

APPENDIX Q

APPROVe TRIAL CARDIOVASCULAR DATA AND WITHDRAWAL OF VIOXX.

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APPENDIX Q

APPROVe TRIAL CARDIOVASCULAR DATA AND WITHDRAWAL OF VIOXX.

A. The APPROVe Trial.

As discussed in Appendix M, the Adenomatous Polyp Prevention on Vioxx (“APPROVe”) Trial, which commenced in February 2000, was a placebo-controlled trial testing whether Vioxx helped prevent the recurrence of adenomatous (i.e., precancerous or cancerous) colon polyps in patients who previously had been treated for such polyps.¹ Although the APPROVe Trial was not designed to test cardiovascular safety, Merck adjudicated cardiovascular adverse events that occurred during the study pursuant to the Cardiovascular Adjudication SOP.²

Cardiovascular data from the APPROVe Trial – which demonstrated a numerically increased relative risk of adjudicated and confirmed cardiovascular events beginning after 18 months of continuous use of Vioxx and a significantly increased risk after 30 months of continuous use – led the APPROVe Trial External Safety Monitoring Board to recommend termination of the trial only weeks before it was scheduled to end, and prompted the Company to voluntarily withdraw Vioxx from the worldwide market.

¹ 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 93.

² 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 93-94. In addition, as explained in Appendix M, the APPROVe Trial was one of three trials included in Protocol 203, Merck’s cardiovascular outcomes study.

This Section reviews: (i) the design of the APPROVe Trial; (ii) the cardiovascular data that the APPROVe Trial External Safety Monitoring Board reviewed during the course of the trial; (iii) the External Safety Monitoring Board's recommendation to terminate the trial before completion; and (iv) Merck's decision to withdraw Vioxx from the worldwide market.

1. Trial Design.

The APPROVe Trial was a placebo-controlled, double-blind study to determine the effect of 156 weeks (3 years) of treatment with Vioxx on the recurrence of adenomatous polyps of the large bowel in patients with a history of colorectal adenomas.³ Sporadic colorectal adenomas were believed to be precursors of 95% of colorectal cancers.⁴ Treatment for colon polyps was typically removal, with subsequent surveillance colonoscopies conducted to ensure that polyps did not reappear.⁵ Scientists at MRL decided to conduct the APPROVe Trial because epidemiologic and pre-clinical studies had suggested that suppression of the Cox-2 enzyme could decrease colon polyp recurrence.⁶

³ 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111, at 121. Although the APPROVe Trial three year "base study" was scheduled to be completed in November 2004 – after patients received their year-three colonoscopy – in August 2003, MRL amended the APPROVe Trial protocol to collect follow-up data on patients during a one-year off-drug extension study to assess off-treatment recurrence of colon polyps. APPROVe Study Update, MRK-AAD0295440, at 40-41.

⁴ 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111, at 133.

⁵ 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111, at 133; 10/3/04 "MRL Managers Questions and Answers," MRK-AFJ0009727, at 27.

⁶ 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111, at 134-35; 10/3/04 "MRL Managers Questions and Answers," MRK-AFJ0009727, at 27.

Enrollment in the APPROVe Trial began in February 2000 and continued on a rolling basis through November 2001.⁷ The APPROVe Trial included 2,586 patients (1,287 in the Vioxx arm and 1,299 in the placebo arm) between the ages of 40 and 96, approximately 62% of whom were male.⁸ Patients who had had an adenomatous polyp removed within 12 weeks of beginning the study were eligible to participate.⁹ Participants took Vioxx 25 mg or placebo each day throughout the study and underwent colonoscopies one and three years after entering the trial to determine whether any polyps had recurred.¹⁰ Patients were allowed to use low-dose aspirin concomitantly with Vioxx (or placebo).¹¹ Upon study entry, approximately 16% of patients used low-dose aspirin for cardiovascular prophylaxis.¹²

⁷ Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 93.

⁸ 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 92, 95.

⁹ 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111, at 122; 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 93.

¹⁰ 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111, at 122. “The original study design included a group assigned to receive 50 mg of rofecoxib per day; 26 patients had been assigned to this treatment before it was decided not to proceed with this group.” 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 94.

¹¹ 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 93. The original APPROVe Trial Protocol did not allow concomitant aspirin use. In response to the results of the VIGOR Trial, the APPROVe Trial Protocol was amended in May 2000 to allow patients to take low-dose aspirin for cardiovascular prophylaxis. Id.

¹² 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 95; 10/3/04 “MRL Managers Questions and Answers,” MRK-AFJ0009727, at 30.

2. Oversight.

The APPROVe Trial was overseen by three separate groups: (i) clinical monitors; (ii) the APPROVe Trial External Safety Monitoring Board; and (iii) the APPROVe Trial Administrative Committee.

a. Clinical monitors.

The APPROVe Trial clinical monitors were Merck employees charged with implementing and monitoring the study by recruiting investigators, reviewing patient records to ensure compliance with the trial protocol, supervising investigator sites to ensure that safety data were appropriately reported, and resolving inconsistencies or inaccuracies in data reporting, including reviewing adverse event reports for events undetected by investigators.¹³ Drs. Eric Mortensen and Peter Callagari were co-clinical monitors of the APPROVe Trial until the fall of 2001, when they left Merck, at which time Dr. Bettina Oxenius became the clinical monitor of the APPROVe Trial.¹⁴ She was joined by co-clinical monitor Dr. Raymond Joseph in mid-October 2002.¹⁵ The clinical monitors were supervised by Dr. Thomas Simon, head of the MRL Gastroenterology group, until early 2004, at which point Dr. Kevin Horgan, a Senior Director in the

¹³ APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 273 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

¹⁴ See 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111, at 114.

¹⁵ 10/14/02 letter from B. Oxenius and R. Joseph to H. Quan, MRK-AGO0003586.

Gastroenterology group, assumed Dr. Simon's responsibilities with regard to the APPROVe Trial.¹⁶

b. External Safety Monitoring Board.

The APPROVe Trial External Safety Monitoring Board was tasked with monitoring safety data and evaluating whether the study should be modified or terminated for safety reasons.¹⁷ The External Safety Monitoring Board was charged with reporting to the Executive Committee, a subset of the APPROVe Trial Administrative Committee, after each External Safety Monitoring Board meeting "either that no change to the study is required, or that the protocol needs to be modified or terminated early."¹⁸

The four outside members of the External Safety Monitoring Board were Dr. James Neaton* (Chair), Professor of Biostatistics at the University of Minnesota School of Public Health; Dr. Marvin Konstam* Professor of Medicine at Tufts University School of Medicine and Chief of Cardiology at the New England Medical Center; Dr. David Bjorkman* gastroenterologist and Professor of Internal Medicine at the University of Utah School of Medicine; and Dr. Richard Logan*, gastroenterologist and

¹⁶ 2/9/04 letter from T. Simon to J. Neaton* MRK-ABS0392050, at 50.

¹⁷ APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 253-54 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111); Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 40-41.

¹⁸ Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 41.

Professor of Clinical Epidemiology at the University of Nottingham Medical School in the United Kingdom.¹⁹

The APPROVe Trial External Safety Monitoring Board members were selected by the Administrative Committee with input on behalf of MRL from Dr. Mortensen, the Merck clinical monitor at the time.²⁰ In November 2000, the Administrative Committee began to compile a list of potential members to serve on the External Safety Monitoring Board.²¹ In June 2001, invitations to join the APPROVe Trial External Safety Monitoring Board were sent to Drs. Neaton*, Konstam*, and Bjorkman*.²² In October 2001, the Administrative Committee decided to invite Dr. Logan* to become a member.²³ At that time, the Administrative Committee intended to invite at least one more person to serve on the External Safety Monitoring Board.²⁴ However, at the External Safety

¹⁹ ESMB and Administrative Committee Guidelines attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111, at 264. Merck statistician, Dr. Hui Quan, was a non-voting member of the External Safety Monitoring Board. Id.

²⁰ Minutes of 4/9/01 APPROVe Administrative Committee meeting, MRK-ABS0200244, at 44, 48-49. Drs. Bjorkman* and Konstam* stated that they did not recall who asked them to become members of the APPROVe External Safety Monitoring Board. Mr. Bolognese assisted in recruiting Dr. Neaton* to join the External Safety Monitoring Board. 5/01 email from J. Bolognese to E. Mortensen, MRK-AGO0026321-22.

²¹ Draft minutes of 11/20/01 APPROVe Administrative Committee meeting, MRK-ABS0300020, at 21, 23.

²² Minutes of 6/11/01 APPROVe Administrative Committee meeting, MRK-ABK0432470, at 70, 72-73; see also 1/11/05 email from K. Horgan to A. Plohoros, MRK-AFS0026166.

²³ Minutes of 10/15/01 APPROVe Administrative Committee meeting, MRK-ABK0432461, at 61, 64.

²⁴ Minutes of 10/15/01 APPROVe Administrative Committee meeting, MRK-ABK0432461, at 64; see also Minutes of 6/11/01 APPROVe Administrative Committee meeting, MRK-ABK0432470, at 70.

Monitoring Board's first meeting on November 7, 2001, it was decided that a fifth member was not needed.²⁵

None of the External Safety Monitoring Board members were investigators in the APPROVe Trial nor affiliated with any institution involved in the trial, although some had previously been consultants for Merck.²⁶ External Safety Monitoring Board members were compensated \$2,500 for in-person meetings, and \$1,250 for teleconferences.²⁷

Merck assigned an unblinded statistician – Dr. Hui Quan – to assist the External Safety Monitoring Board in analyzing the APPROVe Trial data throughout the trial. As the unblinded statistician, Dr. Quan was the only Merck employee who was aware of which study participants were receiving Vioxx and which were receiving placebo.²⁸ With respect to the APPROVe Trial, Dr. Quan reported solely to the External Safety Monitoring Board (and not to Merck) for the duration of the trial, provided statistical

²⁵ Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 42.

²⁶ APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 254-55 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111); Minutes of 4/9/01 APPROVe Administrative Committee meeting, MRK-ABS0200244, at 48. Drs. Bjorkman* and Neaton* previously served as members of the VIGOR Trial Data Safety and Monitoring Board. Minutes of 10/3/99 VIGOR DSMB meeting, MRK-AFL0000889, at 89. Drs. Konstam* and Bjorkman* were consultants to Merck before serving on the APPROVe External Safety Monitoring Board. See 10/18/00 VIGOR Cardiology Consultants meeting participant list, MRK-NJ0272583.

²⁷ 6/6/01 letter from S. Reines to D. Bjorkman* (cc: E. Mortensen), MRK-ABS0216558, at 58; 6/6/01 letter from S. Reines to J. Neaton* (cc: E. Mortensen), MRK-ABS0216579; 6/6/01 letter from S. Reines to M. Konstam* (cc: E. Mortensen), MRK-ABS021657, at 79, 12/5/01 letter from A. Nies to R. Logan* (cc: B. Oxenius), MRK-ABS0216582, at 82.

²⁸ Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 42; APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 255 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

analyses to facilitate the members' review of the safety data, and attended External Safety Monitoring Board meetings in a non-voting capacity.²⁹ Merck also assigned a blinded statistician, Mr. James Bolognese, to resolve inconsistencies in the data and implement any changes to the Data Analysis Plan after Dr. Quan was unblinded.³⁰

c. Administrative Committee.

The APPROVe Trial was guided by an Administrative Committee, composed of six people outside of Merck and three Merck representatives.³¹ The Administrative Committee was responsible for overseeing the study generally, reviewing and approving the External Safety Monitoring Board's recommendations regarding the trial, and providing ongoing consulting input to Merck from academic and investigator perspectives.³² The Administrative Committee received general update information about the trial as early as November 2000 but remained blinded to treatment group assignments.³³

²⁹ Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 42; APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 255 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

³⁰ See APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 269, 274 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

³¹ APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 274 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

³² APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 269 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111); 1/5/05 deposition of T. Simon at 226-27 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

³³ APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 254, 269 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111); Draft minutes of 11/20/00 APPROVe Administrative Committee meeting, MRK-ABS0300020, at 20.

Outside members of the Administrative Committee included Dr. John Baron* (Chair), epidemiologist and Professor of Medicine at Dartmouth Medical School; Dr. Robert Riddell*, pathologist at Mount Sinai Hospital in Toronto, Canada and Professor of Pathology and Molecular Medicine at McMaster University Health Sciences; Dr. Robert Sandler*, Professor of Medicine and Chief of the Division of Gastroenterology and Hepatology at the University of North Carolina at Chapel Hill; Dr. Angel Lanas* gastroenterologist and Professor of Medicine at Zaragoza University in Zaragoza, Spain; Dr. Dion Morton* surgeon affiliated with Queen Elizabeth Hospital and the University of Birmingham in the United Kingdom; and Dr. Robert Bresalier*, gastroenterologist, Professor and Chair of the Gastrointestinal and Nutrition Department of the University of Texas M.D. Anderson Cancer Center.³⁴

Merck representatives on the Administrative Committee were Dr. Oxenius; Dr. Simon, who was Dr. Oxenius's supervisor; and Mr. James Bolognese, the blinded statistician for the APPROVe Trial.³⁵ When Dr. Simon switched jobs in early 2004, Dr. Horgan replaced him on the Administrative Committee.³⁶

The Executive Committee, a subset of the Administrative Committee that evaluated recommendations by the External Safety Monitoring Board regarding the

³⁴ APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 274 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

³⁵ APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 274 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

³⁶ 2/9/04 letter from T. Simon to J. Neaton*, MRK-ABS0392050, at 50.

continuance and/or modification of the trial, included Drs. Baron*, Sandler* and Riddell*.³⁷ Under the rules, Dr. Baron*, as Chair of the APPROVe Trial Executive Committee, would review the External Safety Monitoring Board's recommendation before convening a meeting of the Executive Committee to consider whether to follow the recommendation.³⁸ If the Executive Committee agreed with the recommendation of the External Safety Monitoring Board, it would be taken to the Administrative Committee for review.³⁹

3. External Safety Monitoring Board Meetings.

a. Process.

The External Safety Monitoring Board met twelve times throughout the three-year base study, beginning on November 7, 2001.⁴⁰ The first meeting of the External Safety Monitoring Board at which safety data were reviewed was January 23, 2002, more than

³⁷ Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 40; APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 270 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111). The two-tiered review structure, which involved review of the External Safety Monitoring Board's recommendation by the Executive Committee prior to review by the Administrative Committee, was implemented to limit the number of people unblinded to trial data in case the Executive Committee disagreed with the External Safety Monitoring Board's recommendation and determined not to bring it to the attention of the Administrative Committee. Unblinding the members of the Administrative Committee would "influence their ability to function on the study." Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 41; see also 9/22/99 VIGOR Steering Committee Guidelines and Overall Study Structure, MRK-NJ0244603, at 05.

