug period regardless of when patients discontinued study therapy) the difference in the risk of confirmed thrombotic cardiovascular events between groups initially observed in the on-drug period of the study remained statistically significant.

In the four-year data, there was an increased relative risk of confirmed heart attacks in the VIOXX group compared to the placebo group and an increased relative risk of confirmed ischemic strokes in the VIOXX group compared to the placebo group. Mortality was similar between the VIOXX and placebo groups in the four-year data. These preliminary analyses have been shared with regulatory agencies.

"Our preliminary analyses of the off-drug period did not demonstrate a statistically significant increased risk of confirmed cardiovascular thrombotic events after patients in the APPROVe study stopped taking VIOXX," said Peter S. Kim, Ph.D., president of Merck Research Laboratories. "The limited data in the APPROVe study on stroke have to be interpreted in the context of the extensive data we have previously published, which consistently showed no increased risk of strokes in patients taking VIOXX."

- more -

Appendix R

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The Company reported the results of the three-year APPROVe study (the "base study") in September 2004. As previously reported, in the 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. Given the questions raised by the data in the base study and the perceptions regarding alternative therapies available, the Company decided to voluntarily withdraw VIOXX worldwide at that time. In accordance with the APPROVe clinical study protocol, the Company announced that it planned to follow patients for one year after they came off treatment. The results announced today are the preliminary safety analyses including this follow-up period.

A copy of the summary report of confirmed thrombotic cardiovascular events from the APPROVe off-drug extension, which was shared with regulatory agencies, is attached and available by visiting: **The VIOXX Information Center on www.merck.com.**

About the APPROVe Study

APPROVe (Adenomatous Polyp Prevention on VIOXX) was a multi-center, randomized, placebo-controlled, double-blind study designed to evaluate the efficacy of 156 weeks (three years) of treatment with VIOXX 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. The one-year off-drug extension of APPROVe addressed recurrence of polyps, thrombotic cardiovascular events and mortality. Recurrence of polyps will be addressed in a future publication.

About Merck

Merck & Co., Inc. is a global research-driven pharmaceutical company dedicated to putting patients first. Established in 1891, Merck currently discovers, develops, manufactures and markets vaccines and medicines to address unmet medical needs. The Company devotes extensive efforts to increase access to medicines through far-reaching programs that not only donate Merck medicines but help deliver them to the people who need them. Merck also publishes unbiased health information as a not-for-profit service. For more information, visit www.merck.com.

Forward-Looking Statement

This press release (including the attachment) contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements are based on management's current expectations and involve risks and uncertainties, which

- more -

Appendix R

- 180 -

may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the cautionary statements in Item 1 of Merck's Form 10-K for the year ended Dec. 31, 2005, and in its periodic reports on Form 10-Q and Form 8-K, which the Company incorporates by reference.

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The initial paragraph of the press release focused on the results of the off-drug analysis – i.e., the extension study's secondary analysis that examined the relative risk of cardiovascular events 15 or more days after the participants had discontinued study therapy. The release stated that “[i]n the off-drug follow-up period for patients in the APPROVe study, there was not a statistically significant difference in the risk of confirmed thrombotic cardiovascular events in patients who had previously taken VIOXX compared to those who had previously taken placebo.” The release stated that this pre-specified analysis included patients regardless of when they discontinued study therapy. The release then stated that this same result was found in a post-hoc analysis of year-4 off-drug data for those patients who had completed the full three years of study therapy.⁴⁰¹

⁴⁰¹ 5/11/06 Merck press release, “Merck Announces Preliminary Analyses of Off-Drug Extension of APPROVe Study, MRK-ARQ0002290, at 90.

The release stated that in the study's intention-to-treat analysis, – i.e., the study's primary analysis, which combined data from the on-drug period and the off-drug period – “the difference in the risk of confirmed thrombotic cardiovascular events between groups initially observed in the on-drug period of the study remained statistically significant.”⁴⁰²

As noted above, the four-page summary that was attached to the press release focused on the data and analyses related to the study's primary endpoint of confirmed thrombotic cardiovascular events. The summary did not include any data or analyses of the study's secondary (APTC) endpoint.⁴⁰³

The attached four-page summary provided the number of confirmed thrombotic cardiovascular events (but not APTC events) that occurred in the period beginning 15 days after discontinuation of study therapy through each of the extension study's three censoring dates. Based on the data through the week 210 censoring date, the summary set forth the relative risks for confirmed thrombotic events for the extension study's primary (intention-to-treat) analysis, the secondary (off-drug) analysis, and various subgroup analyses based on the different lengths of on-drug exposure before

⁴⁰² 5/11/06 Merck press release, “Merck Announces Preliminary Analyses of Off-Drug Extension of APPROVe Study, MRK-ARQ0002290, at 90. The press release also noted an increased risk of heart attacks and stroke in the Vioxx group, which was followed by a statement by Dr. Kim that “[t]he limited data in the APPROVe study on stroke have to be interpreted in the context of the extensive data we have previously published, which consistently showed no increased risk of strokes in patients taking VIOXX.” Id.

⁴⁰³ 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 93-96. The summary included a brief section entitled “Mortality” that reported the following information: “Among the 2,587 patients enrolled in the APPROVe study, mortality data for the period beginning on day 15 after discontinuation of study therapy were available for 2,448. Mortality rates were similar between groups in all analyses performed.” Id. at 96.

discontinuing treatment.⁴⁰⁴ Unlike the full report, the summary did not contain any Kaplan-Meier curves, hazard plots, or tables of data. The summary also did not contain any proportionality p-values or other data that would shed light on the proportionality of hazards.

In reporting on the intention-to-treat analysis of events through week 210, the summary stated that the relative risk of experiencing confirmed thrombotic cardiovascular events on Vioxx versus placebo in the 156-week base study was 1.92 (95% confidence interval, 1.19 to 3.11, p=0.008), while in the Intention-to-Treat Analysis through week 210, the relative risk was 1.74 (95% confidence interval, 1.19 to 2.55, p=0.004). Thus, the summary stated that the relative risk remained significant after including data from the off-drug follow-up period.⁴⁰⁵

The summary stated that in the on-drug base-study (through week 156), the relative risk of patients having confirmed thrombotic cardiovascular events on Vioxx versus placebo was not constant over time: 1.18 (95% confidence interval, 0.64 to 2.15) for the first 18 months and 4.45 (95% confidence interval, 1.77 to 13.32) for the period beyond month 18. After then setting out the corresponding data from the Intention-to-Treat Analysis through week 210, the summary said that in comparing these datasets, the

⁴⁰⁴ 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 93-96.

⁴⁰⁵ 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 94. The summary also reported the number of myocardial infarctions and strokes through week 210. The summary said as to myocardial infarction, between group differences were observed in both the base study and in the intention-to-treat analyses, while between-group differences in strokes were observed in the intention-to-treat analyses. Id.

relative risks for the first 18 months are similar, while in the period beyond month 18, the relative risk for Vioxx compared to placebo in the Intention-to-Treat Analysis was approximately half of what had been observed in the on-drug analysis of the 156-week data.⁴⁰⁶

In the section that followed, which reported on the Off-Drug Analyses, the summary provided the data as to the number of events in groups previously on Vioxx and placebo and noted that based on the corresponding relative risks and confidence intervals, the between group difference was not statistically significant.⁴⁰⁷ After then providing the subgroup data and analyses, the final page of the summary set forth the following four conclusions reiterating the key points that were discussed in the previous pages:⁴⁰⁸

⁴⁰⁶ 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 94.

⁴⁰⁷ 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 95.

⁴⁰⁸ 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 96. In contrast to the conclusions regarding the intention-to-treat analyses set forth in the first two bullet points in the four-page summary, an early draft of the extension study safety report prepared for submission to the FDA did not separate the relative risks into two 18 month periods. Instead, the draft listed a single conclusion as to the intention-to-treat (four-year) data, which stated that “there was an increased relative risk of confirmed thrombotic cardiovascular events in the rofecoxib group compared to the placebo group.” 5/29/06 draft of APPROVe Extension Safety Report, MRK-ARQ0011740, at 829. Merck subsequently decided to make the conclusions in the safety report identical to those in the four-page summary since the summary had been sent to the FDA as part of Merck’s May 11 submission and already was in the public domain. See 6/06 email correspondence between N. Braunstein, R. Silverman, S. Loftus, *et al.*, MRK-AFV0502296, at 96.

Conclusions

- For the first 18 months, the relative risk of confirmed thrombotic cardiovascular events for rofecoxib compared to placebo in the ITT analysis was similar to that observed in the on-drug base study.
- Beyond 18 months, the relative risk of confirmed thrombotic cardiovascular events for rofecoxib compared to placebo in the ITT analysis was approximately half of that observed in the on-drug base study. This lowering of the relative risk was mostly due to the off-drug follow-up data observed during the period beyond month 36 and to the off-drug follow-up data in patients who prematurely discontinued study therapy.
- There was no statistically significant increased relative risk of confirmed thrombotic cardiovascular events for rofecoxib compared to placebo in off-drug follow-up data in all patients regardless of when they discontinued therapy as well as in those who completed 150 weeks of on-drug treatment in the base study. In these analyses, data are insufficient to conclude that there was an increased relative risk following discontinuation of therapy.
- Mortality was similar between groups.

Like the summary itself, the conclusions focused exclusively on the confirmed thrombotic cardiovascular event endpoint, and did not provide any information regarding the secondary APTC endpoint, which generally had yielded results that were less favorable to Vioxx than the confirmed thrombotic cardiovascular event endpoint. Although Merck did not initially release the full 107-page report to the public,⁴⁰⁹ two news outlets obtained copies of it.⁴¹⁰ Merck subsequently provided the full report to additional news outlets and made it available on its website, although the posting on Merck's website was delayed while the report was in the process of being updated.⁴¹¹

⁴⁰⁹ Letter from P. Huang to B. Rappaport*, MRK-S0420112017, at 17. As discussed above, the letter was sent to the FDA on May 11, 2006.

⁴¹⁰ See Snigdha Prakash*, Data: Vioxx Heart Risks Began Earlier than Thought, National Public Radio, 5/18/06 (referencing "confidential report" provided by Merck to the FDA last week); Heather Won Tesoriero* & Ron Winslow*, New Merck Data Suggest Risks from Vioxx Begin Earlier in Use, Wall St. Journal, 5/18/06 (referencing the 107-page report).

⁴¹¹ See 6/6/06 memorandum from R. Silverman to S. Korn, MRK-ARQ0003282, at 82-83.

Shortly after Merck provided the updated report to the FDA, Merck posted the updated report (now 137 pages in length) on its website along with an accompanying statement announcing its availability.⁴¹²

ii. Drafting process.

The press release was written by Merck personnel without input from the APPROVe Trial Administrative Committee.⁴¹³ Various people at Merck were involved in writing or reviewing the release including, among others, Dr. Braunstein, Dr. Gertz, Dr. Reiss, and members of Merck's legal department. Dr. Braunstein was the primary author of the four-page summary, which he wrote based on discussions with various scientists at Merck, including Dr. Gertz, Dr. Kim, Dr. Reiss, Dr. Bain, Mr. Bolognese, Dr. Oxenius and Mr. Cook.⁴¹⁴

Neither the press release nor the four-page summary presented any analysis of hazard rates for the entire 210-week period, but instead presented the hazard rates in two 18-month intervals. Dr. Braunstein explained that the reason for this was to show that, in their view, the inclusion of the additional post-discontinuation follow-up data did not

⁴¹² See 6/2/06 email from B. Oxenius *et al.*, MRK-ARQ0006119, at 119;
http://www.merck.com/newsroom/vioxx/pdf/Statement_APPROVe_Extension_Statistical_Package.pdf;
http://www.merck.com/newsroom/vioxx/pdf/APPROVe_Extension_Statistical_Package.pdf.

