

## APPENDIX M

### POST-VIGOR EFFORTS TO DEVELOP AND EVALUATE ADDITIONAL VIOXX-RELATED CARDIOVASCULAR DATA.

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### POST-VIGOR EFFORTS TO DEVELOP AND EVALUATE ADDITIONAL VIOXX-RELATED CARDIOVASCULAR DATA.

#### A. Overview.

Although MRL scientists were persuaded that the between-treatment differential in cardiovascular adverse events observed in the VIGOR Trial was most likely caused by a cardioprotective effect of naproxen, rather than a prothrombotic effect of Vioxx, this post hoc conclusion did not have the probative weight of a conclusion drawn from a prospectively designed clinical trial. The significance of the cardiovascular data in the VIGOR Trial could not be established definitively because the VIGOR Trial did not include a placebo comparator and had not been designed to test either the cardiovascular effects of Vioxx or the cardioprotective effects of naproxen.

As a result, a number of scientists and others outside Merck – including Merck’s chief competitor in the selective Cox-2 inhibitor market, Searle/Pfizer – questioned Merck’s explanation and interpreted the cardiovascular results from the VIGOR Trial as evidence that Vioxx increased the risk of thrombotic events. In response, MRL scientists in the immediate aftermath of the VIGOR Trial in the spring of 2000, and again the following spring, discussed whether to conduct a large-scale, prospectively designed cardiovascular outcomes trial to obtain definitive data concerning Vioxx’s cardiovascular safety profile.

By the end of 2001, the Company had informally decided to conduct two cardiovascular outcomes trials, one for Vioxx and one for Arcoxia. On February 27,

2002, Merck's Human Health Product Approval Committee approved a protocol for the Vioxx cardiovascular outcomes trial, known as VALOR ("Vioxx-Aspirin Long Term Outcomes Research"), and the Company began contracting with external administrators to implement the study protocol.

On March 13, 2002, however, Merck announced internally and to the external VALOR Trial Steering Committee that it would not conduct the VALOR Trial at that time. Instead, the Company decided to design a protocol to pool and analyze cardiovascular event data from three placebo-controlled trials of the efficacy of Vioxx in the treatment or prevention of various forms of cancer. This study, Protocol 203, (i) would be placebo-controlled, which meant that it would provide a relatively clean answer to the question of whether Vioxx was prothrombotic; (ii) would involve at least as many patients as would have been enrolled in a large cardiovascular outcomes trial; and (iii) would be powered to detect a small difference in cardiovascular event rates between Vioxx and placebo.

This Appendix describes the Company's decision-making process regarding a cardiovascular outcomes trial, the various hypotheses that the Company considered to support such a trial, the hurdles MRL scientists encountered in designing such a trial, and the Company's ultimate decision to implement Protocol 203.

B. Discussions in the Spring of 2000.

1. Overview.

MRL scientists first discussed the possibility of conducting a cardiovascular outcomes trial in April and May 2000, shortly after the release of the VIGOR Trial

results. The goal of this trial would be to determine whether Vioxx had played any role in increasing the incidence of cardiovascular adverse events in the Vioxx arm of the VIGOR Trial as compared to the naproxen arm. Externally, Merck's Board of Scientific Advisors suggested in April 2000 that Merck undertake a cardiovascular outcomes trial as part of an overall approach to clarifying the cardiovascular event rate differential observed in the VIGOR Trial. Internally, MRL scientists wanted to conduct such a trial to confirm unequivocally the belief held within the Company that Vioxx did not pose a cardiovascular risk.

The MRL scientists who explored possible designs for a cardiovascular outcomes trial, however, realized that such a trial would be difficult to design and might not answer head-on the question raised by the VIGOR Trial. They also recognized that any new large clinical trial with Vioxx would yield additional gastrointestinal safety data that could potentially compromise the favorable results of the VIGOR Trial. Moreover, based on their data analysis, MRL scientists did not believe that Vioxx was prothrombotic. At the same time, executives in Merck's U.S. Human Health Marketing Division became concerned as a strategic matter that conducting a cardiovascular outcomes trial could undermine Merck's credibility in outwardly expressing its confidence in Vioxx and the naproxen cardioprotection hypothesis.

Ultimately, the Company decided in May 2000 not to conduct a cardiovascular outcomes trial at that time. The discussions leading up to that decision are reviewed below.

2. Post-VIGOR Consideration of Cardiovascular Outcomes Trial.

Dr. Scolnick was one of the first to suggest that MRL undertake a cardiovascular outcomes trial. On April 12, 2000, Dr. Scolnick proposed to Dr. Reicin, a study of Vioxx versus Tylenol (which is not an NSAID and is not associated with cardiovascular risk), with 10,000 patients in each arm:<sup>1</sup>

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From: Scolnick, Edward M.  
Sent: Wednesday, April 12, 2000 10:42 PM  
To: Reicin, Alise S.  
Subject: RE: RA and CV mortality  
Importance: High

**I will tell you my worry quotient is high. I actually am in minor agony. . . . WE WILL NOT KNOW FOR SURE WHAT IS GOING ON UNTIL WE DO THIS STUDY. PLEASE THINK HARD ABOUT THE DESIGN BEFORE THE [HHPAC] MEETING.**

Hi Alise I have been trading email with Doug Greene in real time. we a  
worry quotient is high. I actually am in minor agony. What I really want to do is a 10000 vs 10000 patient study  
in mild -moderate OA Tylenol vs vioxx with prn low dose asa for those judged to need it. safety first primary  
endpoint and efficacy secondary or co primary. WE WILL NOT KNOW FOR SURE WHAT IS GOING ON  
UNTIL WE DO THIS STUDY. PLEASE THINK HARD ABOUT THE DESIGN BEFORE THE PAC MEETING.  
Thanks/ Ed

Although MRL scientists at this time had been persuaded by the totality of data analyzed that naproxen cardioprotection was the most likely explanation for the between-treatment difference in the incidence of cardiovascular events in the VIGOR Trial, Dr. Scolnick “still thought [Merck] needed even more data to have 1,000 percent certainty.”<sup>2</sup>

Accordingly, on April 18, 2000, a group of MRL scientists reviewed with Dr. Scolnick two preliminary ideas for designing a cardiovascular outcomes study with Vioxx:<sup>3</sup> (i) the Vioxx versus Tylenol study that Dr. Scolnick had suggested; and (ii) a

<sup>1</sup> 4/12/00 email from E. Scolnick to A. Reicin, MRK-ABC0033809 (emphasis in original).

<sup>2</sup> 6/1/05 deposition of E. Scolnick at 913 (*In re Vioxx Litig.*, No. 619, N.J. Super. Ct. Law Div.).

<sup>3</sup> See 4/15/00 memorandum from A. Reicin to E. Scolnick, MRK-ABT0014807; Undated slide presentation, “VIOXX Outcomes Study Potential Designs” MRK-ABT0014818-27 (attached to 4/15/00 memorandum from A. Reicin to E. Scolnick, MRK-ABT0014807).

study of Vioxx versus Celebrex.<sup>4</sup> One drawback to the study against Tylenol was that MRL's rheumatology consultants did not believe that Tylenol would provide adequate pain relief to arthritis patients and thus such a study would yield poor patient recruitment and retention.<sup>5</sup> The MRL scientists considered pros and cons of each option.<sup>6</sup>

## VIOXX vs Tylenol

- Pro
  - This study directly addresses the question of the CV safety of COX-2 inhibitors
  - Bolster claim for GI safety similar to placebo if no significant difference is detected
- Con
  - Demonstration of a CV difference would likely be due to a COX-2 CLASS effect but would put VIOXX at extreme disadvantage to celebrex and negate existing OA and Alzheimers data
  - Possibility of detecting small differences from tylenol in GI safety is of concern

## VIOXX vs Celebrex

- Pro
  - Likelihood of a positive study would be high  
No reason to believe CV or GI safety are different at these doses
- Con
  - Addresses Searle marketing tactics but does not address CV safety of the COX-2 inhibitor class

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<sup>4</sup> Undated slide presentation, "Vioxx Outcomes Study Potential Designs," MRK-ABT0014818, at 19 (attached to 4/15/00 memorandum from A. Reicin to E. Scolnick, MRK-ABT0014807).

<sup>5</sup> See 4/29/05 deposition of E. Scolnick at 247-48 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); 10/11/05 transcript of Humeston v. Merck & Co., ATL-L-2272-03 MT, N.J. Super. Ct. Law Div., at 3552-59.

<sup>6</sup> Undated slide presentation, "Vioxx Outcomes Study Potential Designs," MRK-ABT0014818, at 24, 27 (attached to 4/15/00 memorandum from A. Reicin to E. Scolnick, MRK-ABT0014807). The presentation also included calculations as to what the chances were of demonstrating a difference in gastrointestinal bleeds in a trial of Vioxx versus Tylenol. Id. at 22-23.

Merck's Board of Scientific Advisors, which convened from April 26 to April 28, 2000, discussed at length the cardiovascular results of the VIGOR Trial and prospective studies that might be conducted regarding Vioxx's cardiovascular safety profile.<sup>7</sup> Although members of the Board of Scientific Advisors concluded that it was "highly probable" that the cardiovascular event differential in the VIGOR Trial was due to a cardioprotective effect of naproxen rather than a prothrombotic effect of Vioxx,<sup>8</sup> they were concerned that combining aspirin with Vioxx could undermine Vioxx's positive gastrointestinal safety profile (because perforations, ulcers, and bleeds are known side effects of aspirin therapy). As a result, the Board of Scientific Advisors suggested that MRL conduct endoscopy studies to determine the gastrointestinal consequences of adding low-dose aspirin to Vioxx.<sup>9</sup>

Thereafter, if the results of the proposed endoscopy study were favorable, the Board of Scientific Advisors proposed that MRL could conduct a cardiovascular outcomes trial in rheumatoid arthritis patients, which they called "VIGOR-Plus," to determine whether taking Vioxx with aspirin or another antiplatelet agent would result in

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<sup>7</sup> 7/10/00 Merck Board of Scientific Advisors Human Health Chairman's Report, MRK-NJ0025217, at 20-26.

<sup>8</sup> 7/10/00 Merck Board of Scientific Advisors Human Health Chairman's Report, MRK-NJ0025217, at 21.

<sup>9</sup> Endoscopy studies are typically short-term studies where scientists use an endoscope – an instrument for visualizing the interior of a hollow organ – to examine the stomach lining for gastrointestinal complications. The Board of Scientific Advisors and MRL scientists previously had expressed concern about the gastrointestinal toxicity of aspirin in their discussions about the design of Protocol 059, the pre-approval proposed gastrointestinal outcomes trial. See Appendix A.

a similar cardiovascular event rate to that of naproxen in the VIGOR Trial.<sup>10</sup> The members of the Board of Scientific Advisors believed that this trial was likely to demonstrate no difference in the incidence of cardiovascular adverse events between the Vioxx arm and the naproxen arm.<sup>11</sup>

The previous week, at its April 20, 2000 meeting, the Human Health Product Approval Committee had independently considered undertaking an endoscopy study of Vioxx plus low-dose aspirin versus ibuprofen to determine “a GI ‘safe’ CV regimen for Vioxx users.”<sup>12</sup> At the time, the Celebrex label stated that Celebrex could be used concomitantly with low-dose aspirin, but the Vioxx label did not contain parallel language.<sup>13</sup> In evaluating whether to move forward with such a study, the Committee considered, among other things, “the study’s risk” – namely, that adding low-dose aspirin would undermine the gastrointestinal safety advantage of Vioxx, and “that the data will not assist Marketing during the immediate post VIGOR period.”<sup>14</sup>

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<sup>10</sup> 7/10/00 Merck Board of Scientific Advisors Human Health Chairman’s Report, MRK-NJ0025217, at 22-24.

<sup>11</sup> See 7/10/00 Merck Board of Scientific Advisors Human Health Chairman’s Report, MRK-NJ0025217, at 25 (“[T]he trial could demonstrate that cardiovascular outcomes on naproxen were still superior to those in patients on Vioxx plus an antiplatelet drug; we are inclined to think that such an outcome would be unlikely.”).

<sup>12</sup> 4/20/00 slide presentation to HHPAC, “Vioxx® and MK-663 Interim Review,” MRK-ABL0000880, at 888-89.

<sup>13</sup> 4/14/00 background material for 4/20/00 HHPAC meeting, MRK-ABI0002269, at 274-75.

<sup>14</sup> 4/20/00 slide presentation to HHPAC, “Vioxx® and MK-663 Interim Review,” MRK-ABL0000880, at 890.

Despite these concerns, the Vioxx Commercialization Team – a cross-functional committee that participated in developing the commercialization strategy for Vioxx – asked the Committee to approve the plans to move forward with the endoscopy study.<sup>15</sup> With respect to the cardiovascular outcomes trial, the Commercialization Team noted that designing such a study would be complex, and that, because they had not yet identified the appropriate patient population in which to conduct such a study, the Team would not be asking the Human Health Product Approval Committee for additional resources for the trial.<sup>16</sup>

At the same time that the MRL scientists were reviewing potential design options for a cardiovascular outcomes study and endoscopy studies, some individuals in the Marketing Department expressed concerns about conducting a cardiovascular outcomes trial. As Mr. Tim Ruef, a Senior Director in Merck’s Worldwide Human Health Marketing Division, described the issue, undertaking a study that focused on the potential cardiovascular side effects of Vioxx could create the public perception that Merck believed there was cause for concern. Moreover, during the months following the release of the VIGOR Trial data, weekly new prescriptions of Vioxx had actually increased, and by the middle of May 2000, the gap between Vioxx and Celebrex sales had narrowed significantly.<sup>17</sup>

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<sup>15</sup> 4/20/00 slide presentation to HHPAC, “Vioxx® and MK-663 Interim Review,” MRK-ABL0000880, at 907; 4/14/00 background material for 4/20/00 HHPAC meeting, MRK-ABI0002269, at 70, 78-80.

<sup>16</sup> 4/14/00 background material for 4/20/00 HHPAC meeting, MRK-ABI0002269, at 76.

<sup>17</sup> 6/19/00 slide presentation, “Weekly Prescription Update,” MRK-ADM0004460-79.