³⁸ Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 41.

³⁹ Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 41.

⁴⁰ See the timeline at the end of this Appendix for a listing of the APPROVe Trial External Safety Monitoring Board meetings.

22 months after patients first began enrolling in the APPROVe Trial.⁴¹ There was a six-week placebo run-in period, which meant that patients were not monitored for up to 21 months after receiving Vioxx.⁴² Although guidelines recommended that the External Safety Monitoring Board meet “approximately every six months during the study to provide for the longitudinal review of safety reports and to review any questions regarding safety from either the Merck Clinical Monitor or the Administrative Committee,”⁴³ in practice, once it was fully formed, the Board met more frequently than every six months to evaluate safety data.⁴⁴

⁴¹ Minutes of 1/23/02 APPROVe ESMB Open Session meeting, MRK-AFF0000095; 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 93. According to the APPROVe External Safety Monitoring Board and Administrative Committee Guidelines, the first meeting of the External Safety Monitoring Board was to be scheduled within three months of November 2001, which was the date of Last Patient In (“LPI”). APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 256 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

⁴² Minutes of 1/23/02 APPROVe ESMB Open Session meeting, MRK-AFF0000095; 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 93. In February 2005, a peer reviewer for the *New England Journal of Medicine* who reviewed the draft manuscript that the APPROVe Administrative Committee members along with a member of the APPROVe External Safety Monitoring Board had submitted regarding the cardiovascular results of the APPROVe Trial focused on the fact that the External Safety Monitoring Board’s “appointment was delayed” and that patients were not monitored throughout the beginning of the trial. APPROVe Trial Manuscript, “Author’s responses to Reviewer’s Comments,” MRK-AHD0000061, at 61; *see also* 1/13/05 Draft Briefing Document, “WSJ Story on APPROVe External Safety Monitoring Board,” MRK-AHU0007565, at 66.

⁴³ APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 257 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

⁴⁴ See the timeline at the end of this Appendix for a listing of the APPROVe Trial External Safety Monitoring Board meetings.

The first two meetings of the External Safety Monitoring Board were in person, and all subsequent meetings were conducted by teleconference.⁴⁵ Dr. Quan was unblinded shortly before the External Safety Monitoring Board's second meeting, and thereafter he provided the External Safety Monitoring Board members with a formal report analyzing unblinded data several days prior to each meeting.⁴⁶ The reports were printed on numbered, colored paper to prevent copying,⁴⁷ and the External Safety Monitoring Board members returned them to Dr. Quan after each meeting.⁴⁸

Each External Safety Monitoring Board meeting began with an Open Session, which the Merck clinical monitors, other MRL scientists, and members of the Administrative Committee could attend. During the Open Session, operational issues, recruitment, compliance, and data quality were discussed.⁴⁹

⁴⁵ Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 43; Minutes of 1/23/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000097, at 98.

⁴⁶ APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 257 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

⁴⁷ Minutes of 5/29/02 Administrative Committee meeting, MRK-ABS0421641, at 46; APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 262 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

⁴⁸ Minutes of 5/29/02 Administrative Committee meeting, MRK-ABS0421641, at 46; APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 262 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

⁴⁹ Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 40; APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 256 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

Following the Open Session, External Safety Monitoring Board members would meet in a Closed Session, during which Dr. Quan presented unblinded data analyses regarding, among other things, cardiovascular events.⁵⁰

b. Request to unblind data from the APPROVe Trial
for inclusion in cardiovascular meta-analysis.

When the APPROVe Trial began, the Data Analysis Plan setting forth the methods by which trial data would be analyzed was not yet in place. A draft Data Analysis Plan was prepared by Merck statisticians and presented at the External Safety Monitoring Board's second meeting, which took place in January 2002.⁵¹ The draft Data Analysis Plan contemplated that "[a] very small group of [Merck] employees (except the unblinded statistician) may be unblinded to some specific safety data like CV data" during the course of the study so that Merck could include such data in a Vioxx cardiovascular meta-analysis.⁵²

This provision was included so that Merck could pool cardiovascular data from the ongoing APPROVe Trial with data collected from all clinical trials of Vioxx. As explained in Appendices I and O, Merck committed to provide such meta-analyses to the FDA on a regular basis in periodic safety update reports and in connection with the ongoing post-VIGOR label negotiations, and intended to submit an updated analysis in

⁵⁰ Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 40; APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 256 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

⁵¹ Minutes of 1/23/02 APPROVe APPROVe ESMB Open Session meeting, MRK-AFF0000095, at 95-96.

⁵² Minutes of 1/23/02 APPROVe APPROVe ESMB Open Session meeting, MRK-AFF0000095, at 96.

March 2002.⁵³ Merck asked the External Safety Monitoring Board for permission to unblind cardiovascular data at the Board's January 2002 meeting.⁵⁴

Members of the APPROVe Trial External Safety Monitoring Board, according to the January 2002 Open Session meeting minutes, "raised serious concerns" about this proposal.⁵⁵ The External Safety Monitoring Board members "were concerned that making any other use of the data creates the possibility (even if small) that it will leak to the investigator community and affect the perception of the polyp study."⁵⁶ In particular, External Safety Monitoring Board members were concerned that Merck's use of unblinded APPROVe Trial data for inclusion in a meta-analysis would enable some individuals within MRL to divine the study's cardiovascular results to date based on the change, if any, from prior meta-analyses, as APPROVe Trial data were the only new cardiovascular data that could be added to the pre-existing meta-analyses.⁵⁷ The External Safety Monitoring Board members "felt if there was concern on the CV safety based on the interim analyses from this study, they prefer to share the concern with the DSMBs of other studies in a private manner, rather than involve the sponsor [Merck]."⁵⁸

⁵³ 2/25/02 email from T. Simon to J. Baron*, MRK-ABS0372415, at 15.

⁵⁴ Minutes of 1/23/02 APPROVe APPROVe ESMB Open Session meeting, MRK-AFF0000095, at 96.

⁵⁵ Minutes of 1/23/02 APPROVe ESMB Open Session meeting, MRK-AFF0000095, at 96.

⁵⁶ 1/23/02 email from T. Simon to S. Reines, MRK-ABS0346030, at 31.

⁵⁷ 3/6/02 memorandum from T. Simon to S. Reines, MRK-NJ0280058.

⁵⁸ Minutes of 1/23/02 APPROVe ESMB Open Session meeting, MRK-AFF0000095, at 96.

Some MRL scientists disagreed with the External Safety Monitoring Board's position. For example, Dr. Reines, an MRL Vice President overseeing the Central Nervous System, Ophthalmology, and Gastrointestinal Divisions, stated in an internal email to Dr. Simon:⁵⁹

-----Original Message-----
From: Simon, Thomas J.
Sent: Wednesday, January 23, 2002 6:00 PM
To: Reines, Scott A.
Subject: feedback from ESMB meeting--vioxx colon polyp study

Scott,

The ESMB dealt with three important issues during its open session. At that time we had the conversation--that was to occur in a closed session.

1. Unblinding to a small group of senior Merck management to allow that the strongest position is that no unblinding occurs, and that the modification", at scheduled meetings. They were concerned that making any other use of the data creates possibility (even if small) that it will leak to the investigator community and affect the perception of the polyp study. One angle I hadn't considered is that if Merck were to d/c this study early, before a conclusive trend emerged, and allowed others to continue, the company could be accused of cutting off a potentially negative result before it became fully apparent. This needs further discussion within Merck. [Reines, Scott A.] Tom, if VIOXX is associated with a higher risk of CV events it could be unethical to continue the Polyp trial. That issue can't be handled by the ESMB. They have to be aware that there are bigger issues than this single trial, important though it is.

Tom, if VIOXX is associated with a higher risk of CV events it could be unethical to continue the Polyp trial. That issue can't be handled by the ESMB. They have to be aware that there are bigger issues than this single trial, important though it is.

On February 20, 2002, MRL scientists renewed their request for permission to unblind individual patient data from the APPROVe Trial and advised External Safety Monitoring Board members that the unblinded APPROVe Trial data included in the meta-analysis would be "grouped with other trials in a manner such that the APPROVe results cannot be ascertained, e.g., in a group labeled as 'other placebo controlled trials,

⁵⁹ 1/02 email correspondence between S. Reines and T. Simon, MRK-ABS0346030, at 31.

including migraine, cancer prevention, prostatitis, low back pain.”⁶⁰ In response to Merck’s request, Dr. Neaton*, writing on behalf of the External Safety Monitoring Board, sent a letter to Dr. Simon dated February 25, 2002, requesting that Merck “not unblind these data until we have had an opportunity to re-consider this request on our May teleconference.”⁶¹ Dr. Neaton* stated that the External Safety Monitoring Board’s “concerns have not gone away” and that immediate unblinding was not necessary since “the data available to the Merck staff carrying out the meta-analysis” – 10 confirmed adjudicated events to date – “is limited.”⁶²

After hearing of the External Safety Monitoring Board’s decision, Dr. Simon contacted Dr. Baron*, head of the APPROVe Trial Administrative Committee.⁶³

⁶⁰ “APPENDIX z: CV Event Data Unblinding Procedures for the APPROVe Trial,” MRK-NJ0391863 (attached to 2/20/02 email from J. Bolognese to H. Quan, MRK-NJ0391862); 2/20/02 email from H. Quan to J. Neaton*, M. Konstam*, D. Bjorkman*, and R. Logan*, MRK-AGO0028431; see also 2/25/02 email correspondence between T. Simon, B. Gertz, and J. Bolognese, MRK-NJ0393055, at 55.

⁶¹ 2/25/02 letter from J. Neaton* to T. Simon, MRK-ABS0327073, at 73.

⁶² 2/25/02 letter from J. Neaton* to T. Simon, MRK-ABS0327073, at 73.

⁶³ 2/25/02 email from T. Simon to J. Baron*, MRK-ABS0372415, at 15; see also 2/26/02 memorandum from T. Simon to S. Reines, MRK-ABS0327080.

-----Original Message-----
From: Simon, Thomas J.
Sent: Monday, February 25, 2002 2:09 PM
To: John Baron (E-mail)
Subject: unblinding data from colon polyp study for meta analysis

--BUSINESS CONFIDENTIAL, VIA SECURE E-MAIL--
John,

I was informed today that the ESMB is sending us a letter to the effect that it opposes unblinding the cv data to include in the VIOXX CV meta analysis. This is out of concern that it would be possible to conclude what's happening in the colon polyp trial, even if the data were combined with other studies.

I wanted to talk to you about this a bit further--the administrative committee had a different perspective, based on public health concerns. We need to reach a short term resolution, because there's a plan to update the meta-analysis very soon (next month), and to include the colon polyp study, we'd need to decide about unblinding the cv events from 122 by tomorrow.

Can you give me a call? REDACTED

Tom

Dr. Baron* subsequently called Dr. Neaton*, the Chair of the External Safety Monitoring Board, to discuss Merck's request to unblind data from the APPROVe Trial.⁶⁴ According to a memorandum that Dr. Baron* wrote memorializing their conversation, Dr. Neaton* stated that although the External Safety Monitoring Board remained skeptical about unblinding data from the APPROVe Trial before the end of the study, it was open to discussing the issue at its next meeting.⁶⁵ Dr. Neaton* invited Dr. Baron* to participate in

⁶⁴ 2/27/02 memorandum from J. Baron* to Approve Study Files, MRK-ABS0323263, at 63.

⁶⁵ 2/27/02 memorandum from J. Baron* to Approve Study Files, MRK-ABS0323263, at 63.

the Open Session of the next External Safety Monitoring Board meeting to discuss the issue.⁶⁶

A few days later, on March 4, 2002, Drs. Reicin and Simon discussed with Dr. Neaton* “the possibility of including the data from protocol 122 [the APPROVe Trial] in the cardiovascular meta-analysis being prepared” for submission to the FDA.⁶⁷ Dr. Neaton* indicated that the External Safety Monitoring Board had concerns about MRL’s proposal, “specifically the section concerning tests for homogeneity prior to the meta analysis” as “these would display the contribution of each study.”⁶⁸ Drs. Reicin and Simon assured Dr. Neaton* that MRL would not include the data from the APPROVe Trial in the cardiovascular meta-analysis “without concurrence from the ESMB, and agreed to plan a teleconference within the next few days to discuss the matter further.”⁶⁹

On March 6, 2002, the APPROVe Trial External Safety Monitoring Board held an Open Session teleconference, at which Mr. Bolognese presented Merck’s proposal to unblind the data from the APPROVe Trial for the limited purpose of including it in an updated cardiovascular meta-analysis.⁷⁰ “The ESMB strongly endorsed the proposal” to periodically unblind certain Merck employees in order to facilitate a cardiovascular

⁶⁶ 2/27/02 memorandum from J. Baron* to Approve Study Files, MRK-ABS0323263, at 63.

⁶⁷ 3/4/02 memorandum from T. Simon to S. Reines, MRK-ABS0327082, at 82.

⁶⁸ 3/4/02 memorandum from T. Simon to S. Reines, MRK-ABS0327082, at 83.

⁶⁹ 3/4/02 memorandum from T. Simon to S. Reines, MRK-ABS0327082, at 82.

⁷⁰ 3/6/02 memorandum from T. Simon to S. Reines, MRK-NJ0280058, at 58, attaching Proposal, MRK-NJ0280060-62.

meta-analysis but decided that the proposal “*should not* be implemented at this point in time.”⁷¹ However, the External Safety Monitoring Board “did endorse including data from the APPROVe study in analysis to be performed in 4q02-1q03, and later time points, provided that at these subsequent times, sufficient numbers of events have occurred in the VICTOR trial” – a soon-to-be-launched second placebo-controlled study of the effect of Vioxx on colon polyps – which would make it “impossible to infer the contribution from the APPROVe study.”⁷² Given the External Safety Monitoring Board members’ decision, Merck representatives did not receive unblinded data and thus could not include APPROVe Trial data in the May 2, 2002 update of the cardiovascular meta-analysis submitted to the FDA.⁷³

c. Protocol 203.

(i) External Safety Monitoring Board
for Protocol 203.

In the fall of 2002, Merck launched Protocol 203, its cardiovascular outcomes trial. As discussed more fully in Appendix M, Protocol 203 called for prospective cardiovascular data to be collected from three ongoing placebo-controlled trials – the APPROVe Trial, the VICTOR Trial, and the Prostate Cancer Prevention Trial (“ViP”) – and pooled for analysis. Merck asked the APPROVe Trial External Safety Monitoring

⁷¹ 3/6/02 memorandum from T. Simon to S. Reines, MRK-NJ0280058, at 59 (emphasis in original).

