

## APPENDIX F

### FURTHER ANALYSIS AND PUBLIC PRESENTATION OF VIGOR TRIAL CARDIOVASCULAR DATA: APRIL 2000 - JANUARY 2001.

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## APPENDIX F

### FURTHER ANALYSIS AND PUBLIC PRESENTATION OF VIGOR TRIAL CARDIOVASCULAR DATA: APRIL 2000 - JANUARY 2001.

After the public disclosure of the unadjudicated results of the VIGOR Trial on March 27, 2000, Merck continued to collect, analyze and interpret VIGOR Trial cardiovascular data, both internally and with the aid of external consultants. During 2000, Merck publicly discussed data from the VIGOR Trial in several fora, including in the New England Journal of Medicine and presentations at major scientific conferences. This Appendix addresses: (i) Merck's internal review and analysis, from March 27, 2000 onward, of cardiovascular data from the VIGOR Trial; (ii) the Company's public presentation of data from the VIGOR Trial at various scientific conferences and in the New England Journal of Medicine; (iii) epidemiological and pharmacological studies conducted by MRL to explore the cardiovascular risk profile of rheumatoid arthritis patients; (iv) MRL's review of post-marketing spontaneously reported adverse event data for evidence of cardiovascular problems in lupus patients; (v) MRL's meta-analysis of cardiovascular data from all Vioxx trials; and (vi) the reaction of Merck advisors and consultants to cardiovascular data from the VIGOR Trial.

#### A. Post March-2000 Internal Analysis of VIGOR Trial Cardiovascular Data.

##### 1. Data.

As discussed, Merck planned to submit to the FDA a supplemental New Drug Application in June 2000. According to the VIGOR Trial "Closeout Guidelines," adjudication eligible gastrointestinal events had to be reported by midnight on March 9,

2000 – the official “last patient out” date – in order to be adjudicated and included in the June 2000 submission.<sup>1</sup> February 10, 2000 was established as the reporting cut-off date for adjudication-eligible cardiovascular events that would be adjudicated and included in the June 2000 submission.<sup>2</sup> To briefly recap from Appendix D, this four-week difference in the gastrointestinal and cardiovascular reporting cut-off dates came about as follows:

- In January 2000, the VIGOR Trial Steering Committee set February 10 as the “trial termination” date and March 9 as the date by which all patients were required to have exited the study.<sup>3</sup>
- Pursuant to the VIGOR Trial “Closeout Guidelines,” the adjudicated results of all gastrointestinal events reported as of the “last patient out” date (here, March 9, 2000) were to constitute the primary analysis of gastrointestinal events to be submitted to the FDA.<sup>4</sup>
- The VIGOR Trial Data Analysis Plan did not mention the cardiovascular adjudication process, nor did it specify a cut-off date for cardiovascular events, adjudicated or not, to be submitted to the FDA.
- In late January 2000, MRL agreed at the request of the VIGOR Data Safety and Monitoring Board to include an

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<sup>1</sup> 3/99 VIGOR Closeout Guidelines Final (Revised), MRK-ACP0003360, at 68 (attached to 1/9/00 VIGOR Steering Committee meeting agenda, MRK-ACP0003359). The “Closeout Guidelines” specified “midnight on the date chosen for Last Patient Out.”

<sup>2</sup> 2/7/00 letter from A. Reicin to M. Weinblatt\*, MRK-NJ0067266, at 66; 2/10/00 “Plan for the Adjudication and Analysis of Serious Vascular Events in VIGOR,” MRK-AAX0002763; see also 1/17/00 email from H. Guess to G. Williams, MRK-NJ0120249, at 49.

<sup>3</sup> 1/28/00 letter from A. Reicin to A. Weaver\*, MRK-NJ0243243.

<sup>4</sup> 3/99 VIGOR Closeout Guidelines Final (Revised), MRK-ACP0003360, at 68 (attached to 1/9/00 VIGOR Steering Committee meeting agenda, MRK-ACP0003359).

analysis of the adjudicated cardiovascular data in its  
clinical study report to be submitted to the FDA.<sup>5</sup>

- MRL epidemiologists overseeing the adjudication process were concerned that the external cardiovascular adjudication committees would likely not be able to adjudicate all cardiovascular events reported through the end of the study in time to meet MRL's planned deadlines for "freezing" the study database (April 24, 2000) and submitting the clinical study report to the FDA (June 29, 2000).<sup>6</sup>
- Dr. Alise Reicin proposed, and in early February MRL adopted, February 10, 2000 as a cut-off date for cardiovascular events to be included in the clinical study report to be submitted to the FDA on June 29.<sup>7</sup>

Adjudication-eligible cardiovascular events that were reported after February 10 would be sent for adjudication, but would not be included in the June 2000 FDA submission.<sup>8</sup>

During March 2000, cardiovascular events that had been reported on or before the February 10 cut-off date were being adjudicated by external committees. Partial reports were available on March 16, March 31, and April 14. By April 21, all 87 adjudication-eligible events that had been reported by the February 10 cut-off date had

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<sup>5</sup> 1/24/00 letter from M. Weinblatt\* to A. Reicin, MRK-ACG0000457; 2/7/00 letter from A. Reicin to M. Weinblatt\*, MRK-NJ0067266-67.

<sup>6</sup> See 1/17/00 email from H. Guess to G. Williams, MRK-NJ0120249-50; see also Appendix D.

<sup>7</sup> 1/17/00 email from H. Guess to G. Williams, MRK-NJ0120249, at 49; 2/7/00 letter from A. Reicin to M. Weinblatt\*, MRK-NJ0067266, at 66; 2/10/00 "Plan for the Adjudication and Analysis of Serious Vascular Events in VIGOR," MRK-AAX0002763.

<sup>8</sup> Similarly, gastrointestinal events that were reported after March 9, 2000 would be adjudicated and be "available for regulatory agency questions" but would not be included in the June 2000 submission. 3/99 VIGOR Closeout Guidelines Final (Revised), MRK-ACP0003360, at 68 (attached to 1/9/00 VIGOR Steering Committee meeting agenda, MRK-ACP0003359).

been adjudicated.<sup>9</sup> These 87 events (in 85 patients) were the basis for the analysis used in the VIGOR supplemental New Drug Application to the FDA on June 29, scientific conferences in May and June, and the article on the VIGOR Trial published in the New England Journal of Medicine on November 23, 2000.

The adjudicated cardiovascular data based on the February 10 cut-off date were similar to the unadjudicated data that were submitted to the FDA on March 23, 2000 (and which are discussed in Appendices E and I).<sup>10</sup> As summarized in the tables below, there was a statistically significant difference in confirmed thrombotic events between Vioxx and naproxen, with a relative risk of 0.44 (a 56% “reduction”) for naproxen versus Vioxx. There were 41 confirmed thrombotic events in the Vioxx arm, 17 of which were myocardial infarctions and 11 of which were ischemic (i.e. thrombotic) strokes or “mini-strokes” (transient ischemic attacks). In the naproxen group, there were 18 confirmed thrombotic events, 4 of which were myocardial infarctions and 7 of which were ischemic strokes.<sup>11</sup> There were 6 confirmed cardiovascular deaths in each arm. These data are summarized in Tables 1 and 2 below:<sup>12</sup>

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<sup>9</sup> 4/21/00 email from Q. Yu to A. Reicin, MRK-NJ0249213.

<sup>10</sup> See 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, Table C-4 at 029, Table C-5 at 031; 3/23/00 preliminary VIGOR report to FDA, MRK-ABK0460838, Tables 2-3 at 47-48.

<sup>11</sup> There also were 2 hemorrhagic (non-thrombotic) strokes on Vioxx and 1 on naproxen.

<sup>12</sup> 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, Table C-4 at 029, Table C-5 at 031. Note that the event totals in Table 2 include hemorrhagic stroke, which accounts for the difference in totals between the two tables.

Table 1

Summary of Analysis of Confirmed Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences  
VIGOR Study in Patients With Rheumatoid Arthritis<sup>1</sup>

Event Category	Treatment Group	N	Patients With Events	PYR <sup>2</sup>	Rates <sup>3</sup>	Relative Risk <sup>4</sup>	
						Estimate	95% CI
All thrombotic events	Rofecoxib	4047	41	2697	1.52	0.44	(0.25, 0.76)
	Naproxen	4029	18	2698	0.67		
All cardiac events	Rofecoxib	4047	25	2698	0.93	0.40	(0.19, 0.83)
	Naproxen	4029	10	2698	0.37		
All cerebrovascular events	Rofecoxib	4047	11	2699	0.41	0.63	(0.25, 1.64)
	Naproxen	4029	7	2699	0.26		
All peripheral vascular events	Rofecoxib	4047	5	2699	0.19	0.20	(0.00, 1.79)
	Naproxen	4029	1	2699	0.04		

<sup>1</sup> In keeping with the data analysis section of the Adjudication SOP, this table does not include events determined by adjudication to be hemorrhagic cerebrovascular accidents.  
<sup>2</sup> Per 100 patient-years at risk (PYR).  
<sup>3</sup> Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.  
<sup>4</sup> Although a patient may have had two or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Table 2

Summary of Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences VIGOR Study in Patients With Rheumatoid Arthritis

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
<b>Any Event<sup>1</sup></b>	<b>43</b>	<b>(1.1)</b>	<b>19</b>	<b>(0.5)</b>
Arterial Event <sup>1</sup>	39	(1.0)	18	(0.4)
Venous Event	4	(0.1)	1	(0.0)
<b>Cardiovascular Death<sup>1</sup></b>	<b>6</b>	<b>(0.1)</b>	<b>6</b>	<b>(0.1)</b>
Fatal Acute Myocardial Infarction	2	(0.0)	0	(0.0)
Fatal Hemorrhagic Stroke	1	(0.0)	1	(0.0)
Fatal Ischemic Cerebrovascular Stroke	0	(0.0)	1	(0.0)
Sudden Cardiac Death	3	(0.1)	4	(0.1)
<b>Cardiac Events (Fatal/Nonfatal)</b>	<b>25</b>	<b>(0.6)</b>	<b>10</b>	<b>(0.2)</b>
Acute Myocardial Infarction	17	(0.4)	4	(0.1)
Sudden Cardiac Death	3	(0.1)	4	(0.1)
Unstable Angina Pectoris	5	(0.1)	3	(0.1)
<b>Cerebrovascular Events (Fatal/Nonfatal)<sup>1</sup></b>	<b>13</b>	<b>(0.3)</b>	<b>8</b>	<b>(0.2)</b>
Hemorrhagic Stroke	2	(0.0)	1	(0.0)
Ischemic Cerebrovascular Stroke	9	(0.2)	7	(0.2)
Transient Ischemic Attack	2	(0.0)	0	(0.0)
<b>Peripheral Vascular Events (Fatal/Nonfatal)</b>	<b>5</b>	<b>(0.1)</b>	<b>1</b>	<b>(0.0)</b>
Peripheral Arterial Thrombosis	1	(0.0)	0	(0.0)
Peripheral Venous Thrombosis	4	(0.1)	1	(0.0)

<sup>1</sup> Includes patients who experienced a hemorrhagic stroke.  
Patients may be counted in more than one row but are only counted once within a row.

[Attachment 3]

After the February 10 reporting cut-off date for cardiovascular events to be adjudicated for the June 2000 submission, 11 additional potentially thrombotic (adjudication-eligible) cardiovascular events were reported.<sup>13</sup> After adjudication, 5 of these were confirmed as thrombotic events, 4 on Vioxx and 1 on naproxen.<sup>14</sup> The results of the adjudications of the post-February 10 events were sent to Dr. Reicin on May 26, 2000.<sup>15</sup> These additional data were incorporated into the existing tables of VIGOR cardiovascular data and were circulated internally on July 5, 2000<sup>16</sup> and submitted to the FDA on October 13, 2000.<sup>17</sup>

## 2. Subgroup Analyses.

In April 2000, when adjudicated data on cardiovascular events reported by February 10 became available, MRL scientists re-ran the subgroup analyses that they had performed in March 2000 to determine whether the cardiovascular events were associated with any demographic risk factors and whether the difference in cardiovascular events

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<sup>13</sup> 7/5/00 memorandum from D. Shapiro to A. Reicin, E. Barr, and D. Erb, MRK-AAX0001417, at 17; 10/13/00 letter from R. Silverman to FDA (CDER) attaching VIGOR Safety Update Report, MRK-00420027870-72.