At its May 17, 2000 meeting, the Human Health Product Approval Committee addressed the question of whether to conduct a large clinical cardiovascular outcomes trial with Vioxx and further evaluated the endoscopy study proposed at the prior meeting.<sup>18</sup> Representatives of MRL and Merck's Marketing Department recommended to the Committee that a cardiovascular outcomes study not be pursued at that time. A slide presentation prepared for the meeting provided the following rationale:<sup>19</sup>

### CV Outcome Study

- At present, within Clinical Research there is no consensus as to hypothesis and design of such a trial.
  - Properly designed “non-inferiority” trial would need close to 50,000 patients
- At present, there is no compelling marketing need for such a study
  - Data would not be available during the critical period
  - The implied message is not favorable

Additionally, according to Dr. Scolnick, MRL scientists were comfortable with their conclusion that Vioxx had not contributed to the increased incidence of cardiovascular events in the VIGOR Trial and therefore did not feel that an outcomes trial was necessary.

After considering these factors at the May 17 meeting, the Human Health Product Approval Committee approved the decision not to pursue a cardiovascular outcomes trial

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<sup>18</sup> 5/17/00 slide presentation of B. Daniels to HHPAC, “VIOXX® Interim Review,” MRK-ABL0000942, at 43, 71-81; 5/17/00 slide presentation to HHPAC, “Key Marketing Messages,” MRK-ABL0000921, at 36-37.

<sup>19</sup> 5/17/00 slide presentation to HHPAC, “Key Marketing Messages,” MRK-ABL0000921, at 36.

at that time and agreed to proceed with endoscopy study,<sup>20</sup> which Merck hoped would demonstrate that adding low-dose aspirin to Vioxx would not negatively affect its gastrointestinal safety profile.<sup>21</sup>

3. Endoscopy Studies.

Pursuant to the recommendations of the Human Health Product Approval Committee and the Board of Scientific Advisors, in 2000-2001 MRL scientists planned two endoscopy studies to test the gastrointestinal effects of combining Vioxx with aspirin therapy.<sup>22</sup> The first endoscopy study, Protocol 136, was a three-arm study designed to evaluate the comparative effects on the stomach lining of (i) Vioxx 25 mg plus low-dose aspirin, (ii) low-dose aspirin alone, and (iii) ibuprofen alone.<sup>23</sup> The second endoscopy study, Protocol 158, would follow Protocol 136 and would evaluate the comparative effect on the stomach lining of (i) Vioxx 25 mg plus low-dose aspirin and (ii) an NSAID plus low-dose aspirin.<sup>24</sup> In both studies, patients would be assigned randomly to one of

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<sup>20</sup> Minutes of 5/17/00 HHPAC meeting, MRK-ABL0000938, at 39.

<sup>21</sup> See 3/9/00 email from E. Scolnick to D. Shapiro, A. Reicin, and A. Nies, MRK-ABH0016220.

<sup>22</sup> See 6/20/01 Merck Board of Scientific Advisors Human Health Chairman's Report, MRK-NJ0254333, at 60.

<sup>23</sup> 8/11/00 draft Protocol 136 Protocol, MRK-ACR0011184, at 189.

<sup>24</sup> Undated slide presentation, "VIOXX Aspirin Users Endoscopy Study – Protocol 158" MRK-ABP0020136-56 (attached to Summary of 12/19/01 CRRC meeting, MRK-ABP0020124). As discussed in Section D of this Appendix, the comparator for Protocol 158 changed several times before it was cancelled in 2003.

the treatment groups, take the treatment for twelve weeks, and then be examined with an endoscope for signs of developing gastroduodenal ulcers.<sup>25</sup>

MRL scientists hypothesized that these studies would show that Vioxx combined with low-dose aspirin for cardiovascular prophylaxis (i) would cause less gastrointestinal injury than ibuprofen alone, (ii) would not cause any greater gastrointestinal injury than aspirin alone, and (iii) would cause less gastrointestinal injury than ibuprofen plus aspirin.<sup>26</sup> Protocol 136, the first of these studies to be conducted, enrolled its first patient on December 19, 2000, and produced interim results in the fall of 2001.<sup>27</sup> Protocol 158 was in development from mid-2001 until mid-2003, at which point it was cancelled.<sup>28</sup>

C. Subsequent Decision to Conduct a Cardiovascular Outcomes Trial.

From May 2000 – when the Company decided not to conduct a cardiovascular outcomes trial – until the spring of 2001, there was little (if any) discussion within the Company about a cardiovascular outcomes trial. By May 2001, however, the idea of conducting a cardiovascular outcomes trial had resurfaced, prompted by two factors:

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<sup>25</sup> Gastroduodenal ulcers, also known as “peptic ulcers,” are defined as ulcers that occur in the gastrointestinal tract, which occur when there are defects in the mucosal barrier. The common forms of gastroduodenal ulcers are associated with, among other things, the consumption of NSAIDs. <http://www.diseasesdatabase.com/umlsdef.asp?glnUserChoice=9818>.

<sup>26</sup> See 5/17/00 slide presentation of B. Daniels to HHPAC, “VIOXX® Interim Review,” MRK-ABL0000942, at 71; 3/9/00 email from E. Scolnick to D. Shapiro, A. Reicin, and A. Nies, MRK-ABH0016220; Undated slide presentation, “Aspirin Users Endoscopy Study – Protocol 158,” MRK-ABP0020136, at 43 (attached to Summary of 12/19/01 CRRC meeting, MRK-ABP0020124).

<sup>27</sup> Vioxx CSR Tracking Schedule, MRK-NJ0196341, at 50; 11/19/01 email from T. Simon to R. Bain *et al.*, MRK-AAD0111895. As discussed in Section D.2. of this Appendix, the interim results of Protocol 136 did not support MRL’s hypotheses.

<sup>28</sup> See 8/29/01 slide presentation to HHPAC, MRK-AKU0080353, at 393-94; 8/26/03 email from N. Patel to T. Simon *et al.*, MRK-ABS0465511.

(i) statements by FDA representatives and Arthritis Advisory Committee members at the February 2001 FDA Arthritis Advisory Committee Meeting reflecting continuing concern about the cardiovascular safety of Vioxx,<sup>29</sup> and (ii) concern within Merck about the pending publication in the Journal of the American Medical Association (“JAMA”) of an article by Dr. Eric Topol\* of the Cleveland Clinic, which suggested that selective Cox-2 inhibitors might increase patients’ risk of cardiovascular adverse events and called for a prospective trial to further study the issue.<sup>30</sup>

These two factors triggered a series of discussions within the Company – first among the members of the Arthritis and Analgesia Worldwide Business Strategy Team and later moving up to the Human Health Product Approval Committee – about potential designs for a cardiovascular outcomes trial. This Section discusses: (i) the preliminary consideration given to the design of a cardiovascular outcomes trial in the spring and summer of 2001, including a proposal by Dr. Topol\* to study the effects of Vioxx plus aspirin versus aspirin alone in high cardiovascular risk patients; (ii) the additional pressure on the Company generated by the publication of the Topol article in August 2001, the FDA Warning Letter that Merck received in September 2001, and the FDA label negotiations anticipated to begin in October 2001, to conduct a cardiovascular outcomes trial with Vioxx; and (iii) Merck’s informal decision that fall to conduct such a trial.

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<sup>29</sup> See Appendix I.

<sup>30</sup> See Appendix J.

1. May – August 2001: Renewed Discussions  
About Conducting a Cardiovascular Outcomes Trial.

In May 2001, before submitting his manuscript to JAMA, Dr. Topol<sup>\*</sup>, together with his colleague from the Cleveland Clinic, Dr. Deepak Bhatt<sup>\*</sup>, sent Merck a draft protocol for a proposed Vioxx cardiovascular outcomes study in patients with acute coronary syndrome (“ACS”) and elevated markers of inflammation.<sup>31</sup> (As discussed in Appendix J, at this time Dr. Topol<sup>\*</sup> and MRL scientists were engaged in ongoing discussions regarding his draft article.) The proposed study tested the hypothesis noted in the Topol article that, because of their anti-inflammatory properties, selective Cox-2 inhibitors could be cardioprotective in patients at high cardiovascular risk.<sup>32</sup> The proposed study would not, however, directly test whether Vioxx alone was prothrombotic, because (i) it was designed around a cardioprotection hypothesis in a limited set of high-risk patients, and (ii) the design required all patients enrolled in the study to take aspirin for cardiovascular prophylaxis.<sup>33</sup> Nonetheless, because it would analyze cardiovascular safety data as its primary endpoint, it constituted one approach to conducting a Vioxx cardiovascular outcomes trial.

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<sup>31</sup> 5/2/01 email from D. Bhatt<sup>\*</sup> to A. Reicin attaching Topol/Bhatt proposal, MRK-ABA0010314. The Topol/Bhatt proposal stated that “acute coronary syndrome” included “acute myocardial infarction and unstable angina,” and was defined more specifically as “ischemic discomfort at rest lasting at least five minutes.” MRK-ABA0010315, at 16, 20.

<sup>32</sup> Study proposal, “Rofecoxib in the Prevention of Ischemic Events in Patients with Acute Coronary Syndromes and Elevated Markers of Inflammation,” MRK-ABA0010315, at 16-18 (attached to 5/2/01 email from D. Bhatt<sup>\*</sup> to A. Reicin, MRK-ABA0010314). According to the proposal, acute coronary syndrome patients included those with acute myocardial infarction and unstable angina.

<sup>33</sup> Study proposal, “Rofecoxib in the Prevention of Ischemic Events in Patients with Acute Coronary Syndromes and Elevated Markers of Inflammation,” MRK-ABA0010315, at 16-19 (attached to 5/2/01 email from D. Bhatt<sup>\*</sup> to A. Reicin, MRK-ABA0010314).

Beginning in May 2001, the Worldwide Business Strategy Team – a group of senior clinical scientists and marketing executives that, under Dr. Wendy Dixon’s leadership, oversaw the strategic global research and marketing decisions for Vioxx – began discussing whether further outcomes studies, including the one proposed by Drs. Topol\* and Bhatt\*, should be planned with Vioxx or Arcoxia.<sup>34</sup> The Worldwide Business Strategy Team established an “Anti-inflammatory Study Design Working Group,” headed by Drs. Alice Reicin and Sean Harper, a physician in MRL’s gastroenterology group, to evaluate the Topol/Bhatt proposal and other designs and then report back to the Team in July.<sup>35</sup>

In June and July 2001, Dr. Reicin, together with Drs. Peter DiBattiste and Laura Demopoulos – two members of MRL’s cardiovascular group who headed the design efforts for a Vioxx cardiovascular outcomes study – reviewed the study proposal and engaged in an ongoing dialogue with Drs. Topol\* and Nissen\* about the Topol/Bhatt proposal for a trial in post-ACS patients.<sup>36</sup> Throughout these discussions, Drs. Topol\* and Nissen\* indicated that they were simultaneously engaged in discussion with Pfizer about sponsoring their post-ACS study proposal.<sup>37</sup> As Dr. Demopoulos communicated to

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<sup>34</sup> 1/19/05 deposition of W. Dixon at 142-43 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>35</sup> See Summary of 5/17/01 A&A WBST meeting, MRK-AFV0010496, at 97.

<sup>36</sup> See Appendix J.

<sup>37</sup> 6/28/01 email from S. Nissen\* to A. Reicin and P. DiBattiste, MRK-ABA0010456; 7/13/01 email correspondence among E. Topol\* and L. Demopoulos, MRK-ABA0010491-92; 7/27/01 email from S. Nissen\* to L. Demopoulos and P. DiBattiste, MRK-ABA0010638; see also 6/19/01 email correspondence among A. Reicin, M. Whitney, et al., MRK-ABA0010417-18.

Dr. Nissen\*, the Topol/Bhatt proposal remained at the forefront of MRL's internal discussions about designing a cardiovascular clinical outcomes trial with Vioxx:

We have wrangled a bit on what question we want to address, but have sequentially rejected every design (we generated about 20!) other than yours. Now that the "working group" level has bought in, I need to bring it to senior management for review. I hope you will feel confident in my track record that we will get this done. I hope you don't do this with Pfizer.<sup>38</sup>

The Worldwide Business Strategy Team discussed various design options for a cardiovascular outcomes trial at its meeting on July 24 2001, and endorsed a study in high cardiovascular risk patients comparing the effects of Vioxx plus aspirin versus aspirin alone, essentially the Topol/Bhatt study proposal.<sup>39</sup> The Team presented the study design to the Human Health Product Approval Committee in August.<sup>40</sup> At that time, however, no formal decision had been made to pursue any cardiovascular outcomes trial, including the one specifically proposed by Drs. Topol\* and Bhatt\*.<sup>41</sup>

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<sup>38</sup> 7/13/01 email from L. Demopoulos to E. Topol\*, MRK-ABA0010491.

<sup>39</sup> Summary of 7/24/01 A&A WBST meeting, MRK-AFV0010500, at 00.

<sup>40</sup> 8/29/01 slide presentation to HHPAC, MRK-NJ0202897, at 90.

<sup>41</sup> Accordingly, Drs. DiBattiste, Demopoulos, Gertz, and Slater prepared a letter to Dr. Topol\* confirming for him that Merck had not committed to conducting his study. Draft letter from E. Scolnick to E. Topol\*, MRK-ABD0003143-44 (attached to 7/30/01 email from P. DiBattiste to B. Gertz, L. Demopoulos, and E. Slater, MRK-ABD0003142). There is no evidence to suggest that the letter was ever mailed, or that Dr. Scolnick was involved in drafting it.

2. August – September 2001: Additional Pressure to Conduct a Cardiovascular Outcomes Study.
  - a. Public attention following the publication of the Topol article.

The publication of the Topol article on August 22, 2001 triggered renewed external criticism of Vioxx’s cardiovascular safety profile and increased pressure on Merck to conduct a clinical cardiovascular safety trial.<sup>42</sup> In addition, in mid-September, the American Heart Association, the National Stroke Association, and the Arthritis Foundation publicly asked Merck and Pharmacia (Searle/Pfizer) to conduct cardiovascular safety studies of their respective selective Cox-2 inhibitors.<sup>43</sup>

On September 17, 2001, less than a month after the Topol article was published, Merck received a Warning Letter from the FDA (discussed in Appendix G) that, among other things, criticized the Company’s emphasis in certain promotional materials on the naproxen cardioprotection hypothesis as an explanation for the between-treatment differential in cardiovascular adverse event rates observed in the VIGOR Trial.<sup>44</sup> The Warning Letter, which asserted that Merck’s promotional campaign had “minimize[d] the potentially serious cardiovascular findings that were observed in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, and thus, misrepresent[ed] the

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<sup>42</sup> See, e.g., Jim Ritter\*, Pain Pill Linked to Heart Risk, Chi. Sun-Times, Aug. 22, 2001, at 3; Thomas H. Maugh II\*, Study Finds Health Risks in Popular Arthritis Medicines Vioxx, Celebrex, L.A. Times, Aug. 22, 2001, at A15; Thomas M. Burton\*, Note of Caution: Study Raises Specter of Cardiovascular Risk for Hot Arthritis Pills, Wall St. J., Aug. 22, 2001, at A1; see also 4/12/05 deposition of D. Anstice at 247-48 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>43</sup> See 9/13/01 email from D. Wambold to E. Slater et al. including text of article: Ransdell Pierson\*, Groups Urge Heart Safety Trial for Vioxx, Celebrex, Reuters, Sept. 13, 2001, MRK-ABD0003283, at 83.