⁷² 3/6/02 memorandum from T. Simon to S. Reines, MRK-NJ0280058, at 59.

⁷³ 5/22/02 letter from N. Braunstein to L. Simon* (FDA), MRK-AHN0022140, at 40.

Board to take on the additional roles of being the External Safety Monitoring Board for the ViP Trial and for Protocol 203.⁷⁴

The APPROVe Trial External Safety Monitoring Board members agreed to serve as members of the ViP Trial and Protocol 203 External Safety Monitoring Boards.⁷⁵ Because the APPROVe Trial started well before the VICTOR Trial (which started in April 2002) and the ViP Trial (which started in June 2003), data collection from the APPROVe Trial, cardiovascular and otherwise, was farther along than that of the other trials in Protocol 203.⁷⁶ For this reason, and because several meetings of the APPROVe Trial External Safety Monitoring Board already had taken place, the APPROVe Trial External Safety Monitoring Board recommended that the two additional members proposed – a cardiologist and an oncologist/urologist – only be added to the Boards of the ViP Trial and Protocol 203, and not the APPROVe Trial.⁷⁷

(ii) Cardiovascular Event Analysis for the APPROVe Trial and Protocol 203.

The APPROVe Trial Data Analysis Plan specified that serious adverse events, including cardiovascular events, would be collected and analyzed. However, because the primary endpoint of the APPROVe Trial was the recurrence of colorectal adenomas,

⁷⁴ Minutes of 8/7/02 APPROVe ESMB Open Session meeting, MRK-AFF0000103, at 03.

⁷⁵ 8/20/02 letter from J. Neaton* to A. Reicin, MRK-AAD0194876, at 76; 5/6/03 Statistical Data Analysis Plan for Protocol 203, MRK-AAD0200169, at 74.

⁷⁶ In fact, the External Safety Monitoring Board of Protocol 203 did not meet to discuss data before Vioxx was withdrawn from the market.

⁷⁷ 5/19/03 letter from J. Neaton* to T. Simon, MRK-ABS0392059.

detailed analyses of cardiovascular events were not pre-specified. According to the APPROVe Trial Data Analysis Plan, “[d]ata on thrombotic cardiovascular serious adverse experiences from this study will be combined for analysis with those of 2 other placebo-controlled studies to better assess the effect of rofecoxib on these AEs.”⁷⁸ That analysis of cardiovascular data, which “would take place after APPROVe is completed and its data reviewed, corrected, and frozen/locked. . . . is described in VIOXX Protocol 203.”⁷⁹

d. Trends in cardiovascular data.

Throughout the APPROVe Trial, the External Safety Monitoring Board monitored safety data, particularly potential trends with respect to cardiovascular, hypertension, and edema adverse events.⁸⁰ The External Safety Monitoring Board monitored two broad categories of cardiovascular adverse events: confirmed thrombotic cardiovascular adverse events (“confirmed thrombotic” events)⁸¹ and Antiplatelet Trialists’ Collaboration composite cardiovascular endpoint events (“APTC composite

⁷⁸ 1/10/03 APPROVe Trial Data Analysis Plan, MRK-ABS0452604, at 23.

⁷⁹ 1/10/03 APPROVe Trial Data Analysis Plan, MRK-ABS0452604, at 23; see also 1/9/04 Protocol 203 Data Analysis Plan, MRK-AFL0076074.

⁸⁰ Minutes of 8/7/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000103, at 03; Minutes of 11/26/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000091, at 93.

⁸¹ Dr. Quan’s pre-meeting reports refer to these events as “adjudicated/confirmed thromboembolic serious AEs.” As discussed in Appendix E, the terms thromboembolic and thrombotic have slightly different meanings but were used interchangeably to refer to the terms included in Merck’s Cardiovascular Adjudication SOP.

cardiovascular endpoint events”).⁸² The former category encompassed all adjudicated and confirmed thrombotic events under Merck’s Cardiovascular Adjudication SOP.⁸³

The latter category – APTC composite cardiovascular endpoint events – included a smaller group of hard clinical outcomes, including myocardial infarction, stroke (both ischemic and hemorrhagic), cardiovascular death, and death due to unknown cause or due to bleeding, but did not include peripheral vascular events.⁸⁴ The APTC composite cardiovascular endpoint was the “primary” cardiovascular endpoint being monitored by the APPROVe Trial External Safety Monitoring Board.⁸⁵

⁸² See, e.g., 5/8/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AFK0202981, at 83, 99; 11/18/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0007185, at 85. “APTC” stands for the Antiplatelet Trialists’ Collaboration, a group that developed a commonly used composite cardiovascular endpoint that includes myocardial infarction, stroke (both ischemic and hemorrhagic), cardiovascular death, and death due to unknown cause or due to bleeding. See 10/5/00 Statistical Data Analysis Plan, MRK-AFO0014726, at 32.

⁸³ Included events were acute myocardial infarctions (fatal or nonfatal), unstable angina pectoris, sudden and/or unexplained death, resuscitated cardiac arrest, cardiac thrombus, pulmonary embolism (fatal or nonfatal), peripheral arterial or venous thrombosis (fatal or nonfatal), ischemic cerebrovascular stroke (fatal or nonfatal), cerebrovascular venous thrombosis (fatal or nonfatal), and transient ischemic attack. 5/8/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AFK0202981, at 98 (Table 10); 1/9/04 Protocol 203 Data Analysis Plan, MRK-AFL0076074, at 85.

⁸⁴ See 5/8/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AFK0202981, at 98 (listing in Table 10 the types of events included in each endpoint). The APTC composite cardiovascular endpoint was also based on adjudicated and confirmed data, except for hemorrhagic events, which were not adjudicated. *Id.* The differences between these two composite endpoints are discussed in more detail in Appendix F.

⁸⁵ Minutes of 11/24/03 APPROVe ESMB Closed Session meeting, MRK-AFF0000117, at 18; 11/18/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0007185, at 85. In the pre-meeting analyses prepared by Dr. Quan, APTC events were considered primary events and confirmed thrombotic events secondary events, “[t]o be consistent with the current approaches for CV combined analysis.” 5/8/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AFK0202981, at 97. The cardiovascular meta-analyses submitted to the FDA used the APTC composite cardiovascular endpoint. See Appendices F and O. However, the Protocol 203 Data Analysis Plan stated the opposite – primary endpoints were confirmed thrombotic events and secondary endpoints included confirmed APTC events, along with confirmed investigator-reported

Hypertension and edema adverse events did not fall into either category, but the External Safety Monitoring Board members monitored the incidence of hypertension and edema as well.⁸⁶ An increase in hypertension in the Vioxx arm was not unexpected because increased blood pressure was a known side effect of Vioxx (as with all non-selective NSAIDs).

The following Section reviews the External Safety Monitoring Board's monitoring of APPROVe Trial safety data from the beginning of the trial through its early termination in September 2004.

- (i) The first two years:
November 2001 - November 2003.

For the first two years of the APPROVe Trial – November 2001 through November 2003 – the number of confirmed cardiovascular adverse events on Vioxx relative to placebo increased steadily, but the overall numbers remained small and the between-treatment difference did not reach statistical significance. As discussed below, the External Safety Monitoring Board members closely monitored and expressed concern about cardiovascular safety data throughout that period but did not conclude that the trial should be terminated on the basis of those data.

cardiovascular events. See 5/6/03 Statistical Data Analysis Plan for Protocol 203, MRK-AAD0200169, at 80-81.

⁸⁶ Minutes of 1/23/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000097, at 97; Minutes of 8/7/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000103, at 03.

a. January 2002: First review of unblinded safety data.

Dr. Quan presented unblinded safety data to the External Safety Monitoring Board for the first time at its second meeting, held on January 23, 2002.⁸⁷ Dr. Quan had been unblinded one week before the meeting, and the data were not yet “clean,” meaning that the data were raw and had yet to be reviewed for inaccuracies.⁸⁸

The External Safety Monitoring Board noted “some trends” in thromboembolic events, but added that “it was not clear whether thromboembolic events had been adjudicated and what the process was for adjudicating events.”⁸⁹ The minutes of the January 2002 Closed Session meeting stated:

Due to the concerning nature of the [cardiovascular adverse event] trends, even though the numbers are small, we will be exercising diligence to review the data once they are cleaner and urge expeditious updating of the event database for the next look.⁹⁰

⁸⁷ Minutes of 1/23/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000097, at 97.

⁸⁸ Minutes of 1/23/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000097, at 97.

⁸⁹ Minutes of 1/23/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000097, at 97. The pre-meeting report prepared by Dr. Quan for the January 2002 meeting stated that there were 11 “adjudicated thromboembolic” adverse events in the placebo treatment group compared to 24 events in the Vioxx treatment group. 1/21/02 Pre-Meeting Safety Report from H. Quan to APPROVe ESMB, MRK-AGO0006753, at 54. However, those events do not appear to have actually been adjudicated because the pre-meeting report prepared by Dr. Quan for the February 2002 meeting stated that as of February 5, 2002, only “20 of 45 reported cases have been adjudicated.” 2/11/02 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0006667, at 71. The pre-meeting report that Dr. Quan prepared for the External Safety Monitoring Board’s January 2002 meeting did not contain an analysis of APTC composite cardiovascular endpoint events. 1/21/02 Pre-Meeting Safety Report from H. Quan to APPROVe ESMB, MRK-AGO0006753.

⁹⁰ Minutes of 1/23/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000097, at 97.

The External Safety Monitoring Board scheduled a meeting the following month to monitor the adverse event trends that they had observed.⁹¹ The Board also specified a number of additional analyses of the cardiovascular, hypertension, and edema adverse event data for Dr. Quan to perform, including:

- classification of hypertension and edema events by severity;
 - classification of thrombotic events by type;
 - a summary of blood pressure differences between treatment groups (along with clarification of how “a ‘hypertension-related’ AE” was defined for purposes of the ongoing data analysis); and
 - Kaplan-Meier curves to illustrate whether and to what extent the rates of cardiovascular, edema and/or hypertension adverse events may have increased over time.⁹²
- b. Spring 2002: Requests for additional analyses.

Over the next few months, the External Safety Monitoring Board members made several additional requests of Dr. Quan and MRL to facilitate their review of the emerging data. First, in February 2002, the External Safety Monitoring Board expressed concern with “the delay of the [cardiovascular adverse event] adjudication process which has left out significant number [sic] of potential cases.”⁹³ As of February 2002, “only 20 of 45 events (44%) reported that met criteria for adjudication had been adjudicated,” of

⁹¹ Minutes of 1/23/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000097, at 97-98.

⁹² Minutes of 1/23/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000097, at 97-98.

⁹³ Minutes of 2/13/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000099; see also 2/25/02 letter from J. Neaton* to T. Simon, MRK-ABS0327073, at 73.

which 10 had been confirmed.⁹⁴ The External Safety Monitoring Board asked Merck to accelerate the adjudication process of adverse events because of the importance of reviewing “clean” adjudicated cardiovascular data.⁹⁵ Minutes of the External Safety Monitoring Board’s May 2002 Open Session meeting stated that the Board was “pleased with MRL’s effort for expediting the adjudication process.”⁹⁶

Second, in May 2002, the External Safety Monitoring Board members asked Dr. Quan to allow them to retain the pre-meeting safety reports rather than returning them to Dr. Quan after each meeting in accordance with Merck policy.⁹⁷ At that point in time, the number of adjudicated thrombotic adverse events “was small and did not differ substantially by treatment group (11 for Treatment A [placebo] and 16 for Treatment B [Vioxx]).”⁹⁸ The External Safety Monitoring Board members believed that retaining pre-meeting safety reports would “permit easy comparison of the safety results over time to assess how safety trends change.”⁹⁹ Merck suggested instead that Dr. Quan either return the previous report together with the new one to each External Safety Monitoring Board member before each meeting, or summarize key data from the previous reports in

⁹⁴ 2/25/02 letter from J. Neaton* to T. Simon, MRK-ABS0327073, at 73.

⁹⁵ Minutes of 2/13/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000099.

⁹⁶ Minutes of 5/16/02 APPROVe ESMB Open Session meeting, MRK-AFF0000100; see also 5/28/02 letter from J. Neaton* to T. Simon, MRK-ABS0387085.

⁹⁷ Minutes of 5/16/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000100, at 01.

⁹⁸ Minutes of 5/16/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000100, at 00; see also 5/9/02 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AFF0000318, at 21, 26.

⁹⁹ Minutes of 5/16/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000100, at 01.

each new report prepared.¹⁰⁰ Dr. Quan subsequently included relevant data from prior reports in each pre-meeting report.

c. August 2002 – May 2003.

In August 2002, the External Safety Monitoring Board members sought additional data analyses and trial procedures relating to hypertension. The External Safety Monitoring Board noted at that time that there was an increased number of patients with stage 2 or 3 hypertension during follow-up visits and that not all patients with elevated blood pressure at follow-up appeared to have been reported as having hypertension adverse events.¹⁰¹ The External Safety Monitoring Board further noted that while the number of cardiovascular adverse events was still small with no “nominally significant” between-treatment differences, there “appear[ed] to be clear differences in BP [blood pressure] and edema events between treatments.”¹⁰²

The External Safety Monitoring Board members asked Merck to establish procedures for “referring . . . patients [with stage 2 or 3 hypertension] for re-measurement

¹⁰⁰ Minutes of 5/16/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000100, at 01.

¹⁰¹ Minutes of 8/7/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000103, at 03. Stage 2 hypertension is defined as blood pressure greater than 160/100; Stage 3 hypertension, at the time of the External Safety Monitoring Board’s August 2002 meeting, was defined as blood pressure greater than 180/110. Kaplan* NM. Systemic Hypertension: Mechanisms and Diagnosis. In: Braunwald* E, Zipes* DP, Libby* P, eds. Heart Disease. 6th ed. Philadelphia, PA: W.B. Saunders Company; 2001:944. Some clinicians now fold Stage 3 hypertension into the definition of Stage 2 hypertension while others maintain the previous definitions. See, e.g., “Hypertension: Blood Pressure Basics,” <http://www.webmd.com/content/article/96/103783.htm>; Kaplan* NM. Systemic hypertension: Mechanism and diagnosis. In: Zipes* DP, Libby* P, Boniow* RO, Braunwald* E, eds. Braunwald’s Heart Disease. 7th Ed. 2005:962.