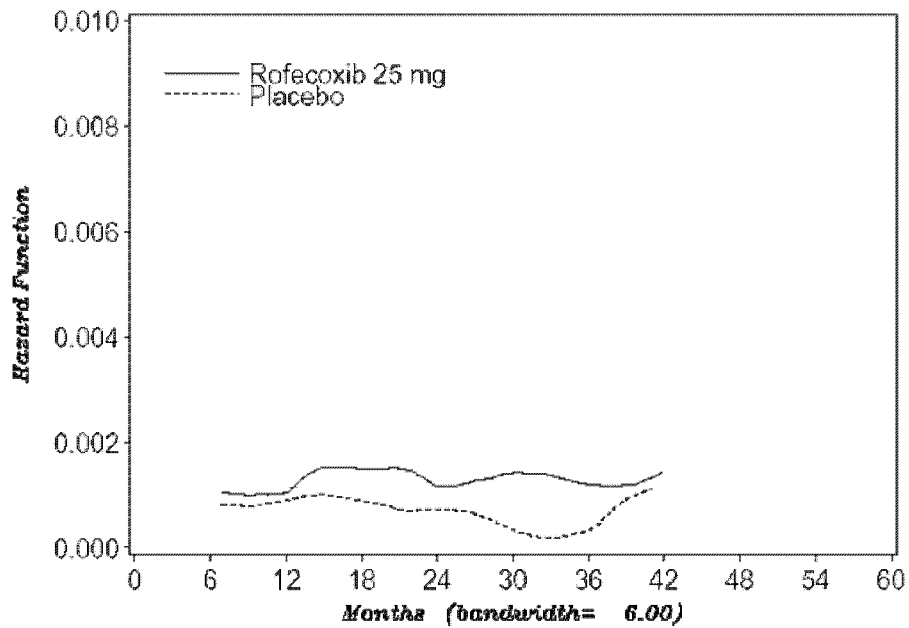
⁴¹³ Although the external authors were not involved in preparing the press release or the four-page summary, Dr. Reiss and Dr. Braunstein called Dr. Baron* on May 11 to advise him that the press release was to be issued later that day and explained its content. They also sent him a copy of the four-page summary that was referenced in the release.

⁴¹⁴ 5/9/06 email from N. Braunstein to B. Oxenius, B. Gertz, T. Reiss, R. Bain, J. Bolognese, T. Cook *et al.*, MRK-AFN0189419 (attaching draft of four-page summary).

change the basic findings pertaining to those periods that were observed in the base study.

Figure 12

APPROVe Extension – Intention-to-Treat Analysis
Plot of Hazard Rate Over Time– Confirmed Thrombotic Events⁴¹⁵



⁴¹⁵ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 220-21.

Figure 13

APPROVe Extension – Intention-to-Treat Analysis
Plot of Hazard Rate Over Time – APTC Events⁴¹⁶

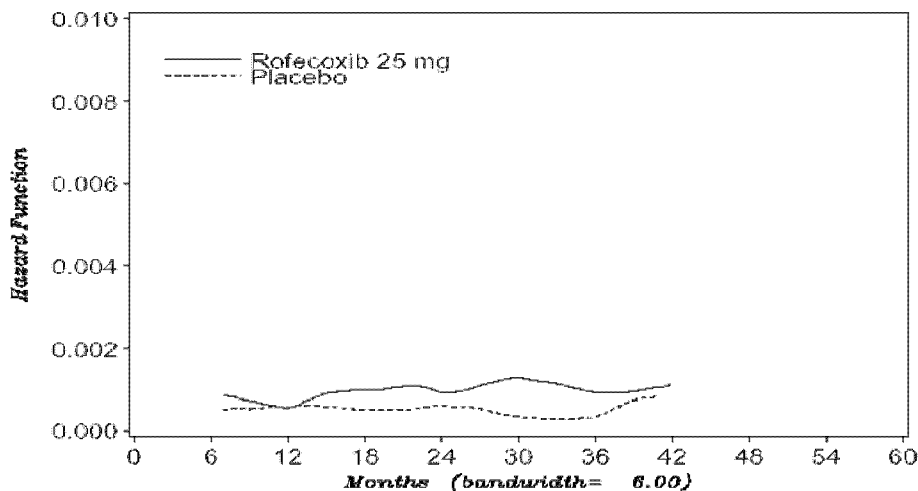
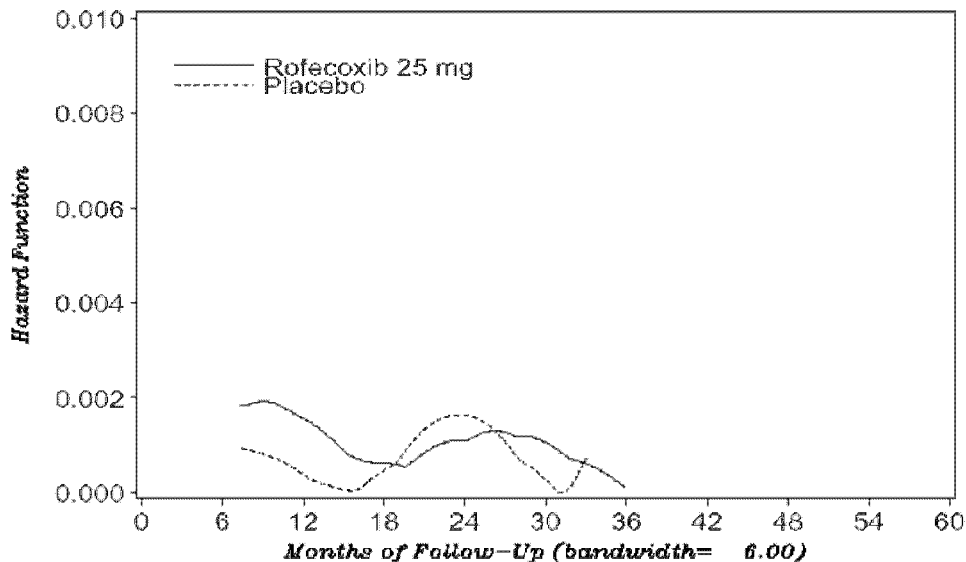


Figure 14

APPROVe Extension – Off-Drug Analysis
Plot of Hazard Rate Over Time – Confirmed Thrombotic Events⁴¹⁷

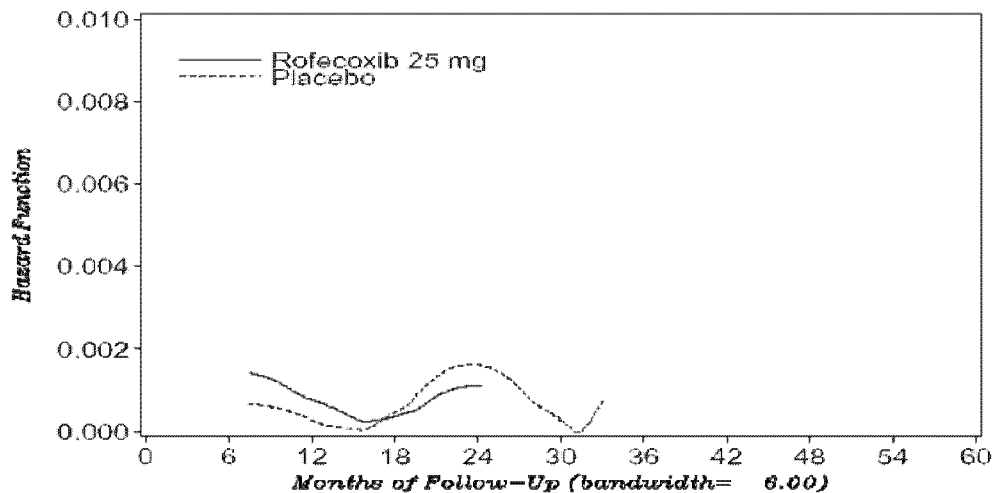


⁴¹⁶ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 231.

⁴¹⁷ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 226.

Figure 15

APPROVe Extension – Off-Drug Analysis
Plot of Hazard Rate Over Time -- APTC Events⁴¹⁸



D. Communications with the *New England Journal of Medicine* Concerning the Impact of the Error and Follow-Up Data on the APPROVe Article.

On May 25, 2006, at a regularly scheduled meeting of the APPROVe Trial Administrative Committee, the co-authors of the APPROVe article discussed two issues pertaining to that article. First, on May 22, 2006, Dr. Gregory Curfman*, Executive Editor of the *New England Journal of Medicine*, had forwarded to Dr. Robert Bresalier*, the lead author of the APPROVe article, two letters that the editors had received that questioned, based on data from the APPROVe follow-up study, the APPROVe article's statements regarding the proportionality of hazards in the APPROVe Trial. Second,

⁴¹⁸ 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 235.

shortly before the May 25 Administrative Committee meeting, MRL scientists had discovered the statistical error in the APPROVe article discussed above.

Over the next month, the authors of the APPROVe article and editors of the New England Journal of Medicine corresponded simultaneously about the authors' response to the two letters and about the scope and content of the correction to be made to the APPROVe article in light of the error. On June 26, 2006 the New England Journal of Medicine published online the two letters it had received, the APPROVe article authors' response, a notice of a correction to the APPROVe article, and an article on the statistical concepts involved in the letters and the correction. On the same day, Merck released an "Open Letter" to the scientific community in response to the correction notice.

The subsections that follow discuss in detail (i) the correspondence between the authors of the APPROVe article and the editors of the New England Journal of Medicine regarding the APPROVe follow-up study, the error in the APPROVe article, and the proposed correction; (ii) the article published in the New England Journal of Medicine on the statistical concepts involved in the letter and correction; and (iii) Merck's "Open Letter" to the scientific community.

1. Correspondence Between the APPROVe Article Authors and the Editors of the New England Journal of Medicine.
 - a. The New England Journal of Medicine's request for responses to the Furberg* and Nissen* letters.

On May 22, 2006, Dr. Curfman* sent a letter to Dr. Bresalier* attaching copies of two letters the New England Journal of Medicine had recently received from Dr. Curt Furberg* of the Wake Forest School of Medicine and Dr. Steven Nissen* of the Cleveland

Clinic Foundation (the “Furberg* and Nissen* letters”). The Furberg* and Nissen* letters stated that the data from the follow-up study raised questions about the findings asserted in the original APPROVe article, as well as about the collection and analysis of the data in the base study. Dr. Curfman* requested that Dr. Bresalier* and his co-authors respond to the issues raised by Drs. Furberg* and Nissen* and highlighted certain issues that he wanted the authors to address. The Furberg* and Nissen* letters and Dr. Curfman’s* letter are described more fully below.

- i. The Furberg* and Nissen* letters.
 - (a) Overview.

The Furberg* and Nissen* letters referenced data that was contained in the report of preliminary analyses that Merck submitted to the FDA on May 11, 2006 but that had not yet been made public. Both writers asserted that the new data called into question statements in the APPROVe article that “[t]he increased relative risk [on Vioxx] became apparent after 18 months of treatment.”⁴¹⁹ In particular, Drs. Furberg* and Nissen* claimed that the Kaplan-Meier time-to-event plots⁴²⁰ for the Intention-to-Treat Analysis in Merck’s May 11, 2006 report to the FDA – unlike that set forth in the APPROVe article – appeared to indicate a separation between Vioxx and placebo beginning prior to 18 months.

⁴¹⁹ Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 092.

⁴²⁰ Dr. Furberg* referred to these as “survival” curves. Undated letter from C. Furberg* to the editor of the New England Journal of Medicine, MRK-ASW0002579 (attached to 5/22/06 letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574-75).

As discussed more fully above, the Kaplan-Meier plot in the APPROVe article was based on confirmed thrombotic cardiovascular events that occurred while patients were on blinded study therapy (Vioxx or placebo) or within 14 days of their discontinuation of treatment.

By contrast, the Kaplan-Meier plots for the Intention-to-Treat Analysis contained in Merck's May 11, 2006 report to the FDA reflected all cardiovascular events experienced during the three-year course of the base study or the one-year follow-up study by patients originally randomized to treatment, regardless of whether the patients had remained enrolled. The "on drug" Kaplan-Meier plot included in the APPROVe article, plus the intention-to-treat Kaplan-Meier plots for the confirmed thrombotic and APTC composite cardiovascular endpoints included in Merck's May 11, 2006 report to the FDA, are presented in Figures 16, 17, and 18 below.⁴²¹

⁴²¹ Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, Figure 2 at 097; 5/11/06 APPROVe Extension Statistical Package, MRK-S0420112022, Figure B1 at 036, Figure B5 at 045.