<sup>44</sup> 9/17/01 FDA Warning Letter from T. Abrams\* to Mr. Gilmartin, MRK-AAF0007777-85.

safety profile for Vioxx,”<sup>45</sup> triggered additional negative publicity concerning Vioxx’s cardiovascular safety.<sup>46</sup>

During September and October 2001, Vioxx prescription volume decreased by approximately 11%, which members of Merck’s Marketing Department attributed to negative publicity following the Topol article and the FDA Warning Letter.<sup>47</sup>

b. Anticipation of upcoming FDA label negotiations.

Some at Merck – including Dr. Robert Silverman, Merck’s principal contact with FDA during the Vioxx label negotiations – were concerned that the negative publicity regarding the cardiovascular safety of selective Cox-2 inhibitors resulting from the Topol article would also affect the Company’s ongoing negotiations with the FDA over proposed post-VIGOR revisions to the Vioxx label. After reading an advance copy of the Topol article just before its publication, Dr. Silverman noted his thoughts in an August 17, 2001 internal email:<sup>48</sup>

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<sup>45</sup> 9/17/01 FDA Warning Letter from T. Abrams\* to Mr. Gilmartin, MRK-AAF0007777, at 77.

<sup>46</sup> See, e.g., Chris Adams\*, FDA Warns Merck for Vioxx Promotions, Wall St. J., Sept. 25, 2001, at B5; Rita Rubin\*, FDA Sends Warning Letter to Vioxx Maker, USA Today, Sept. 25, 2001, at C4.

<sup>47</sup> 10/12/01 email from R. El-Dada to P. Daruwala and S. Kornowski, MRK-ADM0037829, at 29 (“Prescription volume in the US [is] off by roughly 10-12% since the JAMA article . . . .”); see also 3/16/05 deposition of D. Anstice at 77 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>48</sup> 8/17/01 email from R. Silverman to K. Truitt, MRK-NJ0202006; see also 10/26/01 email from S. Vignau to W. Dixon, MRK-ABW0014720 (“Nissen and Topol are starting to attack the next generation products. Obviously they want to keep the pressure on to fund them. I hope we will announce that we are doing a study soon or they will use each approval to question the safety and call for a study. Once we announce we cut them off. Also it may help our approval time if the FDA is feeling less pressure.”).

To: Truitt, Ken E  
From: Silverman, Robert E. (MRL)  
Cc: Simpson, Sandra L.; Gertz, Barry J  
Bcc:  
Date: 2001-08-17 15:14:42  
Subject: RE: decision making on a

Ken, another nuance to consider is the  
Cleveland Clinic press release. I have a growing pre-  
some kind of CV outcome study from FDA as part of  
ourselves at the negotiating table to preclude overly  
internal position/proposal that I can have when we re-  
concerned with undermining the excellent labelling we  
worst from FDA (they will be under pressure to be co-  
marketing safety issues and likely Topol article public

Bob

**I have a growing premonition that we will be getting a Phase 4 requirement to do some kind of CV outcome study from FDA as part of the VIGOR approval. Or perhaps we will offer one ourselves at the negotiating table to preclude overly negative labelling [sic]. . . . I think we must assume the worst from FDA (they will be under pressure to be conservative, eg [sic] taking heat for previous recent post-marketing safety issues and likely Topol article publicity, etc.).**

A demand by the FDA that Merck conduct a cardiovascular outcomes trial as part of the of the VIGOR supplemental New Drug Application approval process would substantially delay the post-VIGOR label change. In addition, as discussed more fully in Appendix N, the Company wanted to avoid a demand by the FDA that the Company include a Cardiovascular Warning in the Vioxx label. MRL scientists did not think such a warning was justified, but Dr. Silverman expressed concern that the FDA was under public pressure in the aftermath of the Topol article to “be conservative.”<sup>49</sup> The anticipation of the FDA’s counterproposal to Merck’s proposed label change for Vioxx thus factored into MRL scientists’ decision that they should conduct a cardiovascular outcomes trial.<sup>50</sup>

<sup>49</sup> 8/17/01 email from R. Silverman to K. Truitt, MRK-NJ0202006.

<sup>50</sup> As discussed in Appendix N, on October 15, 1001, the FDA sent Merck a counterproposal label that in fact included Cardiovascular Warning for Vioxx. Dr. Scolnick and others at Merck strongly objected to the inclusion of a Cardiovascular Warning on the ground that it was not warranted by the data. The FDA ultimately approved a label without a cardiac warning, but that included cardiovascular safety information in the Precautions section.

### 3. Informal Decision to Conduct a Cardiovascular Outcomes Trial

On September 13, 2001, Dr. Scolnick had emphasized in an internal email that in his view a cardiovascular outcomes trial was the “ONLY ESSENTIAL STUDY” for Vioxx for the coming year, even though the Company had not yet settled on an appropriate study design.<sup>51</sup> By September 25, 2001, Merck had assembled a “Vioxx CV Outcomes Study – Merck Steering Committee,” led by Dr. DiBattiste, the Medical Director of Merck’s Cardiovascular Clinical Research Department, to oversee the Company’s efforts to design such a study,<sup>52</sup> signaling that an informal decision, not yet endorsed by the Human Health Product Approval Committee, had been made to proceed with such a trial.

The informal decision to conduct the trial was characterized at that time as a “huge win[.]”<sup>53</sup> by Marketing executives who hoped to “put to rest all the noise in the market” by publicly announcing plans to initiate a cardiovascular outcomes study.<sup>54</sup> By October 19, when marketing and research groups from all of Merck’s drug franchises met to discuss the budget for 2002 studies at the Company’s annual budgeting meeting in

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<sup>51</sup> 9/13/01 email from E. Scolnick to D. Anstice et al., MRK-ABW0011211, at 12 (emphasis in original).

<sup>52</sup> 9/25/01 email from P. DiBattiste to T. Simon et al., MRK-NJ0206741; 8/16/05 deposition of B. Gertz at 511 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>53</sup> 11/7/01 email from T. Cannell to W. Dixon, MRK-ADG0052349.

<sup>54</sup> 9/17/01 email from W. Dixon to S. Nichtberger, MRK-ABW0008875.

Branchburg, New Jersey, the cardiovascular outcomes study had been labeled as the Marketing Department's top priority study for Vioxx for 2002.<sup>55</sup>

The Company informed the FDA of its decision to conduct a cardiovascular safety trial with Vioxx in its November 6, 2001 response to the FDA's proposed label.<sup>56</sup>

D. Designing the Cardiovascular Outcomes Trial.

1. Overview.

Once MRL scientists had decided to recommend that the Company conduct a cardiovascular outcomes trial, they were again faced with the difficult task of designing the trial. In an October 22, 2001 email, Dr. Reicin alluded to the complexity of the task ahead: “[w]e believe that doing a study is the right thing to do—but the logistics will make VIGOR look like a walk in the park (and VIGOR felt like a marathon to me).”<sup>57</sup>

Designing any large clinical outcomes trial requires identifying a hypothesis, a patient population, and comparator drugs. A successful trial would need to be:

(i) effective, in that it unequivocally resolved any doubts about Vioxx's cardiovascular safety; (ii) practical, in that it could be conducted relatively quickly, feasibly, and with a manageable number of patients; and (iii) ethical, in that patients receiving Vioxx or an active comparator could be expected to receive a benefit that outweighed any known risks of the treatments, such as gastrointestinal or hypertensive complications, and

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<sup>55</sup> 10/3/01 slide presentation, “2002 Pre-Branchburg Review – VIOXX and ARCOXIA,” MRK-AFO0155427, at 35.

<sup>56</sup> 11/6/01 letter from R. Silverman to J. Bull\*, MRK-01420163697, at 700.

<sup>57</sup> 10/22/01 email from A. Reicin to C. Bombardier\* (cc: P. DiBattiste), MRK-AAD0085326.

patients receiving placebo not experience a lasting harm as a result of the denial of treatment for the duration of the study.

A primary question that framed the design discussions was whether the study should be constructed around a non-inferiority hypothesis (i.e., one that sought to show that Vioxx was no worse than the comparator), or a superiority hypothesis (i.e., one that sought, like study proposed by Dr. Topol<sup>\*</sup>, to show that Vioxx was better than placebo or a comparator drug). The hypothesis that Vioxx was not prothrombotic was essentially a non-inferiority hypothesis. One difficulty of designing such a trial, however, was that the FDA Division of Cardio-Renal Drug Products generally disfavored non-inferiority studies of cardiovascular endpoints.<sup>58</sup>

Throughout June and July 2001, Drs. Alise Reicin, Sean Harper, Laura Demopoulos, and Peter DiBattiste were among a core group of MRL scientists that considered various design options and the strengths and weaknesses of each.

a. Approaches considered.

MRL scientists considered several alternative hypotheses and design approaches to test those hypotheses. On June 21, 2001, Dr. Reicin emailed to Dr. Scolnick a draft presentation identifying nine different design options for a cardiovascular outcomes trial, including the Vioxx versus Tylenol study design that Dr. Scolnick had originally

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<sup>58</sup> See 12/19/02 letter from L. Goldkind<sup>\*</sup> to N. Braunstein, MRK-YAH0000017, at 18 (“The Division of Cardio-renal products is uncomfortable with the use of a non-inferiority trial. For claims related to the CV system, direct discussion with the Division of Cardio-renal products is recommended.”).

proposed in April 2000.<sup>59</sup> Dr. Reicin's presentation, which was incorporated into a June 22, 2001 presentation to the Human Health Product Approval Committee,<sup>60</sup> listed the same pros and cons for the Tylenol design as had originally been considered, and asked, with respect to that proposed design: "What are the PR implications of Merck doing a study primarily for CV risk?"<sup>61</sup> By the end of August 2001, the Vioxx versus Tylenol design had fallen out of consideration.<sup>62</sup>

The four types of trial designs that primarily remained under consideration are introduced below.

(i) Vioxx versus placebo.

Theoretically, a long-term study of Vioxx versus placebo in the patient population most likely to be taking Vioxx – osteoarthritis and rheumatoid arthritis patients – would have answered cleanly and directly the question of whether Vioxx was prothrombotic. MRL scientists concluded, however, that such a non-inferiority study would be not be feasible for several reasons. First, such a study would need to have a primary hypothesis other than the non-inferiority hypothesis that Vioxx does not cause myocardial infarction

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<sup>59</sup> 6/21/01 email from A. Reicin to E. Scolnick attaching slide presentation, MRK-ABH0002006; Undated draft slide presentation to HHPAC, "Future Plans," MRK-ABH0002007, at 20-24 (attached to 6/21/01 email from A. Reicin to E. Scolnick, MRK-ABH0002006); see also Section B of this Appendix.

<sup>60</sup> 6/22/01 slide presentation to HHPAC, MRK-AAD0025114, at 75-79.

<sup>61</sup> Undated draft slide presentation to HHPAC, "Future Plans," MRK-ABH0002007, at 20, 24 (attached to 6/21/01 email from A. Reicin to E. Scolnick, MRK-ABH0002006). At its June 22, 2001 meeting, the Human Health Product Approval Committee requested that the Worldwide Business Strategy Team "determine if Pfizer is undertaking a long-term outcomes study versus acetaminophen." Minutes of 6/22/01 HHPAC meeting, MRK-ABL0001687, at 88.

<sup>62</sup> See 8/29/01 slide presentation to HHPAC, MRK-NJ0202897, at 982-92.

or adverse cardiovascular events, both because FDA policy required that a placebo-controlled trial be designed to test a potential benefit of the trial drug,<sup>63</sup> and because it would not be feasible to recruit patients for a study intended primarily to prove that the study drug did not cause cardiovascular adverse events. Second, MRL scientists believed that a long-term Vioxx versus placebo study might be seen as unethical with respect to patients in the placebo arm because osteoarthritis and rheumatoid arthritis patients require pain relief.<sup>64</sup> Third, even if there were no ethical concern, the difficulty of recruiting osteoarthritis and rheumatoid arthritis patients for a long-term study that would deny half the subjects pain relief, and the difficulty of retaining patients over the long term in the placebo arm of such a study, would have made the study unfeasible.

A theoretical alternative would have been to conduct a large-scale Vioxx versus placebo study in a non-arthritic patient population. Without a theory under which non-arthritic patients would derive a benefit from Vioxx, however, conducting such a study would not be feasible and would violate FDA policy regarding placebo-controlled trials.<sup>65</sup>

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<sup>63</sup> See “Guidance for Institutional Review Boards and Clinical Investigators (1998 Update) – Drug Study Designs,” <http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#study> (placebo-controlled trials are designed to show a difference between the tested drug and the control, while active-controlled trials can be designed to show either a difference or no difference between the tested drug and the active control.).

<sup>64</sup> 10/11/05 transcript of Humeston v. Merck & Co., ATL-L-2272-03 MT, N.J. Super. Ct. Law Div., at 3552-59 (testimony of A. Reicin).

<sup>65</sup> See “Guidance for Institutional Review Boards and Clinical Investigators (1998 Update) – Drug Study Designs,” <http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#study> (placebo-controlled trials are designed to show a difference between the tested drug and the control, while active-controlled trials can be designed to show either a difference or no difference between the tested drug and the active control.).

At the time, MRL was conducting two placebo-controlled studies examining whether Vioxx provided any benefit to patients with Alzheimer's disease, as well as two placebo-controlled studies examining whether Vioxx had positive effects on cancer patients (the APPROVe and VICTOR Trials). MRL was analyzing cardiovascular data from those and all other Vioxx clinical trials, pursuant to the Cardiovascular Adjudication SOP. Each of these studies on its own, however, was too small and not adequately powered to constitute a clinical outcomes trial sufficient to answer the question of whether Vioxx was prothrombotic.