<sup>14</sup> 7/5/00 memorandum from D. Shapiro to A. Reicin, E. Barr, and D. Erb, MRK-AAX0001417; 10/13/00 letter from R. Silverman to FDA (CDER) attaching VIGOR Safety Update Report, MRK-00420027870-72.

<sup>15</sup> 5/26/00 email from L. Nelson to A. Reicin attaching table of adjudication results, MRK-AJA0119085-87. The results were not broken down by treatment group, but were listed by patient allocation number.

<sup>16</sup> 7/5/00 memorandum from D. Shapiro to A. Reicin, E. Barr, and D. Erb attaching VIGOR cardiovascular data tables, MRK-AAX0001417-29.

<sup>17</sup> 10/13/00 letter from R. Silverman to FDA (CDER) attaching VIGOR Safety Update Report, MRK-00420027870-72.

between Vioxx and naproxen might be isolated in some particular subgroup of patients.

In March, these analyses had been performed using unadjudicated data.<sup>18</sup> The conclusions of these analyses using adjudicated data were similar to those based on unadjudicated data:

- Patients who entered the study with a cardiovascular risk factor (such as advanced age, male sex, smoking, prior cardiovascular events, hypercholesterolemia, or hypertension) experienced more confirmed thrombotic events than those who did not have a risk factor, regardless of whether they were taking naproxen or Vioxx in the study;<sup>19</sup>
- The between-treatment difference in the incidence of confirmed thrombotic events was similar in patients who did and did not have such risk factors;<sup>20</sup> and
- Patients who experienced a hypertension or edema adverse event in the VIGOR Trial (as reported by their study investigator)<sup>21</sup> were not more likely to have a confirmed thrombotic event in the study than those who did not.<sup>22</sup>

3. The “Aspirin-Indicated” Subgroup Analysis.

In April 2000, MRL scientists also conducted a new subgroup analysis, which had not been performed in March, that examined the incidence of confirmed thrombotic

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<sup>18</sup> 4/14/00 memorandum from A. Reicin to E. Scolnick attaching VIGOR cardiovascular data tables, MRK-AJK0005387-401.

<sup>19</sup> 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, at 032, 108-09.

<sup>20</sup> 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, at 032, 108-09.

<sup>21</sup> Hypertension and edema adverse events were reported by study investigators based on their clinical judgments. This does not include patients who experienced elevations in blood pressure during the trial unless these patients were deemed to have had a hypertension- or edema-related adverse event by the investigator.

<sup>22</sup> 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, at 035-38.

events suffered by patients who, based on a post-hoc review by MRL scientists, met the FDA criteria<sup>23</sup> for low-dose aspirin for cardiac prophylaxis (cardioprotection).<sup>24</sup>

Although the VIGOR Trial had excluded patients on aspirin and MRL had warned investigators not to take patients off of aspirin to qualify them to participate in the study, MRL scientists determined that 4% of the total study population had cardiovascular risk factors at baseline that met the FDA criteria for low-dose aspirin (the “aspirin-indicated subgroup”).<sup>25</sup>

Merck performed this analysis of cardiovascular events in the aspirin-indicated subgroup three times as additional cardiovascular events were adjudicated. The first iteration of the analysis (“Version 1”), which was circulated internally on April 14, 2000, was based on thrombotic events reported by February 10 that had been adjudicated as of April 10, 2000 (89% of the total pre-February 10 reported thrombotic events).<sup>26</sup> The second iteration of the analysis (“Version 2”) was based on all adjudicated and confirmed thrombotic events reported by February 10. Merck included this version of the analysis

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<sup>23</sup> Under FDA criteria, patients with a past medical history of stroke, transient ischemic attack (“mini-stroke”), myocardial infarction, unstable angina, stable angina, coronary artery bypass graft surgery, or percutaneous coronary intervention are indicated for aspirin prophylaxis. See 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, at 022 (citing U.S. product circular for aspirin).

<sup>24</sup> To do this, Dr. Eliav Barr reviewed a list of all the entries in the “patient medical history” category of VIGOR Trial patients’ enrollment forms, from which he selected those that matched the FDA’s criteria for cardiovascular prophylaxis. Dr. Shapiro then ran a program to identify those patients whose medical histories contained the terms Dr. Barr had flagged.

<sup>25</sup> 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, at 032.

<sup>26</sup> 4/14/00 memorandum from A. Reicin to E. Scolnick, MRK-AJK0005387, at 401.

in its June 29, 2000 submission to the FDA.<sup>27</sup> The final iteration of the analysis (“Version 3”) was based on the complete set of adjudicated and confirmed thrombotic events, regardless of when the events were reported. This final version was circulated internally on July 5, 2000<sup>28</sup> and was submitted to the FDA on October 13, 2000 as part of the VIGOR Safety Update Report.<sup>29</sup> These three iterations of the aspirin-indicated subgroup analysis are discussed in the following subsections and presented in Tables 3 through 7 below.

a. April 14, 2000 version (“Version 1”) of aspirin-indicated subgroup analysis.

“Version 1” of MRL’s aspirin-indicated subgroup analysis (based on thrombotic events reported by February 10 that had been adjudicated and confirmed as of April 10, 2000 (89% of the total pre-February 10 events)) reflected that the difference in the incidence of confirmed thrombotic events between Vioxx and naproxen was almost completely confined to the aspirin-indicated 4% of the study population. (See Table 3 below.) In the remaining 96% of the patients, there was very little difference between the treatment groups in terms of the incidence of thrombotic events. Specifically, the analysis showed that aspirin-indicated patients on naproxen experienced only 3 thrombotic events while aspirin-indicated patients on Vioxx experienced 15. This meant

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<sup>27</sup> 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, Table C-6 at 034.

<sup>28</sup> 7/5/00 memorandum from D. Shapiro to A. Reicin, E. Barr, and D. Erb, attaching VIGOR cardiovascular data tables, MRK-AAX0001417, at 17, 22, 25-26.

<sup>29</sup> 10/13/00 VIGOR Safety Update Report, MRK-00420027876, Table 9 at 896.

that patients on naproxen experienced a 79% lower incidence of thrombotic events compared to patients on Vioxx. With regard to the non-aspirin-indicated subgroup (comprising 96% of the study population), the between-treatment difference in thrombotic events (18 in the Vioxx arm and 14 in the naproxen arm) was not statistically significant. In this subgroup, patients on naproxen experienced a 22% lower incidence of thrombotic events compared to patients on Vioxx.<sup>30</sup>

Table 3

Aspirin-indicated Subgroup Analysis – Version 1: April 14, 2000<sup>31</sup>

Endpoint for comparison	Aspirin indication (using FDA criteria)	Treatment (number of patients)	Number of patients with events	Event Incidence (per 100 PYRs)	Relative Risk	
					Estimate (naproxen vs. Vioxx)	95% confidence interval (CI)
Confirmed thrombotic events	Aspirin-indicated	Vioxx (169)	15	13.76	0.21	(0.06, 0.72)
		Naproxen (151)	3	2.87		
	Not aspirin-indicated	Vioxx (3878)	18	0.67	0.78	(0.39, 1.56)
		Naproxen (3878)	14	0.52		

On April 14, 2000, Dr. Reicin circulated this version of the analysis, along with other analyses of VIGOR Trial cardiovascular data, to Dr. Scolnick and other MRL scientists.<sup>32</sup> Two days earlier, Dr. Scolnick had emailed Dr. Reicin, stating: “my worry quotient is high. I am actually in minor agony.”<sup>33</sup> However, upon reviewing the

<sup>30</sup> VIGOR cardiovascular data tables, MRK-AJK0005396, 401 (attached to 4/14/00 memorandum from A. Reicin to E. Scolnick, MRK-AJK0005387).

<sup>31</sup> Data for this table taken from: 4/14/00 memorandum from A. Reicin to E. Scolnick, MRK-AJK0005387, 401.

<sup>32</sup> 4/14/00 memorandum from A. Reicin to E. Scolnick, MRK-AJK0005387.

<sup>33</sup> 4/12/00 email from E. Scolnick to A. Reicin, MRK-ABC0033809.

aspirin-indicated analysis that Dr. Reicin had circulated, Dr. Scolnick stated that his

“anxiety level about the drug and the class is much alleviated [sic]” by the data.<sup>34</sup>

Dr. Scolnick immediately forwarded the analysis to several members of Merck’s Management Committee – Messrs. Raymond Gilmartin, Kenneth Frazier, David Anstice, and Per Wold-Olsen – and to Ms. Margie McGlynn and Ms. Judy Lewent, telling them that the aspirin-indicated subgroup analysis could “save the [selective Cox-2 inhibitor] class”.<sup>35</sup>

From: Scolnick, Edward M.  
Sent: Friday, April 14, 2000 9:13 AM  
To: Gilmartin, Raymond; Anstice, David W.; McGlynn, Margie; Frazier, Kenneth C.; Wold-Olsen, Per; Lewent, Judy C.  
Subject: table reassuranceMEMO  
Importance: High

<<File: vioxxcv.doc>>to all: The table 4 in this file.READ IT! This is the latest adjudicated events tabulation. My anxiety level about the drug and the class is much alleviated by this data. It shows that the major major difference in events between Vioxx and naproxen is in patients who by FDA definition should have been on low dose aspirin!!! At Searle CME course Saturday night I have asked Roger to go and to get garrett Fitzgerald there to blunt the expected spin that they will put on their vs our data. With this analysis we can stem the tide and save the class/ ED Scolnick

On April 25, 2000, Dr. Scolnick used this version of the aspirin-indicated subgroup analysis in a presentation he made to the Merck Board of Directors regarding the VIGOR Trial, as described in Appendix T. Dr. Scolnick reported that, based on preliminary data, the difference in myocardial infarctions between Vioxx and naproxen was 8 versus 0 in patients needing aspirin and 6 versus 4 in those who did not.<sup>36</sup> He also

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<sup>34</sup> 4/14/00 email from E. Scolnick to R. Gilmartin et al., MRK-ADI0006059.

<sup>35</sup> 4/14/00 email from E. Scolnick to R. Gilmartin et al., MRK-ADI0006059.

<sup>36</sup> 4/25/00 slide presentation of E. Scolnick to Merck Board of Directors, MRK-AGN00006490, at 502. According to the data in Dr. Scolnick’s presentation, the total number of myocardial infarctions, regardless of aspirin-indication, was 14 to 4 (Vioxx versus naproxen). According to the data

noted that the aspirin-indicated patients experienced 30%-40% of the total cardiovascular events in the study and that there was “no statistical difference in the occurrence of [cardiovascular] events” between Vioxx and naproxen in the non-aspirin-indicated patients.<sup>37</sup>

- b. April 21, 2000 version (“Version 2”) of aspirin-indicated subgroup analysis based on all adjudicated pre-February 10 data.

On April 21, 2000, the aspirin-indicated subgroup analysis was re-run using the complete set of adjudicated events reported prior to the February 10 cut-off.<sup>38</sup> (See Table 4 below.) In this analysis, the confirmed thrombotic events, including myocardial infarctions, were more evenly distributed between the aspirin-indicated and non-aspirin-indicated subgroups. Of the 9 additional thrombotic events, all 9 were in the non-aspirin-indicated subgroup, and 8 of them were on Vioxx.<sup>39</sup>

Using the complete set of pre-February 10 adjudicated data, in the non-aspirin-indicated subgroup, there were 26 confirmed thrombotic events on Vioxx versus 15 on naproxen (a 43% lower incidence in the naproxen arm) and 9 myocardial

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circulated on April 14, 2000 (“Version 1”), the number of acute myocardial infarctions was 16 to 4 (Vioxx versus naproxen). VIGOR cardiovascular data table, MRK-AJK0005397 (attached to 4/14/00 memorandum from A. Reicin to E. Scolnick, MRK-AJK0005387). Dr. Scolnick may have been presenting only non-fatal myocardial infarctions, as 2 myocardial infarctions in the Vioxx group were fatal. Id.