Figure 16

APPROVe Trial – Events on Therapy or Within 14 days of Discontinuation
Kaplan-Meier Plot – Confirmed Thrombotic Events
As Presented in APPROVe Article

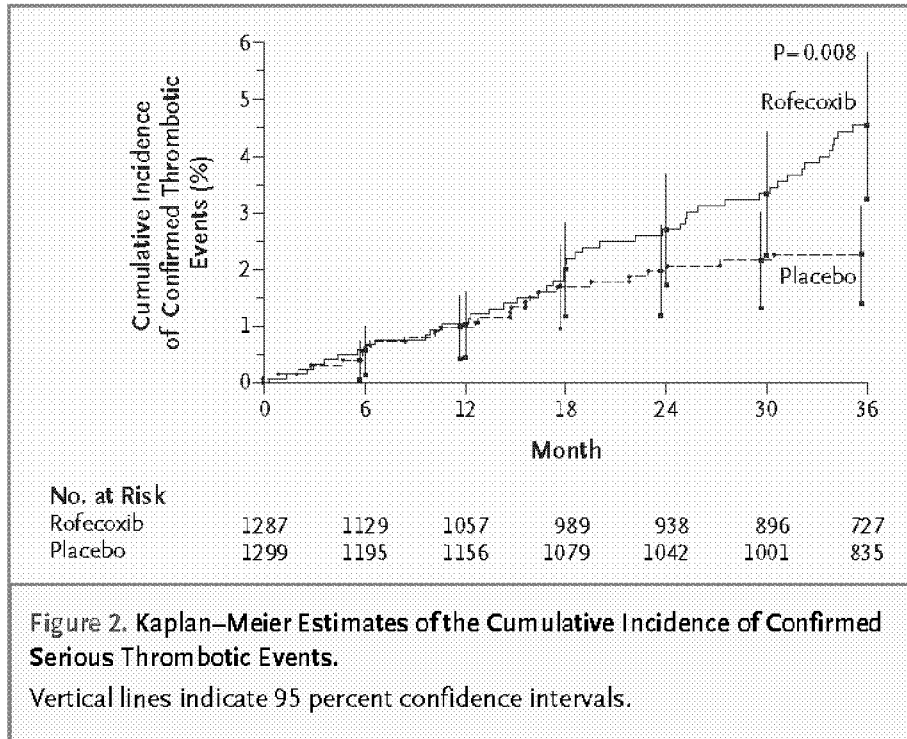
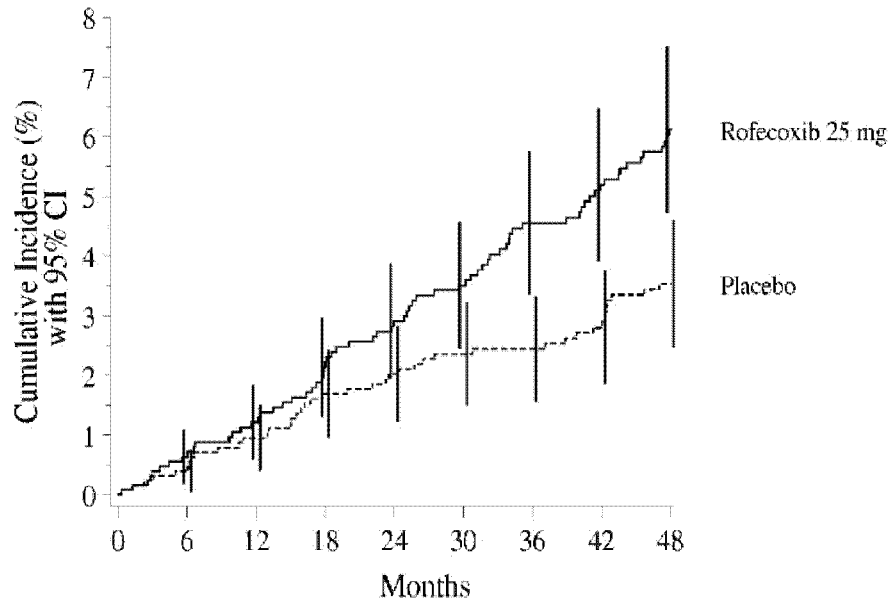


Figure 17

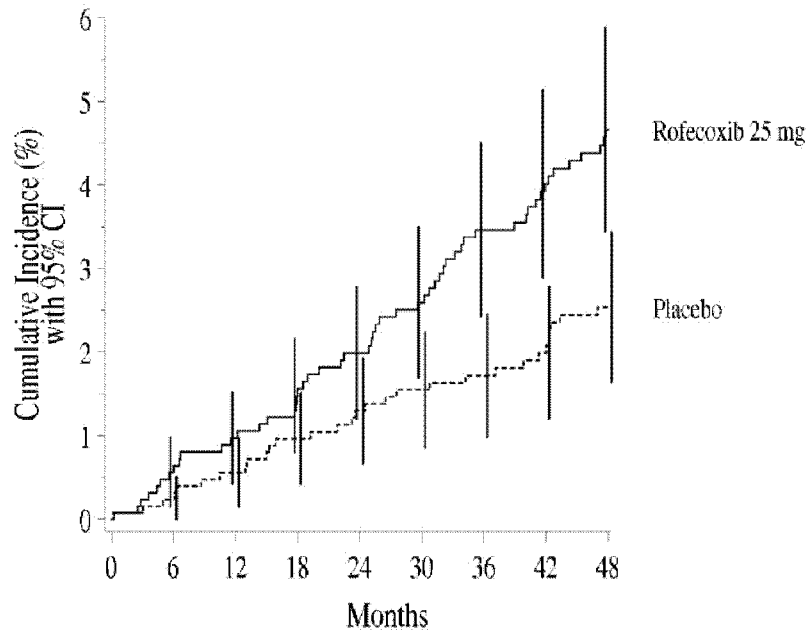
APPROVe Extension – Intention-to-Treat Analysis (Events Through Week 210)
Kaplan-Meier Plot – Confirmed Thrombotic Events
As Presented in May 11, 2006 Report to FDA



Patients at Risk	0	6	12	18	24	30	36	42	48
Rofecoxib 25 mg	1287	1221	1187	1152	1131	1117	1092	1032	989
Placebo	1300	1247	1224	1189	1173	1157	1133	1071	1027

Figure 18

APPROVe Extension – Intention-to-Treat Analysis (Events Through Week 210)
Kaplan-Meier Plot – APTC Events
As Presented in May 11, 2006 Report to FDA



Patients at Risk	0	6	12	18	24	30	36	42	48
Rofecoxib 25 mg	1287	1220	1188	1158	1140	1125	1102	1042	1002
Placebo	1300	1249	1228	1196	1181	1165	1140	1079	1036

(b) Dr. Furberg's* letter.

Dr. Furberg's* letter to the New England Journal of Medicine described the new Kaplan-Meier curves based on the Intention-to-Treat Analysis as “more linear” than the on-drug analyses presented in the APPROVe article and wrote that “the ‘narrowing’ between the rofecoxib and placebo curves at 18 months is almost gone.”⁴²² Dr. Furberg*

⁴²² Undated letter from C. Furberg* to the editor of the New England Journal of Medicine, MRK-ASW0002579 (attached to 5/22/06 letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574-75).

asked, “At the time APPROVe was submitted and published, was the complete data set available to the authors for an ITT analysis? Was a proportionality test performed on the 3-year event data in the published article?”⁴²³

(c) Dr. Nissen’s letter.

Like Dr. Furberg*, Dr. Nissen* expressed the view that the Kaplan-Meier curves based on the Intention-to-Treat Analysis (Figures 21 and 22 above), which were presented in Merck’s May 11, 2006 report, did not support the “post-hoc hypothesis [in the published article] that curves for confirmed thrombotic events do not begin to diverge until 18 months of rofecoxib exposure.”⁴²⁴ Dr. Nissen* stated that the Kaplan-Meier curves for the Intention-to-Treat Analysis began to diverge “much earlier, generally within 4 to 6 months.”⁴²⁵ Dr. Nissen* concluded that the exclusion of events occurring more than 14 days after discontinuation of treatment from the on-drug analysis presented

⁴²³ Undated letter from C. Furberg* to the editor of the New England Journal of Medicine, MRK-ASW0002579 (attached to 5/22/06 letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574-75).

⁴²⁴ Undated letter from S. Nissen* to the editor of the New England Journal of Medicine, MRK-ASW0002576, at 76 (attached to 5/22/06 letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574-75).

⁴²⁵ Undated letter from S. Nissen* to the editor of the New England Journal of Medicine, MRK-ASW0002576, at 76 (attached to 5/22/06 letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574-75). Dr. Nissen* attached to his letter the intention-to-treat Kaplan Meier plot based on the Antiplatelet Trialists’ Collaboration endpoint (Figure 22, above), but did not attach the intention-to-treat Kaplan-Meier plot based on the confirmed thrombotic endpoint. Id. at 78. Further, the Kaplan-Meier plot Dr. Nissen* attached to his letter did not contain “error bars.” Id. However, when it published Drs. Nissen’s* and Furberg’s* letters, the New England Journal of Medicine included intention-to-treat Kaplan-Meier plots based on both endpoints, confirmed thrombotic events and APTC events. Nissen* SE. [letter]. N Engl J Med. 2006; 355:203-04. Both plots included “error bars,” which showed 95% confidence interval at various points along the curves. Id.

in the article “had a significant impact on the results of the APPROVe trial” and that the Intention-to-Treat Analysis “suggests a substantially different conclusion.”⁴²⁶

Dr. Nissen* also suggested that the Intention-to-Treat Analysis was entitled to more weight than the on-drug analysis presented in the March 2005 APPROVe article. Dr. Nissen* wrote: “[i]n the original APPROVe article, the authors reported event rates using an unusual censoring rule in which events occurring more than 14 days after stopping study drug were excluded.”⁴²⁷ Dr. Nissen* added that the data in the new study report was based on a “conventional intention-to-treat . . . analysis” and that patients who discontinued the trial early (and might have experienced events more than 14 days after discontinuation) were likely to represent “a particularly vulnerable group” because these patients “are likely to represent subjects who suffered adverse reactions such as hypertension, heart failure, or renal dysfunction.”⁴²⁸

(d) MRL scientists’ view of the impact of the Intention-to-Treat Analysis on conclusions in the APPROVe article.

Both the Furberg* and Nissen* letters claimed that the results of the Intention-to-Treat Analysis undermined conclusions in the published APPROVe article. In particular,

⁴²⁶ Undated letter from S. Nissen* to the editor of the New England Journal of Medicine, MRK-ASW0002576, at 76 (attached to 5/22/06 letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574-75).

⁴²⁷ Undated letter from S. Nissen* to the editor of the New England Journal of Medicine, MRK-ASW0002576, at 76 (attached to 5/22/06 letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574-75).

⁴²⁸ Undated letter from S. Nissen* to the editor of the New England Journal of Medicine, MRK-ASW0002576, at 76 (attached to 5/22/06 letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574-75).

both authors claimed that the new data did not support the conclusion that an elevated cardiovascular risk associated with Vioxx did not appear until after 18 months of continuous treatment in the APPROVe Trial. All witnesses who expressed an opinion on this subject, however, most of whom were MRL scientists, stated that the Intention-to-Treat Analysis, which included both on-drug and off-drug data, did not undermine this conclusion.

Several witnesses, including Dr. Marvin Konstam^{*}, one of the external authors of the APPROVe article, expressed the view that, in general, intention-to-treat analyses were not useful when assessing safety because they tended to dilute safety signals. In addition:

- Dr. Ned Braunstein stated that, notwithstanding differences between the Kaplan-Meier curves from the base study and the Intention-to-Treat Analysis, the overall shape of both sets of curves was similar.
- Dr. Peter Kim pointed out that these results demonstrated a lower relative risk for Vioxx after the first 18 months of the study than the APPROVe base study had, indicating that the inclusion of off-drug data diluted the safety signal. As a result, he stated, it would not make sense to use these data to assess whether the overall relative risk was constant.
- Dr. Barry Gertz stated that the new analysis included too few additional events for any change in the results to be meaningful. He also stated that the non-significant proportionality p-values in the new analysis did not undercut the original conclusion because the tests have low statistical power and are, therefore, not conclusive.

Several witnesses also expressed the view that the Off-Drug Analysis, and not the Intention-to-Treat Analysis, was the most clinically relevant of the new analyses.

Dr. Janet van Adelsberg and Dr. Braunstein stated that the most pressing outstanding safety question concerning Vioxx after the APPROVe base study was whether a

cardiovascular risk persisted after the discontinuation of treatment. Both Dr. van Adelsberg and Dr. Braunstein stated that an analysis of off-drug data, as opposed to a combination of on-drug and off-drug data, was the most appropriate way to address this concern. According to them, the Intention-to-Treat Analysis provided less probative evidence concerning this issue.

ii. The New England Journal of Medicine's letter to Dr. Bresalier*.