(ii) Vioxx versus non-naproxen NSAIDs: a "Large Simple Trial".

MRL scientists also considered a non-inferiority design that would compare the cardiovascular effects of Vioxx to those of a non-naproxen NSAID such as ibuprofen or diclofenac in an osteoarthritis or rheumatoid arthritis population that included both low-dose aspirin and non-aspirin users. An advantage of this type of trial, considered a "Large Simple Trial,"<sup>66</sup> was that it would reflect real world circumstances, in that the patients studied would be drawn from the broader patient population indicated for Vioxx and that low-dose aspirin, which is widely used for cardiovascular prophylaxis among the older patients likely to be taking Vioxx, would be allowed. In addition, MRL scientists thought that it was highly probable that a study of this sort would yield similar

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<sup>66</sup> 10/19/01 slide presentation for annual Branchburg meeting, "2002 MRL Overview: Human Health " MRK-NJ0216895, at 909. A "Large Simple Trial" is one where "treatment is administered in a naturalistic setting that is intended to mirror standard practice, and the outcomes measured are simple and available in the typical practice setting." Siderowf AD. Evidence from clinical trials: can we do better?" NeuroRx. 2004;1:363-371, at 366.

cardiovascular results in each arm, which would be a positive outcome from the Company's perspective.<sup>67</sup>

At the same time, however, MRL scientists thought that such a study carried a risk of yielding unfavorable gastrointestinal data for Vioxx that was "not insignificant,"<sup>68</sup> both because patients would be allowed to take low-dose aspirin during the study, which is known to result in increased risk of gastrointestinal adverse events,<sup>69</sup> and because some of the non-selective NSAID comparators under consideration (such as diclofenac) were thought to have relatively favorable gastrointestinal safety profiles that might not be significantly different from that of Vioxx.<sup>70</sup>

Moreover, because the cardiovascular adverse event rate is relatively small in a population including both high and low cardiovascular risk patients (*i.e.*, aspirin users and non-aspirin user), it was estimated that a large number of patients – perhaps as many

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<sup>67</sup> Undated draft slide presentation, "Future Plans," MRK-ABH0002007, at 15 (attached to 6/21/01 email from A. Reicin to E. Scolnick *et al.*, MRK-ABH0002006).

<sup>68</sup> Undated draft slide presentation, "Future Plans," MRK-ABH0002007, at 15 (attached to 6/21/01 email from A. Reicin to E. Scolnick *et al.*, MRK-ABH0002006).

<sup>69</sup> 11/21/96 memorandum from T. Musliner to B. Friedman (later: B. Seidenberg) *et al.*, MRK-AAX0002413, at 14-15.

<sup>70</sup> See 12/20/01 email from R. El-Dada to A. Reicin *et al.*, MRK-ADM0063214 (noting that "diclo[fenac] was an option [for the cardiovascular outcomes study comparator] but clinical folks were not inclined due to . . . GI profile"); 2/5/02 email from T. Ruef to R. El-Dada, MRK-ADM0070848 ("GI profile of diclofenac considered quite good."). Among non-selective NSAIDs, diclofenac and lower doses of ibuprofen have the lowest relative risk of gastrointestinal complications. Henry\* D; Lim\* LL-Y, Garcia Rodriguez\* LA, *et al.* Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ*. 1996;312:1563-1566, at 1563.

as 40,000<sup>71</sup> – would be required to power the study to detect small differences (or the lack thereof) in cardiovascular event rates between the Vioxx and NSAID arms.

Additionally, the “Large Simple Trial” design was estimated to require a duration of between five and eight years to adequately power the study.<sup>72</sup> Only a study powered to detect small differences between two treatments would be capable of demonstrating with statistical significance that such a small difference does not exist.

(iii) Vioxx plus aspirin versus NSAID plus aspirin.

MRL scientists also considered a cardiovascular outcomes trial that would show both that (i) taking Vioxx plus aspirin would provide adequate cardiovascular protection for high cardiovascular risk patients, and (ii) taking Vioxx plus aspirin was safe from a gastrointestinal perspective.<sup>73</sup> To this end, MRL scientists discussed a study that would test Vioxx plus aspirin versus an NSAID plus aspirin in patients indicated for cardiovascular prophylaxis – in other words, in patients at high cardiovascular risk. MRL scientists concluded, however, that this approach would not effectively answer the question of whether Vioxx was prothrombotic because (i) it would only address the effects of Vioxx plus aspirin in high cardiovascular risk patients and not in the broader

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<sup>71</sup> Undated slide presentation, “VIOXX: Cardiovascular Outcomes Trial Considerations,” MRK-AFO0094606, at 12 (attached to 8/28/01 email from P. DiBattiste to J. Bolognese, MRK-AFO0094605); Undated draft slide presentation, “Future Plans,” MRK-ABH0002007, at 15 (attached to 6/21/01 email from A. Reicin to E. Scolnick et al., MRK-ABH0002006).

<sup>72</sup> See 8/29/01 slide presentation to HHPAC, MRK-AKU0080353, at 72.

<sup>73</sup> The results of Protocol 136, which demonstrated that the incidence of gastrointestinal adverse events in patients on Vioxx plus aspirin was greater than among patients on aspirin alone and similar to that of patients on ibuprofen alone, were not yet available. See Sections B and D of this Appendix.

patient population indicated for Vioxx;<sup>74</sup> and (ii) the inclusion of aspirin would confound the study's ability to show whether Vioxx itself led to adverse cardiovascular events.<sup>75</sup>

MRL scientists also believed that it might be unethical to require patients with high cardiovascular risk to take aspirin with a traditional non-selective NSAID such as ibuprofen because such a combination could significantly increase the risk of gastrointestinal bleeding, which patients at high cardiovascular risk might be unable to tolerate.<sup>76</sup>

(iv) Vioxx plus aspirin versus aspirin alone.

As discussed in Appendix A, a number of scientists within and outside Merck had raised the question, beginning in or before 1998, of whether Vioxx's anti-inflammatory

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<sup>74</sup> See 6/19/2001 email from S. Harper to B. Gertz and A. Reicin, MRK-NJ0196686 (noting that he did not think a design involving Vioxx plus low-dose aspirin "would really answer question of COX-2 prothrombotic effect in non-ASA requiring [patients]").

<sup>75</sup> Undated draft slide presentation, "Future Plans," MRK-ABH0002007, at 12, 13, 18 (attached to 6/21/01 email from A. Reicin to E. Scolnick *et al.*, MRK-ABH0002006) (noting that designs that include Vioxx plus low-dose aspirin "would not address the VIOXX/Prothrombotic question head on due to use of low dose aspirin").

<sup>76</sup> Undated draft slide presentation, "Future Plans," MRK-ABH0002007, at 13 (attached to 6/21/01 email from A. Reicin to E. Scolnick *et al.*, MRK-ABH0002006). According to The Merck Manual, patients with ischemic heart disease may experience angina or a myocardial infarction after "brisk" gastrointestinal bleeding. Additionally, "[c]oexistent heart failure, hypertension, pulmonary disease, renal failure, and diabetes mellitus may be aggravated by severe GI bleeding." <http://www.merck.com/mrkshared/mmanual/section3/chapter22/22a.jsp>.

In November 2001, MRL scientists analyzed data from non-Vioxx clinical trials in high cardiovascular risk patients to determine whether gastrointestinal adverse events might predispose or trigger cardiovascular adverse events. They concluded, however, that there was "no apparent association between GI events and CV events" in post-ACS patients. 12/01 draft slide presentation to CV Outcomes Internal Steering Committee, "COX-2 Inhibitors and CV Outcomes: A Comprehensive Clinical Evaluation Proposal," MRK-ACD0119327, at 48-52.

quality might make it cardioprotective in certain high-risk patients.<sup>77</sup> A fourth design approach that Merck considered was to test this superiority hypothesis.

In 1997, researchers had observed that the magnitude of aspirin's beneficial cardiovascular effect in male patients was directly related to their baseline levels of C-reactive protein – a marker of systemic inflammation. In other words, low-dose aspirin usage was associated with a greater reduction in the rate of cardiovascular events in patients with high levels of C-reactive protein than in patients with lower levels of C-reactive protein. This observation led the researchers to theorize that aspirin's ability to provide cardioprotection stemmed not only from its antiplatelet effects, but also from its anti-inflammatory effects.<sup>78</sup> By 2001, over 1600 articles had been published about the role of inflammation in cardiovascular disease, plaque destabilization, and acute coronary syndromes.<sup>79</sup>

As discussed above, in the spring of 2001, Drs. Eric Topol\* and Deepak Bhatt\* proposed a study to Merck that would test Vioxx plus aspirin versus aspirin alone in

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<sup>77</sup> 3/18/99 background material for 3/31/99 VIOXX Consultants Meeting, MRK-ABA0004507-22; see generally Appendix A. In addition to MRL scientists' speculations that Vioxx might be cardioprotective due to its anti-inflammatory characteristics, Dr. Scolnick raised the possibility, in a May 2001 email to Mr. Gilmartin, that the magnitude of the differential in cardiovascular events seen in the VIGOR Trial might be due to an extra cardioprotective benefit of naproxen – beyond its antiplatelet effects – achieved through its anti-inflammatory effects. Dr. Scolnick noted that, at the low dosage prescribed for cardiovascular prophylaxis, aspirin did not serve as an anti-inflammatory agent. 5/22/01 email from E. Scolnick to R. Gilmartin, MRK-ACR0009159.

<sup>78</sup> See Ridker\* PM, Cushman\* M, Stampfer\* MJ, Tracy\* RP, Hennekens\* CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336(14):973-979.

<sup>79</sup> Undated slide presentation, "Vioxx CV & GI Outcome Study: The road from prothrombotic to cardioprotective," MRK-ABK0162228, at 32 (attached to 9/27/01 email from A. Moan to B. Gertz, MRK-ABK0162227).

patients with a recent history of acute coronary syndrome (“ACS”) and increased markers of inflammation, with the hypothesis that, because of the potential role of inflammation in atherosclerosis,<sup>80</sup> Vioxx might confer a benefit on such patients. Because all patients would be on low-dose aspirin due to their high cardiovascular risk, such a study would in essence test Vioxx versus placebo. In the fall of 2001, MRL scientists, Drs. Andreas Moan and Ian Rodger, and Dr. Christopher Cannon\*, a Merck external consultant, independently prepared proposals very similar to the post-ACS study initially suggested by Dr. Topol\*.<sup>81</sup>

MRL scientists identified four potential drawbacks of using the post-ACS study idea proposed by Dr. Topol\*. First, such a study would not test the cardiovascular effects of Vioxx in patients with little or no cardiovascular risk – a significant portion of overall Vioxx users. Second, the study would not directly address the question of whether Vioxx alone was prothrombotic because all participants would receive low-dose aspirin.<sup>82</sup> Third, it was not clear that the benefit theory underlying the study was sufficiently well-

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<sup>80</sup> See, e.g., Albert\* MA. The role of C-reactive protein in cardiovascular disease risk. Current Cardiology Report. 2000;2(4):274-279; Fichtlscherer\* S, Rosenberger\* G, Walter\* DH, Breuer\* S, Dimmeler\* S, Zeiher\* AM. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. Circulation. 2000;102:1000-1006; Pasceri\* V, Yeh\* ET. A tale of two diseases: atherosclerosis and rheumatoid arthritis. Circulation. 1999;100:2124-2126.

<sup>81</sup> 9/11/01 email from A. Moan to S. Nichtberger et al. attaching draft study proposal, “Vioxx CV Protection Study,” MRK-ABK0162216-47; 10/27/01 email from C. Cannon\* to P. DiBattiste and L. Demopoulos attaching draft protocol, MRK-ABA0013248-49.

<sup>82</sup> Undated draft slide presentation, “Future Plans,” MRK-ABH0010857, at 68 (attached to 6/21/01 email from A. Reicin to E. Scolnick et al., MRK-ABH0010856).

established to support putting at-risk patients on Vioxx plus aspirin.<sup>83</sup> Fourth, some of Merck's external consultants argued that exposing post-ACS patients to Vioxx, which was known to increase hypertension, would place already unstable patients at undue risk of cardiovascular complications that were not related to thrombotic events.

b. Complicating factor: coxib-aspirin interaction.

Because most of the study designs under consideration involved concomitant use of Vioxx and low-dose aspirin for some or all patients, MRL scientists were necessarily sensitive to the cardiovascular and gastrointestinal consequences of such a combination.

With respect to the cardiovascular consequences of Vioxx plus aspirin, Dr. Scolnick and other MRL scientists were alerted in July 2001 to a discovery made by Dr. Francesca Catella-Lawson,<sup>84</sup> a director of Clinical Research in MRL's Gastroenterology Department, and her former colleagues from the University of Pennsylvania that ibuprofen interfered with the antiplatelet effects of low-dose aspirin.<sup>85</sup>

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<sup>83</sup> For example, Dr. Gertz posed the question, "[H]ow do we support a superiority trial in post-ACS patients? What is the evidence that would support putting patients at any added risk because of going on vioxx plus asa? Peter Libby [Chief of Cardiovascular Medicine at Brigham and Women's Hospital in Boston] just did not see that there was enough support for an anti-inflammatory [sic] message as to the potential benefit [sic] for adding vioxx in such patients." 7/22/01 email from B. Gertz to P. DiBattiste (cc: L. Demopoulos), MRK-NJ0199262. Dr. DiBattiste responded, "If Peter Libby, who has made his recent living describing the role of inflammation in atherosclerosis, doesn't feel that the data are strong enough to support this hypothesis, then this is not a good signal." 7/24/01 email from P. DiBattiste to B. Gertz (cc: L. Demopoulos), MRK-NJ0199262; see also Undated draft summary of consultant input, MRK-YAC0000692, at 93 (attached to 11/2/01 email from P. DiBattiste to L. Connors et al., MRK-YAC0000689); 9/1/05 deposition of B. Gertz at 945-46 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>84</sup> Dr. Catella-Lawson worked with Dr. FitzGerald\* at the University of Pennsylvania from 1994 until December 2000, when she joined MRL.

<sup>85</sup> 7/16/01 email from L. Demopoulos to P. DiBattiste and B. Morrison attaching draft manuscript, "Cyclooxygenase Inhibitors and the Anti-Platelet Effects of Aspirin," MRK-ABA0010496-525.