<sup>37</sup> 4/25/00 slide presentation of E. Scolnick to Merck Board of Directors, MRK-AGN00006490, at 502-03.

<sup>38</sup> VIGOR cardiovascular data table, MRK-NJ0249222 (attached to 4/21/00 email from Q. Yu to A. Reicin, MRK-NJ0249213).

<sup>39</sup> Compare VIGOR cardiovascular data table, MRK-NJ0249222 (attached to 4/21/00 email from Q. Yu to A. Reicin, MRK-NJ0249213), with VIGOR cardiovascular data table, MRK-AJK0005401 (attached to 4/14/00 memorandum from A. Reicin to E. Scolnick, MRK-AJK0005387).

infarctions on Vioxx versus 4 on naproxen (a 56% lower incidence in myocardial infarctions in the naproxen arm). The numbers of thrombotic events in the aspirin-indicated 4% – 15 versus 3 – remained the same.<sup>40</sup>

Table 4

Aspirin-indicated Subgroup Analysis – Version 2: April 21, 2000 (all pre-Feb. 10 data)<sup>41</sup>

Type of Event	Aspirin indication (using FDA criteria)	Treatment (number of patients)	Number of patients with events	Event Incidence (per 100 PYRs)	Relative Risk	
					Estimate (naproxen vs. Vioxx)	95% confidence interval (CI)
Confirmed thrombotic events	Aspirin-indicated	Vioxx (170)	15	14.29	0.20	(0.06, 0.71)
		Naproxen (151)	3	2.94		
	Not aspirin-indicated	Vioxx (3877)	26	1.00	0.57	(0.30, 1.09)
		Naproxen (3878)	15	0.58		
Confirmed myocardial infarctions	Aspirin-indicated	Vioxx (170)	8	7.60	0.00	(0.00, 0.60)
		Naproxen (151)	0	0.00		
	Not aspirin-indicated	Vioxx (3877)	9	0.35	0.44	(0.14, 1.44)
		Naproxen (3878)	4	0.15		

Although the difference in confirmed thrombotic events (or myocardial infarctions) between Vioxx and naproxen in the non-aspirin-indicated patients was still not significant, the differences were closer to reaching statistical significance. Some MRL scientists – including Dr. Barr and statisticians Drs. Thomas Capizzi and Deborah Shapiro – expressed concern about highlighting the analysis in regulatory or academic journal submissions. Dr. Barr stated that the between-treatment difference in

<sup>40</sup> 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, Table C-6 at 034, Table C-11 at 041-42.

<sup>41</sup> Data for this table taken from: 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, Tables C-6, C-11 at 34, 42.

cardiovascular events in the non-aspirin-indicated group “cannot be ignored.”<sup>42</sup>

Dr. Capizzi pointed out that the fact that the difference in cardiovascular events in the non-aspirin-indicated subgroup did not reach statistical significance was unsurprising given the small overall number of cardiovascular events and could not be given too much weight.<sup>43</sup>

Further, Drs. Barr and Shapiro raised the fact that according to a statistical test (called a subgroup interaction test),<sup>44</sup> the subgroups were not sufficiently different in terms of the Vioxx/naproxen relative risk for thrombotic events to justify drawing any conclusions about confinement of the Vioxx/naproxen difference to one subgroup.<sup>45</sup> Thus, in their view, there was no reliable difference between the aspirin-indicated and non-indicated subgroups in terms of between-treatment relative risk for thrombotic events. While it was statistically valid to separate out the subgroups and to note that the 4% of the patient population who met FDA criteria for low-dose aspirin use experienced a disproportionate number (31%) of the thrombotic events, based on the results of this subgroup interaction test, one could not draw the statistical conclusion that the difference

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<sup>42</sup> 6/12/00 email from E. Barr to N. Braunstein et al., MRK-NJ0122865.

<sup>43</sup> Undated draft VIGOR manuscript with tracked changes and T. Capizzi’s comments, MRK-AAB0103832, at 43, 48.

<sup>44</sup> “A test for interaction between treatment and subgroup is the appropriate way to examine whether treatment effects differ between subgroups.” Brookes ST, Whitely E, Egger M, et al. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol. 2004;57:229-236, at 230.

<sup>45</sup> 6/12/00 email from E. Barr to N. Braunstein et al., MRK-NJ0122865.

in relative risk for thrombotic events between Vioxx and naproxen was confined to the aspirin-indicated patients.

c. July 5, 2000 version (“Version 3”)  
of aspirin-indicated subgroup analysis.

By May 26, 2000, the 11 potentially thrombotic (adjudication-eligible) events reported after the February 10 cut-off had been adjudicated.<sup>46</sup> As noted above, of these 11 additional events sent for adjudication, 5 were confirmed as thrombotic events. All 5 of these events were in the non-aspirin-indicated group, and 4 were on Vioxx, including 3 myocardial infarctions. These additional data in the third version of the analysis further narrowed the difference between the aspirin-indicated and non-aspirin-indicated subgroups in terms of relative risk for myocardial infarctions and confirmed thrombotic events. (See Table 5 below.) On July 5, 2000, Dr. Shapiro circulated tables incorporating the updated data to Drs. Reicin and Barr, who then shared these data with others at MRL.<sup>47</sup>

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<sup>46</sup> 5/26/00 email from L. Nelson to A. Reicin attaching table of adjudication results, MRK-AJA0119085-87.

<sup>47</sup> 7/5/00 memorandum from D. Shapiro to A. Reicin, E. Barr, and D. Erb attaching VIGOR cardiovascular data tables, MRK-AAX0001417-29; 7/10/00 email from L. Valdez to B. Gertz et al. attaching 7/5/00 memorandum from D. Shapiro to A. Reicin, E. Barr, and D. Erb, MRK-NJ0272442.

Table 5

Aspirin-indicated Subgroup Analysis – Version 3: July 5, 2000 (complete VIGOR data)<sup>48</sup>

Type of Event	Aspirin indication (using FDA criteria)	Treatment (number of patients)	Number of patients with events	Event Incidence (per 100 PYRs)	Relative Risk	
					Estimate (naproxen vs. Vioxx)	95% confidence interval (CI)
Confirmed thrombotic events	Aspirin-indicated	Vioxx (170)	15	14.29	0.20	(0.06, 0.71)
		Naproxen (151)	3	2.94		
	Not aspirin-indicated	Vioxx (3877)	30	1.16	0.53	(0.29, 0.97)
		Naproxen (3878)	16	0.62		
Confirmed myocardial infarctions	Aspirin-indicated	Vioxx (170)	8	7.60	0.00	(0.00, 0.60)
		Naproxen (151)	0	0.00		
	Not aspirin-indicated	Vioxx (3877)	12	0.46	0.33	(0.11, 1.03)
		Naproxen (3878)	4	0.15		

The new data were reported to the FDA on October 13, 2000 in a Safety Update Report.<sup>49</sup>

Tables 6 and 7 below summarize the results of the aspirin-indicated subgroup analysis at the three time points discussed above:<sup>50</sup>

<sup>48</sup> Data for this table taken from: 10/13/00 VIGOR Safety Update Report, MRK-00420027870, Table 9 at 896.

<sup>49</sup> 10/13/00 letter from R. Silverman to FDA (CDER) attaching VIGOR Safety Update Report, MRK-00420027870-72.

<sup>50</sup> Data for Table 6 taken from: 4/14/00 memorandum from A. Reicin to E. Scolnick, MRK-AJK0005387, at 401; 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, Table C-6 at 34; 10/13/00 VIGOR Safety Update Report, MRK-00420027870, Table 9 at 896. Data for Table 7 taken from: 4/25/00 slide presentation of E. Scolnick to Merck Board of Directors, MRK-AGN00006490, at 502; 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, Table C-11 at 041-42; 10/13/00 VIGOR Safety Update Report, MRK-00420027870, Table 19 at 904-06.

Table 6

Summary of Aspirin-indicated Subgroup Analysis at Three Time Points  
Endpoint: Confirmed Thrombotic Events

Time/Version of Analysis	Aspirin indication (using FDA criteria)	Treatment	Number of patients with events	Event Incidence (per 100 PYR)	Relative Risk	
					Estimate (naproxen vs. Vioxx)	95% confidence interval (CI)
Version 1: April 14, 2000	Aspirin-indicated	Vioxx (169)	15	13.76	0.21	(0.06, 0.72)
		Naproxen (151)	3	2.87		
	Not aspirin-indicated	Vioxx (3878)	18	0.67	0.78	(0.39, 1.56)
		Naproxen (3878)	14	0.52		
Version 2: April 21, 2000 (all pre-Feb.10 data)	Aspirin-indicated	Vioxx (170)	15	14.29	0.20	(0.06, 0.71)
		Naproxen (151)	3	2.94		
	Not aspirin-indicated	Vioxx (3877)	26	1.00	0.57	(0.30, 1.09)
		Naproxen (3878)	15	0.58		
Version 3: July 5, 2000 (complete VIGOR data)	Aspirin-indicated	Vioxx (170)	15	14.29	0.20	(0.06, 0.71)
		Naproxen (151)	3	2.94		
	Not aspirin-indicated	Vioxx (3877)	30	1.16	0.53	(0.29, 0.97)
		Naproxen (3878)	16	0.62		

Table 7

Summary of Aspirin-indicated Subgroup Analysis at Three Time Points  
Endpoint: Confirmed Myocardial Infarctions

Time/Version of Analysis	Aspirin indication (using FDA criteria)	Treatment	Number of patients with events	Event incidence (per 100 PYR)	Relative Risk	
					Estimate (naproxen vs. Vioxx)	95% confidence interval (CI)
Version 1: * April 14, 2000	Aspirin-indicated	Vioxx	8	*	*	*
		Naproxen	0	*		
	Not aspirin-indicated	Vioxx	6*	*	*	*
		Naproxen	4	*		
Version 2: April 21, 2000 (all pre-Feb.10 data)	Aspirin-indicated	Vioxx	8	7.60	0.00	(0.00, 0.60)
		Naproxen	0	0.00		
	Not aspirin-indicated	Vioxx	9	0.35	0.44	(0.14, 1.44)
		Naproxen	4	0.15		
Version 3: July 5, 2000 (complete VIGOR data)	Aspirin-indicated	Vioxx	8	7.60	0.00	(0.00, 0.60)
		Naproxen	0	0.00		
	Not aspirin-indicated	Vioxx	12	0.46	0.33	(0.11, 1.03)
		Naproxen	4	0.15		

\* These numbers may reflect only non-fatal myocardial infarctions. See note 36. The event incidence and relative risks for the myocardial infarctions in "Version 1" were not presented in internal documents.