In forwarding the Furberg* and Nissen* letters to Dr. Bresalier*, Dr. Curfman* listed specific issues that the Journal wanted the authors to address:⁴²⁹

- Dr. Curfman* requested that the authors provide two new sets of Kaplan-Meier plots based on intention-to-treat data: (i) a Kaplan-Meier plot reflecting intention-to-treat data for the same time period (the 3-year base study) and endpoint (confirmed thrombotic events) as the “on drug” Kaplan-Meier plot in the published APPROVe article; and (ii) Kaplan-Meier plots, based on both the APTC and confirmed thrombotic endpoints, that extended out in time to 210 weeks (4 years).
- Dr. Curfman* also asked the authors to comment on how those new Kaplan-Meier plots affected “[their] post-hoc speculation in the original APPROVe article that the risk of cardiovascular events with rofecoxib did not appear until 18 months of drug exposure.”
- He requested that the authors comment on “whether the data meet the proportional hazards assumption under both rules (14-day censoring and ITT)” – in other words, provide p-values resulting from tests of the assumption that the hazard rates are proportional.
- Dr. Curfman* asked whether “the ‘cardiovascular analysis plan’ mentioned in the APPROVe study is different from the January 2003 statistical analysis plan [i.e., the Protocol 203 data analysis plan].”

⁴²⁹ 5/22/06 Letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574, at 74.

- Dr. Curfman* repeated Dr. Furberg's* question as to whether, when the APPROVe article was published, the complete data set was available to the authors for an intention-to-treat analysis.
- Dr. Curfman* asked the authors to provide data on the level of residual cardiovascular risk following discontinuation of treatment in APPROVe.
 - b. May 25 APPROVe Trial Administrative Committee meeting.

The issue of how to respond to the Furberg* and Nissen* letters was first discussed on May 25, 2006 at the regularly scheduled meeting of the APPROVe Trial Administrative Committee, which was composed of both Merck and external scientists who were responsible for overseeing the base and extension studies and providing ongoing input to Merck.⁴³⁰ In addition, Dr. Marvin Konstam* ; who was not a member of the Administrative Committee but had served by invitation as an external author of the APPROVe article, had been invited to attend the meeting and participated by telephone. Also in attendance were Dr. Bain, Mr. Bolognese, Mr. Cook, Dr. Oxenius, Dr. Reiss, and other individuals from Merck.⁴³¹

The main item on the planned agenda for the meeting had been been a discussion of hypertension issues in the APPROVe Trial,⁴³² but the meeting date fell just days after Dr. Bresalier* had received the Nissen* and Furberg* letters from Dr. Curfman* and after

⁴³⁰ Draft minutes of 5/25/06 APPROVe Administrative Committee meeting, MRK-ASP0000001, at 01. The role of the APPROVe Trial Administrative Committee is described more fully in Appendix Q.

⁴³¹ Draft minutes of 5/25/06 APPROVe Administrative Committee meeting, MRK-ASP0000001, at 01.

⁴³² Draft minutes of 4/25/06 APPROVe Administrative Committee Meeting, MRK-ARQ0002839, at 840; Draft presentation for 5/25/06 APPROVe Administrative Committee Meeting, MRK-ARQ0001016-44 (attached to 5/19/06 email from J. van Adelsberg to T. Reiss et al., MRK-ARQ0001015).

Merck had learned of the error in the APPROVe article concerning the description of the method Merck had used to test the proportional hazards assumption.⁴³³ As a result, those items dominated the discussion at the meeting.

i. The error in the APPROVe article.

The meeting began with a presentation by Mr. Cook of the preliminary results of the off-drug extension study, followed by a discussion of the error in the APPROVe article (discussed above in Section B of this Appendix).⁴³⁴ Dr. Bain and Mr. Bolognese had informed Dr. Baron*, the chair of the APPROVe Trial Administrative Committee and one of the lead authors of the APPROVe article, of the error in person earlier that week, but this was the Company's first opportunity to speak to the broader group of co-authors.

According to draft minutes of the meeting, Dr. Bain made a presentation regarding the nature of the error and "noted that this did not change the results of the study regarding changes in relative risk over time, including the results of the Kaplan-Meier plot and [the analysis of relative risk by time intervals]."⁴³⁵ Dr. Bain's presentation was followed by a scientific discussion of the error among those in attendance, including both Merck representatives and the external authors. Merck representatives told participants at the meeting that Merck planned to issue a press release about the error the following day. The external authors, however, felt that they had not

⁴³³ 5/22/06 letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574, at 74. The proportionality of hazard statistical test error is discussed above, in Section B of this Appendix.

⁴³⁴ Draft minutes of 5/25/06 APPROVe Administrative Committee meeting, MRK-ASP0000001, at 01.

⁴³⁵ Draft minutes of 5/25/06 APPROVe Administrative Committee meeting, MRK-ASP0000001, at 01.

had sufficient time to assess the scientific implications of the error and asked the Company to give them additional time before issuing the press release. Merck agreed to delay issuing the press release.

ii. Responding to the New England Journal of Medicine.

The participants at the meeting discussed how to respond to the questions raised by the New England Journal of Medicine and inform the Journal of the recently discovered error in the APPROVe article. After the issues raised in the Journal's letter were presented, the external authors discussed the matter in a closed session and emerged with the decision to write to the Journal separately from the Merck authors.⁴³⁶

The external authors we interviewed recalled various reasons why they decided to write a separate letter. According to Dr. Konstam^{*}, the external authors were initially torn as to whether they should write a separate response, but thought that a separate response from them might carry more weight since they were not employees of, or otherwise financially obligated to, Merck. Drs. Bresalier^{*} and Baron^{*} stated that the external authors had not been involved in preparing Merck's May 11, 2006 report to the FDA, which was the basis of the questions that had been raised by Drs. Nissen^{*} and Furberg^{*}, and therefore felt that Merck should respond separately to questions specific to it. Dr. Baron^{*} also recalled that the external authors did not want to get caught in the middle of tensions between the editors of the New England Journal of Medicine and Merck. According to Dr. Baron^{*}, the external authors were concerned that the Journal

⁴³⁶ Draft minutes of 5/25/06 APPROVe Administrative Committee meeting, MRK-ASP0000001, at 01.

had treated the external authors of the VIGOR article, which had recently been the subject of an “Expression of Concern” by the Journal,⁴³⁷ as though they were simply taking directions from Merck and they believed that writing a separate response was a good way for them to demonstrate their independence.

According to Dr. Theodore Reiss, a Merck scientist who was not involved in the closed session, the idea of sending separate letters stemmed from Dr. Nissen’s* comment that the “14-day toxicity censoring” in the base study was “unusual.”⁴³⁸ Dr. Reiss recalled that Dr. Baron* was concerned about his lack of familiarity with the regulatory underpinnings and Merck’s practices as to the 14-day censoring rule – two issues that Merck sought to raise in response to Dr. Nissen’s* assertion – and, as a result, suggested that these issues could best be addressed by Merck. Dr. Reiss noted that Merck did not object to the external authors’ decision.

c. Authors’ responses to the Furberg* and Nissen* letters.

On May 30, 2006, the external authors and Merck authors⁴³⁹ sent separate letters to the New England Journal of Medicine responding to the issues raised by Drs. Furberg*

⁴³⁷ Curfman* GD, Morrissey* S, Drazen* JM. Expression of concern: “Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis,” N Engl J Med. 2000;343:1520-8. [editorial]. N Engl J Med. 2005;353:2813-14; Curfman* GD, Morrissey* S, Drazen* JM. Expression of concern reaffirmed [editorial]. N Engl J Med. 2006;354:1193.

⁴³⁸ Undated letter from S. Nissen* to the editor of the New England Journal of Medicine, MRK-ASW0002576, at 76 (attached to 5/22/06 letter from G. Curfman* to R. Bresalier*, MRK-ASW0002574-75).

⁴³⁹ The Merck authors’ letter was signed by Dr. Oxenius and Mr. Bolognese on behalf of the MRL authors of the APPROVe article. 5/30/06 Letter from J. Bolognese and B. Oxenius to the editor of the New England Journal of Medicine, MRK-AQU0000001.

and Nissen^{*}.⁴⁴⁰ Both letters explained that comprehensive data on off-drug cardiovascular events was not available at the time the APPROVe article was written. Both letters also addressed the 14-day censoring rule used in the base study for cardiovascular events and reported on the recently discovered error in the APPROVe article. Unlike the external authors' letter, the Merck authors' letter cited external support for the 14-day censoring rule, provided some context for the error in the APPROVe article, and included a proposed correction. The two responses are discussed below.

i. External authors' response.

On May 30, 2006, Dr. Bresalier^{*} emailed Dr. Curfman^{*} a letter on behalf of the external authors of the APPROVe article responding to the issues raised by Drs. Furberg^{*} and Nissen^{*}.⁴⁴¹ The letter stated that the original APPROVe Trial protocol specified that patients would be followed only while they were on treatment and for 14 days after discontinuation, and that systematic toxicity follow-up beyond 14 days after discontinuation was initiated in the winter of 2004-2005 based on the cardiovascular findings reported in September 2004. Thus, the letter reported, the off-drug follow-up data were not available at the time the APPROVe article was published.⁴⁴²

⁴⁴⁰ 5/30/06 email from R. Bresalier^{*} to G. Curfman^{*} MRK-AQU0000007-08, attaching letter to the editor, MRK-AQU0000009-10; 5/30/06 Letter from J. Bolgonese and B. Oxenius to the editor of the New England Journal of Medicine, MRK-AQU0000001.

⁴⁴¹ 5/30/06 email from R. Bresalier^{*} to G. Curfman^{*}, MRK-AQU0000007-08, attaching letter to the editor, MRK-AQU0000009-10.

⁴⁴² Letter from R. Bresalier^{*} et al. to the editor of the New England Journal of Medicine, MRK-AQU0000009, at 09 (attached to 5/30/06 email from R. Bresalier^{*} to G. Curfman^{*},

Addressing Dr. Nissen's* characterization of the APPROVe Trial's 14-day censoring rule as "unusual," the external authors wrote: "Such follow-up is actually common and is usually conservative, since it avoids the dilution of a toxicity signal that may occur when an active drug is discontinued."⁴⁴³ The external authors stated that their Merck colleagues would discuss "the toxicity monitoring practices in the pharmaceutical industry and the rationale for them."⁴⁴⁴

Finally, the external authors noted that they had been informed of the error in the published APPROVe article relating to the description of the statistical test used to assess proportionality of hazards (discussed in Section B of this Appendix), and added:

It was stated [in the APPROVe article] that the modeling for the test of proportionality of hazards contained a treatment*log(time) term, with a p value of 0.014. That p value was actually derived from a model that used a treatment*time term. The p value using the treatment*log(time) term was 0.07. The main conclusion of the paper – that there is cardiovascular toxicity associated with rofecoxib – is unaffected, as is the post-hoc suggestion of differences over time in the rofecoxib relative

MRK-AQU0000007-08). Further, responding to Dr. Furberg's* request for information regarding a test for proportionality of hazards in the "three-year event data," the non-Merck authors answered that such a test was presented in the published APPROVe report. The letter stated that a similar test using three-year intention-to-treat data had not yet been performed, but that an in-depth analysis of the "extended experience of subjects in APPROVe" including "an independent statistical analysis of cardiovascular data" was underway. Id.

⁴⁴³ Letter from R. Bresalier* et al. to the editor of the New England Journal of Medicine, MRK-AQU0000009, at 09 (attached to 5/30/06 email from R. Bresalier* to G. Curfiman*, MRK-AQU0000007-08).

⁴⁴⁴ Letter from R. Bresalier* et al. to the editor of the New England Journal of Medicine, MRK-AQU0000009, at 09 (attached to 5/30/06 email from R. Bresalier* to G. Curfiman*, MRK-AQU0000007-08).

risks for thrombotic cardiovascular diseases in the
APPROVe trial.⁴⁴⁵

ii. Merck's response.

Also on May 30, 2006, Mr. Bolognese and Dr. Oxenius responded on behalf of the Merck authors of the APPROVe article to the questions the New England Journal of Medicine had raised and addressed the error in the APPROVe article.⁴⁴⁶

(a) Response to questions raised by
Drs. Nissen* and Furberg*.

The Merck authors' letter discussed in more detail the points addressed in the external authors' letter. It noted that the APPROVe Trial "was not designed to systematically collect these [cardiovascular] events off-therapy" and that, as a result, an analysis combining both on- and off-therapy events was not possible at the time the article was published.⁴⁴⁷ Further, the Merck authors' letter stated that "[a]nalyzes including all on- and off- therapy information are often less sensitive for the detection of safety signals than those including only on-therapy information, because they combine treatment-related observations with measurements off-drug that may no longer reflect

⁴⁴⁵ Letter from R. Bresalier* et al. to the editor of the New England Journal of Medicine, MRK-AQU0000009, at 10 (attached to 5/30/06 email from R. Bresalier* to G. Curfman*, MRK-AQU0000007-08).