¹⁰² Minutes of 8/7/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000103, at 04.

of BP (confirmation) and if necessary treatment or treatment modification.”¹⁰³ The External Safety Monitoring Board members also asked for clarification of “the definition of hypertension-related AEs [adverse events] and serious hypertension-related AEs,” and “why some patients who have BP elevations during follow-up do not have AE reports and why some who do [have adverse event reports] do not appear to have elevated follow-up BPs.”¹⁰⁴

In response to the External Safety Monitoring Board’s requests, Dr. Oxenius sent a letter to all trial investigators reminding them that “hypertension is known to be a possible side effect of all NSAIDs including VIOXX®.”¹⁰⁵ Dr. Oxenius further instructed investigators that “if clinically relevant increases in blood pressure are found in any APPROVe patient, he or she should undergo re-measurement of blood pressure and potential initiation or modification of antihypertensive therapy.”¹⁰⁶

Minutes from the August 7, 2002 Closed Session meeting of the External Safety Monitoring Board also noted that notwithstanding the “clear” between-treatment differences in hypertension and edema adverse events, “treatment differences for serious

¹⁰³ Minutes of 8/7/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000103, at 04; see also 8/20/02 letter from J. Neaton* to T. Simon, MRK-ABS0386152.

¹⁰⁴ Minutes of 8/7/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000103, at 04; see also 8/20/02 letter from J. Neaton* to T. Simon, MRK-ABS0386152.

¹⁰⁵ 9/27/02 example letter from B. Oxenius to R. Baerg*, MRK-AFO0045326; see also 11/15/02 letter from T. Simon to J. Neaton*, MRK-AFO0045323, at 23.

¹⁰⁶ 9/27/02 example letter from B. Oxenius to R. Baerg* MRK-AFO0045326; see also 11/15/02 letter from T. Simon to J. Neaton*, MRK-AFO0045323, at 23.

clinical AEs, which number 241 total, have become smaller.”¹⁰⁷ The same trend was noted in the minutes of the External Safety Monitoring Board’s following meeting on November 26, 2002, and it continued into the spring.¹⁰⁸

By the time of the External Safety Monitoring Board’s meeting on May 15, 2003, the External Safety Monitoring Board minutes noted that although the “treatment difference for serious AEs (404 patients total) was not nominally significant,” the “clear differences in BP and edema events between treatments” apparently remained.¹⁰⁹ In May 2003, based on cumulative safety data up to April 21, 2003 and adjudicated “data of deaths, thromboembolic events and PUB events received from the clinical/Epi groups on [April 16, 2003],”¹¹⁰ the relative risk for confirmed APTC composite endpoint events for Vioxx versus placebo was 1.23 (95% confidence interval, 0.60 to 2.52), suggesting a slightly increased risk in the Vioxx arm, although there were only 2 more events in the Vioxx arm than in the placebo arm.¹¹¹ The tables below summarize the data on

¹⁰⁷ Minutes of 8/7/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000103, at 04.

¹⁰⁸ Minutes of 11/26/02 APPROVe ESMB Closed Session meeting, MRK-AFF0000092, at 93.

¹⁰⁹ Minutes of 5/15/03 APPROVe ESMB Closed Session meeting, MRK-AFF0000113, at 14.

¹¹⁰ 5/8/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AFK0202981, at 97. Dr. Quan noted, in each pre-meeting report he prepared, the date that cumulative safety data were extracted from the Merck CTS database versus the date that adjudicated data on cardiovascular, mortality, and gastrointestinal events were received from the Clinical/Epidemiology groups. *See, e.g.*, 11/18/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0007185, at 85. Thus, hypertension and edema adverse events taken from the CTS database may have a different extraction date than adjudicated cardiovascular event data received from the Clinical/Epidemiology groups.

¹¹¹ 5/8/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AFK0202981, at 99, 08; Minutes of 9/17/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000124, at 24. As mentioned above, the APTC composite cardiovascular endpoint was the “primary” pre-specified

cardiovascular, hypertension, and edema adverse events that the External Safety

Monitoring Board reviewed as of their May 2003 meeting:

Table 1
Cardiovascular Adverse Event Data in the APPROVe Trial
Reviewed as of May 2003

Type of Adverse Event	APTC				Thrombotic			
	Treatment Group	A (Placebo)	B (Vioxx)	Relative Risk (95% CI)	P-Value	A (Placebo)	B (Vioxx)	Relative Risk (95% CI)
5/3/02 Data	7	12	1.783 (0.702-4.529)	0.2239	11	16	1.507 (0.700-3.248)	0.2948
7/25/02 Data	7	14	2.105 (0.850-5.216)	0.1078	12	19	1.668 (0.810-3.436)	0.1654
11/11/02 Data	9	16	1.873 (0.828-4.239)	0.1320	16	22	1.447 (0.760-2.755)	0.2611
4/16/03 Data	14	16	1.229 (0.600-2.518)	0.5735	20	25	1.343 (0.746-2.418)	0.3254

cardiovascular endpoint being tracked by the APPROVe External Safety Monitoring Board. The secondary pre-specified cardiovascular endpoint was the composite of confirmed thrombotic events as defined by Merck's Cardiovascular Adjudication SOP. At this meeting, the relative risk for this confirmed thrombotic event composite for Vioxx versus placebo was 1.34 (95% confidence interval, 0.75 to 2.42) based on 25 events in the Vioxx arm and 20 in the placebo arm. 5/8/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AFK0202981, at 97, 08.

Table 2
Hypertension and Edema Adverse Event Data in the APPROVe Trial
Reviewed as of May 2003

Type of Adverse Event	Hypertension				Edema			
	Treatment Group	A (Placebo)	B (Vioxx)	Relative Risk (95% CI)	P-Value	A (Placebo)	B (Vioxx)	Relative Risk (95% CI)
4/30/02 Data*	66	148	2.393 (1.790-3.198)	0.0000	26	58	2.320 (1.461-3.685)	0.0004
7/25/02 Data	86	193	2.437 (1.890-3.142)	0.0000	37	68	1.932 (1.294-2.883)	0.0013
11/11/02 Data	108	230	2.343 (1.864-2.945)	0.0000	44	77	1.851 (1.278-2.680)	0.0011
4/21/03 Data	134	269	2.239 (1.820-2.755)	0.0000	53	79	1.566 (1.106-2.218)	0.0116

*In April 2002, Merck's Adverse Event Reporting System converted from classifying adverse events according to CRISP terms – a less specific, non-industry standard adverse event dictionary – to MedDRA (Medical Dictionary for Regulatory Activities) terms, the industry standard used by the FDA. March/April 2002 presentation on MedDRA CTS Implementation, MRK-AFV0284205, at 06, 12; 8/4/05 deposition of D. Watson at 396-97 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).


(ii) November 24, 2003 External Safety
Monitoring Board meeting.

At the External Safety Monitoring Board's November 24, 2003 Closed Session meeting, External Safety Monitoring Board members expressed greater concern about the cardiovascular adverse event trend than they had previously. According to the minutes,

differences [between Vioxx and placebo] were noted in many categories of AEs including all reported CV events excluding non-CVD [cardiovascular disease] deaths, adjudicated/confirmed APTC/thromboembolic CV combined with CHF [congestive heart failure] AEs . . . hypertension-related AEs, edema-related AEs . . . AEs of cardiovascular system and AEs of renal and urinary disorders.¹¹²

¹¹² Minutes of 11/24/03 APPROVe ESMB Closed Session meeting, MRK-AFF0000117, at 17. As this passage indicates, the External Safety Monitoring Board had begun tracking, as of May 2003, a new non-pre-specified composite endpoint, consisting of all events falling into either of the two primary

The relative risk for confirmed APTC composite cardiovascular endpoint events for Vioxx versus placebo had risen to 1.40 (95% confidence interval, 0.74 to 2.64), based on 22 events in the Vioxx treatment group and 17 events in the placebo treatment group.¹¹³ The difference in the number of patients in the Vioxx treatment group versus those in the placebo group experiencing stage two hypertension as measured in follow-up visits had also increased.¹¹⁴ The External Safety Monitoring Board members noted:¹¹⁵



The ESMB recommended the tabulation of consent and lost to follow up by treatment group results should also be provided. In addition, assessment of the relationship between blood

The number of primary CV adverse events (A) treatment and there was no convincing evidence for the hard endpoints and the differences for the worrisome and the ESMB felt close monitoring

The number of primary CV adverse events (APTC) was still small and the between-treatment difference was not statistically significant. For these “harder” clinical events there was no convincing evidence of a safety problem; however, the trend for the APTC hard endpoints and the differences for the other safety outcomes noted above were worrisome and the ESMB felt close monitoring of accumulating data was important.

composite cardiovascular endpoints (the APTC composite cardiovascular endpoint or the confirmed thrombotic endpoint) plus reported (unadjudicated) cases of congestive heart failure, pulmonary edema, and cardiac failure. 5/8/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AFK0202981, at 983, 008.

¹¹³ Minutes of 9/17/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000124, at 24; 11/18/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0007185, at 99. The relative risk for confirmed thrombotic events for Vioxx versus placebo was 1.49 (95% confidence interval, 0.88 to 2.52) based on 33 events in the Vioxx treatment group and 24 events in the placebo treatment group. 11/18/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0007185, at 99.

¹¹⁴ Minutes of 11/24/03 APPROVe ESMB Closed Session meeting, MRK-AFF0000117, at 17.

¹¹⁵ Minutes of 11/24/03 APPROVe ESMB Closed Session meeting, MRK-AFF0000117, at 18.

To better monitor the accumulating data, the External Safety Monitoring Board requested additional procedures regarding the collection and analysis of mortality data, in particular on patients who had discontinued the study.¹¹⁶ The External Safety Monitoring Board had tracked patient discontinuation as it steadily increased from 15.4% at the end of July 2002,¹¹⁷ to 18.1% in November 2002,¹¹⁸ to 22% in May 2003,¹¹⁹ and finally to 24% in November 2003.¹²⁰ The primary reason for patient discontinuation was an adverse event (not necessarily cardiovascular in nature), and the second most common reason was the more opaque “withdrawal of consent.”¹²¹

Under the terms of the APPROVe Trial Protocol, mortality data were collected (i) for patients who were actively enrolled in the trial at the time of death and (ii) for those who died within 14 days of having completed or discontinued the study.¹²² Mortality data were not collected beyond the pre-specified 14-day period.¹²³ To gain a

¹¹⁶ Minutes of 11/24/03 APPROVe ESMB Closed Session meeting, MRK-AFF0000117, at 18.

¹¹⁷ Minutes of 8/7/02 APPROVe APPROVe ESMB Open Session meeting, MRK-AFF0000103.

¹¹⁸ Minutes of 11/26/02 APPROVe APPROVe ESMB Open Session meeting, MRK-AFF0000091, at 91.

¹¹⁹ Minutes of 5/15/03 APPROVe ESMB Open Session meeting, MRK-AFF0000112, at 12.

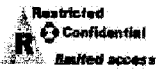
¹²⁰ Minutes of 11/24/03 APPROVe ESMB Open Session meeting, MRK-AFF0000116, at 16.

¹²¹ Minutes of 9/9/04 Administrative Committee meeting, MRK-ACM0000715, at 15.

¹²² 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111, at 160, 167. This 14-day post-discontinuation cut-off applied to the reporting of all serious adverse experiences. Id. at 167.

¹²³ One exception, as stated in the Protocol, was that “any serious adverse experience considered by the investigator to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator at any time outside of the [14-day post discontinuation] time period . . . must be reported immediately.” Further, the Protocol stated that “any adverse experiences

fuller understanding of study discontinuations and patient mortality that may have been due to cardiovascular events, the External Safety Monitoring Board decided at its November 24, 2003 Closed Session meeting to ask MRL to consider collecting additional mortality data.¹²⁴



The ESMB recommended the tabulation of discontinuation rates due to withdrawal of consent and lost to follow up by treatment group in the future updates. Adjudicated PUB results should also be provided. In addition, the ESMB would like to see some kind of assessment of the relationship between blood pressure levels and CV events.

The number of primary CV adverse events (APTC) was still small and the between-treatment difference was not statistically significant. For these "harder" clinical events there was no convincing evidence of a safety benefit. The ESMB felt close monitoring of these events was warranted and the ESMB felt close monitoring of these events was warranted.

The ESMB recommended the study be continued through the end of the trial irrespective of whether participants discontinue from the trial or stay in the trial.

The ESMB . . . would like MRL to consider the collection of mortality data on all participants through the end of the trial irrespective of whether the participants are taking study treatment, discontinue from the trial or stay in the trial.

Accordingly, Dr. Neaton* sent a letter to Dr. Simon setting forth the External Safety Monitoring Board's request.¹²⁵ Both Merck and the APPROVe Trial

which are present at the time of discontinuation/withdrawal" should be "followed up for outcome." 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111, at 160, 167.

¹²⁴ Minutes of 11/24/03 APPROVe ESMB Closed Session meeting, MRK-AFF0000117, at 18. Dr. Bjorkman* stated that the External Safety Monitoring Board tracked the discontinuation rate and requested that MRL collect data past the pre-specified 14-day period after a patient discontinued from the study because of concern that cardiovascular effects may take longer than 14 days to manifest.

¹²⁵ 11/25/03 letter from J. Neaton* to T. Simon, MRK-AFL0000978.

Administrative Committee agreed to amend the Protocol and informed consent form to collect mortality data on all patients who discontinued the trial.¹²⁶

In addition to an updated safety report on the APPROVe Trial, the External Safety Monitoring Board at the Open Session of its November 24, 2003 meeting received an update on cardiovascular data from Protocols 078 and 091, two of Merck's three placebo-controlled trials of the efficacy of Vioxx in slowing the onset and/or progression of Alzheimer's disease. (The third Alzheimer's trial, Protocol 126, had been terminated early when Protocol 091 showed no efficacy, and was excluded from the update.)¹²⁷

The Alzheimer's disease data, which were presented by Dr. Alise Reicin, showed that the relative risk for confirmed thrombotic events for Vioxx 25 mg versus placebo was 1.01 (95% confidence interval, 0.67 to 1.53).¹²⁸ "Similar results were observed for the APTC combined endpoint."¹²⁹ (A relative risk of 1.0 means that risk is equal in both arms of the study.) The External Safety Monitoring Board requested "full safety reports

¹²⁶ 2/9/04 letter from R. Joseph and B. Oxenius to J. Neaton*, MRK-ABS0399128; Minutes of 2/9/04 Administrative Committee meeting, MRK-AFN0001694, at 94; Minutes of 2/18/04 APPROVe ESMB Open Session meeting, MRK-AFF0000120, at 20; 3/2/04 letter from J. Neaton* to K. Horgan, MRK-AFO0066556.

¹²⁷ Minutes of 11/24/03 APPROVe ESMB Open Session meeting, MRK-AFF0000116, at 17.