B. April 2000 Meeting of Merck's Board of Scientific Advisors.

On April 27, 2000, Dr. Nies presented the VIGOR Trial results at the annual meeting of Merck's Board of Scientific Advisors.<sup>51</sup> After laying out the design of the study and the gastrointestinal and efficacy results, Dr. Nies presented cardiovascular data. His slides reflected the complete set of adjudicated data based on the February 10 cut-off date, in which there were 41 patients with confirmed thrombotic events in the Vioxx arm compared to 18 in the naproxen arm, reflecting a statistically significant difference in the incidence of such events.<sup>52</sup>

Dr. Nies also presented the aspirin-indicated subgroup analysis. Here, Dr. Nies used the same numbers that Dr. Scolnick had presented to the Board of Directors on

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<sup>51</sup> The role of Merck's Board of Scientific Advisors is discussed in Appendix A. Dr. John Oates\* of Vanderbilt University was the temporary chair of the Board, replacing Dr. Douglas Greene of the University of Michigan School of Medicine, who had committed to join MRL in the near future. Dr. Greene still attended the meeting as an advisor. The other 25 members of the Board of Scientific Advisors in April 2000 were: Dr. Dennis A. Ausiello\*, Massachusetts General Hospital; Dr. Henry G. Bone III\*, Michigan Bone & Mineral Clinic, P.C.; Dr. Barbara A. Gilchrest\*, Boston University School of Medicine; Dr. Sid Gilman\*, University of Michigan Medical Center; Dr. Diane E. Griffin\*, Johns Hopkins University School of Hygiene and Public Health; Dr. Stephen T. Holgate\*, University of Southampton (UK); Dr. King K. Holmes\*, Center for AIDS and STD, University of Washington; Dr. D. Roger Illingworth\*, Oregon Health Sciences University; Dr. Richard P. Lifton\*, Yale University; Dr. James E. McGuigan\*, University of Florida College of Medicine; Dr. Barbara J. McNeil\*, Harvard Medical School; Dr. Herbert Y. Metzler\*, Vanderbilt University School of Medicine; Dr. William W. Muir, III\*, Ohio State University; Dr. Keith Peters\*, University of Cambridge School of Medicine (UK); Dr. Donald L. Price\*, Johns Hopkins University School of Medicine; Dr. David Robertson\*, Vanderbilt University; Dr. P. Frederick Sparling\*, University of North Carolina at Chapel Hill; Dr. Bruce Stillman\*, Cold Spring Harbor Laboratory; Dr. Andrew Tait\*, University of Glasgow Veterinary School (UK); Dr. Carol A. Tamminga\*, University of Maryland School of Medicine; Dr. Daniel D. Von Hoff\*, University of Arizona; Dr. Stephen G. Waxman\*, Yale Medical School; Dr. Myron L. Weisfeldt\*, Columbia Presbyterian Medical Center; Dr. Scott L. Zeger\*, Johns Hopkins University School of Hygiene and Public Health; Dr. Huda Y. Zoghbi\*, Baylor College of Medicine. 4/00 Merck Board of Scientific Advisors meeting agenda, MRK-ACR0034285, at 297-303.

<sup>52</sup> 4/27/00 slide presentation of A. Nies to BSA, MRK-ABC0022825, at 53.

April 25 based on “Version 1” of the analysis, which showed that in the non-aspirin indicated subgroup, there were 6 Vioxx patients with myocardial infarctions compared to 4 naproxen patients (not a statistically significant difference in the incidence of myocardial infarctions).<sup>53</sup>

Dr. Nies presented the naproxen cardioprotection and FitzGerald prostacyclin hypotheses as possible explanations for the cardiovascular results. He presented scientific background for these hypotheses, including the results of Dr. FitzGerald’s\* studies on Vioxx (Protocol 023) and Celebrex (the McAdam Study), and the results of Merck’s clinical pharmacological study (Protocol 061) showing that naproxen provided a relatively high degree of sustained platelet inhibition.<sup>54</sup> In addition, Dr. Nies presented cardiovascular data from the Phase IIb/III osteoarthritis studies and the ongoing Alzheimer’s studies.<sup>55</sup> Dr. Nies’ presentation concluded that, in MRL’s view, the VIGOR Trial cardiovascular results likely reflected a cardioprotective effect of naproxen but that an adverse effect of Vioxx could not be completely ruled out.<sup>56</sup> Finally, Dr. Nies noted that MRL’s future plan was to develop a Data Analysis Plan for “combined cross

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<sup>53</sup> 4/27/00 slide presentation of A. Nies to BSA, MRK-ABC0022825, at 59.

<sup>54</sup> 4/27/00 slide presentation of A. Nies to BSA, MRK-ABC0022825, at 45-51. These studies are discussed in Appendix A.

<sup>55</sup> 4/27/00 slide presentation of A. Nies to BSA, MRK-ABC0022825, at 62-68.

<sup>56</sup> 4/27/00 slide presentation of A. Nies to BSA, MRK-ABC0022825, at 71-74.

study thromboembolic event analyses.”<sup>57</sup> After Dr. Nies’ presentation, the members of the Board of Scientific Advisors discussed the VIGOR Trial data in closed session.

Following the meeting, Dr. John Oates\* prepared a Chairman’s Report on behalf of the Board of Scientific Advisors. The report, which was submitted to Merck in July 2000, stated that “it is highly probable that the greater cardiovascular event rate on VIOXX is attributable to a substantial extent to the aspirin-like antiplatelet effect of naproxen which VIOXX lacks.”<sup>58</sup> The report also noted, however, that the “evidence does not exclude” a prothrombotic effect of Vioxx “that is peculiar to rheumatoid arthritis.”<sup>59</sup> The report further noted that “[t]here is no evidence other than that in the VIGOR trial that addresses the use of a COX-2 inhibitor in patients who have an accelerated rate of cardiovascular endpoints [such as rheumatoid arthritis patients], and the VIGOR trial does not distinguish between the two hypotheses.”<sup>60</sup>

The report proposed to Merck a two-pronged approach toward addressing the cardiovascular question raised by the VIGOR Trial.<sup>61</sup> First, the report proposed that Merck conduct an endoscopy study to investigate the gastrointestinal effects of taking

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<sup>57</sup> 4/27/00 slide presentation of A. Nies to BSA, MRK-ABC0022825, at 75.

<sup>58</sup> 7/10/00 Merck Board of Scientific Advisors Human Health Chairman’s Report, MRK-AAX0004179, at 183.

<sup>59</sup> 7/10/00 Merck Board of Scientific Advisors Human Health Chairman’s Report, MRK-AAX0004179, at 183.

<sup>60</sup> 7/10/00 Merck Board of Scientific Advisors Human Health Chairman’s Report, MRK-AAX0004179, at 184.

<sup>61</sup> 7/10/00 Merck Board of Scientific Advisors Human Health Chairman’s Report, MRK-AAX0004179, at 184-88.

low-dose aspirin with Vioxx. Second, the report proposed that Merck conduct a cardiovascular outcomes trial comparing Vioxx plus an antiplatelet agent (such as aspirin or clopidogrel) to naproxen plus an antiplatelet agent. These proposals and MRL's attempt to design a cardiovascular outcomes trial are discussed in Appendix M.

C. Public Presentations of the VIGOR Trial Results at Scientific Conferences.

After the March 27, 2000 press release, the VIGOR Trial results were next publicly presented on May 24, 2000, at the Digestive Disease Week annual conference in San Diego, California.<sup>62</sup> The VIGOR Trial was subsequently discussed at the annual conferences of the European League Against Rheumatism in June 2000, and the American College of Rheumatology in October 2000 (although at the latter, Merck's poster on the VIGOR Trial did not include cardiovascular data). Preparing for the conferences was a group effort involving members of the Clinical Research, Marketing, and Public Affairs Departments. These conferences not only attracted scientists but also were significant press and financial analyst events. They are discussed below.

1. Digestive Disease Week – May 19-26, 2000.

The first major scientific conference at which the VIGOR Trial results were presented was the Digestive Disease Week (DDW) conference in San Diego, held from May 19 to 26, 2000. The VIGOR Trial results were presented at a conference plenary session by Dr. Loren Laine\*, a gastroenterologist from the University of Southern California and the co-chair of the VIGOR Trial Steering Committee. VIGOR Trial Data

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<sup>62</sup> 3/31/00 memorandum from M. Brill to Distribution, MRK-AHY0192002, at 02.

Safety and Monitoring Board member Dr. David Bjorkman\* also presented the VIGOR Trial results a Digestive Disease Week-sponsored symposium, titled “Evidence-Based Approach to Preventing GI Complications of NSAIDs.” Finally, Merck sponsored a Continuing Medical Education symposium, entitled “Cox-2 Specific Inhibition for the Gastroenterologist,” at which VIGOR Trial results were again presented.<sup>63</sup>

Dr. Laine’s\* morning presentation focused on the gastrointestinal results of the VIGOR Trial, but four slides were devoted to cardiovascular data.<sup>64</sup>

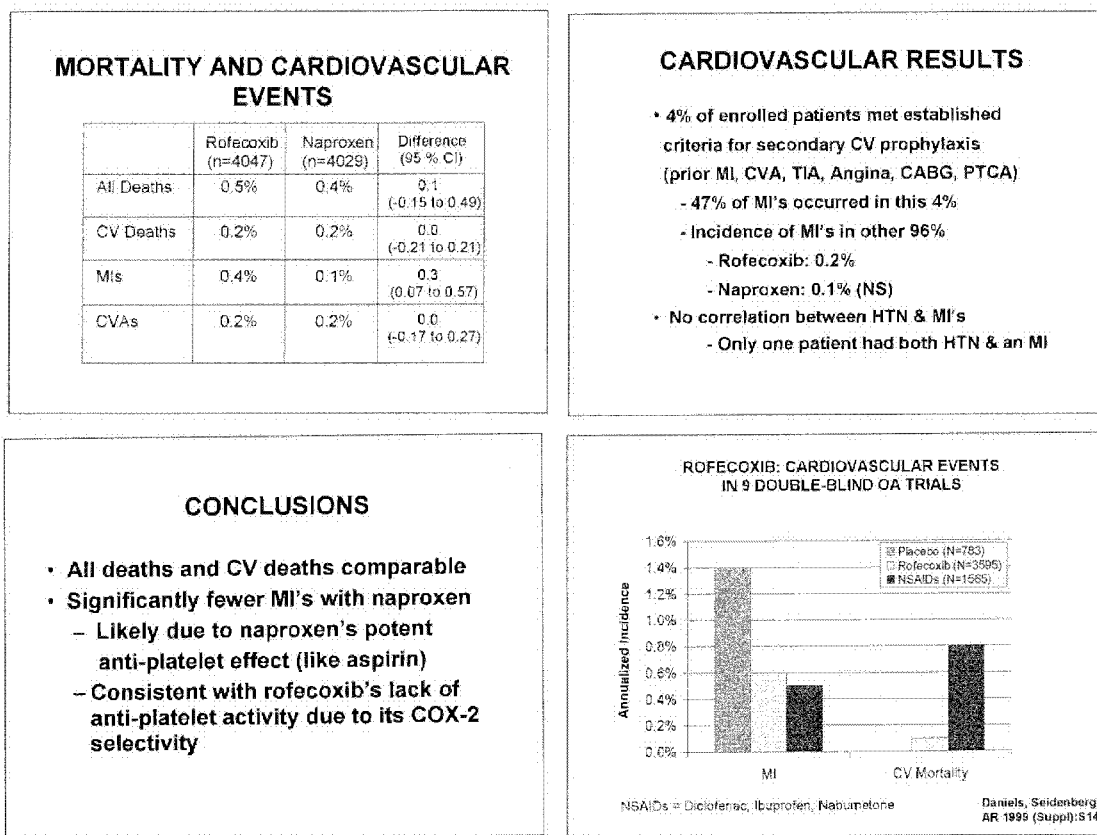
- A table of “Mortality and Cardiovascular Events” (based on all confirmed adjudicated events reported by the February 10 cut-off date, as discussed above);
- A “Cardiovascular Results” slide, presenting “Version 2” of the aspirin-indicated subgroup analysis and noting the lack of correlation between hypertension and myocardial infarctions in the study;
- A “Conclusions” slide that stated that there were “[s]ignificantly fewer MI’s with naproxen” and that this was “[l]ikely due to naproxen’s potent anti-platelet effect (like aspirin);” and
- Cardiovascular results from the Phase II and III osteoarthritis trials, which showed Vioxx as equal to or better than placebo and other non-selective NSAIDs in terms of myocardial infarctions and cardiovascular mortality.

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<sup>63</sup> 3/31/00 memorandum from M. Brill to Distribution, MRK-AHY0192002-03; Digestive Disease Week agendas and programs, MRK-AHY0192004-09 (attached to 5/5/00 email from M. Brill to VIOXX: WW Marketing Directors et al., MRK-AHY0192000).