Specifically, the study concluded that “the prior administration of a conventional NSAID, but not rofecoxib or acetaminophen, antagonizes the irreversible platelet inhibition induced by aspirin” and that this antagonism “may limit the cardioprotective effects of aspirin.”<sup>86</sup>

Additionally, scientists at Merck Frosst had demonstrated that the higher the level of Cox-2 selectivity a given NSAID provided, the lower the risk that the NSAID would interfere with aspirin’s antiplatelet effects.<sup>87</sup> Because Vioxx had the highest level of Cox-2 selectivity of the then-available selective Cox-2 inhibitors, MRL scientists thought that it was the least likely of any of the current NSAIDs (including Celebrex) to interfere with the antiplatelet effects of aspirin, which could potentially confer on Vioxx a competitive advantage with respect to aspirin-indicated NSAID users.<sup>88</sup> Dr. Scolnick told Drs. Douglas Greene, Barry Gertz, and Peter Kim that he was “psyched” about the

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<sup>86</sup> Draft manuscript, “Cyclooxygenase Inhibitors and the Anti-Platelet Effects of Aspirin,” MRK-ABA0010498, at 499 (attached to 7/16/01 email from L. Demopoulos to P. DiBattiste and B. Morrison, MRK-ABA0010496). Dr. Catella-Lawson’s study was published in the New England Journal of Medicine in December 2001. Catella-Lawson F, Reilly\* MP, Kapoor\* SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. New Eng J Med. 2001;345(25):1809-1817. The conclusion of the published article was confined to the interaction between ibuprofen and low-dose aspirin and not, as the quote above states, to “conventional NSAIDs.” The published article states: “the concomitant administration of a ibuprofen but not rofecoxib, acetaminophen, or diclofenac antagonizes the irreversible platelet inhibition induced by aspirin” and that this antagonism “may limit the cardioprotective effects of aspirin.”

<sup>87</sup> See 7/12/01 email from D. Percival to E. Scolnick attaching draft manuscript, “A High Level of Cyclooxygenase-2 Inhibitor Selectivity is Associated with a Lower Risk of Interference with Aspirin Inactivation of Platelet Cyclooxygenase-1,” MRK-AEG0041363-93.

<sup>88</sup> 7/26/01 email from P. Kim to D. Anstice et al., MRK-ACR0008956.

data and requested that they “expeditiously plan” a study to determine whether Celebrex interfered with aspirin in a similar manner to ibuprofen.<sup>89</sup>

Dr. Greene also considered the impact of the ibuprofen-aspirin interaction finding on the cardiovascular outcomes study. In July 2001, he suggested that after Merck completed the proposed Celebrex-aspirin interaction studies, MRL should “reinstate the aspirin/Vioxx/ibuprofen endoscopy study” and prepare to do a gastrointestinal and cardiovascular outcomes study with Vioxx plus aspirin versus ibuprofen plus aspirin.<sup>90</sup>

Dr. Greene reasoned that “if the [ibuprofen-aspirin interaction] concept is correct and the GI endoscopy study results are as expected, we should win on GI and not lose on cardiovascular outcomes.”<sup>91</sup> At this point, no ethical concern was raised about designing a study on a background of aspirin where the comparator – in this case, ibuprofen – was known to interfere with the effects of aspirin.

With respect to the gastrointestinal consequences of Vioxx plus aspirin, the results of Protocol 136, the endoscopy study looking at the gastrointestinal effects of Vioxx plus aspirin that had commenced in December 2000, were not yet known.<sup>92</sup> Many of the designs discussed in the fall of 2001 were contingent on the interim results of that study,

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<sup>89</sup> 7/17/01 email from E. Scolnick to B. Gertz, D. Greene (cc: P. Kim), MRK-ACR0009268.

<sup>90</sup> 7/17/01 email from D. Greene to E. Scolnick, B. Gertz (cc: P. Kim), MRK-ACR0009268. Given that Protocol 136, the endoscopy study of Vioxx plus aspirin versus ibuprofen alone and aspirin alone, was ongoing at this point in time, Dr. Greene was likely referring to the other proposed endoscopy study testing Vioxx plus aspirin versus ibuprofen plus aspirin.

<sup>91</sup> 7/17/01 email from D. Greene to E. Scolnick, B. Gertz (cc: P. Kim), MRK-ACR0009268.

<sup>92</sup> See Vioxx CSR Tracking Schedule, MRK-NJ0196341, at 50.

which were scheduled to be released in at the end of the year.<sup>93</sup> If a positive outcome were reached in Protocol 136 (as expected), then a cardiovascular outcomes study that allowed for aspirin use would be less likely to compromise the positive gastrointestinal effects that had been demonstrated in the VIGOR Trial.<sup>94</sup> If, however, the results of Protocol 136 showed that Vioxx plus aspirin caused more gastrointestinal adverse events than aspirin or ibuprofen, it would “eliminate some of [the design] options” for the cardiovascular outcomes trial.<sup>95</sup>

## 2. Oversight of Trial Design.

After MRL scientists had committed in the fall of 2001 to conducting a cardiovascular outcomes trial, the internal committee for the Vioxx cardiovascular outcomes study narrowed trial designs to three primary options:

- Option A: Vioxx plus aspirin versus an NSAID plus aspirin in patients with high cardiovascular risk;
- Option B: Vioxx plus aspirin versus aspirin alone in patients with high cardiovascular risk;
- Option C: Vioxx versus an NSAID in a mixed-use aspirin population (a “Large Simple Trial”).<sup>96</sup>

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<sup>93</sup> See 8/17/01 email from K. Truitt to A. Silverman, et al., MRK-NJ0202006-07.

<sup>94</sup> See 8/17/00 email from K. Truitt to A. Silverman et al. with handwritten notes, MRK-ADM0018148-49.

<sup>95</sup> 9/17/01 email from T. Ruef to W. Dixon, MRK-ADM0016046, at 47.

<sup>96</sup> 10/19/01 slide presentation for annual Branchburg meeting, “2002 MRL Overview – Human Health,” MRK-NJ0216895 at 908-09.

These three design options had been winnowed down from nine options originally presented by Dr. Reicin in June 2001.<sup>97</sup>

a. Consultants' meeting.

At a meeting held on October 29, 2001, members of MRL's cardiovascular outcomes trial internal steering committee presented the three study options to a group of external consultants, including Drs. Claire Bombardier\* (University of Toronto), Christopher P. Cannon\* (Harvard Medical School), Garret A. FitzGerald\* (University of Pennsylvania), Marvin Konstam\* (New England Medical Center), Loren Laine\* (University of Southern California), and Carlo Patrono\* (University of Chieti, Italy).<sup>98</sup> Prior to the meeting, the consultants received a background package that included information on: (i) the relationship between inflammation, atherosclerosis, and thrombosis; (ii) the role of cyclooxygenase in prostanoid synthesis; (iii) mechanistic issues related to cyclooxygenase inhibition and the cardiovascular system; and (iv) Vioxx's efficacy, gastrointestinal safety, and cardiovascular safety.<sup>99</sup>

The consultants considered, among other things, which comparator should be used if options A or C above – Vioxx versus an NSAID either with or without low-dose

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<sup>97</sup> Undated draft slide presentation, "Future Plans," MRK-ABH0010857, at 61 (attached to 6/21/01 email from A. Reicin to E. Scolnick et al., MRK-ABH0010856).

<sup>98</sup> 10/25/01 email from P. DiBattiste to T. Simon et al. attaching background material for 10/29/01 Cardiovascular Outcomes Study Consultant Meeting, MRK-AAZ0002664, at 65-66.

<sup>99</sup> Background material for 10/29/01 Cardiovascular Outcomes Study Consultant Meeting, MRK-AAZ0002664, at 70-78 (10/25/01 email from P. DiBattiste to T. Simon et al., MRK-AAZ0002664).

aspirin – were pursued. According to an Executive Summary prepared after the meeting

by Dr. DiBattiste, the consultants believed that:

- using ibuprofen would be a “win” for Vioxx from both cardiovascular and gastrointestinal perspectives, but that its interaction with aspirin’s antiplatelet effects would be problematic from an ethical perspective;<sup>100</sup>
- using diclofenac was likely to produce a “draw” from both cardiovascular and gastrointestinal perspectives;<sup>101</sup> and
- using naproxen would be a “draw” or “win” for Vioxx on cardiovascular, but a guaranteed “win” from a gastrointestinal perspective.<sup>102</sup>

The consultants therefore concluded that testing Vioxx plus aspirin versus naproxen plus aspirin would be the best approach if a study with an active comparator were pursued.<sup>103</sup>

With respect to option B – Vioxx plus aspirin versus aspirin alone – the consultants discussed the underlying theory that Vioxx might provide a benefit in post-ACS patients. The consultants agreed that the cardiovascular community now regarded atherosclerosis as an inflammatory process, but the consultants could not achieve consensus as to whether selective suppression of Cox-2 would influence

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<sup>100</sup> Draft summary of 10/29/01 Cardiovascular Outcomes Study Consultant Meeting, MRK-YAC0000974, at 74.

<sup>101</sup> Draft summary of 10/29/01 Cardiovascular Outcomes Study Consultant Meeting, MRK-YAC0000974, at 74.

<sup>102</sup> Draft summary of 10/29/01 Cardiovascular Outcomes Study Consultant Meeting, MRK-YAC0000974, at 74.

<sup>103</sup> Draft summary of 10/29/01 Cardiovascular Outcomes Study Consultant Meeting, MRK-YAC0000974, at 74.

atherosclerosis in a beneficial way.<sup>104</sup> At the meeting, Dr. FitzGerald\* expressed concern that such a trial design was unethical because: (i) the Vioxx cardioprotection theory was tenuous, (ii) post-ACS patients are highly susceptible to thrombosis, and (iii) an increase in blood pressure, a known side-effect of Vioxx and other NSAIDs, could be hazardous to such patients.

The external consultants' recommended – and MRL ultimately agreed – that two studies might be appropriate: (i) Vioxx plus aspirin versus aspirin alone in patients at high cardiovascular risk and with no anti-inflammatory indication (option B above), and (ii) Vioxx plus aspirin versus a non-selective NSAID plus aspirin in patients indicated for an anti-inflammatory drug and cardiovascular prophylaxis (similar to option A above).<sup>105</sup> With respect to the first option, “VALOR” already had been circulated as a possible name for the trial,<sup>106</sup> and after the external consultants meeting, plans proceeded for the development of the VALOR Trial.<sup>107</sup>

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<sup>104</sup> 11/01 slide presentation to CV Outcomes Internal Steering Committee, “COX-2 Inhibitors and CV Outcomes: A Comprehensive Clinical Evaluation Plan,” MRK-ABA0057793, at 97.

<sup>105</sup> Undated draft summary of consultant input, MRK-AAZ0002802, at 04 (attached to 11/2/01 email from P. DiBattiste to L. Connors *et al.*, MRK-AAZ0002799); Draft summary of 10/29/01 Cardiovascular Outcomes Study Consultant Meeting, MRK-YAC0000974, at 76. In the end, MRL decided to conduct the second study with its next-generation selective Cox-2 inhibitor, Arcoxia. The patient population in that study was arthritis patients, both with and without an indication for aspirin usage (closer to a “Large Simple Trial”). 1/12/05 FDA Advisory Committee Background Document, at 8, 34m at [http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B2\\_01\\_Merck-Etoricoxib.pdf](http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B2_01_Merck-Etoricoxib.pdf); 11/30/01 background material for 12/6/01 HHPAC meeting, MRK-ACD0119319-93.

<sup>106</sup> 10/11/01 email from P. DiBattiste to K. Srocki, MRK-ABA0012475-77.

<sup>107</sup> 11/30/01 background material for 12/6/01 HHPAC meeting, MRK-ACD0119319, at 20 (“[MRL] has completed a scientific review of the proposed study designs at DMC (11/27/01).”).

b. Endoscopy study results.

On November 19, 2001, Dr. Thomas Simon forwarded to a group of senior MRL scientists the interim results of the endoscopy study, Protocol 136.<sup>108</sup> The study results, replicated in Table 1 below, were disappointing: the incidence of PUBs in patients who took Vioxx plus aspirin was not significantly different from that in patients who took ibuprofen and was actually higher than that in patients who took aspirin alone.<sup>109</sup>

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<sup>108</sup> 11/19/01 email from T. Simon to R. Bain et al., MRK-AAD0111895.

<sup>109</sup> 11/19/01 memorandum from T. Simon and H. Quan to S. Reines and R. Bain, MRK-AAD0111896, at 96, 98. The difference in the percent incidence of ulcers between patients treated with Vioxx plus low-dose aspirin and those treated with ibuprofen (14.7% versus 16.35%) was not statistically significant. 11/19/01 memorandum from H. Quan to T. Simon, MRK-AAD0111900, at 00. Both Vioxx plus aspirin and ibuprofen showed a statistically significant increase in the percent incidence of ulcers over placebo and over aspirin. Id.

Table 1  
Protocol 136 Interim Results

|   | Placebo | Low-dose aspirin | Vioxx (25 mg) + Low-dose aspirin | Ibuprofen (2400 mg) |
|---|---------|------------------|----------------------------------|---------------------|
|   | N=306   | N=303            | N=301                            | N=290               |
| Percent Incidence of Gastroduodenal Ulcers ( $\geq 3$ mm) | 5.54%   | 8.59%            | 14.70%                           | 16.35%              |

These results prompted MRL scientists to revisit the design of both the planned cardiovascular outcomes trial, which included a Vioxx plus aspirin arm, and Protocol 158, a companion endoscopy study to Protocol 136 that was in the planning stages, as discussed below.

(i) Impact on cardiovascular outcomes trial design.

On November 21, 2001, in light of the interim results of Protocol 136, Dr. Scolnick sent an email to Messrs. Gilmartin and Anstice and Drs. Kim and Greene stating: “I do not think we should announce the Cv outcomes study since now I am not at all sure what the design should be.”<sup>110</sup> The same day, in an email to MRL scientists working on the study, Dr. Scolnick wrote:<sup>111</sup>

<sup>110</sup> 11/19/01 email from E. Scolnick to R. Gilmartin and D. Anstice, MRK-ADI0007471-72. In response, Mr. Anstice expressed concern that the results of Protocol 136 might compromise Vioxx’s competitive position vis-à-vis the labeling of other selective Cox-2 inhibitors, particularly Celebrex, which already had labeling language stating that Celebrex could be taken with low-dose aspirin. Mr. Anstice also suggested that MRL conduct additional endoscopy studies with ibuprofen, Celebrex, and valdecoxib (a second-generation selective Cox-2 inhibitor from Searle/Pfizer), hoping to demonstrate that the gastrointestinal effect of Vioxx plus aspirin was no worse than the gastrointestinal effect of other coxibs plus aspirin. 11/21/01 email from D. Anstice to E. Scolnick, P. Kim, and D. Greene, MRK-ADI0007471.