¹²⁸ Minutes of 11/24/03 APPROVe ESMB Open Session meeting, MRK-AFF0000116, at 17; 12/12/03 Alzheimer's Disease Combined Safety Analysis, MRK-AFL0059959, at 64.

¹²⁹ 12/12/03 Alzheimer's Disease Combined Safety Analysis, MRK-AFL0059959, at 64. The relative risk of APTC composite cardiovascular endpoint events for Vioxx versus placebo was 0.96 (95% confidence interval, 0.60 to 1.52). Id. at 60022.

for these two studies combined including results of deaths, SAEs [serious adverse events], edema-related AEs and hypertension-related AEs when they are available.”¹³⁰

(iii) February 18, 2004 and March 1, 2004 meetings.

The External Safety Monitoring Board next met three months later, on February 18, 2004. At the Open Session, Dr. Reicin, as requested, presented further safety results, including mortality data, from Protocols 078 and 091.¹³¹ Although the overall relative risks for Vioxx versus placebo in Protocols 078 and 091 were “very close to 1.0 for both adjudicated confirmed thrombotic CV events and APTC events” (42 thrombotic events on Vioxx versus 48 events on placebo, and 33 APTC events on Vioxx versus 40 on placebo), the relative risk for Vioxx versus placebo of all-cause mortality, which had been tracked up to 14 days after discontinuation, was 2.23 (95% confidence interval, 1.33 to 3.73).¹³² In addition, for both confirmed thrombotic cardiovascular serious adverse events and confirmed APTC composite cardiovascular endpoint events, the relative risk for Vioxx versus placebo was less than 1.0 for the first 18 months of continuous treatment during the trial – meaning that the risk of experiencing a confirmed

¹³⁰ Minutes of 11/24/03 APPROVe ESMB Open Session meeting, MRK-AFF0000116, at 17. The Alzheimer’s disease mortality data had been the subject of discussion within Merck and between Merck and the FDA in 2001 and 2002. See Appendices J and O.

¹³¹ Minutes of 2/18/04 APPROVe ESMB Open Session meeting, MRK-AFF0000120, at 20.

¹³² Minutes of 2/18/04 APPROVe ESMB Open Session meeting, MRK-AFF0000120, at 20; 12/12/03 Alzheimer’s Disease Combined Safety Analysis, MRK-AFL0059959, at 60000, 60022. The Alzheimer’s Disease Combined Safety Analysis was included in the background material for the 2/18/04 APPROVe External Safety Monitoring Board Open Session meeting. 2/13/04 email from H. Quan to R. Joseph *et al.*, MRK-AFL0069950-51, attaching 12/12/03 Alzheimer’s Disease Combined Safety Analysis, MRK-AFL0059959.

thrombotic or APTC composite cardiovascular endpoint event on Vioxx was less than on placebo during this time period – then rose above 1.0 for the remainder of the trial.¹³³

The relative risks for confirmed APTC composite cardiovascular endpoint events in Protocols 078 and 091 combined, broken down into 6-month time intervals, are shown in the table below:¹³⁴

Table 3
Incidence Rates Over Time of Confirmed APTC Composite Cardiovascular
Endpoint Events of Vioxx vs. Placebo in Protocols 078 and 091 Combined

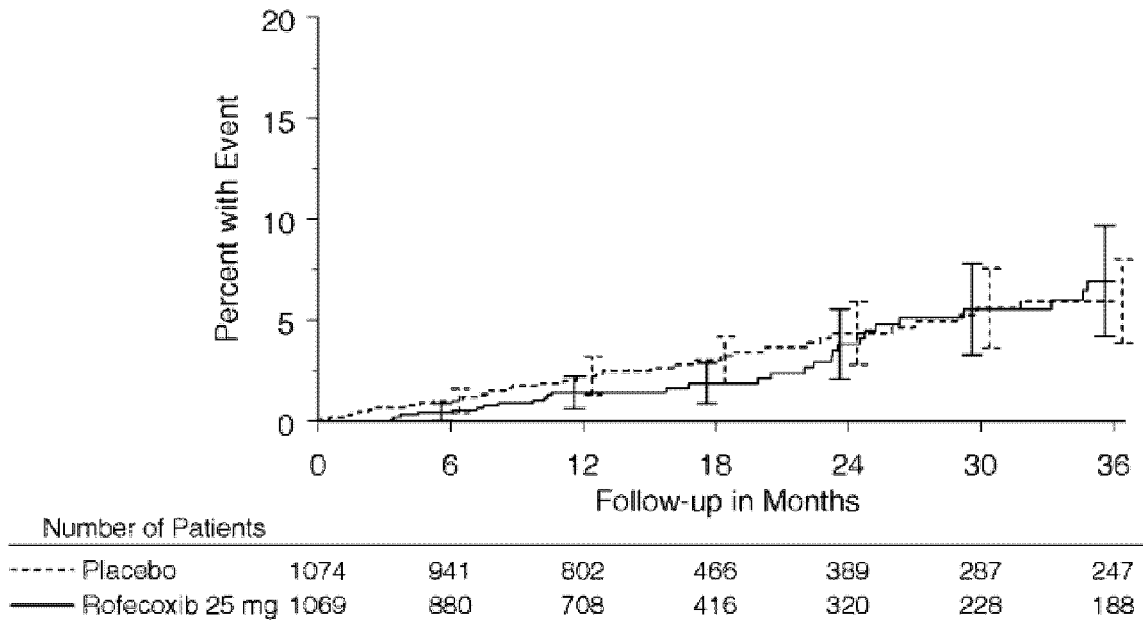
Time Interval	Rofecoxib 25 mg			Placebo			Relative Risk [†] (95% CI)
	Number At Risk	Cases/PYR (Rate [‡])	95% CI	Number At Risk	Cases/PYR (Rate [‡])	95% CI	
0 to 6 Month	1069	4/482 (0.83)	(0.31, 2.21)	1074	10/501 (2.00)	(1.07, 3.71)	0.416 (0.130, 1.326)
6 to 12 Month	830	8/399 (2.01)	(1.00, 4.01)	941	11/435 (2.53)	(1.40, 4.57)	0.793 (0.319, 1.971)
12 to 18 Month	708	2/243 (0.82)	(0.21, 3.29)	802	5/320 (1.56)	(0.65, 3.75)	0.527 (0.102, 2.715)
18 to 24 Month	416	7/185 (3.78)	(1.80, 7.94)	466	6/216 (2.78)	(1.25, 6.18)	1.362 (0.458, 4.053)
24 to 30 Month	320	5/131 (3.82)	(1.59, 9.17)	389	4/159 (2.52)	(0.94, 6.70)	1.517 (0.407, 5.650)
30 to 36 Month	228	3/105 (2.86)	(0.92, 8.86)	287	1/134 (0.75)	(0.11, 5.30)	3.829 (0.398, 36.808)
>36 Month	188	4/124 (3.23)	(1.21, 8.60)	247	3/164 (1.83)	(0.59, 5.67)	1.763 (0.395, 7.879)

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

The Kaplan-Meier time-to-event curves illustrating the cumulative incidence of APTC composite cardiovascular endpoint events in Protocols 078 and 091 are reproduced below:¹³⁵

¹³³ 12/12/03 Alzheimer's Disease Combined Safety Analysis, MRK-AFL0059959, at 60020, 60024.
¹³⁴ 12/12/03 Alzheimer's Disease Combined Safety Analysis, MRK-AFL0059959, at 60024. A corresponding table for confirmed thrombotic events showed a similar distribution of relative risk. 12/12/03 Alzheimer's Disease Combined Safety Analysis, MRK-AFL0059959, at 60020.
¹³⁵ 12/12/03 Alzheimer's Disease Combined Safety Analysis presented at 2/18/04 APPROVe ESMB Open Session meeting, MRK-AFL0059959, at 60025. The corresponding Kaplan-Meier curves based on confirmed thrombotic events showed a similar pattern. 12/12/03 Alzheimer's Disease Combined Safety Analysis, MRK-AFL0059959, at 60021.

Figure 1
Kaplan-Meier Curves of Time to Confirmed APTC Composite Cardiovascular
Endpoint Event in Protocols 078 and 091 Combined



According to Mr. Bolognese, the Open Session attendees did not view these crossed curves as signaling an actual change in risk or as evidence that Vioxx was prothrombotic, because the overall relative risk for Vioxx in the Alzheimer’s disease studies was similar to that of placebo. Dr. Reicin concluded that the crossed curves were due to chance variances around the mean and did not signify an actual change in the thrombotic risk attributable to Vioxx, an opinion that Dr. Peter Kim (who did not attend the meeting) shared.¹³⁶ Dr. Kim has testified that, in his view, if one believes that the

¹³⁶ 3/16/05 deposition of P. Kim at 532-33 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

increase in hazard rate in the latter half of the curve demonstrates that Vioxx is prothrombotic, then it stands to reason that the first half of the curve indicates that Vioxx is cardioprotective for the first 18 months of continuous use, an unlikely occurrence.¹³⁷ The External Safety Monitoring Board members requested additional safety information from Protocols 078 and 091, as well as the safety report from the third Alzheimer's disease trial, Protocol 126.¹³⁸

In the Closed Session of the February 18, 2004 meeting, the External Safety Monitoring Board members, increasingly concerned by the trend in cardiovascular adverse event data in the APPROVe Trial, weighed the pros and cons of continuing the trial.¹³⁹ Based on the adjudicated and confirmed cardiovascular safety data received on January 30, 2004 from the Clinical/Epidemiology groups, there were 26 confirmed APTC composite cardiovascular endpoint events in the Vioxx arm and 16 in the placebo arm.¹⁴⁰ The relative risk of confirmed APTC composite cardiovascular endpoint events for Vioxx versus placebo had risen to 1.77 (95% confidence interval, 0.95 to 3.29), but the

¹³⁷ 3/16/05 deposition of P. Kim at 504, 532 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

¹³⁸ Minutes of 2/18/04 APPROVe ESMB Open Session meeting, MRK-AFF0000120, at 21.

¹³⁹ Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 21-22.

¹⁴⁰ Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 21-22; 2/12/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0006866, at 81.

underlying between-treatment difference on which it was based was still not statistically significant.¹⁴¹

The External Safety Monitoring Board noted that, although “the number of primary CV adverse events (APTC) was still small . . . and the between-treatment difference was not statistically significant . . . the trend for the APTC hard endpoint and the differences for the other safety outcomes noted above continued to be worrisome.”¹⁴² While the Board noted that the between-treatment difference in APTC composite cardiovascular endpoint events “could be due to chance,” it also noted that “this is less likely for all reported thromboembolic outcomes where the difference is larger.”¹⁴³ In fact, the between-treatment differences in both investigator-reported cardiovascular events and also in confirmed thrombotic events had reached statistical significance, a fact that was reflected in the pre-meeting report prepared by Dr. Quan.¹⁴⁴

¹⁴¹ Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 22. The 95% confidence interval for the relative risk of 1.77 ranged from 0.95 to 3.29, with an associated p-value of 0.07. 2/12/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0006866, at 81.

¹⁴² Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 22.

¹⁴³ Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 22. The relative risk for all reported (regardless of status of adjudication) APTC composite cardiovascular endpoint events or thrombotic events (excluding non-cardiovascular death) was 1.83 (95% confidence interval, 1.24 to 2.71) with a p-value less than 0.01. This reflected 67 such events on Vioxx versus 40 on placebo. 2/12/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0006866, at 81.

¹⁴⁴ 2/12/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0006866, at 81. The relative risk of confirmed thrombotic events for Vioxx versus placebo was 1.75 (95% confidence interval, 1.04 to 2.94) with a p-value of 0.04. This reflected 37 confirmed thrombotic events on Vioxx versus 23 on placebo. *Id.* The minutes of the February 18, 2004 External Safety Monitoring Board Closed Session meeting do not specifically reference the fact that the between-treatment difference in confirmed thrombotic events was statistically significant. Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 21-22.

The cumulative cardiovascular, hypertension, and edema adverse event data that the External Safety Monitoring Board had reviewed as of February 2004 are summarized in the tables below.

Table 4
Cardiovascular Adverse Event Data in the APPROVe Trial
Reviewed as of February 2004

Type of Adverse Event	APTC				Thrombotic			
	Treatment Group	A (Placebo)	B (Vioxx)	Relative Risk (95% CI)	P-Value	A (Placebo)	B (Vioxx)	Relative Risk (95% CI)
11/11/02 Data	9	16	1.873 (0.828-4.239)	0.1320	16	22	1.447 (0.760-2.755)	0.2611
4/16/03 Data	14	16	1.229 (0.600-2.518)	0.5735	20	25	1.343 (0.746-2.418)	0.3254
11/5/03 Data	17*	22	1.402 (0.744-2.640)	0.2957	24*	33	1.488 (0.880-2.518)	0.1384
1/30/04 Data	16	26	1.765 (0.947-3.291)	0.0737	23	37	1.745 (1.037-2.936)	0.0361

* As explained in the pre-meeting report circulated by Dr. Quan before the February 2004 External Safety Monitoring Board meeting, there was an additional event in Treatment Group A in the November 2003 pre-meeting report because “one patient who was assigned an ‘acute MI’ in the previous (November 03) data base did not actually have the event in this safety update.” 2/12/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0006866, at 66.

Table 5
Hypertension and Edema Adverse Event Data in the APPROVe Trial
Reviewed as of February 2004

Type of Adverse Event	Hypertension				Edema			
	Treatment Group	A (Placebo)	B (Vioxx)	Relative Risk (95% CI)	P-Value	A (Placebo)	B (Vioxx)	Relative Risk (95% CI)
11/11/02 Data	108	230	2.343 (1.864-2.945)	0.0000	44	77	1.851 (1.278-2.680)	0.0011
4/21/03 Data	134	269	2.239 (1.820-2.755)	0.0000	53	79	1.566 (1.106-2.218)	0.0116
11/11/03 Data*	92	193	2.303 (1.796-2.952)	0.0000	55	83	1.586 (1.128-2.231)	0.0080
2/4/04 Data	174	327	2.167 (1.803-2.605)	0.0000	58	84	1.549 (1.108-2.164)	0.0104

*As previously mentioned, Merck began using MedDRA terms to classify adverse events beginning in April 2002. MedDRA was updated annually with new versions every March and September. Merck implemented new MedDRA versions within two months of their receipt. March/April 2002 presentation on MedDRA CTS Implementation, MRK-AFV0284205, at 06, 08. In November 2003, Dr. Quan was still using MedDRA definitions from April 2003, so it is unclear why the cumulative number of hypertension adverse events is less than in the previous pre-meeting report. 11/18/03 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0007185, at 09. The decrease in the number of hypertension-related adverse events is not mentioned in the minutes of the External Safety Monitoring Board meeting on November 24, 2003. Minutes of 11/24/03 APPROVe ESMB Closed Session meeting, MRK-AFF0000117-18.