<sup>64</sup> While Dr. Laine\* created these slides himself, Dr. Reicin reviewed and edited them with him. See 5/16/00 email from A. Reicin to R. El-Dada and R. Shah, MRK-AFI0105358.

The four slides are reproduced below:<sup>65</sup>



Merck's Public Affairs Department prepared plans to communicate the VIGOR Trial results to the press, both via news releases and interviews, at Digestive Disease Week.<sup>66</sup> Merck's press release, issued on May 24, focused on the gastrointestinal results of the VIGOR Trial, but also discussed cardiovascular data.<sup>67</sup> The cardiovascular

<sup>65</sup> Slide presentation of L. Laine\* for DDW conference, MRK-ABA0029566, at 83-84, 87-88 (attached to 5/25/00 email from G. Kylish to VIOXX: WWLISTING et al., MRK-ABA0029565).

<sup>66</sup> See 5/19/00 email from A. Kaufman to G. Reaves et al. attaching table of activities, MRK-ADI0014487-89.

<sup>67</sup> 5/24/00 Merck press release, "Vioxx® significantly reduced the reduced the risk of serious gastrointestinal side effects by more than half compared to naproxen in a new study," MRK-ADK0000794-97.

discussion in the press release essentially mirrored the information provided in

Dr. Laine's\* slides. On May 24, Dr. Alise Reicin spoke with a reporter from The Wall Street Journal, and representatives of Merck's Public Affairs Department spoke with a Reuters reporter.<sup>68</sup>

The day after Merck's presentation at Digestive Disease Week, Ms. Margaret McGlynn, a Senior Vice President in Worldwide Human Health Marketing, emailed Dr. Reicin thanking her for "the tremendous support [she] provided for the marketing organization" and forwarding an analyst report, which she said "most clearly demonstrate[s] the success of our efforts to defuse the CV risk issue for Vioxx."<sup>69</sup> The analyst report, titled "Vioxx Reduces GI Side Effects Versus NSAIDs, Cardiac Events Not an Issue," focused on the fact that there was "no statistical difference in heart attack rates" between Vioxx and naproxen in the 96% percent of patients not indicated for aspirin, and that the heart attack rate for Vioxx in this population (0.2%) "was the same rate as reported for Celebrex in non-aspirin patients in the CLASS trial."<sup>70</sup>

Similarly, a memorandum from Merck's Public Affairs Department, recapping the "Coverage of VIGOR and CLASS at DDW," stated:

[W]e successfully managed discussions of the heart attack data. Dow Jones and the Los Angeles Times . . . did not mention cardiovascular events, and other outlets discussed the MI rate with appropriate perspective. . . . [Reuters']

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<sup>68</sup> 6/5/00 memorandum from Public Affairs to W. Dixon et al., MRK-ACZ0020795.

<sup>69</sup> 5/25/00 email from M. McGlynn to A. Reicin, MRK-NJ0320174, at 74.

<sup>70</sup> 5/25/00 email from M. McGlynn to A. Reicin, MRK-NJ0320174, at 74-75.

Ransdell Pierson filed three stories on VIGOR and CLASS. After repeated discussions with Public Affairs, the final of these stories, which was filed the evening of May 24<sup>th</sup> for morning television and newspapers, provided the best context we've seen to date from Reuters on the MI data.<sup>71</sup>

The Reuters story emphasized the aspirin-indicated subgroup analysis and included quotes from two analysts. One quote read: "When you exclude consideration of the 4 percent who have had previous cardiovascular incidents, the difference in heart attacks between the Vioxx and naproxen patients are less a problem than previously speculated. I don't think it's an issue at all."<sup>72</sup> The other analyst, however, was quoted as saying that "the targeted population is vulnerable to cardiovascular problems," so "[t]here's no way to say, 'This is nothing.'"<sup>73</sup> The Public Affairs memorandum concluded: "[We] have already started planning for the next battle: EULAR."<sup>74</sup>

2. European League Against Rheumatism (EULAR).

Merck next presented VIGOR Trial results at the annual conference of the European League Against Rheumatism (EULAR) in Nice, France on June 21-22, 2000. Dr. Claire Bombardier\*, a rheumatologist from the University of Toronto and co-chair of the VIGOR Trial Steering Committee, presented the VIGOR Trial results on June 22, as

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<sup>71</sup> 6/5/00 memorandum from Public Affairs to W. Dixon et al., MRK-ACZ0020795.

<sup>72</sup> Vioxx shown safer on GI tract than older drug, Reuters, May 24, 2000, MRK-ACZ0020800, at 801 (attached to 6/5/00 memorandum from Public Affairs to W. Dixon et al., MRK-ACZ0020795).

<sup>73</sup> Vioxx shown safer on GI tract than older drug, Reuters, May 24, 2000, MRK-ACZ0020800, at 802 (attached to 6/5/00 memorandum from Public Affairs to W. Dixon et al., MRK-ACZ0020795).

<sup>74</sup> 6/5/00 memorandum from Public Affairs to W. Dixon et al., MRK-ACZ0020795.

part of the official program.<sup>75</sup> Dr. Bombardier\* also presented the VIGOR Trial results at a Merck-sponsored “Satellite Symposium”<sup>76</sup> and a Merck “Journalists Workshop”<sup>77</sup> where she was joined by other scientists who provided scientific context and discussed some of the study’s implications.

One of Dr. Bombardier’s\* co-presenters for the satellite symposium was Dr. Carlo Patrono\*, an internationally-renowned scientist and antiplatelet agent expert and a long-time MRL consultant. Dr. Patrono\* had given a presentation on the biochemical specificity of Vioxx at the Asia Pacific League of Associations for Rheumatology (APLAR) conference in May, and the Merck marketers arranging the EULAR symposium anticipated that he would give a similar presentation. On June 15, 2000, however, less than a week before the symposium, Dr. Patrono\* informed a Merck representative that he had decided to change his slides to “revisit the whole issue of cardiovascular implications of COX inhibition.”<sup>78</sup>

Dr. Patrono’s\* revised slides, which he sent to Merck, included a slide which listed as a “Commonly Held Misconception” the idea that “[c]onventional NSAIDs have antiplatelet effects similar to aspirin and, therefore, are likely to afford comparable

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<sup>75</sup> 5/11/00 email correspondence among A. Reicin, J. Kasperzik, A. Kaufman, et al., MRK-ADI0008240.

<sup>76</sup> 6/16/00 email from A. Kaufman to C. Bombardier\*, MRK-NJ0320180; 6/15/00 email from C. Patrono\* to J. Kasperzik, MRK-ABK0052046.

<sup>77</sup> Workshop agenda and summary, MRK-EC030592-94 (attached to 6/18/00 email from D. Bolton to A. Diaz et al., MRK-EC030590).

<sup>78</sup> 6/15/00 email from C. Patrono\* to J. Kasperzik, MRK-ABK0052046.

cardiovascular protection.”<sup>79</sup> Another proposed slide presented data on myocardial infarctions in both the CLASS and VIGOR Trials<sup>80</sup> and was followed by a slide titled, “At Least Three Possible Explanations:”<sup>81</sup>

**At Least Three Possible Explanations**

1. A cardioprotective effect of naproxen? But, no evidence that conventional NSAIDs reduce risk of MI at prescribed doses.
2. A thrombogenic effect of coxibs? But, size of the effect not biologically plausible; not substantiated by CLASS results, though a smaller class effect cannot be excluded.
3. The play of chance? Based on uneven distribution of a small number of events occurring over a short time frame in a low-risk population; an overview of all coxib trials might answer the question.

The MRL scientists and Merck marketers involved with the conference asked Dr. Patrono\* to reconsider his focus.<sup>82</sup> Dr. Reicin “spent many hours working with” Dr. Patrono\* regarding his proposed presentation.<sup>83</sup> On June 20, 2000, Merck’s Dr. Martino Laurenzi reported that Dr. Patrono\* had “accepted not to focus his presentation tomorrow at EULAR on the CV [adverse events] of VIGOR,” on the

<sup>79</sup> Draft slide presentation of C. Patrono\* for EULAR conference, MRK-ABK0080762, at 67 (attached to 6/15/00 email from J. Kasperzik to A. Reicin and B. Daniels, MRK-ABK0080760).

<sup>80</sup> Draft slide presentation of C. Patrono\* for EULAR conference, MRK-ABK0080762, at 75 (attached to 6/15/00 email from J. Kasperzik to A. Reicin and B. Daniels, MRK-ABK0080760).

<sup>81</sup> Draft slide presentation of C. Patrono\* for EULAR conference, MRK-ABK0080762, at 76 (attached to 6/15/00 email from J. Kasperzik to A. Reicin and B. Daniels, MRK-ABK0080760).

<sup>82</sup> See 8/28/00 email correspondence between A. Reicin and L. Beauchard et al., MRK-ABK0104367-68; 6/20/00 email from M. Laurenzi to B. Daniels et al., MRK-ADL0082197.

<sup>83</sup> 8/28/00 email from A. Reicin to L. Beauchard et al., MRK-ABK0104367.

condition that (i) “[t]he presentation of the VIGOR data must not mislead the audience into thinking that the difference in CV events could be explained by an anti-thrombotic effect of naproxen, which is not demonstrated” and (ii) Merck “ma[ke] clear that one possible explanation of the data is chance.”<sup>84</sup> Consistent with Dr. Patrono’s\* request, the slides presented by Dr. Bombardier\* at this symposium did not mention the antiplatelet effects of naproxen or the possibility of naproxen affording cardioprotection.<sup>85</sup> The press release that Merck issued in connection with the European League Against Rheumatism conference, however, emphasized the aspirin-indicated subgroup analysis and stated: “The reduction in heart attacks is consistent with naproxen’s ability to block platelet aggregation by inhibiting COX-1.”<sup>86</sup>

According to Dr. Patrono\*, Merck’s interactions with him regarding his presentations at this conference were appropriate. (As discussed in Section G of this Appendix, Dr. Patrono\* later changed his view about the cardioprotective effects of

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<sup>84</sup> 6/20/00 email from M. Laurenzi to B. Daniels et al., MRK-ADL0082197.

<sup>85</sup> Slide presentation of C. Bombardier\* for EULAR conference, MRK-ABK0496096-123 (attached to 7/6/00 email from J. Kasperzik to C. Bombardier\*, MRK-ABK0496027).

<sup>86</sup> 6/21/00 Merck press release, “New Study: Vioxx® Reduced Risk of Serious Gastrointestinal Side Effects by More than Half Compared to Naproxen,” MRK-EC030600, at 03-04 (“In the VIGOR study there was no difference in cardiovascular mortality between the VIOXX and naproxen treatment groups, and excluding the small subset of patients (4%) with a history of cardiac events, there was no significant difference in heart attack rates between the two groups, according to Dr. Bombardier.”).

naproxen and concluded that the antiplatelet effects of naproxen likely impacted the between-treatment event rate differential in the VIGOR Trial.)<sup>87</sup>

3. American College of Rheumatology.

The VIGOR Trial results were next presented at the annual conference of the American College of Rheumatology (ACR), held from October 28 through November 2, 2000 in Philadelphia. As with Digestive Disease Week, Merck sponsored a Continuing Medical Education (“CME”) symposium at the conference.<sup>88</sup> The Accreditation Council for Continuing Medical Education’s then current “Standards for Commercial Support of Continuing Medical Education” stated that “[c]ommercial supporters of [Continuing Medical Education] activities shall not control the planning, content or execution of the activity.”<sup>89</sup> The external organization running the Merck-funded symposium selected Dr. Patrono\* to give a presentation regarding “Cyclooxygenase Inhibition and Thrombogenesis” and selected Drs. Patrono\* and Catella-Lawson\* (who had worked with Dr. Garret FitzGerald\* on Protocol 023) to lead a discussion on that same topic.<sup>90</sup>

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<sup>87</sup> See Capone\* ML, Tacconelli\* S, Sciulli\* MG, Grana\* M, Riccieti\* E, Minuz\* P, Di Gregorio\* P, Merciaro\* G, Patrono\* C, Patrignani\* P. Clinical pharmacology of platelet, monocyte, and vascular cyclooxygenase inhibition by naproxen and low-dose aspirin in healthy subjects. Circulation. 2004;109:1468-71, at 68, 70.