<sup>111</sup> 11/21/01 email from E. Scolnick to D. Greene, et al., MRK-NJ0302933.

-----Original Message-----

From: Scolnick, Edward M.  
Sent: Wednesday, November 21, 2001 9:11 AM  
To: Greene, Douglas Alan; Kim, Peter S; Nichtberger, Steven A.; Schechter, Adam H; Demopoulos, Laura A.  
Cc: Goldmann, Bonnie J; Gertz, Barry J.; Nies, Alan S.  
Subject: Cv study design  
Importance: High

To ALL: I cannot restrain the activist side of me as I continue to mull the results of the low dose ASA endoscopy study. Looking up Clopidogrel, I think the question we should answer now is NOT whether Vioxx or any Coxib is safe for Cv outcomes. I think the question NOW is what is the best antiplatelet regimen to use with a Coxib. I think that is THE medical question and if we answer it, the problem will dissipate. Thus studies 1. Vioxx low dose asa and pump inhibitor vs naproxen and pump inhibitor in patients with arthritis and some level of CV risk. 2 Vioxx and clopidogrel vs naproxen and pump inhibitor in same kind of patients. If you think it through, this will answer the questions that are medically needed. Safety committee monitors the studies and stops them if the arms separate statistically with predefined stopping rules. Power for noninferiority based on the incidence and differences seen in our own OA, RA studies/ Ed

In other words, Dr. Scolnick wanted to design a trial focused on determining which would be the best antiplatelet agent to use with Vioxx, rather than on the hypothesis that Vioxx is not prothrombotic or that Vioxx provides cardioprotection.<sup>112</sup>

Additionally, Dr. Scolnick proposed adding to both arms of the proposed cardiovascular outcomes study a proton pump inhibitor, which would provide protection against gastrointestinal ulcers.<sup>113</sup> Dr. Scolnick and others recognized, however, that adding a proton pump inhibitor to the study design might at best equalize the gastrointestinal safety of Vioxx plus aspirin to that of aspirin alone, but would not eliminate the risk that Vioxx could “lose” on gastrointestinal safety.<sup>114</sup>

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<sup>112</sup> Specifically, Dr. Scolnick has testified that he was concerned about whether, “knowing that aspirin and Vioxx elevated the rate of ulcers over aspirin alone one could develop a regimen where a person who was on Vioxx and who also needed a platelet blocker could take something besides aspirin.” 8/16/05 deposition of E. Scolnick at 1278 (*In re Vioxx Litig.*, No. 619, N.J. Super. Ct. Law Div.).

<sup>113</sup> 11/21/01 email from E. Scolnick to D. Greene *et al.*, MRK-NJ0302933.

<sup>114</sup> 11/30/01 background material for 12/6/01 HHPAC meeting, MRK-ACD0119319, at 54-58.

(ii) Impact on Protocol 158.

The Protocol 136 interim results available in November 2001 also prompted renewed discussion of the design of Protocol 158, the companion endoscopy study to Protocol 136 that had not yet been started. Protocol 158 originally had been designed to study the gastrointestinal effects of Vioxx plus aspirin versus ibuprofen plus aspirin.<sup>115</sup> The design of Protocol 136 had been nearly identical, except that the comparator in Protocol 136 had been ibuprofen alone as opposed to ibuprofen plus aspirin. At this point, however, MRL scientists also considered adding a third arm – Vioxx plus clopidogrel – to Protocol 158, reasoning that “if clopidogrel acceptance [as an antiplatelet agent] increases, study may define more optimal intervention (from GI perspective) than VIOXX/ASA.”<sup>116</sup>

In the minds of many MRL scientists, the unfavorable interim results of Protocol 136 increased the importance of Protocol 158, which they viewed as a more “real world” comparison in that it involved aspirin in both arms. In addition, although Vioxx plus aspirin had not fared well against ibuprofen alone in Protocol 136, MRL scientists believed that the combination would prove superior from a gastrointestinal safety perspective to ibuprofen plus aspirin in Protocol 158.<sup>117</sup> If so, then any unfavorable gastrointestinal data resulting from the planned cardiovascular outcomes

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<sup>115</sup> 12/19/01 slide presentation to CRRC, “VIOXX™ Aspirin User Endoscopy Study: Protocol 158,” MRK-ACR0016409, at 10-12.

<sup>116</sup> 11/30/01 background material for 12/6/01 HHPAC meeting, MRK-ACD0119319, at 89.

<sup>117</sup> See 1/2/02 email from T. Simon to S. Reines, MRK-ABS0343998.

trial – Vioxx plus aspirin versus aspirin alone – would be much less significant because (i) in the real world, low-dose aspirin alone does not provide adequate pain relief for the arthritis patients who comprise most of the Vioxx market, and (ii) the Company could point to Protocol 158 as evidence that Vioxx plus aspirin is safer from a gastrointestinal perspective than ibuprofen (and perhaps other NSAIDs) plus aspirin.<sup>118</sup>

In light of the results of Dr. Catella-Lawson’s study regarding ibuprofen’s interference with the cardioprotective effects of aspirin (discussed above), MRL scientists considered using one of two alternative comparators, naproxen and diclofenac, instead of ibuprofen for Protocol 158.<sup>119</sup> Although the clinical research team favored using naproxen plus aspirin as a comparator because Vioxx had the “best chance of winning from a GI standpoint,” individuals within the Marketing Department expressed concern about that choice:<sup>120</sup>

To: El-Dada, Riad H.  
From: Ruef, Tim F  
Cc:  
Bcc:  
Date: 2002-02-05 20:44:07  
Subject: Marketing Position on Endoscopy Comparator

- \* USHH Marketing has concerns about naproxen for the following reasons
- \* We have hypothesized that a key reason for the VIGOR findings was the anti-platelet effect of naproxen. If this hypothesis is accurate, we could be questioned as to why we feel the addition of low dose asa to naproxen is necessary. This disconnect creates a significant credibility issue.

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<sup>118</sup> See 12/28/01 email from T. Simon to S. Reines, MRK-ABS0343998.

<sup>119</sup> 12/19/01 slide presentation to CRRC, “VIOXX™ Aspirin User Endoscopy Study: Protocol 158,” MRK-ACR0016409, at 13-15; 4/3/02 slide presentation to CRRC, “Diclofenac Plus Aspirin Pilot Erosion Endoscopy Study,” MRK-ACR0020663-81. Dr. Catella-Lawson expressed her personal belief that Protocol 158 should include a comparator other than ibuprofen plus aspirin. 12/19/01 email from F. Catella-Lawson to B. Gertz, MRK-NJ0439354; 1/3/02 email from F. Catella-Lawson to S. Reines, MRK-ABS0344100;

<sup>120</sup> 2/5/02 email from T. Ruef to R. El-Dada, MRK-ADM0070848, at 48. The relevant text of this email has been excerpted in the document image below.

Diclofenac was therefore seriously considered as the comparator for Protocol 158 because it did not interfere with the antiplatelet effects of aspirin and it did not compromise Merck's position on naproxen's cardioprotective characteristics.<sup>121</sup>

A year later, however, on December 3, 2002 the Company settled on ibuprofen rather than diclofenac as the comparator in Protocol 158 based on the results of another endoscopy study: Protocol 184.<sup>122</sup> Protocol 184 was a one-week, four-arm study that had demonstrated the gastrointestinal safety superiority of diclofenac, and diclofenac plus aspirin, over both ibuprofen and ibuprofen plus aspirin.<sup>123</sup> Because Protocol 136 had already demonstrated that there was no gastrointestinal safety difference between ibuprofen and Vioxx plus aspirin, the results of Protocol 184 suggested that diclofenac plus aspirin would outperform Vioxx plus aspirin in terms of gastrointestinal safety.<sup>124</sup>

In February 2003, MRL was still considering conducting Protocol 158 with ibuprofen, either in aspirin users or in non-users. Another article about ibuprofen's interference with the cardiovascular protective qualities of aspirin was published in the

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<sup>121</sup> 4/3/02 slide presentation to CRRC, "Diclofenac Plus Aspirin Pilot Erosion Endoscopy Study," MRK-ACR0020663, at 64.

<sup>122</sup> See 9/23/02 email from L. Beebe to T. Baney *et al.*, MRK-ABS0445361, at 62 (noting a decision to move forward with two draft protocols, one with ibuprofen and one with diclofenac); 1/9/03 email from E. Maller to L. LaMond (cc: R. El-Dada), MRK-ADM0158226 (documenting ultimate decision to use ibuprofen).

<sup>123</sup> Undated slide presentation, "Diclofenac + Aspirin Pilot Erosion Endoscopy Study (0966-184): Results & Implications for Protocol 158," MRK-ADM0158227-51 (attached to 1/9/03 email from E. Maller to L. LaMond (cc: R. El-Dada), MRK-ADM0158226).

<sup>124</sup> Undated slide presentation, "Diclofenac + Aspirin Pilot Erosion Endoscopy Study (0966-184): Results & Implications for Protocol 158," MRK-ADM0158227, at 38 (attached to 1/9/03 email from E. Maller to L. LaMond (cc: R. El-Dada), MRK-ADM0158226).

Lancet in early 2003, raising further ethical concerns about the proposed study design.<sup>125</sup>

Protocol 158 was cancelled in August 2003.<sup>126</sup>

c. Decision to announce the study.

Once the decision had informally been made in September 2001 to conduct a cardiovascular outcomes study, discussion began among members of the Marketing Department, MRL, and senior management about when to announce that decision to the public. Dr. Scolnick opposed making an early announcement because “he did not want to appear reactive” to negative publicity about the cardiovascular effects of Vioxx, and because he wished “to avoid the possibility that the competition would secure sites, etc[.] before [Merck did].”<sup>127</sup>

However, individuals within the Marketing Department – particularly Dr. Dixon – expressed a desire for the study to be announced as early as possible. On September 17, 2001, Dr. Dixon wrote to a cardiologist in Merck’s Worldwide Human Health Marketing Division, Dr. Steven Nichtberger:<sup>128</sup>

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<sup>125</sup> MacDonald\* TM, Wei\* L. Effect of ibuprofen on cardioprotective effect of aspirin. Lancet. 2003;361:573-574, MRK-ABS0454265; 2/28/03 email from S. DeVandry to N. Reinhardt et al., MRK-AFV0217982-83.

<sup>126</sup> 8/26/03 email from N. Patel to T. Simon et al., MRK-ABS0465511.

<sup>127</sup> 9/01 email correspondence among B. Gertz and P. Kim, MRK-NJ0207343.

<sup>128</sup> 9/17/01 email from W. Dixon to S. Nichtberger, MRK-ABW0011210.

-----Original Message-----  
From: Dixon, Wendy L.  
Sent: Monday, September 17, 2001 9:09 AM  
To: Nichtberger, Steven A.  
Subject: RE: confidential

I believe that we need to do a study. It is the only way we can eventually put to rest all the noise in the market by doing a definitive study in high CV risk patients. The results will not be available for some time but handled correctly there is some positive Pr we can gain from saying we are conducting a study ( there are industry examples of other products who benefited in this way). I think the consensus is that the study should be on Viof. There are risks depending on study design, especially re. GI effects but we must do one

On September 28, 2001, Dr. Dixon also told Mr. Anstice and Dr. Gertz that she thought that the study should be announced as soon as possible, even before finalizing the design. Dr. Dixon noted that a press release announcing the study “gets most of its value from just saying we are doing the study,” regardless of whether a design had been finalized.<sup>129</sup> She also stated that she wanted to make sure Merck issued a press release before it looked as if “the FDA . . . ‘made us do it.’”<sup>130</sup> In Dr. Dixon’s view, if the public perception were that the FDA had forced Merck to conduct a cardiovascular outcomes study, the Company would lose the public relations benefit of having decided to conduct the study of its own accord.<sup>131</sup>

Ms. Christine Fanelle and Ms. Joan Wainwright, members of Merck’s Public Affairs Department, also pressed to announce the study.<sup>132</sup> However, Dr. Eve Slater, Senior Vice President of Regulatory Affairs and a Merck spokesperson, told them that “even if [a draft protocol] had been signed off on, it would be highly inappropriate to

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<sup>129</sup> 9/28/01 email from W. Dixon to D. Anstice and B. Gertz, MRK-ABI0005120.

<sup>130</sup> 10/1/01 email from W. Dixon to D. Anstice, MRK-ABI0005120.

<sup>131</sup> 10/1/01 email from W. Dixon to D. Anstice, MRK-ABI0005120.

<sup>132</sup> 9/17/01 email correspondence among C. Fanelle, J. Weiner, and J. Wainwright, MRK-ADI0006587.

make a public announcement about it.”<sup>133</sup> Dr. Slater “went on to say that when [the protocol] is signed off, it will be confidential.”<sup>134</sup> Nonetheless, by September 28, the Public Affairs Group had drafted a press release announcing the study so that the Company would be positioned to issue a statement when the decision to do so was made.<sup>135</sup>

After Merck scientists and external consultants had reviewed study options in October and November 2001, the Company’s General Counsel, Mr. Kenneth Frazier, and strategists from the Marketing Department identified the December 11, 2001 financial analysts’ meeting, an annual forum for the Company to present information to the business community, as the target date for making the announcement.<sup>136</sup> When Dr. Scolnick expressed reluctance to make the announcement in light of the low-dose aspirin endoscopy study results, Mr. Anstice responded that an announcement could be made even if the design were not finalized. He pointed out that “[t]he CV study announcement press release is relatively bland and non-descriptive on study design. . . . [O]pen study [design] issues per se shouldn’t be a stopper.”<sup>137</sup> Dr. Scolnick, however,

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<sup>133</sup> 9/18/01 email from C. Fanelle to J. Weiner and J. Wainwright, MRK-ADI0006587.

<sup>134</sup> 9/18/01 email from C. Fanelle to J. Weiner and J. Wainwright, MRK-ADI0006587.