After the February 18, 2004 Closed Session meeting, the External Safety Monitoring Board members continued to discuss in post-meeting emails whether or not to modify or terminate the study.¹⁴⁵ On February 20, 2004, Dr. Neaton* wrote to Drs. Bjorkman*, Konstam*, and Logan*:¹⁴⁶

¹⁴⁵ 2/20/04 email from J. Neaton* to D. Bjorkman*, M. Konstam*, R. Logan*, and H. Quan, MRK-AGO0028233, at 33; 2/21/04 email correspondence between J. Neaton* and M. Konstam*, JDN 03878-79.

¹⁴⁶ 2/20/04 email from J. Neaton* to D. Bjorkman*, M. Konstam*, R. Logan*, and H. Quan, MRK-AGO0028233, at 33.

To: david.bjorkman@hsc.utah.edu <david.bjorkman@hsc.utah.edu>; Konstam, Marvin
<mkonstam@tufts-nemc.org>; Richard.Logan@nottingham.ac.uk <Richard.Logan@nottingham.ac.uk>; Quan,
Hui <hui_quan@merck.com>
From: James Neaton <jim@cchr.umn.edu>
Cc:
Bcc:
Received Date: 2004-02-20 21:28:49
Subject: Follow-up to APPROVe Call

David, Marv, and Richard,

In follow-up to our call earlier this week, attached are some points
for discussion and your consideration before our next call on
March 1 at 1PM EST.

1. With Hui's help, attached is a summary of lines 3 and 7 of Table 6
from earlier reviews. I think this history will be helpful in
assessing the role of chance in our decision.

2. One argument for recommending stopping now is that if the results
remain as we currently see them, they will be interpreted as very damning
to the drug. Thus, if we think that the results are not going to change,
we should alert people now. The difference in the number of events
observed between May 03 and Feb 04 probably may be a good estimate
many new events will be added between now and Nov 04. If so, we will
12 APTC events and 29 TE or APTC events excluding CVD

It seems likely that the line 7 difference will remain significant in Nov
04. However, there is much more uncertainty about the primary endpoint
(line 3). Another 7 events, could substantially attenuate the difference
or could make the difference nominally significant.

3. Another argument is that in our reviews we are only looking at the risk side of the equation. The 3-year data indicated a treatment effect on colorectal cancer. Week 52 data indicated a treatment effect on polyps. The 3-year data are needed to balance risk and benefits.

One argument for recommending stopping now is that if the results remain as we currently see them, they will be interpreted as very damning to the drug. Thus, if we think that the results are not going to change, we should alert people now.

Another argument is that in our reviews we are only looking at the risk side of the equation. There may be favorable effects on colorectal cancer. Week 52 data indicated a treatment effect on polyps. The 3-year data are needed to balance risk and benefits.

Dr. Neaton^{*}, the biostatistician on the External Safety Monitoring Board, also attached a few tables summarizing some of the cardiovascular data that had been presented by Dr. Quan to the Board in advance of each of their prior meetings, noting that “this history will be helpful in assessing the role of chance in our decision.”¹⁴⁷

In a subsequent email, Dr. Neaton^{*} suggested that “if patients develop stage 2 hypertension they should be taken off study treatment,” and noted that Dr. Quan was “running some analyses that might change or enforce that view.”¹⁴⁸ However,

¹⁴⁷ 2/20/04 email from J. Neaton^{*} to D. Bjorkman^{*}, M. Konstam^{*}, R. Logan^{*}, and H. Quan, MRK-AGO0028233, at 33, attaching “CV summary over time,” MRK-AGO0028235.

¹⁴⁸ 2/21/04 email from J. Neaton^{*} to M. Konstam^{*}, JDN 03879.

Dr. Neaton* advised against stopping the trial based on the APTC composite cardiovascular endpoint because the numbers were too small.¹⁴⁹ In response to Dr. Neaton's* suggestion, Dr. Konstam* questioned whether taking patients with stage two hypertension out of the study would "dampen the magnitude of adverse drug effect during the remaining months of the trial," increasing the likelihood of a less or non-significant outcome and leading to "the conclusion that our quick judgment now is truth: that the only patients at risk are those with elevated blood pressures."¹⁵⁰

On March 1, 2004, the External Safety Monitoring Board held a special meeting to review analyses, prepared by Dr. Quan, on the relationship between blood pressure and cardiovascular events in the APPROVe Trial and to "reach consensus on whether the trial should continue as planned, by [sic] stopped, or be modified."¹⁵¹ The results of these analyses indicated that over 150 patients in the trial had stage two hypertension upon entering the trial and that more patients with baseline elevated blood pressure had discontinued from the Vioxx arm than from the placebo arm.¹⁵² In addition, "stage 2 hypertension during follow-up visits [was] associated with a 2.5 fold increased risk for

¹⁴⁹ 2/21/04 email from J. Neaton* to M. Konstam*, JDN 03879.

¹⁵⁰ 2/21/04 email from M. Konstam* to J. Neaton*, JDN 03879.

¹⁵¹ 2/29/04 email from J. Neaton* to H. Quan (cc: D. Bjorkman*, M. Konstam*, R. Logan*), MRK-AGO0028236-37, attaching 2/26/04 analyses for 3/1/04 APPROVe ESMB meeting, MRK-AGO0028241-49; Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 21.

¹⁵² Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 21; 2/29/04 email from J. Neaton* to H. Quan (cc: D. Bjorkman*, M. Konstam*, R. Logan*), MRK-AGO0028236-37.

CV events.”¹⁵³ The data also showed, however, that the between-treatment difference in the risk of cardiovascular events was not confined to those patients with elevated blood pressure levels at baseline. Indeed, patients with lower baseline blood pressure levels demonstrated greater between-treatment differences in cardiovascular events than those with higher baseline blood pressure.¹⁵⁴ According to Drs. Bjorkman* and Konstam* the External Safety Monitoring Board members discussed hypertension and its association with cardiovascular adverse events, but did not reach any definitive conclusions.

After considering all the data, and factoring in that there were likely to be few adverse events between this meeting and the completion of the study, the External Safety Monitoring Board members “recommended the study continue as planned.”¹⁵⁵

¹⁵³ Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 21; 2/29/04 email from J. Neaton* to H. Quan (cc: D. Bjorkman*, M. Konstam*, R. Logan* MRK-AGO0028236-37.

¹⁵⁴ Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 21; 2/29/04 email from J. Neaton* to H. Quan (cc: D. Bjorkman*, M. Konstam*, R. Logan* MRK-AGO0028236-37.

¹⁵⁵ Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 22.



between-treatment differences were greater for those at lower risk of developing Stage 2 hypertension in the control group during treatment.

The number of primary CV adverse events (APTC) was still small (16 versus 13) and the between-treatment difference was not statistically significant. However, the APTC hard endpoint and the differences for the other safety outcomes noted in the interim analyses had become smaller on subsequent reviews. The difference in outcomes could be due to chance; however, that is less likely for all reported thromboembolic outcomes where the difference is larger. Since few events occurred between now and the end of the trial due to completion of year 3 examinations and discontinuations, the safety data in the report is not likely to change much.

The ESMB considered all of these data and decided it was important to finish the trial to obtain the Year 3 efficacy data so that an overall benefit/risk assessment could be made. The ESMB recommended the study continue as planned with one exception. The

Since few events will occur between now and the end of the trial due to completion of year 3 examinations and discontinuations, the safety data in the report is not likely to change much.

The ESMB considered all of these data and decided it was important to finish the trial to obtain the Year 3 efficacy data so that an overall benefit/risk assessment could be made.


The External Safety Monitoring Board requested, however, that Merck “more aggressively treat patients who have hypertension and . . . discontinue treatment for those patients whose blood pressure is not controlled.”¹⁵⁶

(iv) September 17, 2004 External Safety
Monitoring Board meeting.

On Friday, September 17, 2004, the APPROVe Trial External Safety Monitoring Board members met telephonically to review cumulative confirmed cardiovascular safety

¹⁵⁶ Minutes of 2/18/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000121, at 22. Dr. Neaton* communicated this request to Merck in a March 2, 2004 letter to Dr. Kevin Horgan, Dr. Simon’s replacement and the person to whom the APPROVe Trial clinical monitors reported after Dr. Simon left his position as head of the Gastroenterology group. Specifically, Dr. Neaton* advised Merck to discontinue study treatment for those patients who developed uncontrolled hypertension defined (as in the APPROVe Trial Protocol) as blood pressure >95 mm Hg diastolic or >165 mm Hg systolic with antihypertensive medication. 3/2/04 letter from J. Neaton* to K. Horgan, MRK-AKS0002770.

data through August 16, 2004, the contents of which prompted them to recommend that the study be terminated.¹⁵⁷ According to the minutes:¹⁵⁸



Final

APPROVe ESMB MEETING MINUTES

Mtg Date: 17-September- 2004

Closed Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James

Cumulative safety data up to 8/16/04 were reviewed. Significant between-treatment differences were observed in many categories of AEs including adjudicated/confirmed APTC and adjudicated/confirmed thromboembolic CV events. These adjudicated findings were supported by the unadjudicated (all reported) event analysis and by adverse trends in a heart failure, pulmonary edema and cardiac failure composite outcome. In addition, as before, more patients on treatment B than treatment A are experiencing stage 2 hypertension (DBP 100+ or SBP 160+ mmHg) during follow-up. average DBP and SBP are increased by about 2 and 4 mmHg, respectively, on treatment B.

Significant between-treatment differences were observed in many categories of AEs including adjudicated/confirmed APTC and adjudicated/confirmed thromboembolic CV events. These adjudicated findings were supported by the unadjudicated (all reported) event analysis and by adverse trends in a heart failure, pulmonary edema and cardiac failure composite outcome. In addition, as before, more patients on treatment B [Vioxx] than treatment A are experiencing stage 2 hypertension (DBP 100+ or SBP 160+ mmHg) during follow-up.


Although the External Safety Monitoring Board had noted a cardiovascular adverse event trend against Vioxx beginning at its January 23, 2002 meeting, the numbers of cardiovascular events had been small and the between-treatment differences had not been statistically significant.¹⁵⁹ At the September 17, 2004 meeting, however, for the first time, the between-treatment differences in confirmed APTC composite

¹⁵⁷ Minutes of 9/17/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000124, at 24; see also Notes of H. Quan, MRK-AGO0035920, at 20; 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 17.

¹⁵⁸ Minutes of 9/17/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000124, at 24.

¹⁵⁹ Minutes of 1/23/02 APPROVe Closed Session ESMB meeting, MRK-AFF0000097, at 97; 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 33.

cardiovascular endpoint events reached statistical significance based on 33 events in the Vioxx treatment group and 16 events in the placebo treatment group (relative risk 2.25; 95% confidence interval, 1.24 to 4.08).¹⁶⁰ The minutes of the External Safety Monitoring Board noted:¹⁶¹



Final

APPROVe ESMB MEETING MINUTES

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The trend for excess risk for treatment B [Vioxx] for confirmed APTC events has continued to grow at each meeting over the last 1-2 years. In May 2003, the hazard ratio was 1.2; in November 2003 it was 1.4; last February it 1.8; and currently it is 2.2. Whereas there was an excess of 2 events on treatment B [Vioxx] in May 2003, there are now 17.

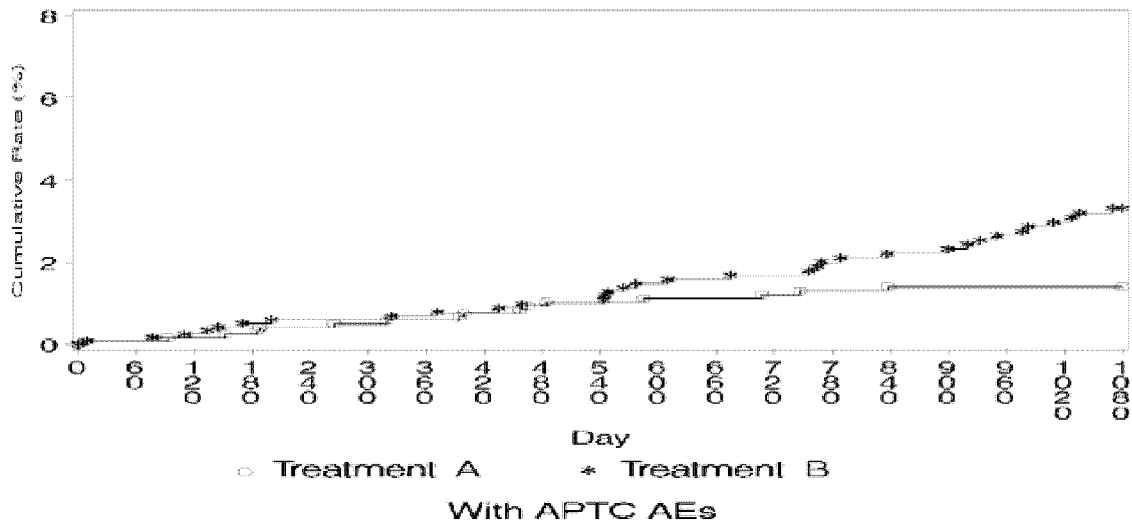
The pre-meeting safety update report prepared by Dr. Quan for the External Safety Monitoring Board members included the Kaplan-Meier plot excerpted in Figure 2

¹⁶⁰ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 33. As noted above, the between-treatment difference in confirmed thrombotic events had reached statistical significance by the February 18, 2004 meeting. 2/12/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0006866, at 81.

¹⁶¹ Minutes of 9/17/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000124, at 24.

below, reflecting the cumulative incidence of confirmed APTC composite cardiovascular endpoint events in the trial through August 16, 2004:¹⁶²

Figure 2
Kaplan-Meier Curves of Confirmed APTC Composite Cardiovascular Endpoint Events
in the APPROVe Trial



The vertical axis of the Kaplan-Meier plot, which measures cumulative rate, is the estimated probability of experiencing an APTC composite cardiovascular endpoint event with continuous use of each treatment as measured in days along the horizontal axis. The above chart reflected that the increased risk of confirmed APTC composite cardiovascular endpoint events in the Vioxx treatment group became apparent after 18 months of continuous use of Vioxx and continued to rise thereafter. According to

¹⁶² 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 36. Kaplan-Meier curves plot the incidence of patient events over time, taking into account patient drop-out and treatment for different amounts of time.