⁴⁴⁶ 5/30/06 letter from J. Bolgonese and B. Oxenius to the editor of the New England Journal of Medicine, MRK-AQU0000001-02.

⁴⁴⁷ 5/30/06 letter from J. Bolgonese and B. Oxenius to the editor of the New England Journal of Medicine, MRK-AQU0000001, at 01.

treatment-related effect.”⁴⁴⁸ The letter stated that “regulatory guidance focuses on the duration of exposure to drug and not duration of off-drug follow-up” and that “unless there is evidence for delayed risk, collection of safety data should focus on the time on-drug and for a period off-drug consistent with drug exposure.”⁴⁴⁹ The Merck authors’ letter stated that these principles are consistent with Merck’s standard procedure for drugs such as NSAIDs, which is “to collect all safety data within 14-days of discontinuation of treatment.”⁴⁵⁰

⁴⁴⁸ 5/30/06 letter from J. Bolgonese and B. Oxenius to the editor of the New England Journal of Medicine, MRK-AQU0000001, at 01.

⁴⁴⁹ 5/30/06 letter from J. Bolgonese and B. Oxenius to the editor of the New England Journal of Medicine, MRK-AQU0000001, at 01 (citing ICH E1A: Guideline for Industry – The extent of population exposure to assess clinical safety: For drugs intended for long-term treatment of non-life-threatening conditions (1995); CIOMS VI: Management of Safety Information from Clinical Trials (2005)).

The ICH guidelines focus on the size of the study population and the duration of therapy necessary to assess the relationship between use of a drug and the occurrence of adverse events. See Guidelines for Industry – The Extent of Population Exposure to Assess Clinical Safety For Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions, ICH-E1A, March 1995. The report of the CIOMS Working Group VI, which was comprised of senior safety officials from major regulatory agencies and the pharmaceutical industry, as well as academics with experience in clinical trials, “recommends that in general, safety data event-collection should continue after the last dose of the drug for at least an additional five half-lives.” Management of Safety Information from Clinical Trials – Report of CIOMS Working Group VI (2005), at 15, 17, 96. The half-life of Vioxx is approximately 17 hours. See 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 29. The CIOMS VI report adds, however, that while the proposed rule might apply to most drugs, it might not be appropriate in all cases due to the diversity of drugs in development and patient-specific circumstances. As an example, the report notes that some agents may have delayed toxicity that need to be monitored over longer periods of time. Id. at 96.

⁴⁵⁰ 5/30/06 letter from J. Bolgonese and B. Oxenius to the editor of the New England Journal of Medicine, MRK-AQU0000001, at 01.

(b) Proportionality of hazards error and
proposed correction notice.

The letter from the Merck authors also noted the recently discovered error regarding the description of the proportionality of hazard test in the APPROVe article and proposed that the Journal publish the following correction to the “Methods, Statistical Analysis” section of the article:

<p align="center">Published APPROVe Article Methods Section⁴⁵¹</p>	<p align="center">Merck Authors’ Proposed Correction (5/30/06) Methods Section⁴⁵²</p>
<p>A test of the proportional-hazards assumption was specified in the cardiovascular-analysis plan. This was accomplished by evaluating the interaction between logarithm of time and the assigned treatment in the Cox proportional-hazards model.</p>	<p>A test of the proportional-hazards assumption was specified in the cardiovascular-analysis plan. This was accomplished by evaluating the interaction between time and the assigned treatment in the Cox proportional-hazards model.</p>

The Merck authors explained:

The context for this change is as follows: The cardiovascular data from the APPROVe trial was to be analyzed as part of a combined analysis plan with 2 additional trials (ViP, VICTOR). That plan called for multiple pre-specified, statistical and graphical methods to assess whether the relative risk of VIOXX compared to placebo was constant or if it changed over time (see attached). The use of the variable, logarithm of time, was the primary method specified. The reference to logarithm of time in the methods section of the manuscript and the corresponding regulatory submissions was in error. The reported result (p-value = 0.01) came from a method using linear time, not logarithm of time. Recent tests show that the result using logarithm of time has a p-value = 0.07. Results of diagnostics analyses indicate that a model using linear time is more representative of the data than one using logarithm of time. Thus the linear time analysis is an appropriate method to assess the changes in relative risk over time.

⁴⁵¹ Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 095.

⁴⁵² 5/30/06 letter from J. Bolgonese and B. Oxenius to the editor of the New England Journal of Medicine. MRK-AQU0000001, at 01.

In essence, the Merck authors requested that the word “logarithm” be removed from the sentence describing the proportional hazards test so that the Methods section would reflect the test – the “Linear Time Test” – that was actually used to generate the proportionality p-value presented in the Results section of the paper. The Merck authors did not propose to state the p-value for the result using logarithm of time or to change any of the conclusions or interpretive statements in the article regarding the proportionality of the hazard rate or shape of the Kaplan-Meier curves.

d. May 31, 2006 letter from the New England Journal of Medicine.

On May 31, 2006, Dr. Jeffrey Drazen^{*}, Editor-in-Chief of the New England Journal of Medicine, and Dr. Curfman^{*} sent Dr. Bresalier^{*} a letter acknowledging receipt of correspondence from both the external and the Merck authors.⁴⁵³ The editors did not, however, send a separate letter to the Merck authors, nor did they copy them on their letter to Dr. Bresalier^{*}. According to Dr. Reiss, around this time, Merck proposed a scientific discussion with representatives of the Journal about the error and its significance, but the editors declined and would communicate only with the external authors.⁴⁵⁴

i. Response to questions raised by Drs. Nissen^{*} and Furberg^{*}.

The editors notified Dr. Bresalier^{*} of their intent to publish the Furberg^{*} and Nissen^{*} letters, and asked that the external authors and the Merck authors send a single

⁴⁵³ 5/31/06 letter from J. Drazen^{*} and G. Curfman^{*} to R. Bresalier^{*}, MRK-AQU0000005-06.

⁴⁵⁴ The request for the scientific discussion was conveyed to the Journal editors by Dr. Baron.

response.⁴⁵⁵ At the end of the letter, the editors stated they understood that an additional outside statistical analysis was planned for the cardiovascular safety data, and acknowledged that “[m]any of the questions posed by Drs. Furberg and Nissen, as well as questions posed by us, can be answered only after this statistical analysis is performed.”⁴⁵⁶ The editors expressed their interest in reviewing the analysis when it was completed.⁴⁵⁷

ii. Proportionality of hazards error
and proposed correction notice.

The editors agreed that a correction was required as a result of the proportionality of hazards error and set forth a proposed correction notice. The editors did not accept the Merck authors’ proposed correction, which involved simply modifying the description of the specified proportional hazards test in the Methods section to match the test that was actually performed (the Linear Time Test). Instead, the correction proposed by the editors kept the Methods section intact while modifying the Results section to state the p-value that would have been generated had the test specified in the Methods section (the

⁴⁵⁵ 5/31/06 letter from J. Drazen* and G. Curfman* to R. Bresalier*, MRK-AQU0000005, at 05. The editors also proposed a few edits to the external authors’ letter. Id. at 06.

⁴⁵⁶ 5/31/06 letter from J. Drazen* and G. Curfman* to R. Bresalier*, MRK-AQU0000005, at 06. As mentioned above, the external authors May 30, 2006 letter had noted that an in-depth analysis of the “extended experience of subjects in APPROVe” including “an independent statistical analysis of cardiovascular data” was underway. Letter from R. Bresalier* et al. to the editor of the New England Journal of Medicine, MRK-AQU0000009, at 09 (attached to 5/30/06 email from R. Bresalier* to G. Curfman*, MRK-AQU0000007-08). The Administrative Committee retained Dr. David DeMets* of the University of Wisconsin to conduct this independent analysis.

⁴⁵⁷ 5/31/06 letter from J. Drazen* and G. Curfman* to R. Bresalier*, MRK-AQU0000005, at 06.

Logarithm of Time Test) been performed.⁴⁵⁸ The editors' proposed modification to the Results section follows:

Published APPROVe Article Results Section⁴⁵⁹	Editors' Proposed Correction (5/31/06) Results Section⁴⁶⁰
<p>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 (Fig. 2 and Table 3). The changing pattern of the treatment effect over time was confirmed by a failed test for proportionality of hazards (P=0.01). Findings for the APTC end point were similar (Table 3).</p>	<p>In a post-hoc assessment, visual inspection of Figure 2 suggested that the Kaplan-Meier curves separated 18 months after randomization. However, the results of an overall test of the proportional-hazards assumption for the entire 36-month observation period did not reach statistical significance (P=0.07).</p>

The editors' proposed correction also listed various conclusions and interpretive statements relating to the assertion of delayed onset of increased cardiovascular risk that they wanted revised or removed from the article because of the error and the corrected results. Specifically, they proposed that "statements regarding an increase in risk after 18 months should be removed from the Abstract . . . and from the Discussion section" and that a passage in the Discussion section be changed as follows:⁴⁶¹

⁴⁵⁸ 5/31/06 letter from J. Drazen* and G. Curfman* to R. Bresalier*, MRK-AQU0000005, at 05.

⁴⁵⁹ Bresalier* RS, Sandler* RS, Quan H, *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med.* 2005;352:1092-102, at 097.

⁴⁶⁰ 5/31/06 letter from J. Drazen* and G. Curfman* to R. Bresalier*, MRK-AQU0000005, at 05.

⁴⁶¹ 5/31/06 letter from J. Drazen* and G. Curfman* to R. Bresalier*, MRK-AQU0000005, at 05.

Published APPROVe Article Discussion Section ⁴⁶²	Editors' Proposed Correction (5/31/06) Discussion Section ⁴⁶³
<p>In our randomized, placebo-controlled trial, we found an increased risk of confirmed thrombotic events associated with the long-term use of rofecoxib. The increase in adjudicated thrombotic events associated with rofecoxib therapy was not evident during the first 18 months of the trial.</p>	<p>In our randomized, placebo-controlled trial, we found an increased risk of confirmed thrombotic events associated with the use of rofecoxib. Visual inspection of the Kaplan-Meier curves suggested that there was an increased frequency of thrombotic events associated with rofecoxib therapy after 18 months.</p>

- e. Further correspondence between the New England Journal of Medicine and the APPROVe article authors concerning the correction notice.

- i. June 9, 2006 letter from all APPROVe article authors.

On June 9, 2006, Drs. Bresalier* and Baron* submitted a letter to the New England Journal of Medicine editors on behalf of all authors of the APPROVe article. This letter provided a counterproposal to the editors' proposed correction notice.⁴⁶⁴

Like the Merck authors' original proposed correction, the APPROVe article authors' new proposed correction altered the Methods section of the article. The correction stated that a "battery" of proportionality tests were specified in the cardiovascular analysis plan and that, while the Logarithm of Time Test was listed as

⁴⁶² Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 100.

⁴⁶³ 5/31/06 letter from J. Drazen* and G. Curfman* to R. Bresalier*, MRK-AQU0000005, at 05.

⁴⁶⁴ Letter from the Authors of the APPROVe Trial to the editor of the New England Journal of Medicine, MRK-ARQ0007328-30 (attached to 6/9/06 email from R. Bresalier* to G. Curfman*, MRK-ARQ0007326-27). According to Dr. Baron*, the text of the letter was suggested by Mr. Bolognese on a conference call that took place on June 8, 2006. The final letter was later agreed to by all APPROVe authors.

“primary,” the Linear Time Test was also carried out. The APPROVe article authors’ proposed correction to the Methods section was as follows:

Published APPROVe Article Methods Section⁴⁶⁵	APPROVe Article Authors’ Proposed Correction (6/9/06) Methods Section⁴⁶⁶
<p>A test of the proportional-hazards assumption was specified in the cardiovascular-analysis plan. This was accomplished by evaluating the interaction between logarithm of time and the assigned treatment in the Cox proportional-hazards model.</p>	<p>The cardiovascular analysis plan specified a battery of statistical assessments of the proportional hazards assumption. Among these was a test of the interaction between logarithm of time and the assigned treatment in the Cox proportional hazards model, which was designated as primary (i.e., the initial test of the battery of statistical assessments), as well as graphical assessments of HR over time, computation of HR by time interval, and other diagnostic assessments. Among the other diagnostic assessments, a test of the interaction between (linear) time and assigned treatment was also carried out.</p>

In addition, the new proposed correction included a short modification to the Results section. Instead of simply replacing the published proportionality p-value from the Linear Time Test with the p-value from the Logarithm of Time Test, as the New England Journal of Medicine editors had proposed, the APPROVe article authors proposed to include both p-values in the corrected version. The APPROVe article authors’ proposed correction to the Results section was as follows:

⁴⁶⁵ Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1095.