<sup>135</sup> See 9/29/01 email from C. Fanelle to R. Silverman attaching draft Merck press release, “Merck to Conduct Clinical Outcomes Study of Vioxx®,” MRK-ACD0013192-95.

<sup>136</sup> See 11/21/01 email from D. Anstice to E. Scolnick, P. Kim, and D. Greene (cc: R. Gilmartin et al.), MRK-ADI0007471.

<sup>137</sup> See 11/21/01 email from D. Anstice to E. Scolnick, P. Kim, and D. Greene (cc: R. Gilmartin et al.), MRK-ADI0007471.

has said that he remained uneasy about making the announcement before a study design was finalized, notwithstanding the Company's firm commitment to conduct such a study.

The first draft of a protocol synopsis summarizing the study design for the planned cardiovascular outcomes trial was circulated by Dr. Peter DiBattiste on December 4, 2001.<sup>138</sup> Two days later, the Human Health Product Approval Committee approved an official request to announce the Vioxx cardiovascular outcomes trial.<sup>139</sup>

As planned, Dr. Scolnick announced at the December 11 financial analysts' meeting Merck's plan to conduct two large cardiovascular outcomes studies – one with Vioxx and one with Arcoxia.<sup>140</sup> According to The Pink Sheet, a publication specializing in prescription pharmaceuticals and biotechnology, Dr. Scolnick provided a few details of the design of the studies: together the studies would enroll 30,000 patients and the studies would allow patients to take low-dose aspirin.<sup>141</sup>

3. January – March 2002: Implementation of the Cardiovascular Outcomes Trial (VALOR).

During the first three months of 2002, planning for the VALOR Trial moved forward. In early January, Drs. Demopoulos and DiBattiste arranged for Drs. Eugene

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<sup>138</sup> 12/4/01 email from P. DiBattiste to L. Demopoulos and W. Shaw attaching draft VALOR protocol synopsis, MRK-AAZ0003934.

<sup>139</sup> See 12/5/01 background material for 12/6/01 HHPAC meeting, MRK-AAX0003153, at 157.

<sup>140</sup> 12/17/01 email from D. Manulkin to P. Alberti *et al.* including text of 12/17/2001 article from The Pink Sheet entitled "Merck COX-2 Cardiovascular Safety Studies Will Enroll 30,000 Subjects," MRK-ADF0027642-44.

<sup>141</sup> 12/17/01 email from D. Manulkin to P. Alberti *et al.* including text of 12/17/2001 article from The Pink Sheet entitled "Merck COX-2 Cardiovascular Safety Studies Will Enroll 30,000 Subjects" MRK-ADF0027642, at 42.

Braunwald\* and Christopher Cannon\*, leading cardiologists at the Brigham and Women's Hospital in Boston, in conjunction with the TIMI Study Group<sup>142</sup> to assume responsibility for implementing the VALOR Trial, and together they selected members for its External Steering Committee.<sup>143</sup> Internally, a "VALOR Task Force" – comprised of MRL scientists, statisticians, epidemiologists, and FDA liaisons – convened on a weekly basis to address study logistics and to recruit centers and investigators for the trial.<sup>144</sup> In addition, by the end of January 2002, MRL scientists had prepared a formal draft study protocol.<sup>145</sup> By the end of February, MRL scientists had determined that the VALOR Trial would enroll 20,000 patients for thirteen months beginning in June 2002, and that the data would be available in the second quarter of 2004.<sup>146</sup>

a. Continued concerns about the VALOR Trial.

Despite this progress, some MRL scientists and external consultants continued to have concerns about the trial, and MRL scientists began to reconsider earlier design options as well as new options. In early February 2002, the Clinical Regulatory Review Committee – a committee of Merck Vice Presidents with sign-off authority on study protocols – revisited the three primary design options that had been identified in the fall of 2001 and considered a new option, a three-arm study comparing (i) Vioxx plus aspirin

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<sup>142</sup> The TIMI Group was an organization run by Drs. Braunwald\* and Cannon\* that routinely coordinated studies regarding thrombolysis (the breaking up of blood clots) in myocardial infarction.

<sup>143</sup> See 1/18/02 email from A. Esposito to B. Pica, et al., MRK-ABA0018791.

<sup>144</sup> See 1/28/02 email from A. Altameyer to P. DiBattiste et al., MRK-ABA0020191.

<sup>145</sup> 1/24/02 draft VALOR Protocol, MRK-ABK0175555-622.

<sup>146</sup> 2/26/02 background material for 2/27/02 HHPAC meeting, MRK-ADM0035287, at 95.

versus (ii) either a non-selective NSAID or a competing selective Cox-2 inhibitor plus aspirin versus (iii) aspirin alone.<sup>147</sup> Ultimately, the idea of conducting a three-arm study was rejected due to the significant increase in sample size, study duration and cost, and concern that introducing an active comparator would “heighten the scrutiny and impact of GI outcomes.”<sup>148</sup>

The Committee also reviewed the design options (now four in number) in terms of how each might address the clinical impact (if any) of Dr. FitzGerald’s\* prostacyclin hypothesis.<sup>149</sup> Prior design discussions regarding cardiovascular non-inferiority hypotheses had not explicitly drawn a link to the FitzGerald prostacyclin hypothesis. The presentation to the Clinical Regulatory Review Committee stated that the new three-arm trial, as well as the Vioxx plus aspirin versus NSAID plus aspirin design, “potentially mitigate[] GI risk” and “mitigate[] CV risk if [the] prostacyclin hypothesis is correct.”<sup>150</sup> This discussion of the FitzGerald prostacyclin hypothesis reflected continued uncertainty about whether the goal of the study should be to disprove the prostacyclin hypothesis, to find an antiplatelet regimen to use with Vioxx, or to prove the anti-inflammatory hypothesis.

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<sup>147</sup> See post-1/22/02 slide presentation, “VIOXX CV Outcomes Study Protocol,” MRK-ACD0099800, at 06-09; Minutes of 2/6/02 CRRC meeting, MRK-ABP0020539, at 43-44.

<sup>148</sup> Minutes of 2/21/02 CRRC meeting, MRK-AFV0195306, at 10; see also 2/26/02 background material for 2/27/02 HHPAC meeting, MRK-ABH0006434, at 459.

<sup>149</sup> See post-1/22/02 slide presentation, “VIOXX CV Outcomes Study Protocol” MRK-ACD0099800, at 08-09.

<sup>150</sup> Post-1/22/02 slide presentation, “VIOXX CV Outcomes Study Protocol” MRK-ACD0099800, at 09.

In early 2002, Dr. Catella-Lawson expressed what she characterized as “significant concerns” about the VALOR Trial design, based upon a study by Dr. Benedict Lucchesi\*, Professor of Pharmacology at the University of Michigan Medical School.<sup>151</sup> Dr. Lucchesi’s\* study, which examined the effects of Cox-2 inhibition on the vascular responses of canines, suggested that Cox-2-derived prostacyclin may play a role in the cardioprotective effects of aspirin and that inhibition of Cox-2-derived prostacyclin (such as that caused by a selective Cox-2 inhibitor) may lead to an increased risk of thrombosis, especially in high risk patients.<sup>152</sup> To address this potential risk, Dr. Catella-Lawson recommended that the proposed Vioxx cardiovascular outcomes study add a non-selective NSAID to the aspirin arm, testing Vioxx plus aspirin versus a non-selective NSAID plus aspirin.<sup>153</sup>

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<sup>151</sup> 1/30/02 email from F. Catella-Lawson to S. Reines, MRK-ABS0346719.

<sup>152</sup> Hennan\* JK, Huang\* J, Barrett\* TD, et al. Effects of selective cyclooxygenase-2 inhibition on vascular responses and thrombosis in canine coronary arteries. Circulation. 2001;104:820-825.

<sup>153</sup> 1/30/02 email from F. Catella-Lawson to S. Reines and K. Horgan, MRK-ABS0346720. The “4 S Study” (“Scandinavian Simvastatin Survival Study”), a double-blind, placebo-controlled trial in patients with coronary heart disease, demonstrated that long-term treatment with simvastatin (a cholesterol-lowering drug) was safe and improved survival rates in coronary heart disease patients. See Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383-1389.

---Original Message---

From: Lawson, Francesca  
Sent: Tuesday, January 29, 2002 4:03 PM  
To: Reines, Scott A.; Horgan, Kevin J  
Subject: RE: CV outcomes trial

Scott and Kevin,

Yes, the 4 S study was not a sure thing, but there was no alternative study design (and there was no known biochemical reason to justify an increased mortality by lipid lowering drugs). The Vioxx CV outcome trial could be performed with almost no risks by adding an NSAID to the control aspirin arm = Vioxx plus asa versus NSAID plus asa. Both arms would have the same inhibition of prostacyclin and the study would show that Vioxx is as safe as any other NSAID when given to patients with high cardiovascular risk. In contrast, if there is any truth in the "prostacyclin hypothesis", patients receiving vioxx plus asa will have a higher risk of CV events as compared to asa alone.

Regards,  
Francesca

According to Dr. Catella-Lawson, her concern about the potential effect of suppressing prostacyclin pertained to a high cardiovascular risk patient population, and she believed it was unethical to subject such an unstable patient population to potentially serious cardiovascular-related consequences.

Another open issue in early 2002 was whether and to what extent the study design should take into account increased cardiovascular risk resulting from increased blood pressure.<sup>154</sup> An early 2002 presentation to the Clinical Regulatory Review Committee noted that "in observational studies, [there is a] clear association between hypertension and cardiovascular events in general," and discussed whether the study design should minimize the impact of a small increase in systolic blood pressure.<sup>155</sup>

The presentation also noted the following:

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<sup>154</sup> See Post-1/22/02 slide presentation, "VIOXX CV Outcomes Study Protocol," MRK-ACD0099800, at 02 (listing the "influence of hypertension on event rates" as an "outstanding issue" in the design of the VALOR Trial); see also 2/26/02 background material for 2/27/02 HHPAC meeting, MRK-ABH0006434, at 45 (listing "increase in blood pressure" as an "issue associated with [the] current design and hypothesis").

<sup>155</sup> Post-1/22/02 slide presentation, "VIOXX CV Outcomes Study Protocol," MRK-ACD0099800, at 03-06.

- Vioxx was associated with “small but consistent” increases in systolic and diastolic blood pressure,<sup>156</sup> and
- The LIFE trial<sup>157</sup> found that each 1mmHg increase in systolic blood pressure was associated with a “relative increase of 0.6% in primary endpoint” (a composite cardiovascular endpoint including cardiovascular mortality, fatal and non-fatal myocardial infarction, and non-fatal stroke).<sup>158</sup>

The recommendation presented to the Clinical Regulatory Review Committee for the VALOR Trial was to manage blood pressure aggressively by measuring blood pressure in triplicate at each subject visit and recording the mean of the three values.<sup>159</sup>

As design options continued to be discussed, some scientists, both inside and outside of Merck, who had not been involved in the preliminary design discussions, expressed concern about the ethical implications of the VALOR Trial hypothesis. For example, Dr. Lars Wallentin\*, a Swedish professor of cardiology whom Merck invited to be on the VALOR Trial external steering committee, was reluctant to participate because he believed that its hypothesis – i.e., that Vioxx would be non-inferior or superior to placebo in the incidence of cardiovascular adverse events in patients with a recent history

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<sup>156</sup> Post-1/22/02 slide presentation, “VIOXX CV Outcomes Study Protocol,” MRK-ACD0099800, at 03.

<sup>157</sup> The Losartan Intervention For Endpoint (“LIFE”) Trial – conducted by the LIFE Study Group affiliated with Ostra University Hospital in Goteborg, Sweden – tested the effect of two drugs used to treat hypertension – Losartan and Atenolol – on risk of cardiovascular events in high cardiovascular risk hypertensive patients.

<sup>158</sup> Post-1/22/02 slide presentation, “VIOXX CV Outcomes Study Protocol,” MRK-ACD0099800, at 06.

<sup>159</sup> Post-1/22/02 slide presentation, “VIOXX CV Outcomes Study Protocol,” MRK-ACD0099800, at 03. The Clinical Regulatory Review Committee ultimately rejected that proposal. See Minutes of 2/6/02 CRRC meeting, MRK-ABP0020539, at 43-44.

of acute coronary syndromes<sup>160</sup> – was “an unacceptable objective, as we cannot expose patients to new treatments if our main objective is to show that they are no worse than placebo, especially if there are indications that in other patient categories there really is some suspicion of harmful effects.”<sup>161</sup> Similarly, Dr. Francois Bertrand, Senior Director of Clinical Research at Merck Frosst, noted that “there is a significant ethical issue on the table with regards to giving a drug to patients not needing this drug.”<sup>162</sup> Both Dr. Wallentin\* and Dr. Bertrand seemed unconvinced that the VALOR Trial’s superiority hypothesis was sufficiently well established to justify placing high cardiovascular risk patients on placebo, and believed that a non-inferiority hypothesis would be insufficient to justify exposing patients to new treatments.

In a letter to Dr. Braunwald\*, dated February 4, 2002, Dr. Carlo Patrono\* articulated his views about the VALOR Trial design, which stood in contrast to those raised by Drs. Wallentin\* and Bertrand. Dr. Patrono\* argued that a non-inferiority hypothesis for the trial did not make sense to him because (i) a “broad rationale” existed for expecting that selective Cox-2 inhibition, in combination with aspirin, would confer a benefit; and (ii) the cardiovascular safety concern raised by the VIGOR Trial findings – “the so-called TXA<sub>2</sub>/PGI<sub>2</sub> ‘inbalance’ [sic] hypothesis” – would not apply to the patient

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<sup>160</sup> 1/24/02 draft VALOR Protocol, MRK-ABK0175555, at 58.

<sup>161</sup> Letter from L. Wallentin\* to S. Reines and P. DiBattiste, MRK-ABA0024064 (attached to 2/19/02 email from C. Cannon\* to P. DiBattiste, MRK-ABA0024063).