Dr. Kim, the between-treatment difference in APTC composite cardiovascular endpoint events became statistically significant by approximately 30 months of continuous use of Vioxx.¹⁶³

Dr. Quan also prepared a table analyzing the hazard ratio over time broken down into six month increments. Over the course of the trial, the hazard ratio of Vioxx to placebo per six month period varied from above 1.0 – indicating a greater cardiovascular risk of Vioxx versus placebo – to below 1.0 – indicating a greater cardiovascular risk on placebo versus Vioxx – back to above 1.0. As indicated below in the chart prepared by Dr. Quan for the External Safety Monitoring Board members, the hazard ratio of confirmed APTC composite cardiovascular endpoint events comparing Vioxx to placebo was 2.07 during the first 6 months of drug use, dropped to 0.54 between months 6 to 12 of drug use, and rose slightly to 0.66 between months 12 to 18.¹⁶⁴

¹⁶³ 3/15/05 deposition of P. Kim at 114-15 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); 6/8/05 deposition of P. Kim at 949-50 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); see also 1/10/06 Merck press release, “VIOXX® Trial Update: Statement on VIOXX® Product Liability Trial Scheduled in Starr County, Texas,” http://www.merck.com/newsroom/press_releases/corporate/2006_0110.html. Patients were enrolled in the APPROVe Trial from February 2000 through November 2001, which resulted in drug use beginning at varying dates or points in time. The time axis in the Kaplan-Meier analysis is based on days of continuous use per patient. Thus, events that occurred months apart on the calendar could appear at the same point on the Kaplan-Meier curve if they both occurred the same number of days after the patient started the study. For this reason, the time period covered in the Kaplan-Meier analysis cannot be correlated to any particular dates.

¹⁶⁴ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 36.

Table 6
Hazard Ratio Over Time of Confirmed APTC Composite Cardiovascular Endpoint Events in the APPROVe Trial

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

After the 18-month mark, the hazard ratio of confirmed APTC composite cardiovascular endpoint events on Vioxx versus placebo rose to its highest level, measuring 3.84 between 18 and 24 months of drug use and 3.32 between 24 and 30 months of drug use.¹⁶⁵

The last row of the chart listed APTC composite cardiovascular endpoint events that occurred after 30 months of continuous use of Vioxx, a period shorter than six months due to the trial's termination. During that period, there were 9 APTC events on Vioxx compared to 0 events on placebo.¹⁶⁶ The between-treatment trends in APTC composite cardiovascular endpoint events were similar for confirmed thrombotic serious adverse events.¹⁶⁷

¹⁶⁵ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 36.

¹⁶⁶ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 36.

¹⁶⁷ 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517, at 37. The cardiovascular data from the APPROVe Trial was first published in the electronic version of the New England Journal of Medicine on February 15, 2004. Bresalier^{*} RS, Sandler^{*} RS, Quan H, et al.

In minutes of its September 2004 meeting, the APPROVe Trial External Safety Monitoring Board noted that “the changing relative risk with increasing follow-up indicating adverse effects with longer treatment exposure was also present in the Alzheimer analyses reviewed by the ESMB last February.”¹⁶⁸ The Alzheimer’s Disease Combined Safety Analysis presented to the Board prior to its February 2004 meeting had revealed that the relative risk for thrombotic or APTC events on Vioxx versus placebo in the two completed Alzheimer’s disease trials – Protocols 078 and 091 – was less than 1.0 for the first 18 months of continuous use of Vioxx, but rose above 1.0 after 18 months of continuous use (see Table and Figure at pp. 35-36 above).¹⁶⁹

The minutes from the External Safety Monitoring Board Closed Session meeting indicate that, in weighing alternatives, members took into account the fact that the APPROVe Trial was very close to completion, but concluded that “it was important to communicate their safety concerns to the Executive Committee.”¹⁷⁰ The External Safety Monitoring Board members “unanimously recommend[ed] that the Executive Committee be unblinded to the safety data and that participating patients be instructed to discontinue study treatment.”¹⁷¹ Furthermore, the External Safety Monitoring Board listed a series of

Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial.
N Engl J Med. 2005;352:1092-102.

¹⁶⁸ Minutes of 9/17/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000124, at 24.

¹⁶⁹ 12/12/03 Alzheimer’s Disease Combined Safety Analysis, MRK-AFL0059959, at 60020, 60024;
Minutes of 2/18/04 APPROVe ESMB Open Session meeting, MRK-AFF0000120, at 21.

¹⁷⁰ Minutes of 9/17/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000124, at 24.

¹⁷¹ Minutes of 9/17/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000124, at 24.

related issues to discuss with Merck, including the “importance of further analyses to understand the extent to which BP differences between treatment groups explains the adverse CVD [cardiovascular disease] findings.”¹⁷² The External Safety Monitoring Board Closed Session meeting minutes do not contain a recommendation that Vioxx be withdrawn from the market.¹⁷³

e. Recommendation to stop the APPROVe Trial.

On the same day as their meeting, September 17, 2004, the External Safety Monitoring Board members notified the Chair of the APPROVe Executive Committee, Dr. John Baron*, in accordance with the protocol for study modification or termination agreed upon at the first External Safety Monitoring Board meeting.¹⁷⁴ On Sunday, September 19, 2004, a teleconference was held with members of the External Safety Monitoring Board and the Executive Committee (a subset of the APPROVe Administrative Committee formed to conduct a preliminary review of External Safety Monitoring Board recommendations) to discuss the Board’s recommendation.¹⁷⁵ On Wednesday, September 22, 2004, in accordance with the termination protocol, the

¹⁷² Minutes of 9/17/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000124, at 25.

¹⁷³ Minutes of 9/17/04 APPROVe ESMB Closed Session meeting, MRK-AFF0000124-25.

¹⁷⁴ Notes of H. Quan, MRK-AGO0035920, at 20; J. Neaton* handwritten notes of 9/17/04 meeting, JDN 01973; Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 41; APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 270 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

¹⁷⁵ Notes of H. Quan, MRK-AGO0035920, at 20; J. Neaton* handwritten notes of 9/19/04 meeting, JDN 01955; List of September 2004 APPROVe teleconferences, JAB 02016; APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 270 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111).

External Safety Monitoring Board and non-Merck members of the Administrative Committee discussed the decision to terminate the APPROVe Trial via teleconference.¹⁷⁶

Following the meeting, Dr. Quan faxed tables from the pre-meeting safety report prepared for the External Safety Monitoring Board's September 17 meeting to the non-Merck members of the Administrative Committee.¹⁷⁷ At a follow-up teleconference among the External Safety Monitoring Board and the non-Merck members of the Administrative Committee on Thursday, September 23, the decision was made to inform Merck of the External Safety Monitoring Board's recommendation to terminate the APPROVe Trial.¹⁷⁸

B. Decision to Withdraw Vioxx From Worldwide Market.

1. Decision-Making Process.

a. Thursday, September 23, 2004.

On the evening of Thursday, September 23, 2004, Dr. Baron* called Dr. Kevin Horgan to inform him that the External Safety Monitoring Board members had recommended stopping the trial based on their concern about the cardiovascular events in

¹⁷⁶ Notes of H. Quan, MRK-AGO0035920, at 20; J. Neaton* handwritten notes of 9/22/04 meeting, JDN 01954; Minutes of 11/7/01 APPROVe ESMB meeting, MRK-ABS0392239, at 41; APPROVe ESMB and Administrative Committee Guidelines, MRK-ABS0326250, at 270 (attached as Appendix 12 to 1/17/02 APPROVe Trial Protocol, MRK-ABS0326111); see also List of September 2004 APPROVe teleconferences, JAB 02016.

¹⁷⁷ Notes of H. Quan, MRK-AGO0035920, at 20.

¹⁷⁸ Notes of H. Quan, MRK-AGO0035920, at 20; see also J. Neaton* handwritten notes of 9/23/04 meeting, JDN 01639; List of September 2004 APPROVe teleconferences, JAB 02016.

the Vioxx treatment group.¹⁷⁹ Dr. Baron* faxed to Dr. Horgan a copy of the External Safety Monitoring Board Closed Meeting Minutes of the September 17, 2004 meeting.¹⁸⁰

Dr. Horgan then left a voicemail message for Dr. Barry Gertz, MRL Clinical Sciences Senior Vice-President, who in turn left a message for Dr. Peter Kim, President of MRL, stating that the External Safety Monitoring Board had recommended that the APPROVe Trial be stopped. Dr. Kim received the message the following morning.¹⁸¹

b. Friday, September 24, 2004.

In the morning, on Friday, September 24, 2004, Dr. Horgan faxed a copy of the Closed Session minutes to Drs. Kim and Gertz.¹⁸² On the cover sheet, Dr. Horgan stated: “There is a consensus among the ESMB members and also the members of the administrative committee for the study that it should be terminated because of trends noted with respect to adverse events.”¹⁸³

Dr. Kim convened an ad hoc group of MRL scientists, including Drs. Gertz, Quan, Oxenius, Reicin, Horgan, Peter Honig, and Raymond Bain, to review data from the APPROVe Trial.¹⁸⁴ At the meeting, the group reviewed the safety report prepared by

¹⁷⁹ Notes of H. Quan, MRK-AGO0035920, at 20; MRL Managers Q&A 10/3/04, MRK-AFJ0009727, at 29.

¹⁸⁰ Notes of H. Quan, MRK-AGO0035920, at 20; MRL Managers Q&A 10/3/04, MRK-AFJ0009727, at 29.

¹⁸¹ 9/28/05 deposition of B. Gertz at 1083-84 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

¹⁸² 9/24/04 facsimile from K. Horgan to P. Kim and B. Gertz, MRK-AFJ0000067, at 67.

¹⁸³ 9/24/04 facsimile from K. Horgan to P. Kim and B. Gertz, MRK-AFJ0000067, at 67.

¹⁸⁴ Notes of H. Quan, MRK-AGO0035920, at 20-21.

Dr. Quan for the External Safety Monitoring Board's September 17, 2004 meeting, which Dr. Quan had brought with him to the meeting.¹⁸⁵ According to Dr. Honig, the increase in hazard rate at 18 months of continuous use of Vioxx in the APPROVe Trial indicated a latent effect, which was rare, so the group's first thought was that high blood pressure or hypertension, which has a lag time until cardiovascular effects occur, was responsible.

At some point during the meeting, Dr. Kim left to call Mr. Gilmartin to inform him of the events that had transpired.¹⁸⁶ According to Dr. Kim, Mr. Gilmartin stated during the call that Merck would "do the right thing, figure out what's the best thing to do in terms of patient safety," and asked to be kept updated.¹⁸⁷ Dr. Kim subsequently made clear to the group that the ultimate decision about how to proceed rested with him and that he would make a recommendation to Mr. Gilmartin and the Board of Directors.

c. Saturday-Sunday, September 25-26, 2004.

During the rest of the day on Friday and over the weekend, Dr. Kim and the group of scientists he had assembled reanalyzed the APPROVe Trial data, requested additional data and analyses from the VIGOR and Alzheimer's disease Trials, and arranged to confer with external consultants regarding the data.¹⁸⁸ Drs. Bain and Quan prepared the

¹⁸⁵ Notes of H. Quan, MRK-AGO0035920, at 20-21; 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AGO0029517-69.

¹⁸⁶ Notes of H. Quan, MRK-AGO0035920, at 20; 6/8/05 deposition of P. Kim at 951-53 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

¹⁸⁷ 6/8/05 deposition of P. Kim at 953 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

¹⁸⁸ 6/8/05 deposition of P. Kim at 954-55 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); Notes of H. Quan, MRK-AGO0035920, at 21.

various analyses that the scientists requested, the results of which were delivered to Dr. Kim and his direct reports, Drs. Gertz, Honig, and Elizabeth Stoner.

The scientists analyzed, among other things, whether and to what extent blood pressure was responsible, whether the prophylactic use of low-dose aspirin had mitigated the results, and whether patient demographics played a role in patients' cardiovascular risk susceptibility. The group concluded that the small increase in blood pressure could not account for all of the difference in cardiovascular effects, based on the known correlation between blood pressure and cardiovascular risk, and that there seemed to be a residual drug effect – meaning that some of the cardiovascular effects seen in the APPROVe Trial must be due to a non-hypertensive effect of Vioxx.

The group also focused on data from the long-term, placebo-controlled combined Alzheimer's disease trials.¹⁸⁹ As noted above, before seeing cardiovascular data from the APPROVe Trial, Dr. Kim believed that the apparent change in the cardiovascular event relative risk in the Alzheimer's Trials was a play of chance.¹⁹⁰ However, after seeing data from the APPROVe Trial, Dr. Kim and other MRL scientists reevaluated the Alzheimer's data and noted that both the Alzheimer's and APPROVe Trial hazard rate curves reflected a change after 18 months of continuous use of Vioxx.

On Sunday morning, September 26, MRL scientists, Ms. Joanne Lahner from the Legal Department, and Dr. Brian White-Guay, a Vice-President in the European

¹⁸⁹ 9/25/04 email from R. Bain to P. Kim, B. Gertz, and P. Honig, MRK-AFJ0008493.

¹⁹⁰ 3/16/05 deposition of P. Kim at 532-33 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

Regulatory Department of Merck, Sharpe, & Dohme, participated in a teleconference focused on understanding the available data and identifying additional sources of data. The studies discussed included the APPROVe Trial, the VIGOR Trial, Protocol 069, the Alzheimer's trials, the ViP Trial, and the VICTOR Trial.¹⁹¹

That evening, Dr. Kim led a teleconference with MRL scientists, External Safety Monitoring Board members, and members of the APPROVe Trial Administrative Committee.¹⁹² Agenda items included: (i) gaining an understanding of the reasoning behind the External Safety Monitoring Board's recommendation to terminate the study; (ii) discussing the implications of the APPROVe Trial data and the External Safety Monitoring Board's recommendation for ongoing Vioxx studies; and (iii) an item added with the characterization "LESS IMPORTANT:" exploring the "implications for use of drug in clinical practice versus PPI [proton pump inhibitor for suppression of gastric acid] + naproxen."¹⁹³

According to Dr. Konstam*, MRL scientists did not challenge the External Safety Monitoring Board's recommendation, or raise questions regarding whether the results were accidental or due to a play of chance. The call initially focused on attempting to

¹⁹¹ 9/26/04 email from B. Gertz to B. White-Guay, E. Stoner, K. Horgan, R. Bain, D. Erb, A. Reicin, P. Honig, B. Oxenius, P. Kim, and J. Lahner, MRK-AFJ0008559, at 59.

¹⁹² 9/26/04 email from K. Horgan to A. Reicin, B. Gertz, R. Bain, H. Quan, P. Honig, B. Oxenius, and P. Kim, MRK-AFJ0000189, at 89; 9/25/04 email from C. Inoa* to K. Horgan, B. Gertz, et al., with handwritten notes, JDN 01620.