⁴⁶⁶ Letter from the Authors of the APPROVe Trial to the editor of the New England Journal of Medicine, MRK-ARQ0007328, at 328 (attached to 6/9/06 email from R. Bresalier* to G. Curfman* MRK-ARQ0007326-27).

<p align="center">Published APPROVe Article Results Section⁴⁶⁷</p>	<p align="center">APPROVe Article Authors' Proposed Correction (6/9/06) Results Section⁴⁶⁸</p>
<p>The changing pattern of the treatment effect over time was confirmed by a failed test for proportionality of hazards (P=0.01).</p>	<p>The changing pattern of the treatment effect over time was not statistically significant by the test for proportionality of hazards based on logarithm of time (P=0.07), but was confirmed by the failed test of proportionality of hazards based on linear time (P=0.01).</p>

The authors of the APPROVe article did not propose altering the Discussion section or changing any of their conclusions or interpretive statements regarding the apparent increase in cardiovascular risk beginning only after 18 months on treatment.

The APPROVe article authors' letter provided their rationale for the proposed changes and for their decision not to propose changes to their conclusions or other interpretive statements. The letter explained that because the APPROVe Trial did not itself have a specific cardiovascular data analysis plan, Merck's assessment of cardiovascular data, including the assessment of the proportional hazards assumption, "proceeded in a manner consistent with good statistical practice and guided by the DAP [data analysis plan] for Protocol 203," which was a study designed to demonstrate the cardiovascular non-inferiority of Vioxx to placebo by analyzing the combined

⁴⁶⁷ Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1097.

⁴⁶⁸ Letter from the Authors of the APPROVe Trial to the editor of the New England Journal of Medicine, MRK-ARQ0007328, at 328-29 (attached to 6/9/06 email from R. Bresalier* to G. Curfman*, MRK-ARQ0007326-27).

cardiovascular data from three placebo-controlled studies (including the APPROVe Trial).⁴⁶⁹

According to the letter from the authors of the APPROVe article, the Data Analysis Plan for Protocol 203 called for a “battery” of tests of the proportional hazards assumption.⁴⁷⁰ In this context, the letter stated, the use of the word “primary” to describe the Logarithm of Time Test simply meant that it would be the “initial” approach of many.⁴⁷¹

The letter noted that many assessments “aimed at modeling the [hazard ratio] over time” were performed and that the “Cox model with terms for treatment and treatment-by-time interaction [*i.e.*, the Linear Time Test] fit the [hazard ratio] over time data better than one with terms for treatment and treatment-by-logarithm(time) [*i.e.*, the Logarithm

⁴⁶⁹ Letter from the Authors of the APPROVe Trial to the editor of the New England Journal of Medicine, MRK-ARQ0007328, at 329 (attached to 6/9/06 email from R. Bresalier* to G. Curfman*, MRK-ARQ0007326-27).

⁴⁷⁰ According to the APPROVe authors’ letter, the assumption of a constant hazards ratio over time, which underlay the non-inferiority hypothesis of Protocol 203, could never actually be proven. Thus, the purpose of the battery of statistical assessments specified in the Statistical Data Analysis Plan for Protocol 203 was to show that there was no substantial evidence that was inconsistent with that assumption. Letter from the Authors of the APPROVe Trial to the editor of the New England Journal of Medicine, MRK-ARQ0007328, at 329 (attached to 6/9/06 email from R. Bresalier* to G. Curfman*, MRK-ARQ0007326-27).

⁴⁷¹ Letter from the Authors of the APPROVe Trial to the editor of the New England Journal of Medicine, MRK-ARQ0007328, at 330 (attached to 6/9/06 email from R. Bresalier* to G. Curfman*, MRK-ARQ0007326-27). Dr. Marvin Konstam*, however, said that he was out of the country when the final letter was submitted, and when interviewed he did not agree with this interpretation of “primary.”

of Time Test].”⁴⁷² The letter then noted that the result using the better fitting model, the Linear Time Test, supported a non-constant hazard ratio over time.⁴⁷³

The APPROVe article authors’ letter also listed other factors that persuaded them that there was a non-constant hazard ratio over time. Those factors included an analysis of risk ratios in the APPROVe trial by 6-month intervals and the visual appearance of the Kaplan-Meier curves. Based on these factors, the APPROVe article authors stated that they did not believe further changes to the manuscript were warranted.⁴⁷⁴

- ii. June 12, 2006 letter from the editors
with second proposed correction notice.

By letter dated June 12, 2006 Drs. Drazen* and Curfman* rejected the APPROVe article authors’ proposed corrections⁴⁷⁵ and proposed an alternative that was identical to their May 31, 2006 proposal but added language to make it even more clear that, in their view, the statements in the published article suggesting a delayed onset of cardiovascular risk at 18 months were not statistically supported. The editors’ new proposed alteration

⁴⁷² Letter from the Authors of the APPROVe Trial to the editor of the New England Journal of Medicine, MRK-ARQ0007328, at 329-30 (attached to 6/9/06 email from R. Bresalier* to G. Curfman*, MRK-ARQ0007326-27).

⁴⁷³ The letter referred to a January 27, 2005 memorandum by Drs. Jennifer Ng and Hongwei Wang, which plotted the data using various proportional hazards models, which, according to the letter, demonstrated non-constant hazard over time. Letter from the Authors of the APPROVe Trial to the editor of the New England Journal of Medicine, MRK-ARQ0007328, at 330 (attached to 6/9/06 email from R. Bresalier* to G. Curfman* MRK-ARQ0007326-27).

⁴⁷⁴ Letter from the Authors of the APPROVe Trial to the editor of the New England Journal of Medicine, MRK-ARQ0007328, at 330 (attached to 6/9/06 email from R. Bresalier* to G. Curfman*, MRK-ARQ0007326-27).

⁴⁷⁵ 6/12/06 letter from J. Drazen* and G. Curfman* to APPROVe Authors, MRK-AQU0000104, at 04. The letter was physically sent to Dr. Bresalier*.

to the Discussion section is presented below, next to the published text and the editors’ first proposed alteration (with the newly added language in italics):

Published APPROVe Article Discussion Section⁴⁷⁶	Editors’ First Proposed Correction (5/31/06) Discussion Section⁴⁷⁷	Editors’ Second Proposed Correction (6/12/06) Discussion Section⁴⁷⁸
<p>In our randomized, placebo-controlled trial, we found an increased risk of confirmed thrombotic events associated with the long-term use of rofecoxib. The increase in adjudicated thrombotic events associated with rofecoxib therapy was not evident during the first 18 months of the trial.</p>	<p>In our randomized, placebo-controlled trial, we found an increased risk of confirmed thrombotic events associated with the use of rofecoxib. Visual inspection of the Kaplan-Meier curves suggested that there was an increased frequency of thrombotic events associated with rofecoxib therapy after 18 months.</p>	<p>In our randomized, placebo-controlled trial, we found an increased risk of confirmed thrombotic events associated with the use of rofecoxib. <i>Although post hoc</i> visual inspection of the Kaplan-Meier curves suggested that there was an increased frequency of thrombotic events associated with rofecoxib therapy after 18 months, <i>the fact that the test of the proportional-hazards assumption failed puts any conclusion of a time-differential response on uncertain grounds.</i></p>

The editors stated that the evidence supporting “a divergence in risks 18 months after the start of therapy” was tenuous to begin with and that, in 2005, the editors had been “persuaded to publish these statements in part because of the [statistically

⁴⁷⁶ Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 100.

⁴⁷⁷ 5/31/06 letter from J. Drazen* and G. Curfman* to R. Bresalier*, MRK-AQU0000005, at 05.

⁴⁷⁸ 6/12/06 letter from J. Drazen* and G. Curfman* to APPROVe Authors, MRK-AQU0000104, at 05. This proposed correction referred to a “failed” test of the proportional hazards assumption to indicate that the result was not statistically significant and, thus, that there was insufficient evidence to reject the assumption of proportional hazards over time. The Journal editors used this same phrasing to indicate that there had been a significant result elsewhere in the same letter. Id.

significant result from] tests for proportional hazards”⁴⁷⁹ The editors interpreted “the error on the part of [Merck] statisticians” to mean that the proportional hazards test had not in fact failed (because the p-value for the Logarithm of Time Test was 0.07, which is greater than the threshold for significance of $p=0.05$ specified in the Protocol 203 Statistical Data Data Analysis Plan) and stated that this fact necessitated changes to the statements in the text relating to the claim of a divergence in risk beginning after 18 months.⁴⁸⁰

Further, the editors noted that, while the cardiovascular analysis plan (for Protocol 203) listed many techniques for assessing the proportional hazards assumption, they could not find any mention of using the Linear Time Test as a primary analysis.⁴⁸¹ Therefore, they were unwilling to list the results of the Linear Time Test, and concluded: “We do not know how many tests you have tried in search of ones that were especially ‘significant’; thus, it makes scientific sense to stick to the planned analysis.”⁴⁸²

⁴⁷⁹ 6/12/06 letter from J. Drazen* and G. Curfman* to APPROVe Authors, MRK-AQU0000104, at 05.

⁴⁸⁰ 6/12/06 letter from J. Drazen* and G. Curfman* to APPROVe Authors, MRK-AQU0000104, at 05.

⁴⁸¹ 6/12/06 letter from J. Drazen* and G. Curfman* to APPROVe Authors, MRK-AQU0000104, at 05-06.

⁴⁸² 6/12/06 letter from J. Drazen* and G. Curfman* to APPROVe Authors, MRK-AQU0000104, at 06.

iii. APPROVe article authors' response to the
New England Journal of Medicine editors'
second proposed correction notice.

The APPROVe external authors discussed by email how to respond to the New England Journal of Medicine editors' June 12, 2006 letter.⁴⁸³ Dr. Baron* wrote on June 12, 2006: "Looks like they are insisting on their own text. Perhaps the best thing is to let the Journal publish their correction[;] at least it will be labeled as theirs. Then we can write a letter or present a different version in another journal."⁴⁸⁴ On or before June 15, 2006, Dr. Bresalier* contacted Dr. Curfman* and came to the understanding that the New England Journal of Medicine would publish, without attribution, a slight variation of the editors' initial proposed correction as set forth in their May 31, 2006 letter.⁴⁸⁵ According to Dr. Bresalier*, the Merck authors were aware that he was in contact with the Journal's editors in an attempt to resolve the matter. However, a draft letter to the editor circulated internally at Merck on June 16, 2006 began: "The correction notice from Dr. Bresalier of

⁴⁸³ 6/12/06 email from R. Bresalier* to J. Baron*, R. Sandler*, D. Morton*, A. Lanas*, R. Riddell*, and M. Konstam*, MRK-AQU0000102, at 102; 6/12/06 email from J. Baron* to R. Bresalier*, R. Sandler*, D. Morton*, A. Lanas*, R. Riddell* and M. Konstam*, MRK-AQU0000101; 6/13/06 email from M. Konstam* to J. Baron*, R. Bresalier*, R. Sandler*, D. Morton*, A. Lanas* and R. Riddell*, MRK-AQU0000097, at 97.

⁴⁸⁴ 6/12/06 email from J. Baron* to R. Bresalier*, R. Sandler*, D. Morton*, A. Lanas*, R. Riddell* and M. Konstam*, MRK-AQU0000101.

⁴⁸⁵ See 6/15/06 email from R. Bresalier* to G. Curfman*, MRK-AQU0000108, at 108-110; 6/17/06 email from G. Curfman* to R. Bresalier*, MRK-AQU0000119, at 119 (confirming publication without attribution).

In his email confirming their understanding, Dr. Bresalier* explained to Dr. Curfman* that because wording regarding the differences in relative risks over time for adjudicated thrombotic events would be deleted from the abstract, similar wording in the abstract regarding timing of separation between groups for non-adjudicated investigator-reported events also needed to be deleted. 6/15/06 email from R. Bresalier* to G. Curfman*, MRK-AQU0000108, at 108-09.

June 15, 2006, does not represent the views of the Merck authors. We regret that this was sent without our consent or knowledge.”⁴⁸⁶ It was decided not to send the letter after Dr. Bresalier* confirmed with Dr. Curfman* that the correction was to be published without attribution.

f. Further correspondence concerning the authors’ responses to the Furberg* and Nissen* letters.