<sup>88</sup> 10/29/00 American College of Rheumatology – Master Memo, MRK-ABK0431530, at 34-36.

<sup>89</sup> Accreditation Council for Continuing Medical Education “Standards for Commercial Support of Continuing Medical Education” (approved March 1992), MRK-AFI0019546, at 46. In September 2004, these standards were revised to require that “[s]election and presentation of content” and “[s]election of all persons and organizations that will be in a position to control the content of the CME” be done “free of the control of a commercial interest,” such as the sponsoring entity. Accreditation Council for Continuing Medical Education “Standards for Commercial Support” (approved September 2004), <http://www.accme.org>.

<sup>90</sup> 10/29/00 American College of Rheumatology – Master Memo, MRK-ABK0431530, at 35.

When Dr. Reicin learned in late August of the proposed symposium schedule, she sent an email to the Merck organizers of the symposium:<sup>91</sup>

From: Reicin, Alise S.  
Sent: Monday, August 28, 2000 5:30 PM  
To: Beauchard, Lucine E.; Roberts, Rick; El-Dada, Riad H.  
Subject: RE: ACR-2000 Master MEMO-Final

I have some concerns about the choice of patrono and catella lawson for the CV discussion. Do you know where they will come out? Carlo caused us alot of trouble at Euler. He wanted to do a totally unacceptable presentation that took great effort to talk him out of and he "sprung" it on us at the last moment. All went well in the end but it was touch and go until the end. He will not support our "naproxen" is a cardioprotective agent hypothesis. Francesca has been promoting the potential thrombotic effects of decreasing prostacyclin. Do you know what their presentations look like and how they plan to present this? We are having Carlo in for a consultants meeting hopefully prior to ACR which may help. Just a warning to proceed with great caution. I am not sure these would have been my top choices-in the end everything may work out ok but there may be a lot of headaches along the way  
Alise

After being informed that the speakers already had been confirmed, Dr. Reicin responded:<sup>92</sup>

To: Beauchard, Lucine E.; El-Dada, Riad H.; Alberti, Peter M; Roberts, Rick M; Shah, Raksha  
From: Reicin, Alise S.  
Cc:  
Bcc:  
Date: 2000-08-28 22:23:21  
Subject: RE: ACR-2000 Master MEMO-Final

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Raksha

I know that clinical is usually not consulted (which is fine) but had you asked me in June I would have given you the same response. In fact, someone asked me about catella lawson in may and I said to beware. I think that the CV issue is sensitive enough that we really need to be careful. The ACR symposium is just too important. Carlo sent one version of his talk and then 4 days before the meeting completely revised it with the main focus being that NSAIDs CANNOT WORK AS CARDIOPROTECTIVE AGENTS. Unless we are lucky and change his mind in October you are likely up for the same thing. Showing me the slides is fine but I spent many hours working with Carlo before Euler and I dont have the time to run through the same fire drill before every meeting. In addition because this is for CME credit we have much less imput than we did at Euler.  
Alise

Dr. Patrono\* did not share his slides with Merck prior to the symposium, but he sent them to the external organization running the Merck-funded symposium, Scientific

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<sup>91</sup> 8/28/00 email from A. Reicin to L. Beauchard et al., MRK-ABK0104367-68

<sup>92</sup> 8/28/00 email from A. Reicin to L. Beauchard et al., MRK-ABK0104367.

Therapeutics Information, Inc. (“STI”). An employee of STI, John Romankiewicz\*, contacted Dr. Patrono\* and suggested some changes, including removing a notation indicating that the between-treatment difference in myocardial infarctions in the VIGOR Trial was statistically significant and adding in a slide presenting a subgroup analysis of myocardial infarctions.<sup>93</sup> Mr. Romankiewicz\* also called to Dr. Patrono’s\* attention two studies showing that the NSAIDs flurbiprofen and indobufen, respectively, reduced the incidence of cardiovascular events in clinical trials.<sup>94</sup>

Mr. Romankiewicz\* kept Merck informed of his interactions with Dr. Patrono.\*<sup>95</sup> On October 23, 2000, Ms. Tracy Mills, a Merck Marketing Senior Director, emailed Dr. Reicin and members of the Marketing Department that Ms. Susan Baumgartner and Mr. William Griffing, both Merck Marketing Directors, were “working to follow-up on some discrepancies around [Dr. Patrono’s] talk.”<sup>96</sup> After Dr. Patrono\* rejected Mr. Romankiewicz’s\* suggestions, Mr. Romankiewicz\* wrote to Ms. Baumgartner and Ms. Raksha Shah, a Merck Scientific Conference Coordinator: “Dear Friends: Can’t say we have not tried.”<sup>97</sup>

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<sup>93</sup> See 10/18/00 email from J. Romankiewicz\* to C. Patrono\*, MRK-ABK0116717-18; 10/18/00 email from J. Romankiewicz\* to R. Shah and S. Baumgartner, MRK-ABK0127529.

<sup>94</sup> See 10/18/00 email from J. Romankiewicz\* to C. Patrono\*, MRK-ABK0116717-18; 10/18/00 email from J. Romankiewicz\* to R. Shah and S. Baumgartner, MRK-ABK0127529.

<sup>95</sup> See 10/18/00 email from J. Romankiewicz\* to R. Shah and S. Baumgartner, MRK-ABK0127529; 10/19/00 email from J. Romankiewicz\* to S. Baumgartner and R. Shah, MRK-AFI0184899.

<sup>96</sup> 10/23/00 email from T. Mills to A. Reicin et al., MRK-AFI0185024.

<sup>97</sup> 10/19/00 email from J. Romankiewicz\* to S. Baumgartner and R. Shah, MRK-AFI0184899.

In the end Dr. Patrono\* did not revise his presentation. He highlighted his own recently published epidemiological study which did not show a cardioprotective effect of NSAIDs, noted the FitzGerald prostacyclin hypothesis, and included the slide discussed and displayed above (in Section C.2 of this Appendix) presenting three possible explanations for the between-treatment cardiovascular event rate difference in the VIGOR Trial and concluding that the most likely explanation was chance.<sup>98</sup>

Merck also prepared and hosted two poster presentations on the VIGOR Trial at the conference. Because of the American College of Rheumatology's "long-standing policy that new data be presented at the meeting,"<sup>99</sup> the primary results of the VIGOR Trial were presented in one poster, and a new gastrointestinal sub-analysis was presented in the other.<sup>100</sup> Neither of these posters nor their corresponding abstracts mentioned cardiovascular data from the VIGOR Trial.<sup>101</sup>

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<sup>98</sup> Slide presentation of C. Patrono\* for ACR conference, MRK-ABK0165902-914 (attached to 10/23/00 email from S. Baumgartner to W. Griffing, MRK-ABK0165901).

<sup>99</sup> Draft of "Timeline and Events Related to Communications of VIGOR Results to the Medical Community," MRK-S006810, at 11 (attached to 1/26/01 email from J. Weiner to K. Frazier, et al., MRK-S006808-09).

<sup>100</sup> American College of Rheumatology – Merck Meeting Guide, MRK-ABK0307693, at 723-24.

<sup>101</sup> American College of Rheumatology – Merck Meeting Guide, MRK-ABK0307693, at 723-24; see also 1/9/01 letter from J. Fries\* to R. Gilmartin, MRK-ABO0000250, at 51. In a letter to Mr. Gilmartin in January, 2001, Dr. James Fries\* of Stanford University stated that he had "tried unsuccessfully to get the [cardiovascular and renal] data" at the American College of Rheumatology meeting; Dr. Reicin stated that she had the relevant cardiovascular data on hand at the poster presentation and recalled reviewing the data with Dr. Fries\*. 1/9/01 letter from J. Fries\* to R. Gilmartin, MRK-ABO0000250, at 51; Draft of "Timeline and Events Related to Communications of VIGOR Results to the Medical Community," MRK-S006810, at 11 (attached to 1/27/01 email from A. Reicin to K. Frazier, et al., MRK-S006808-09).

D. VIGOR Trial New England Journal of Medicine Article.

In April 2000, Dr. Reicin and members of the VIGOR Trial Steering Committee began preparing a manuscript about the VIGOR Trial for publication in a scientific journal. A manuscript was submitted to the New England Journal of Medicine on May 18, 2000 and was published November 23, 2000 (the “VIGOR article”). The process of drafting and the content of this article are discussed below.

1. Process of Drafting and Revising for Publication.

The primary authors of the VIGOR article were Dr. Alise Reicin of MRL and the non-Merck chairs of the VIGOR Trial Steering Committee: Dr. Claire Bombardier\*, a rheumatologist, and Dr. Loren Laine\*, a gastroenterologist. This group shared primary responsibility for drafting the article and communicating with the New England Journal of Medicine editors regarding proposed and actual revisions. Dr. Deborah Shapiro, a Merck statistician, also participated extensively in drafting and revising the manuscript. The remaining nine non-Merck members of the VIGOR Trial Steering Committee also participated in the drafting process, although to a lesser extent, and were listed as authors of the VIGOR article.<sup>102</sup>

In late April 2000, the VIGOR Trial Steering Committee met to review the unblinded data and jointly to revise an initial draft of the manuscript that Drs. Laine\*, Bombardier\*, and Reicin had prepared. Drs. Barr, Blois, Daniels and Nies then reviewed

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<sup>102</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28. Merck statistician Dr. Thomas Capizzi was a member of the VIGOR Trial Steering Committee but was not listed as an author.

the draft manuscript internally at Merck.<sup>103</sup> On May 18, Dr. Bombardier\*, on behalf of all of the authors, submitted the manuscript to the New England Journal of Medicine, which circulated it for anonymous peer review.<sup>104</sup>

On June 30, 2000, the editors of the New England Journal of Medicine sent Dr. Bombardier\* a letter stating that they would consider the paper if it were revised based on the attached comments of the New England Journal of Medicine editors and the three peer reviewers.<sup>105</sup> Over the course of the next few months, the New England Journal of Medicine editors and the authors engaged in a dialogue regarding revisions to manuscript,<sup>106</sup> as discussed more fully below. Dr. Reicin characterized the editing process as difficult and stated that the dialogue with the New England Journal of Medicine editors was at times heated. On September 13, 2000, the New England Journal of Medicine officially accepted the manuscript for publication,<sup>107</sup> and the article appeared in the November 23, 2000 edition.<sup>108</sup>

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<sup>103</sup> See 5/1/00 email from A. Reicin to D. Blois, A. Nies, and B. Daniels attaching draft VIGOR manuscript, MRK-AAD0019783-809.

<sup>104</sup> 5/18/00 letter from C. Bombardier\* to R. Utiger\*, MRK-AAD0019335-36.

<sup>105</sup> 6/30/00 letter from M. Kaplan\* to C. Bombardier\*, MRK-NJ0163720-22.

<sup>106</sup> 7/17/00 letter from C. Bombardier\* to M. Kaplan\*, MRK-AAB0009785-86; 8/16/00 letter from R. Steinbrook\* to C. Bombardier\*, MRK-NJ0245617; 8/22/00 letter from C. Bombardier\* to R. Steinbrook\*, MRK-NJ0123258-60; 8/28/00 letter from R. Steinbrook\* to C. Bombardier\*, MRK-NJ0245675; 8/30/00 letter from C. Bombardier\* to R. Steinbrook\*, MRK-NJ0245667; 9/13/00 letter from J. Drazen\* to C. Bombardier\*, MRK-NJ0070478-79; 10/12/00 facsimile from V. Cullmann\* to A. Reicin and C. Bombardier\*, MRK-NJ0246697.

<sup>107</sup> 9/13/00 letter from J. Drazen\* to C. Bombardier\*, MRK-NJ0070478.

<sup>108</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28.

2. Discussion of Cardiovascular Data in the VIGOR Article.

Although the focus of the published VIGOR article was on gastrointestinal data from the VIGOR Trial, the article also reviewed cardiovascular data, as discussed below.

a. Presentation of cardiovascular results.