<sup>162</sup> 1/7/02 email from F. Bertrand to P. DiBattiste, MRK-ABA0017748.

population in the VALOR Trial, because they would be receiving both Cox-1 and Cox-2 inhibition.<sup>163</sup>

Additionally, MRL scientists began to reconsider the design of the second cardiovascular outcomes trial – Arcoxia versus a non-selective NSAID – which was not as far along in development as the VALOR Trial. On January 3, 2002, Dr. Scolnick questioned whether that trial still made sense. His concern arose from recent studies conducted by Dr. FitzGerald\* that suggested that the rate of atherosclerosis (an inflammatory disease) in animal models is the same among animals treated with selective Cox-2 inhibitors as with placebo, but that it is slowed in animals treated with traditional non-selective NSAIDs.<sup>164</sup> According to Dr. Scolnick, these observations raised the possibility that the cardiovascular event rate differential seen in the VIGOR Trial was not due solely to naproxen's antiplatelet effect, but perhaps also was attributable in part to an anti-atherosclerotic effect of naproxen. Therefore, Dr. Scolnick's concern was that a study comparing Arcoxia and ibuprofen would demonstrate fewer cardiovascular events in the ibuprofen arm because of this theoretical slowing of atherosclerosis by traditional non-selective NSAIDs.<sup>165</sup>

Following the meetings of the Clinical Regulatory Review Committee and the Human Health Product Approval Committee in January and February 2002, the original

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<sup>163</sup> 2/4/02 letter from C. Patrono\* to E. Braunwald\*, MRK-ABA0003490, at 90.

<sup>164</sup> 1/3/02 email from E. Scolnick to D. Greene et al., MRK-AAZ0004638.

<sup>165</sup> 1/3/02 email from E. Scolnick to D. Greene et al., MRK-AAZ0004639; 1/4/02 email correspondence among E. Scolnick and L. Demopoulos, MRK-AAZ0004638-39.

VALOR Trial design for Vioxx (Vioxx plus aspirin versus aspirin alone in post-ACS patients) and the “Large Simple Trial” for Arcoxia (Arcoxia versus an NSAID in a mixed aspirin-use population), remained the presumptive selections for each drug.<sup>166</sup> The VALOR Trial Task Force, the VALOR Trial Steering Committee, and Drs. Braunwald\* and Cannon\* were devoting substantial time and energy to finalizing the VALOR Trial design, and MRL scientists hoped to begin enrolling patients in the third quarter of 2002.<sup>167</sup> Even as these efforts progressed, however, MRL’s senior management, including Drs. Kim, Gertz, and Scolnick, began to contemplate canceling the VALOR Trial.<sup>168</sup>

Additionally, the FDA expressed concerns about the design of the VALOR Trial. In late February 2002, once Merck had come close to finalizing a protocol for the VALOR Trial based on the post-ACS study design, Dr. Silverman proposed the study to Dr. Lawrence Goldkind\*, Deputy Division Director at the FDA’s Division of Anti-Inflammatory, Analgesics & Ophthalmic Drug Product, at an informal meeting.<sup>169</sup> According to Dr. Silverman, Dr. Goldkind’s\* reaction was that Merck might need to convene an FDA Advisory Committee Meeting to discuss the study design, because he

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<sup>166</sup> See 3/9/02 email from B. Gertz to P. Kim et al., MRK-NJ0452635; 3/9/02 email from L. Demopoulos to E. Scolnick et al., MRK-AAZ0008111.

<sup>167</sup> See 1/28/02 email from A. Esposito to P. DiBattiste, MRK-ABA0020169; see also 3/1/02 email from N. Braunstein to D. Greene et al. attaching draft VALOR Protocol and background packages to send to the FDA, MRK-NJ0451445.

<sup>168</sup> See 9/28/05 deposition of B. Gertz at 1364-66 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>169</sup> Undated handwritten memorandum from R. Silverman to B. Goldmann et al., MRK-ACD0119123-24; see also 2/13/02 handwritten notes of R. Silverman, MRK-ACD0119117, at 19-20.

questioned whether there was enough data to support the “appropriateness of embarking on such a huge study in patients without an existing indication for VIOXX and with some clinical data that suggest at least the possibility of a negative outcome for the patients getting VIOXX.”<sup>170</sup> Dr. Silverman communicated Dr. Goldkind’s\* criticisms to the Worldwide Business Strategy Team and to senior MRL scientists, including Drs. Kim, Gertz, and Reicin,<sup>171</sup> which prompted them to revisit the viability and ethics of the VALOR Trial’s design.

As it became increasingly apparent that senior scientists might decide not to proceed with the VALOR Trial, Dr. DiBattiste, who had spearheaded the efforts to design a cardiovascular outcomes trial with Vioxx, noted the potentially negative implications of a decision to cancel the VALOR Trial: “Any reversal of the decision to go forward with this trial will certainly communicate a message of lack of confidence, uncertainty and concern that may have important and untoward consequences.”<sup>172</sup>

b. Cancellation of VALOR.

The VALOR Trial – which was planned to test Vioxx plus aspirin versus aspirin alone in a high cardiovascular risk population – was formally cancelled by Dr. Kim on March 13, 2002.<sup>173</sup> His decision was predicated on a number of factors:

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<sup>170</sup> Undated handwritten memorandum from R. Silverman to B. Goldmann et al., MRK-ACD0119123-24; see also 2/24/02 email from B. Gertz to D. Greene, MRK-NJ0450791.

<sup>171</sup> Undated handwritten memorandum from R. Silverman to B. Goldmann et al., MRK-ACD0119123-24.

<sup>172</sup> 3/9/02 email from P. DiBattiste to B. Gertz, MRK-NJ0394689.

<sup>173</sup> 3/13/02 email from A. Esposito to B. Baird et al., MRK-ABA0028398.

First, there were continuing concerns – both within MRL and externally – about the validity of the hypothesis that Vioxx might be cardioprotective in a high cardiovascular risk population. Many had expressed the view that from an ethical standpoint, this superiority claim was not strong enough to justify conducting the study.

Second, the study also was ethically questionable in that high cardiovascular risk patients might be harmed by the gastrointestinal and hypertensive effects of taking Vioxx plus aspirin.

Third, the inclusion of aspirin would not produce a result that clearly answered the question of whether Vioxx alone had negative cardiovascular effects as compared to non-selective NSAIDs alone or placebo.

Fourth, the required size and duration of the study would not produce an answer in a reasonable period of time.

Fifth, the FDA had expressed concerns about the design of the VALOR Trial.

Finally, Dr. Kim recognized that ongoing placebo-controlled clinical trials would provide substantial cardiovascular data within the coming months which MRL scientists would continue to analyze.

E. Decision to Capture Cardiovascular Outcomes  
Data In a Pooled Analysis: Protocol 203.

Around the time that senior management cancelled the VALOR Trial, MRL scientists again considered several of the previously discarded trial design options, including a study of Vioxx versus Celebrex<sup>174</sup> (as had been discussed in April 2000) and

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<sup>174</sup> 3/4/02 slide presentation, “CV Outcomes with Merck COXIB,” MRK-NJ0451798, at 98-01 (attached to 3/3/02 email from A. Reicin to P. DiBattiste et al., MRK-NJ0451797).

a study of Vioxx versus an NSAID (diclofenac) in osteoarthritis and rheumatoid arthritis patients.<sup>175</sup> Additionally, MRL scientists considered some new approaches, such as two three-arm pilot studies in post-ACS patients – Vioxx versus diclofenac versus placebo, and Arcoxia versus Celebrex versus placebo – which would then be used to determine whether to go forward with a large clinical study in post-ACS patients.<sup>176</sup>

By June 2002, however, MRL scientists had determined that the best way to test the hypothesis underlying the initial decision to conduct an outcomes trial – that Vioxx was not prothrombotic – was to analyze cardiovascular data from three placebo-controlled studies in cancer patients, two of which were already underway.<sup>177</sup> As discussed above, the idea of collecting cardiovascular data from placebo-controlled trials had begun circulating as early as June 21, 2001 as an alternative to a large outcomes trial,<sup>178</sup> but MRL scientists had recognized that the two ongoing cancer studies, APPROVe and VICTOR, lacked sufficient power to answer any open questions about Vioxx’s cardiovascular safety.<sup>179</sup> Based on the significant ethical and practical

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<sup>175</sup> 3/11/02 slide presentation to Management Committee, MRK-ABX0032041, at 96; 6/26/02 draft slide presentation to HHPAC, MRK-ABL0002116, at 20-24.

<sup>176</sup> Undated draft slide presentation to HHPAC, “Cardiovascular Safety Study Plans: VIOXX and Arcoxia,” MRK-NJ0453702, at 02-03, 17-18 (attached to 3/19/02 email from S. Morris to A. Reicin et al., MRK-NJ0453701).

<sup>177</sup> 7/10/02 slide presentation to HHPAC, “Update on Studies and Plans to Evaluate Cardiovascular Safety of VIOXX and ARCOXIA,” MRK-ABL0002136, at 40.

<sup>178</sup> Undated draft slide presentation, “Future Plans,” MRK-ABH0002007, at 10 (attached to 6/21/01 email from A. Reicin to E. Scolnick et al., MRK-ABH0002006).

<sup>179</sup> APPROVe (Protocol 122) was designed to test the efficacy of Vioxx in preventing the recurrence of colon polyps, and enrolled 2612 patients. 1/17/02 Amended APPROVe Protocol, MRK-ABS0326111, at 121; 6/11/03 Protocol 203 Protocol, MRK-YAH0000137, at 140. VICTOR (Protocol 145) was also designed to observe Vioxx’s effects on colon cancer, and was anticipated to

complexities that the VALOR Trial design had presented, however, MRL senior management decided to add to the other two trials the ViP Trial (Protocol 201), a prostate cancer prevention study originally planned to be conducted with Arcoxia, in order to obtain a sample size large enough to power a cardiovascular analysis.<sup>180</sup> The ViP Trial was expected to enroll 15,000 participants,<sup>181</sup> bringing the total anticipated enrollment for the proposed cardiovascular outcomes trial close to 25,000 patients (yielding approximately 38,000 patient-years of exposure).<sup>182</sup> On July 10, 2002, the Human Health Product Approval Committee approved this design, which became Protocol 203.<sup>183</sup>

Although the three studies comprising Protocol 203 had pre-specified endpoints that did not relate to cardiovascular safety, Protocol 203 nonetheless was powered to demonstrate a relatively small difference in cardiovascular event rates across the patient populations that were involved.<sup>184</sup> Dr. Kim and other senior scientists at MRL believed that Protocol 203 provided a simpler and quicker answer to the Vioxx cardiovascular question: simpler, because it did not implicate the difficult ethical and design questions

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enroll approximately 7000 patients. 11/13/00 memorandum B. Morrison to R. Silverman et al., MRK-ACD0073684; 6/11/03 Protocol 203 Protocol, MRK-YAH0000137, at 140.

<sup>180</sup> See 6/26/02 draft slide presentation, "Strategy to Further Evaluate the Cardiovascular Safety of Vioxx] and Arcoxia," MRK-ABL002116, at 25-26; 7/10/02 slide presentation to HHPAC, "Update on Studies and Plans to Evaluate Cardiovascular Safety of VIOXX and ARCOXIA," MRK-ABL0002136, at 40-43.

<sup>181</sup> 6/11/03 Protocol 203 Protocol, MRK-YAH0000137, at 140.

<sup>182</sup> 1/9/04 Protocol 203 Statistical Data Analysis Plan, MRK-YAH0000302, at 06.

<sup>183</sup> Minutes of 7/10/02 HHPAC meeting, MRK-ABL0002147; 7/10/02 slide presentation to HHPAC, "Update on Studies and Plans to Evaluate Cardiovascular Safety of VIOXX and ARCOXIA," MRK-ABL0002136, at 40.

<sup>184</sup> See 1/9/04 Protocol 203 Statistical Data Analysis Plan, MRK-YAH0000302, at 06.

that had stymied the cardiovascular outcomes trial; and quicker because it piggybacked on two trials (APPROVe and VICTOR) that had already begun and a third trial that was already in development.

On October 10, 2002, Merck forwarded the Protocol 203 protocol to the FDA to be evaluated, along with a set of “MRL Questions to the Agency.”<sup>185</sup> The FDA responded to Merck’s questions on December 27, 2002. With respect to the concept of a pooled analysis of the ongoing placebo-controlled trials, the FDA’s answer suggested that such a study was acceptable, provided that the model for pooling and analyzing the data was carefully constructed:<sup>186</sup>

**SPONSOR QUESTIONS with FDA RESPONSE**

- 1A. Does the Agency agree that a prospective combined analysis of 3 similarly conducted, long-term studies comparing a single dose of rofecoxib (25 mg) to placebo would provide clinically important information about the effects of rofecoxib on the incidence of thrombotic events and would therefore constitute a cardiovascular outcomes study with rofecoxib?

**FDA Response:**

**A study with the proposed exposure (size and duration) would provide clinically important safety information about rofecoxib.**

- 1B. Does the Agency agree with MRL’s plans to combine the cardiovascular data from the APPROVe, VICTOR, and Prostate Cancer Prevention studies as described in the protocol?

**FDA Response:**

**a. Conceptually a meta-analysis is reasonable.**

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<sup>185</sup> 10/10/02 letter from N. Braunstein to L. Simon\* attaching “MRL Questions to the Agency,” MRK-AFL0003139-45.

<sup>186</sup> 12/19/02 letter from L. Goldkind\* to N. Braunstein, MRK-YAH0000017, at 17-18.

Dr. Braunstein has stated that from a scientific rigor standpoint, there was no difference between Protocol 203 and VALOR, and that the only difference between the trials would be the patient population. The proposed VALOR Trial would have included 100% high cardiovascular risk patients indicated for low-dose aspirin, whereas Protocol 203 would have a significantly smaller percentage of high cardiovascular risk patients because the component studies were cancer prevention studies.<sup>187</sup>

Although the cardiovascular data collection and data analysis for Protocol 203 were not completed before the Company withdrew the drug in September 2004 on the basis of the APPROVe Trial data, the data produced by the APPROVe, VICTOR, and ViP Trials before withdrawal continue to be analyzed.

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<sup>187</sup> In its review of the draft Protocol 203 Protocol, the FDA expressed the position that at least 20% of the patients included in Protocol 203 be low-dose aspirin users. 12/19/02 letter from L. Goldkind\* to N. Braunstein, MRK-YAH0000017, at 18. Merck responded that it was “unable to guarantee” the enrollment of 20% low-dose aspirin users in Protocol 203. 1/17/03 letter from N. Braunstein to L. Simon\*, MRK-YAH0000024, at 29. Ultimately, the FDA determined that the percentage of low-dose aspirin users and other design issues, such as the proposed non-inferiority bounds for the study, would become review issues that could potentially influence the way the FDA interpreted the results of the trial once they were available. See 5/21/04 letter from B. Harvey\* to D. Louie, MRK-AFV0304388, at 90, 91.