As discussed above, on May 30, 2006, the APPROVe article authors initially sent two separate responses to the New England Journal of Medicine – one from the Merck authors and one from the external, non-Merck authors.⁴⁸⁷ These letters responded to the questions raised by the Furberg* and Nissen* letters, in particular whether the intention-to-treat analysis affected the APPROVe base study’s conclusions. On May 31, 2006, the Journal editors responded that a single letter from all authors would be required for publication.⁴⁸⁸

i. June 8, 2006 letter from APPROVe article external authors.

Notwithstanding the editors’ request for a single letter, on June 8, 2006, the external authors submitted to the Journal a slightly revised letter addressing the Furberg*

⁴⁸⁶ See draft letter to G. Curfman*, MRK-ARQ0007827, at 827 (attached to 6/16/06 email from P. Huang to J. Bolognese, et al., MRK-ARQ0007826).

⁴⁸⁷ Letter from R. Bresalier* et al. to the editor of the New England Journal of Medicine, MRK-AQU0000009, at 09 (attached to 5/30/06 email from R. Bresalier* to G. Curfman*, MRK-AQU0000007-08); 5/30/06 Letter from J. Bolognese and B. Oxenius to the editor of the New England Journal of Medicine, MRK-AQU0000001, at 02.

⁴⁸⁸ 5/31/06 letter from J. Drazen* and G. Curfman* to R. Bresalier*, MRK-AQU0000005, at 05.

and Nissen* letters.⁴⁸⁹ Like the external authors' May 30, 2006 letter, this letter stated that the original APPROVe Trial protocol included adverse event follow-up of patients only during treatment and for 14-days afterward, and that systematic follow-up of events more than 14-days after discontinuation was initiated in the winter of 2004-2005 and was motivated by the cardiovascular findings first reported in September 2004.⁴⁹⁰ Also, commenting on Dr. Nissen's* characterization of the APPROVe Trial's "unusual" 14-day censoring rule, the external authors reiterated that such follow-up is common and conservative, and left further elaboration to their Merck colleagues.⁴⁹¹

ii. June 9, 2006 letter from the Merck authors.

The next day, June 9, 2006, the Merck authors also submitted to the New England Journal of Medicine editors a revised version of their May 30, 2006 response letter, and asked that it be published alongside that of the external authors.⁴⁹² Like their previous letter, the June 9, 2006 letter concurred with the points made by Dr. Bresalier*. In particular, the Merck authors reiterated that the APPROVe study was designed to evaluate the effect of treatment with Vioxx on colon polyps and had the objective of

⁴⁸⁹ Letter from R. Bresalier* et al. to the editor of the New England Journal of Medicine, MRK-ARQ0007348-49 (attached to 6/12/06 email from R. Bresalier* to T. Reiss, MRK-ARQ0007347); see also 6/9/06 email from J. Bolognese to J. Lahner et al., MRK-ARQ0007254.

⁴⁹⁰ Letter from R. Bresalier* et al. to the editor of the New England Journal of Medicine, MRK-ARQ0007348, at 348 (attached to 6/12/06 email from R. Bresalier* to T. Reiss, MRK-ARQ0007347).

⁴⁹¹ Letter from R. Bresalier* et al. to the editor of the New England Journal of Medicine, MRK-ARQ0007348, at 348 (attached to 6/12/06 email from R. Bresalier* to T. Reiss, MRK-ARQ0007347).

⁴⁹² 6/9/06 email from J. Bolognese to G. Curfman* attaching letter to the editor, MRK-ARQ0007338-40.

collecting on-therapy safety data; the APPROVe study was not designed to systematically collect cardiovascular events off-therapy.⁴⁹³ The Merck authors again noted their view that “[a]nalyzes including all on- and off- therapy information are often less sensitive for the detection of safety signals than those including only on-therapy information, because they combine treatment-related observations with measurements off-drug that may no longer reflect treatment-related effects.”⁴⁹⁴

In contrast to their May 30, 2006 letter to the editors of the Journal, however, the June 8, 2006 letter from the Merck authors did not discuss in detail the discovery of the error or set forth a proposed correction notice. Instead, the Merck authors’ letter mentioned the discovery of the error in the article and noted that a correction notice was being submitted separately.⁴⁹⁵

iii. June 12, 2006 response from the Journal editors.

In response to both the external authors and the Merck authors, on June 12, 2006, Drs. Drazen* and Curfman* sent a letter to Dr. Bresalier* reiterating their request that the APPROVe article authors provide a single response.⁴⁹⁶ The editors called attention to the fact that the APPROVe article was written by a group of joint authors and contained a

⁴⁹³ 6/8/06 letter from J. Bolognese et al. to the editor of the New England Journal of Medicine, MRK-ARQ0007339, at 39.

⁴⁹⁴ 6/8/06 letter from J. Bolognese et al. to the editor of the New England Journal of Medicine, MRK-ARQ0007339, at 39.

⁴⁹⁵ 6/8/06 letter from J. Bolognese et al. to the editor of the New England Journal of Medicine, MRK-ARQ0007339, at 39.

⁴⁹⁶ 6/12/06 letter from J. Drazen* and G. Curfman* to R. Bresalier*, MRK-AQU0000014, at 14.

statement that the investigators – i.e., the external authors – had full access to the data.⁴⁹⁷

The editors also attached a copy of the International Committee of Medical Journal Editors' joint editorial, "Sponsorship, Authorship and Accountability," stating that external authors were responsible for the content of articles published in collaboration with commercial sponsors.

On these bases, Drs. Drazen* and Curfman* concluded that the external authors were fully accountable for the content of the article and the New England Journal of Medicine wanted a single letter responding to the Furberg* and Nissen* letters. The deadline for this response was the close of business on Friday, June 16, 2006.

iv. June 15, 2006 response from all APPROVe article authors.

On June 15, 2006, Dr. Bresalier* emailed Dr. Curfman* a letter, signed by Drs. Bresalier* and Baron* on behalf of all of the APPROVe article authors, responding to the Furberg* and Nissen* letters.⁴⁹⁸ The letter was substantively very similar to the letter the external authors originally submitted on May 30, 2006 and mentioned the proportionality of hazards test error in the APPROVe article.

g. June 26, 2006 online publication in the New England Journal of Medicine of the letters to the editor and the correction notice.

On June 26, 2006, the New England Journal of Medicine posted on its website Drs. Nissen's* and Furberg's* letters to the editor, the response letter by Drs. Bresalier*

⁴⁹⁷ 6/12/06 letter from J. Drazen* and G. Curfman* to R. Bresalier* MRK-AQU0000014, at 14.

⁴⁹⁸ 6/15/06 email from R. Bresalier* to G. Curfman* attaching letter to the editor, MRK-AQU0000111-12, 115-116.

and Baron* on behalf of the APPROVe article authors, and the notice of a correction to the March 2005 APPROVe article, which was posted without attribution.⁴⁹⁹ These letters and the correction notice were subsequently published in the July 13, 2006 print version of the New England Journal of Medicine.⁵⁰⁰

The published correction notice was identical to the initial proposed correction that the New England Journal of Medicine editors sent to the APPROVe article authors on May 31, 2006, not the June 12, 2006 revised version. Below is the correction, as it appeared in the Journal:

⁴⁹⁹ Adverse Cardiovascular Effects of Rofecoxib, www.nejm.org (updated June 28, 2006). We did not interview Drs. Curfman* or Drazen* in connection with our investigation, but it is clear from documentary evidence that the relationship between the New England Journal of Medicine and Merck is strained. For example, a few days after publishing the notice of correction, the editors of the journal sent Dr. Baron* a letter notifying him that the paper on the efficacy results of the APPROVe Trial, which had been on track for publication in the journal, would no longer be considered unless the data were re-analyzed by someone outside of Merck. 6/30/06 letter from J. Drazen* to J. Baron*, MRK-ASW0005714; 6/26/06 email from M.B. Hamel* to J. Baron*, MRK-AFO0300157. This new requirement, which suddenly had been raised by the editors in a phone conversation with Dr. Baron* the previous day, was based on a number of concerns posited by the editors including the fact that Merck had publicly stated its disagreement with the journal's notice of correction. In an email to Dr. Bresalier*, Dr. Baron* stated that "[t]he Journal's concern is that we are withholding data – not necessarily because we are not disclosing something we haven't disclosed, but because we may not have asked the right questions of Merck." 6/29/06 email from J. Baron* to R. Bresalier* et al., MRK-ASW0005710-11.

⁵⁰⁰ Furberg* CD. [letter]. N Engl J Med. 2006; 355:204; Nissen* SE. [letter]. N Engl J Med. 2006; 355:203-04; Bresalier* RS, Baron* JA. [letter]. 2006; 355:204-205; [Correction]. N Engl J Med. 2006; 355:221.

CORRECTION

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial (March 17, 2005;352:1092-102). In the reported results, the test for proportionality of hazards used linear time rather than the logarithm of time that was specified in the Methods section. Analysis using the logarithm of time leads to the following changes:

The first complete paragraph on page 1097 should have read, "In a post hoc assessment, visual inspection of Figure 2 suggested that the Kaplan-Meier curves separated 18 months after randomization. However, the results of an overall test of the proportional-hazards assumption for the entire 36-month observation period did not reach statistical significance ($P=0.07$)."

Therefore, statements regarding an increase in risk after 18 months should be removed from the Abstract (the sentence "The increased relative risk became apparent after 18 months of treatment; during the first 18 months, the event rates were similar in the two groups" should be deleted, as should the sentence beginning "There was earlier separation . . .") and from the Discussion section (the sentence "In post hoc analyses, the increased relative risk of adjudicated thrombotic events was first observed after approximately 18 months of treatment" should be deleted).

In addition, the first full paragraph on page 1100 should have read, "In our randomized, placebo-controlled trial, we found an increased risk of confirmed thrombotic events associated with the use of rofecoxib. Visual inspection of the Kaplan-Meier curves suggested that there was an increased frequency of thrombotic events associated with rofecoxib therapy after 18 months. Other investigators reported . . ."

2. Dr. Lagakos^{*} "Perspective" Article.

Alongside the letters from Drs. Furberg^{*} and Nissen^{*}, the response by the APPROVe article authors, and the correction to the APPROVe article, the New England Journal of Medicine published a "Perspective" article by Dr. Stephen Lagakos^{*}, a professor of biostatistics at the Harvard School of Public Health and a statistical consultant to the Journal. This article, which Dr. Lagakos^{*} prepared at the request of the Journal's editors, set forth Dr. Lagakos^{*} views concerning three issues presented by the letters and correction:

- how to determine the appropriate amount of time after discontinuation of treatment that safety data should be collected in clinical trials;
- how to assess the constancy of hazard ratio over time; and
- the inferences concerning short-term drug use that may be made from data on long-term drug use.

This section summarizes Dr. Lagakos’* article with respect to these three issues.

With regard to the first issue – setting the length of post-discontinuation follow-up – Dr. Lagakos* identified a number of considerations that bear on the appropriate amount of follow-up time. He began by noting the reasons why using a follow-up period shorter than the planned course of treatment (like the 14-day period used in the APPROVe base study) may be advisable:

There are several reasons why using such windows might be desirable. First, events occurring during treatment or the subsequent window may be the most relevant clinically for assessing the safety of the treatment. Second, any increased risk attributable to the treatment might diminish shortly after the discontinuation of treatment, so that power of the log-rank or Cox test might be diluted if events that occurred after the window period were counted. And third, patients might receive other therapy after discontinuation of the study treatment that could affect their risk of a safety endpoint.⁵⁰¹

Next, Dr. Lagakos* identified what in his view are the key considerations in setting the length of this follow-up period. At the most basic level, Dr. Lagakos* wrote, the optimal length of follow-up time depends on “the way in which the relative risk of the outcome

⁵⁰¹ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 113.

changes during treatment and after the discontinuation of treatment.”⁵⁰² Dr. Lagakos*

also noted that uneven discontinuations between treatment groups was an important consideration:

For example, if the treatment (in this case, rofecoxib) causes a side effect that increases the likelihood of both the discontinuation of treatment and the outcome event, then following these patients for a short time (say ... 14 days) after discontinuation might cause a real difference to be obscured by the differential exclusion of events that occur in the treatment group after the 14-day window.⁵⁰³

He further noted that 32% of the patients taking Vioxx in the APPROVe base study as opposed to 25% of those taking placebo discontinued.⁵⁰⁴ In light of this uneven discontinuation rate, Dr. Lagakos* concluded that “the premature discontinuations may have biased the Kaplan-Meier estimates of cumulative incidence . . . and the estimated relative risk associated with treatment.”⁵⁰⁵

With regard to assessing the constancy of the hazard ratio over time, Dr. Lagakos* first identified the most common methods for testing the assumption of proportional hazards as well as proposed a method for investigating the change in hazard ratio further. According to Dr. Lagakos*, “[t]he most common analytic way of testing the proportional-

⁵⁰² Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 114.