Cardiovascular data were presented in the “Abstract” (or summary) at the front of the VIGOR article and in the “Results” and “Discussion” sections. The Abstract stated: “The incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.”<sup>109</sup> In the “Results” section, the article included cardiovascular data in a section on “General Safety.” The relevant portion stated:

The safety of both rofecoxib and naproxen was similar to that reported in previous studies. The mortality rate was 0.5 percent in the rofecoxib group and 0.4 percent in the naproxen group. The rate of death from cardiovascular causes was 0.2 percent in both groups. Ischemic cerebrovascular events occurred in 0.2 percent of the patients in each group. Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent; 95 percent confidence interval for the difference, 0.1 to 0.6 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7).<sup>110</sup>

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<sup>109</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 20.

<sup>110</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 23.

The discussion of cardiovascular data also addressed the aspirin-indicated subgroup analysis described in Section A of this Appendix:

Four percent of the study subjects met the criteria of the [FDA] for the use of aspirin for secondary cardiovascular prophylaxis . . . but were not taking low-dose aspirin therapy. These patients accounted for 38 percent of the patients in the study who had myocardial infarctions. In the other patients the difference in the rate of myocardial infarction between groups was not significant (0.2 percent in the rofecoxib group and 0.1 percent in the naproxen group). When the data showing a reduction in the rate of myocardial infarction in the naproxen group became available after the completion of this trial, Merck, the manufacturer of rofecoxib, notified all investigators in ongoing studies of a change in the exclusion criteria to allow patients to use low-dose aspirin.<sup>111</sup>

These data were again summarized in the “Discussion” section.

This presentation of cardiovascular data in the final article was similar to the presentation of cardiovascular data in the manuscript originally submitted to the New England Journal of Medicine on May 18, 2000,<sup>112</sup> although drafts circulated among the authors and internally at Merck prior to May 18 had included an additional table of cardiovascular data.<sup>113</sup> The table had listed the raw numbers of total deaths, cardiovascular deaths, myocardial infarctions, and ischemic strokes that had occurred in each treatment group, as well as the percentages of the total patients within each

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<sup>111</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 23.

<sup>112</sup> See 5/18/00 draft VIGOR manuscript, MRK-AAD0019337, at 52-54 (attached to 5/18/00 letter from C. Bombardier\* to R. Utiger\*, MRK-AAD0019335-36).

<sup>113</sup> 5/4/00 facsimile sending draft VIGOR manuscript, MRK-NJ0245917, at 36.

treatment group who experienced such events. The table also had included raw numbers and percentages of patients in each treatment group who experienced an event that qualified for a composite endpoint (the “Antiplatelet Trialists’ Collaboration” or “APTC” composite cardiovascular endpoint), which consisted of cardiovascular death, myocardial infarction, stroke (both ischemic and hemorrhagic), and death due to unknown cause or due to bleeding.<sup>114</sup> The table is reproduced below as Table 8:<sup>115</sup>

Table 8

Cardiovascular Events Table From VIGOR Article Internal Draft Manuscript

Table 5. Cardiovascular events

<b>Set of Events</b>	<b>Rofecoxib (N=4047)</b>	<b>Naproxen (N=4029)</b>	<b>Difference (95% CI)</b>
All deaths	22 (0.5%)	15 (0.4%)	0.1 (-0.15 to 0.49)
Cardiovascular deaths <sup>1</sup>	7 (0.2%)	7 (0.2%)	0.0 (-0.21 to 0.21)
Cardiovascular deaths <sup>1</sup> , nonfatal MI or CVA <sup>2</sup>	32 (0.8%)	17 (0.4%)	0.4 (0.01 to 0.73)
MI <sup>3</sup>	17 (0.4%)	4 (0.1%)	0.3 (0.07 to 0.57)
Ischemic CVA <sup>4</sup>	9 (0.2%)	7 (0.2%)	0.0 (-0.17 to 0.27)

<sup>1</sup> includes sudden death, unknown cause of death, fatal MI, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage and fatal GI bleeding episode.

<sup>2</sup> includes ischemic and hemorrhagic strokes

<sup>3</sup> includes fatal and non-fatal MI

<sup>4</sup> includes fatal and non-fatal CVAs

<sup>114</sup> 10/5/00 Statistical Data Analysis Plan, MRK-AFO0014726, at 32.

<sup>115</sup> 5/4/00 facsimile sending draft VIGOR manuscript, MRK-NJ0245917, at 36.

This table was deleted from the draft manuscript on May 16, 2000.<sup>116</sup> Data on all of the individual endpoints from that table were included in the text of the article in percentage form (as opposed to raw numbers). Thus, the article stated that “the mortality rate was 0.5 percent in the rofecoxib group and 0.4 percent in the naproxen group,” and characterized the overall mortality rate in the two groups as “similar.”<sup>117</sup> The raw numbers, which were not presented, showed that there were 37 total deaths in the VIGOR Trial – 22 among patients taking Vioxx and 15 among patients taking naproxen.<sup>118</sup> The between-treatment difference in deaths did not reach the level of statistical significance.

The composite cardiovascular endpoint that had been presented in the table was not included in the text of the article. The table had shown that there was a statistically

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<sup>116</sup> Undated draft VIGOR manuscript with dated tracked changes, MRK-AAB0103574, at 618-19. One peer reviewer noticed that the manuscript referenced a “Table 6,” which did not appear to exist. 7/17/00 letter from C. Bombardier\* to M. Kaplan\*, MRK-AAB0009785, at 95. In response, the authors wrote to the reviewer and the journal: “We apologize for the confusion created by the inadvertent reference to Table 6, which never existed. This should have been ‘Table 5,’ rather than ‘Table 6.’” Id.

<sup>117</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 23, 26.

<sup>118</sup> VIGOR Clinical Study Report, MRK-00420012526, Table 54 at 711; 2/1/01 Vioxx Cardiovascular Safety Review by S. Targum\*, MRK-ABK0457094, at 111. The percentage of deaths in each treatment group was 0.54% (or 22 ÷ 4047) in the Vioxx group versus 0.37% (or 15 ÷ 4029) in the naproxen group. Although, in this instance, rounding to one decimal place reduced the appearance of a difference unfavorable to Vioxx, rounding of other statistics to one decimal place in the VIGOR article increased the appearance of a difference against Vioxx. For example, the relative risk ratio for myocardial infarctions was presented in the article as 0.2 (a five-fold difference between naproxen and Vioxx), although based on the data set used in the article (pre-February 10 events), the relative risk was actually 0.24 (approximately a four-fold difference between naproxen and Vioxx). Compare Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 23 with 7/17/00 draft VIGOR manuscript, MRK-AAB0009797, at 811-12 (attached to 7/17/00 letter from C. Bombardier\* to M. Kaplan\*, MRK-AAB0009785-86).

significant difference in the number of composite cardiovascular endpoint (APTC) events between the Vioxx and naproxen arms.<sup>119</sup>

Neither the anonymous peer reviewers nor the editors at the New England Journal of Medicine requested that the authors include the raw cardiovascular data or insert a cardiovascular data table.<sup>120</sup> On the contrary, the New England Journal of Medicine editors required the authors to eliminate some of their other tables and figures to meet the journal's limit of five total tables and figures.<sup>121</sup> One peer reviewer requested inclusion of the relative risk and confidence interval for myocardial infarctions, and these data were included in the revised manuscript and final article.<sup>122</sup>

b. Aspirin-indicated subgroup analysis.

The VIGOR article also presented the aspirin-indicated subgroup analysis (“Version 2”) discussed in Section A of this Appendix:

Four percent of the study subjects met the criteria of the [FDA] for the use of aspirin for secondary cardiovascular prophylaxis (presence of a history of myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, angioplasty, or coronary bypass) but were not taking low-dose aspirin therapy. These patients accounted for 38

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<sup>119</sup> 5/4/00 facsimile sending draft VIGOR manuscript, MRK-NJ0245917, at 36.

<sup>120</sup> 6/30/00 letter from M. Kaplan\* to C. Bombardier\* attaching reviewers' comments, MRK NJ0163720-29.

<sup>121</sup> 6/30/00 letter from M. Kaplan\* to C. Bombardier\* attaching reviewers' comments, MRK NJ0163720, at 21.

<sup>122</sup> 6/30/00 letter from M. Kaplan\* to C. Bombardier\* attaching reviewers' comments, MRK NJ0163720, at 24; Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 23.

percent of the patients in the study who had myocardial infarctions. In the other patients the difference in the rate of myocardial infarction between groups was not significant (0.2 percent in the rofecoxib group and 0.1 percent in the naproxen group).<sup>123</sup>

(Citations omitted.) The “Discussion” section included a similar passage:

This difference [in myocardial infarctions] was primarily accounted for by the high rate of myocardial infarction among the 4 percent of the study population with the highest risk of a myocardial infarction, for whom low-dose aspirin is indicated. The difference in the rates of myocardial infarction between the rofecoxib and naproxen groups was not significant among the patients without indications for aspirin therapy as secondary prophylaxis.<sup>124</sup>

(Citations omitted.)

Drafts of the manuscript before its initial submission to the New England Journal of Medicine had included the raw numbers of myocardial infarctions in the aspirin-indicated subgroup analysis – 8 to 0 (Vioxx versus naproxen) among aspirin-indicated patients and 9 to 4 (Vioxx versus naproxen) among non-aspirin-indicated patients.<sup>125</sup> The raw numbers for the aspirin-indicated subgroup

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<sup>123</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 23 (“Results” section).

<sup>124</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000; 343:1520-28, at 26.

<sup>125</sup> Undated draft VIGOR manuscript with dated tracked changes, MRK-AAB0103574, at 589.

analysis were not included in the manuscript submitted to the New England Journal of Medicine, nor did they appear in the published article.<sup>126</sup>

Both passages quoted above concluded with the statement that there was not a significant difference in the risk of myocardial infarction between Vioxx and naproxen among non-aspirin-indicated patients.<sup>127</sup> Several MRL scientists, notably Drs. Barr and Capizzi, did not agree that such a statement was appropriate given the data and so advised the authors during the drafting of the VIGOR article.

An early internal draft of the manuscript had stated that “there was no significant difference between rofecoxib and naproxen in the rate of myocardial infarctions in the 96% of the population without indications for aspirin as secondary prophylaxis.”<sup>128</sup> After this text, Dr. Reicin inserted the comment that Dr. Barr “thinks we need to tone down the wording and say the difference was ‘much less pronounced.’” In handwritten comments next to this passage in the draft manuscript, Dr. Blois wrote: “AGREE.”<sup>129</sup> On another

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<sup>126</sup> 5/18/00 draft VIGOR manuscript, MRK-AAD0019337, at 53 (attached to 5/18/00 letter from C. Bombardier\* to R. Utiger\*, MRK-AAD0019335-36); Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000; 343:1520-28, at 23.

<sup>127</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000; 343:1520-28, at 23, 26.

<sup>128</sup> 5/1/00 draft VIGOR manuscript with D. Blois’ comments, MRK-AAD0019783, at 797-98 (sent by facsimile from D. Blois to A. Reicin on 5/3/00).

<sup>129</sup> 5/1/00 draft VIGOR manuscript with D. Blois’ comments, MRK-AAD0019783, at 798 (sent by facsimile from D. Blois to A. Reicin on 5/3/00).

copy of the draft, Dr. Alan Nies wrote next to the comment from Dr. Barr: “Maybe say ‘much less pronounced and not significant.’”<sup>130</sup>

In a later draft, still prior to the initial New England Journal of Medicine submission, Dr. Capizzi commented on a passage in the “Discussion” section of the manuscript that stated (as Dr. Nies had suggested) that the between-treatment difference in myocardial infarctions was “much less pronounced and not significant” in the non-aspirin-indicated 96%:

[G]ive me a break[.] [O]ne barely has enough power (with just 21 events) to detect an overall difference with so few events[,] so you probably have high ‘power’ to see a nonsignificant result in the low risk group when you break up the overall results into a high risk and low risk group.<sup>131</sup>

Commenting on another passage, which stated that the between-treatment difference in myocardial infarctions in the non-aspirin-indicated group was “much less apparent” than in the aspirin-indicated group, Dr. Capizzi wrote: “I think that this is a stretch for a post-hoc analysis – there is considerable overlap in the CIs [confidence intervals] – Clearly the difference on an absolute scale has to appear less pronounced in the low risk group vs the high risk group.”<sup>132</sup> With regard to a different subgroup analysis included in the paper that examined gastrointestinal events based on steroid use,

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<sup>130</sup> 5/1/00 draft VIGOR manuscript with A. Nies’ comments, MRK-NJ0245793, at 807.