¹⁹³ 9/26/04 email from K. Horgan to A. Reicin, B. Gertz, R. Bain, H. Quan, P. Honig, B. Oxenius, and P. Kim, MRK-AFJ0000189, at 89-90; see also Handwritten notes of P. Kim, MRK-AFJ0000167, at 72-76; Notes of H. Quan, MRK-AGO0035920, at 20; Handwritten notes, MRK-EC049385-96; J. Neaton* handwritten notes of 9/26/04 meeting, JDN 01637.

understand the data, for instance, by analyzing whether patients on aspirin exhibited a different risk level.¹⁹⁴ The group also discussed whether Merck should continue other ongoing studies using Vioxx and whether the label could be re-written to define a population for whom the drug would be safe.¹⁹⁵ The participants did not discuss whether Merck should withdraw Vioxx from the market.¹⁹⁶

d. Monday, September 27, 2004.

Dr. Kim led two morning meetings with external consultants.¹⁹⁷ The consultants were faxed data from the APPROVe and Alzheimer's Trials on Sunday. The first teleconference was attended by rheumatologists, Drs. Claire Bombardier*, Marc Hochberg* and Thomas Schnitzer*, and a cardiologist, Dr. Robert Califf*.¹⁹⁸ Drs. Garret FitzGerald* and John Oates*, both prostaglandin experts, participated in the second consultants' teleconference.¹⁹⁹

Dr. Kim began the meetings with Merck's external consultants by stating that Merck wanted to hear their interpretations of the data without debating them at this

¹⁹⁴ Handwritten notes of P. Kim, MRK-AFJ0000167, at 72-76.

¹⁹⁵ Handwritten notes of P. Kim, MRK-AFJ0000167, at 72-76.

¹⁹⁶ Handwritten notes of P. Kim, MRK-AFJ0000167, at 72-76.

¹⁹⁷ 6/8/05 deposition of P. Kim at 954-56 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

¹⁹⁸ Handwritten notes of P. Kim, MRK-AFJ0000167, at 77-78, 80.

¹⁹⁹ Handwritten notes of P. Kim, MRK-AFJ0000167, at 77, 79. Dr. Kim attempted to contact Dr. Carlo Patrono* for this second teleconference, but was unable to reach him.

time.²⁰⁰ Although Dr. Kim “tried to keep the discussion away from what it is that Merck should do and instead tried to keep it focused on the science,” the consultants ultimately ended up discussing their recommendations regarding whether or not Merck should withdraw Vioxx from the market.²⁰¹ According to Dr. Kim, the consultants’ beliefs fell into three camps.²⁰²

- Rheumatologists, including Dr. Claire Bombardier*, thought that Merck should not withdraw Vioxx because the cardiovascular risk was small and manageable, and withdrawal was detrimental to patient welfare because some patients only responded to Vioxx to treat their pain.²⁰³
- Another group believed that Vioxx should be withdrawn because an increased risk of a serious adverse event existed, Vioxx was not essential to maintain life, and alternative therapies existed.²⁰⁴
- A third group, including Dr. Oates*, was torn and did not express an opinion either way, although Dr. Oates* later told Dr. Gertz that he thought Merck should withdraw the drug.²⁰⁵

Internally, MRL scientists – including Drs. Gertz and Honig – continued to discuss what course of action was consistent with Merck’s values, and they concluded

²⁰⁰ 6/8/05 deposition of P. Kim at 955 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

²⁰¹ 6/8/05 deposition of P. Kim at 955 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

²⁰² 6/8/05 deposition of P. Kim at 955-57 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

²⁰³ 6/8/05 deposition of P. Kim at 955-56 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

²⁰⁴ 6/8/05 deposition of P. Kim at 956-57 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

²⁰⁵ 6/8/05 deposition of P. Kim at 956 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

that withdrawal was the right outcome. There were a variety of opinions expressed internally about what the data meant and what course Merck should take with respect to Vioxx.²⁰⁶

According to Dr. Kim, MRL scientists believed that the drug theoretically could be kept on the market if the label were modified with a black box warning to reflect the new data.²⁰⁷ However, because (i) there was now a known risk with potentially serious consequences (albeit at a low probability for occurrence), and (ii) alternatives existed for treatment of a non life-threatening disease, Dr. Kim and other MRL scientists concluded that the Company should withdraw Vioxx.²⁰⁸ According to Dr. Kim, marketing, commercial, and litigation considerations did not factor into his decision to recommend withdrawal of Vioxx.²⁰⁹

On that Monday afternoon, Dr. Kim presented the APPROVe Trial data and the consultants' recommendations to Mr. Gilmartin.²¹⁰ Dr. Kim told Mr. Gilmartin that Merck could re-label the drug, but advised that in his opinion, the best course was to withdraw Vioxx from the market because there was a known risk that appeared to be

²⁰⁶ Handwritten notes of P. Kim, MRK-AFJ0000167, at 80.

²⁰⁷ See slide presentation, "Labeling Scenario," MRK-ACM0000585-93.

²⁰⁸ 6/8/05 deposition of P. Kim at 957-58 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

²⁰⁹ 6/8/05 deposition of P. Kim at 965 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

²¹⁰ 3/15/05 deposition of P. Kim at 170-71 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); 6/8/05 deposition of P. Kim at 959-60 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); 3/24/05 deposition of R. Gilmartin at 156-57 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

real.²¹¹ Mr. Gilmartin accepted Dr. Kim's recommendation to withdraw Vioxx from the market.²¹²

After their meeting, Mr. Gilmartin convened a meeting of a subset of Merck's Management Committee, at which Drs. Kim, Honig, and Gertz briefed the group on the APPROVe Trial data and on the discussions that had taken place over the weekend and that morning.²¹³ Mr. Gilmartin then informed the group that he agreed with Dr. Kim's recommendation voluntarily to withdraw Vioxx from the market and asked the Management Committee members for their input.²¹⁴ According to Mr. Gilmartin, no one dissented from his decision. Mr. Gilmartin has testified that he made the ultimate decision voluntarily to withdraw Vioxx from the market.²¹⁵

e. Tuesday, September 28, 2004.

On Tuesday, September 28, 2004, Merck's Board of Directors convened for a regularly scheduled Board meeting. Mr. Gilmartin "advised the Board that the Company had recently received new safety information from the APPROVe trial," and told them of the APPROVe External Safety Monitoring Board's recommendation that the Company stop the trial based on the increased relative risk of cardiovascular events in patients

²¹¹ 3/15/05 deposition of P. Kim at 170-71 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); 6/8/05 deposition of P. Kim at 959-60 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.);

²¹² 3/24/05 deposition of R. Gilmartin at 157 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); 6/8/05 deposition of P. Kim at 959-61 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.);

²¹³ 6/8/05 deposition of P. Kim at 959-60 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.);

²¹⁴ 3/24/05 deposition of R. Gilmartin at 157 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.);

²¹⁵ 3/24/05 deposition of R. Gilmartin at 160 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.);

taking Vioxx compared to placebo.²¹⁶ Mr. Gilmartin “informed the Board . . . that management had concluded that the Company should voluntarily withdraw VIOXX worldwide.”²¹⁷ Dr. Kim then presented and discussed the APPROVe Trial data with the Board.²¹⁸

After hearing Mr. Gilmartin’s and Dr. Kim’s presentations regarding the APPROVe Trial data, and after considerable discussion, the Board endorsed the Management Committee’s recommendation to withdraw Vioxx from the market.²¹⁹

2. Process of Withdrawal.

After the decision to withdraw Vioxx was made, senior management, including Mr. Gilmartin, Dr. Kim, and Dr. Honig, focused on the logistical challenge of how to implement the withdrawal worldwide.²²⁰ A crisis management team called the “VIOXX Management Task Force” was established “to develop plans and actions to deal with the immediate issues arising from the voluntary withdrawal of VIOXX, and also put in place plans and strategies to deal with mid and longer-term secondary impacts of this

²¹⁶ Minutes of 9/28/04 Merck Board of Directors meeting, MRK-AAV0000075, at 76.

²¹⁷ Minutes of 9/28/04 Merck Board of Directors meeting, MRK-AAV0000075, at 76; 3/24/05 deposition of R. Gilmartin at 157 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

²¹⁸ Minutes of 9/28/04 Merck Board of Directors meeting, MRK-AAV0000075, at 76-77.

²¹⁹ Minutes of 9/28/04 Merck Board of Directors meeting, MRK-AAV0000075, at 77; 3/24/05 deposition of R. Gilmartin at 160 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.). Several members of Merck’s Management Committee also attended the meeting, including Dr. Kim, Mr. Kenneth Frazier (Merck’s General Counsel), Ms. Judith Lewent (Merck’s Chief Financial Officer), Dr. Marsha Avedon (Senior Vice-President, Human Resources), Mr. Richard Clark (President, Merck Manufacturing Division, and Dr. Bradley Sheares (President, U.S. Human Health). Minutes of 9/28/04 Merck Board of Directors meeting, MRK-AAV0000075, at 75.

²²⁰ 6/8/05 deposition of P. Kim at 961-62 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

action.”²²¹ The task force included approximately 50 Merck employees, who, among other things, created communications materials that would allow the Company to deliver its message worldwide.²²² Those materials included a press release and list of questions and answers about the withdrawal of Vioxx, as well as websites and letters to physicians to inform the public about the withdrawal.²²³

a. Communication to the public.

On September 30, 2004, Merck issued a press release announcing the voluntary worldwide withdrawal of Vioxx from the market, effective immediately, based on the new data from the APPROVe Trial.²²⁴ The press release stated that the APPROVe Trial found “an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo.”²²⁵ The press release included the following statement by Mr. Gilmartin:²²⁶

²²¹ 10/7/04 email correspondence between W. Yamo, J. Wainwright, B. White-Guay, et al., MRK-AFJ0008764, at 64.

²²² 6/8/05 deposition of P. Kim at 961-62 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

²²³ 9/30/04 email from J. Wainwright to P. Wold-Olsen et al., MRK-ABI0011771; 6/8/05 deposition of P. Kim at 961-62 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

²²⁴ 9/30/04 Merck press release, “Merck Announces Voluntary Worldwide Withdrawal of VIOXX,” MRK-AFJ0008607, at 07. The contents of Merck’s press release were reiterated by Dr. Kim at a press conference that morning. 9/30/04 remarks of Peter S. Kim at Merck press conference, MRK-ABI0011790.

²²⁵ 9/30/04 Merck press release, “Merck Announces Voluntary Worldwide Withdrawal of VIOXX,” MRK-AFJ0008607, at 07.

²²⁶ 9/30/04 Merck press release, “Merck Announces Voluntary Worldwide Withdrawal of VIOXX,” MRK-AFJ0008607, at 07.

MERCK News Release

Media Contact: Anita Larsen (908) 423-8022 | Investor Contact: Michael Rabinowitz (908) 423-5185

Merck Announces Voluntary Worldwide Withdrawal of VIOXX ©

WHITEHOUSE STATION, N.J., Sept. 30, 2004 – Merck & Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company's decision, which is effective immediately, is based on new, three-year data from a prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial.

The trial, which is being stopped, was designed to evaluate the effect of VIOXX in preventing recurrence of colorectal polyps in patients with a history of colorectal adenoma. In this study, there was an increased relative risk for confirmed cardiovascular events, including heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results for the first 18 months of the trial did not show any increased risk of confirmed cardiovascular events on VIOXX. The results in respect, are similar to the results of two placebo-controlled studies described in the current labeling for VIOXX.

“We are taking this action because we believe it best serves the interests of patients,” said Raymond V. Gilmartin, chairman, president and chief executive officer of Merck. “Although we believe it would have been possible to continue to market VIOXX with labeling that would incorporate these new data, given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take.”

“We are taking this action because we believe it best serves the interests of patients,” said Raymond V. Gilmartin, chairman, president and chief executive officer of Merck. “Although we believe it would have been possible to continue to market VIOXX with labeling that would incorporate these new data, given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take.”

APPROVe was a multi-center, randomized, placebo-controlled, double-blind trial designed to determine the effect of 156 weeks (three years) of treatment with VIOXX on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal adenoma. The trial enrolled 2,500 patients and compared VIOXX 25 mg to placebo. The trial began enrollment in 2000.

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The press release also stated that Merck had informed the FDA and regulatory authorities in other countries of its decision, and was in the process of notifying health care practitioners in the United States and other countries where Vioxx was marketed.²²⁷

In a press release issued by the FDA on September 30, 2004, Dr. Lester Crawford*, Acting Commissioner of the FDA, stated: “Merck did the right thing by promptly

²²⁷ 9/30/04 Merck press release, “Merck Announces Voluntary Worldwide Withdrawal of VIOXX,” MRK-AFJ0008607, at 08.

reporting these findings to FDA and voluntarily withdrawing the product from the market.”²²⁸

All Vioxx clinical trials conducted by the Company were halted on September 30, 2004, including the APPROVe Trial, which was eight weeks from completion.²²⁹ Trials of Arcoxia (etoricoxib), however, were not terminated. In a letter to investigators assigned to Arcoxia trials, Dr. William Keane, Merck’s Vice President of U.S. Medical and Scientific Affairs, described the findings of the APPROVe Trial and distinguished Arcoxia, stating that “[t]he results of clinical studies with one molecule in a given class are not necessarily applicable to others in the class.”²³⁰

b. Communication to Merck employees.

On the morning of September 30, 2004, Merck began informing its employees of the Company’s decision.²³¹ Senior management, including Mr. Gilmartin, Dr. Kim, Dr. Bradley Sheares, President of U.S. Human Health, and Mr. Tyrone Edwards, Senior Vice President of Primary Care Sales in U.S. Human Health, conducted several

²²⁸ 9/30/04 FDA press release, “FDA Issues Public Health Advisory on Vioxx as its Manufacturer Voluntarily Withdraws the Product,” MRK-ABS0401084, at 84.

²²⁹ 10/3/04 MRL Managers Questions and Answers, MRK-AFJ0009727, at 27, 29; 9/30/04 letter from A. Reicin to APPROVe Trial Investigators, MRK-AFF0000089.

²³⁰ 9/30/04 letter from W. Keane to investigators in etoricoxib trials, MRK-GAR0016608, at 08; see also 9/30/04 Merck press release, “Merck Announces Voluntary Worldwide Withdrawal of VIOXX,” MRK-AFJ0008607, at 08.

²³¹ Communications timeline, MRK-GAR0016327, at 27; 1/5/05 deposition of T. Simon at 92-93 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

teleconferences and a town hall meeting.²³² Dr. Honig briefed the top members of MRL's scientific staff after the withdrawal. Information about the Company's decision to withdraw Vioxx subsequently cascaded through the organization.

* * *

²³² Communications timeline, MRK-GAR0016327, at 27.