⁵⁰³ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 114.

⁵⁰⁴ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 114.

⁵⁰⁵ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 114.

hazards assumption is by fitting a Cox model with one term representing the treatment group and another term representing an interaction between the treatment group and either time or the logarithm of time” – i.e., by the Linear Time Test or the Logarithm of Time Test.⁵⁰⁶ With regard to interpreting the results from these tests, Dr. Lagakos* wrote, “rejection of the proportional hazards assumption [i.e., a significant p-value] does not mean that the true relative risk follows the form assumed in an expanded Cox model, nor does the failure to reject the assumption [i.e., an insignificant p-value] necessarily mean that the assumption holds.”⁵⁰⁷

Dr. Lagakos* expressed the view that when there is an indication that the hazard ratio is not constant over time, “visual inspection of the Kaplan-Meier curves for the treatment groups can be misleading and should be avoided.”⁵⁰⁸ Instead, Dr. Lagakos* proposed examining “confidence bands.” The approach he described involves plotting an area centered on the difference in cumulative incidence between the two treatment groups

⁵⁰⁶ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 114.

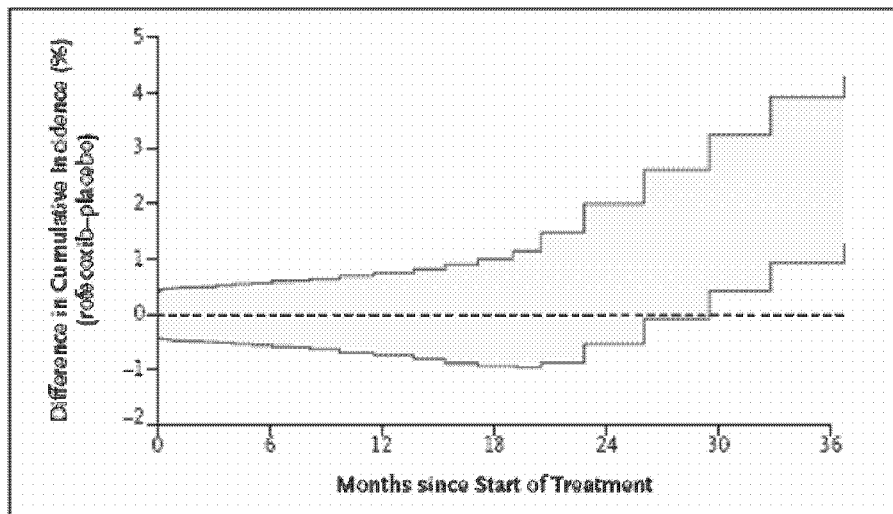
⁵⁰⁷ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 115.

⁵⁰⁸ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 115.

over time.⁵⁰⁹ Dr. Lagakos^{*} article included a hypothetical plot of this kind for the APPROVe Trial data, reproduced below:⁵¹⁰

Figure 19

Confidence Bands Showing Difference in Cumulative Risk
Between Vioxx and Placebo in Hypothetical Clinical Trial



The upper and lower boundaries of the plotted area represent the upper and lower bounds of the 95% confidence interval (i.e., the 5% margin of error) around the difference in cumulative incidence at each point in time. Any point within the shaded area represents a value for the difference in cumulative incidence between the treatment groups that is consistent with the hypothetical data set.

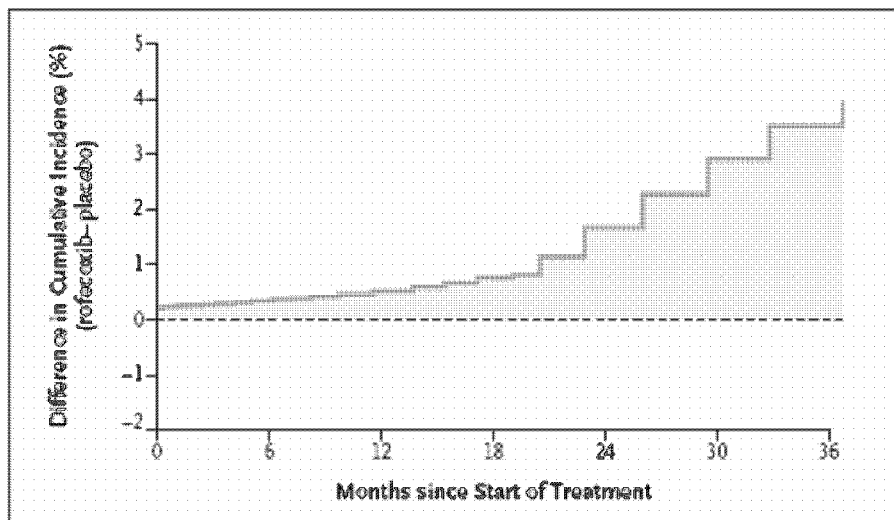
⁵⁰⁹ Lagakos^{*} SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 115.

⁵¹⁰ Lagakos^{*} SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, Figure 1 at 115.

Finally, Dr. Lagakos* discussed what inferences concerning short-term use of Vioxx could be drawn from the long-term data from the APPROVe Trial. Again, Dr. Lagakos* concluded that the confidence band approach was the best method for drawing this inference. For these purposes, Dr. Lagakos* assumed monotonicity – that the risk over a 12-month course of treatment is at least as high as that of placebo and is no greater than the risk during a 36-month course of treatment.⁵¹¹ Figure 20 below represents the confidence band approach to this question based on the same hypothetical data set as in Figure 19 above.⁵¹²

Figure 20

Confidence Band Approach to Assessing Excess Risk of Vioxx
Based on Hypothetical Clinical Trial Data



⁵¹¹ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 116.

⁵¹² Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, Figure 3 at 117.

This plot includes only the top half of the confidence band in the first plot, thus reflecting the assumption of monotonicity. The bottom of the shaded area aligns with zero, indicating no increase in cumulative incidence on Vioxx. The top of the confidence band is identical to the top of the confidence band in Figure 19, indicating that, all else equal, the risk during a 12-month course should not be different than the risk during the first 12 months of a 36-month course. Overall, the plot indicates that there may be no difference in cumulative incidence over the first twelve months, but also that there may be an increased risk. As Dr. Lagakos* concluded:

When applied to the data from the APPROVe trial, a confidence band . . . would provide a plausible range of excess risks associated with a shorter (less than 18 months) course of rofecoxib. If all the differences represented in this band were clinically unimportant, one could conclude that the data were inconsistent with a clinically important increase in risk for the shorter course of rofecoxib. However, since the band would necessarily include the estimated excess risk associated with the 36-month course reflected in Figure 2 of the original APPROVe trial, one could not conclude that a shorter course of rofecoxib is safe.⁵¹³

3. June 26, 2006 Open Letter from Merck.

On June 26, 2006, the same day that the New England Journal of Medicine published online the correction to the APPROVe article, Merck posted on its website an open letter to the scientific community from Dr. Peter Kim, president of MRL (the “Open Letter”). The purpose of the Open Letter was to provide Merck’s response to the

⁵¹³ Lagakos* SW. Time-to-event analyses for long-term treatments – the APPROVe Trial. N Engl J Med. 2006;355:113-17, at 117.

correction published in the New England Journal of Medicine. The Open Letter attached a detailed assessment of the error in the APPROVe manuscript prepared by MRL scientists (the “Assessment”). These documents, unlike the published correction notice, took the position that the discovery of the error did not change the conclusions of the APPROVe article.⁵¹⁴ Many of the points set forth in these documents mirror closely the positions taken by the APPROVe article’s authors in their correspondence with the New England Journal of Medicine editors described above. This section summarizes the key points made in both the Open Letter and the Assessment.

First, both the Open Letter and the Assessment concluded that the use of the Linear Time Test to test the proportional hazards assumption was appropriate. The Open Letter stated:

Results of diagnostic analyses indicate that a model using linear time is more representative of the data than one using logarithm of time. Thus, the linear time analysis is an appropriate method to assess the changes in relative risk over time.⁵¹⁵

The Assessment also concluded that using the Linear Time Test was appropriate, notwithstanding the fact that the Protocol 203 Statistical Data Analysis Plan pre-specified use of the Logarithm of Time Test. The Assessment explained that the Protocol 203

⁵¹⁴ Merck also issued a press release in connection with the release of the Open Letter. 1/26/06 Merck press release, “Merck Stands Behind Original APPROVe Study Results,” MRK-ASW0005632-34. This release reflected the content of the Open Letter and Assessment.

⁵¹⁵ 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152, at 52. These “diagnostic analyses,” discussed more fully in Section B.5 of this Appendix, were those conducted by Dr. Jennifer Ng in connection with her efforts to model the hazard ratio over time in the APPROVe Trial.

Statistical Data Analysis Plan was designed to test a non-inferiority hypothesis, and, as a result, provided for a battery of tests: “Although the results of a single test may be consistent with this null hypothesis [*i.e.* assumption] of constant [hazard ratio] over time, it is common statistical practice to conduct more than one assessment because no single test alone can prove that null hypothesis.”⁵¹⁶ According to the Assessment, the use of multiple tests of the proportionality of hazards, therefore, was “consistent with good statistical practice and consistent with the DAP for Protocol 203.”⁵¹⁷

Second, the Open Letter and Assessment both stated that the error did not affect the results of other statistical tests that provided support for the conclusion that the hazard ratio was not constant. These results included the Kaplan-Meier plot of the data (included in the article as Figure 2),⁵¹⁸ the different relevant risks and confidence intervals for 6-month time intervals;⁵¹⁹ the significant p-value produced by the Linear Time Test,⁵²⁰ and the results of the hazard ratio modeling.⁵²¹

⁵¹⁶ “APPROVe Assessment,” MRK-AFO030154, at 54 (attached to 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152-53).

⁵¹⁷ “APPROVe Assessment,” MRK-AFO030154, at 54 (attached to 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152-53).

⁵¹⁸ 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152, at 52; “APPROVe Assessment,” MRK-AFO030154, at 55 (attached to 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152-53).

⁵¹⁹ 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152, at 52 (refers to Table 3 in the APPROVe article, which contained these results); “APPROVe Assessment,” MRK-AFO030154, at 55 (attached to 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152-53).

⁵²⁰ “APPROVe Assessment,” MRK-AFO030154, at 55 (attached to 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152-53).

Third, the Open Letter and the Assessment both stated that the result of the Logarithm of Time Test was not inconsistent with these results. The Open Letter stated that the proportionality p-value of 0.07, though “borderline[,] . . . justifies concern regarding changes in relative risk over time.”⁵²² Similarly, the Assessment stated, “[e]ven the treatment-by-log(time [sic] interaction p-value 0.07 approaches statistical significance, consistent with all the other analyses, which support a conclusion of non-constant HR [hazard ratio] over time.”⁵²³

Based on these three considerations – that the Linear Time Test was an appropriate test; that numerous analyses supported the conclusion that the hazard ratio was not constant over time; and that the results of the specified test (the Logarithm of Time Test) were not inconsistent with these other results – the Open Letter and the Assessment concluded that the error in the APPROVe article did not affect the article’s conclusions. The Open Letter stated, “we conclude that this correction to the description of the statistical method does not change the results of the APPROVe study.”⁵²⁴ Likewise, the Assessment stated: “We conclude, based on these facts, that the correction to the description of the statistical method does not change the result that, in the APPROVe study, the relative risk for confirmed thrombotic cardiovascular events was

⁵²¹ “APPROVe Assessment,” MRK-AFO030154, at 55 (attached to 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152-53).

⁵²² 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152, at 52.

⁵²³ “APPROVe Assessment,” MRK-AFO030154, at 55 (attached to 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152-53).

⁵²⁴ 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152, at 53.

not constant over time, and that an increased relative risk . . . was observed after 18
months of continuous daily treatment.”⁵²⁵

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⁵²⁵ “APPROVe Assessment,” MRK-AFO030154, at 56 (attached to 6/26/06 letter from P. Kim, “An Open Letter from Merck,” MRK-AFO0300152-53).