<sup>131</sup> Undated draft VIGOR manuscript with tracked changes and T. Capizzi’s comments, MRK-AAB0103832, at 48.

<sup>132</sup> Undated draft VIGOR manuscript with tracked changes and T. Capizzi’s comments, MRK-AAB0103832, at 43.

Dr. Capizzi stated that the very same breakdown occurred: there was no statistically significant difference between Vioxx and naproxen in gastrointestinal events in the non-steroid using subgroup. Dr. Capizzi pointed out that, in that instance, the authors stated that steroid users and non-steroid-users showed a similar reduction in gastrointestinal events in the Vioxx arm, whereas the authors claimed that aspirin-indicated and non-indicated patients differed in terms of the reduction in cardiovascular events in the naproxen arm.<sup>133</sup>

Although neither the journal nor any of the anonymous peer reviewers initially commented on the aspirin-indicated subgroup analysis, one of the peer reviewers asked that the steroid-use subgroup analysis of gastrointestinal events be discussed in a similar way as the aspirin-indicated subgroup analysis – in other words, that the lack of a statistically significant reduction in gastrointestinal events (PUBs) among non-steroid-users be noted even though the subgroup interaction test did not affirm that there was a statistical difference between the steroid-user and non-steroid-user subgroups. The reviewer wrote: “The steroid finding is worthy of comment, even if the interaction is not statistically significant (the power for interactions is low). It may well be that the new agent [Vioxx] has little benefit for those not treated with steroids.”<sup>134</sup>

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<sup>133</sup> See Undated draft VIGOR manuscript with tracked changes and T. Capizzi’s comments, MRK-AAB0103832, at 43.

<sup>134</sup> Reviewer B comments, MRK-NJ0163723 (attached to 6/30/00 letter from M. Kaplan\* to C. Bombardier\*, MRK-NJ0163720-22).

The authors, however, resisted the reviewer's suggestion, writing in their response letter to the journal:

While there was not a significant reduction in relative risk of confirmed PUBs in the subgroup not taking steroids at baseline, VIGOR was only designed to detect a significant reduction overall, and not within any specific subgroup. There were, however, reductions in relative risk in this subgroup albeit not significant. Whenever many subgroups are examined, it becomes likely that there will be no apparent effect in some of them purely by chance. That is why the test for interaction, although underpowered as you rightly pointed out, is the appropriate way to assess subgroup effects.<sup>135</sup>

The authors' response concluded:

For these reasons, one cannot conclude that there is a lack of benefit of rofecoxib in the steroid subgroup. The effect within the subgroup of patients not taking steroids at baseline should be considered no different than the effect within any other subgroup in which the interaction effect was not significant.<sup>136</sup>

As noted above, prior to initially submitting the manuscript to the journal, Merck had "toned down" the description of the between-treatment difference in myocardial infarctions in the non-aspirin-indicated subgroup by stating that it was "much less pronounced and not significant" and "much less apparent" than the between-treatment difference in myocardial infarctions in the aspirin-indicated four percent. When the New

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<sup>135</sup> Response to Reviewer B's comments, MRK-AAB0009790-91 (attached to 7/17/00 letter from C. Bombardier\* to M. Kaplan\*, MRK-AAB0009785-86).

<sup>136</sup> Response to Reviewer B's comments, MRK-AAB0009790-91 (attached to 7/17/00 letter from C. Bombardier\* to M. Kaplan\*, MRK-AAB0009785-86). There was further correspondence between Merck and the journal before final language regarding the steroid use subgroup was finalized. See 8/30/00 letter from C. Bombardier\* letter to R. Steinbrook\*, MRK-NJ0245667-70.

England Journal of Medicine editors revised Merck's manuscript and prepared page proofs, however, they changed both passages back to "not significant."<sup>137</sup> The authors accepted this revision without further discussion.

c. Explanations of cardiovascular data.

The "Discussion" section of the VIGOR article set forth the naproxen cardioprotection hypothesis as the likely explanation for the differential in cardiovascular events between the two arms of the study. The relevant portion of the "Discussion" section read as follows:

Naproxen inhibits the production of thromboxane by 95 percent and inhibits platelet aggregation by 88 percent, and this effect is maintained throughout the dosing interval; therefore, the effects of regular use of naproxen may be similar to those of aspirin. Flurbiprofen, another NSAID that is a potent inhibitor of platelet-derived thromboxane, led to a 70 percent reduction in the rate of reinfarction as compared with placebo among patients in whom acute myocardial infarction was successfully treated with thrombolysis, angioplasty, or both.

Analyses of 7535 patients in double-blind trials comparing rofecoxib with placebo and other NSAIDs (diclofenac, ibuprofen, and nabumetone) that do not produce sustained, maximal inhibition of platelet aggregation revealed similar rates of myocardial infarction in all groups. Thus, our results are consistent with the theory that naproxen has a coronary protective effect and highlight the fact that rofecoxib does not provide this type of protection owing to its selective inhibition of cyclooxygenase-2 at its therapeutic dose and at higher doses. The finding that naproxen therapy was associated with a lower rate of

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<sup>137</sup> Page proofs of VIGOR manuscript, MRK-NJ0246698, at 708, 732, 734 (attached to 10/12/00 facsimile from V. Cullmann to A. Reicin and C. Bombardier, MRK-NJ0246697).

myocardial infarction needs further confirmation in larger  
studies.<sup>138</sup>

(Citations omitted.)

The original manuscript submitted by the authors to the New England Journal of  
Medicine had also included several sentences describing the FitzGerald prostacyclin  
hypothesis:

COX-2 selective inhibitors and non-selective NSAIDs both  
may decrease production of prostacyclin, a vasodilator and  
an inhibitor of platelet aggregation. It has been theorized  
that the inhibition of prostacyclin without the concomitant  
inhibition of thromboxane could potentially be  
pro-thrombotic. However, this theoretical risk was not  
demonstrated with rofecoxib in placebo-controlled  
studies.<sup>139</sup>

(Citations omitted.) The authors eliminated this passage, however, in response to an  
anonymous peer reviewer's comment that: "The conclusion section is somewhat  
awkward. I understand that the emphasis on the apparent increased comparative rate of  
cardiovascular events in the rofecoxib group is relevant. However, this needs to be  
tightened up."<sup>140</sup>

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<sup>138</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib  
and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 26-27.

<sup>139</sup> 5/18/00 draft VIGOR manuscript, MRK-AAD0019337, at 61 (attached to 5/18/00 letter from  
C. Bombardier\* to R. Utiger\*, MRK-AAD0019335-36).

<sup>140</sup> Response to Reviewer C's comments, MRK-AAB0009792, at 95-96 (attached to 7/17/00 letter from  
C. Bombardier\* to M. Kaplan\*, MRK-AAB0009785-86); 7/17/00 draft VIGOR manuscript,  
MRK-AAB0009797, at 817-18 (attached to 7/17/00 letter from C. Bombardier\* to M. Kaplan\*,  
MRK-AAB0009785-86); Reviewer C's comments, MRK-NJ0163725, at 26 (attached to 6/30/00  
letter from M. Kaplan\* to C. Bombardier\*, MRK-NJ0163720-22); see also 10/14/05 transcript of  
Humeston v. Merck & Co., No. ATL-L-2272-03MT, N.J. Super. Ct., at 3741 (testimony of  
A. Reicin).

In describing the Cardiovascular Adjudication SOP, the article stated that the adjudication process had been put in place because of the possibility that “the incidence of thrombotic cardiovascular events would be lower among patients treated with nonselective cyclooxygenase inhibitors [NSAIDs] than among those treated with cyclooxygenase-2-selective inhibitors.”<sup>141</sup> The article did not mention the FitzGerald prostacyclin hypothesis, which was a primary reason that Merck’s Board of Scientific Advisors had recommended in 1998 that the Company implement a Cardiovascular Adjudication SOP.<sup>142</sup>

d. Data on hypertension and edema.

The VIGOR article did not mention the hypertension and edema rates in the VIGOR Trial. Instead, the “General Safety” portion of the results section noted that “the safety of both rofecoxib and naproxen was similar to that reported in previous studies” and cited the Vioxx and naproxen product labeling (package inserts).<sup>143</sup> In the VIGOR Trial, there was a statistically significant difference between the Vioxx and naproxen arms in hypertension and edema, but the rate of hypertension and edema seen in the Vioxx arm of the VIGOR Trial was similar to that reported in the label for the 50 mg

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<sup>141</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 21.

<sup>142</sup> See discussion of the origins of the Cardiovascular Adjudication SOP in Appendix A.

<sup>143</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 23.

dose of Vioxx. As a result, Dr. Reicin has testified that she did not feel that it was necessary to use limited journal space to include the actual statistics.<sup>144</sup>

The version of the manuscript submitted to the New England Journal of Medicine stated: “Since both nonselective NSAIDs and COX-2 selective inhibitors are occasionally associated with hypertension, the association between hypertension and myocardial infarctions was explored.”<sup>145</sup> The published article did not include that statement, but included the following sentence regarding hypertension: “There was no association between hypertension and myocardial infarction; only a single patient (in the rofecoxib group) had both hypertension and a myocardial infarction as adverse events.”<sup>146</sup>

In their initial set of comments, the New England Journal of Medicine editors requested that the authors “add a sentence or two with regard to the effects of the two medications on renal function.”<sup>147</sup> The editors did not specify what the term “renal function” should encompass. Although hypertension and edema may be considered “renal” or “cardiorenal” adverse effects, the authors interpreted the editors’ request, according to Dr. Reicin, as referring to a different group of adverse events – those having

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<sup>144</sup> 10/11/05 transcript of Humeston v. Merck & Co., No. ATL-L-2272-03MT, N.J. Super. Ct., at 3511-12 (testimony of A. Reicin).

<sup>145</sup> 5/18/00 draft VIGOR manuscript, MRK-AAD0019337, at 53 (citations omitted) (attached to 5/18/00 letter from C. Bombardier\* to R. Utiger\*, MRK-AAD0019335-36).

<sup>146</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 23.

<sup>147</sup> 6/30/00 letter from M. Kaplan\* to C. Bombardier\*, MRK-NJ0163720, at 20.

to do specifically with indices of renal function or dysfunction. Therefore, the authors responded to the request by stating in the article that the “incidence of adverse effects related to renal function was low and similar in the two groups (1.2 percent in the rofecoxib group and 0.9 percent in the naproxen group).”<sup>148</sup> These figures did not include hypertension or edema adverse events.<sup>149</sup>

### 3. Additional Adjudicated Data.

As discussed above, the cardiovascular discussion in the VIGOR article was based on adjudicated and confirmed thrombotic cardiovascular events reported on or before February 10, 2000. As discussed above, 5 confirmed thrombotic events in the VIGOR Trial were reported after February 10, 4 on Vioxx and 1 on naproxen. All 5 of these additional events occurred in patients not indicated for prophylactic low-dose aspirin use. Three of these additional events were myocardial infarctions, all experienced by patients on Vioxx.

Dr. Reicin received an email on May 26, 2000 attaching a table listing the adjudication results for the post-February 10 events.<sup>150</sup> On July 5, Dr. Shapiro circulated

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<sup>148</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 24-25.

<sup>149</sup> During a taping session for a Merck video news release about the VIGOR article, Dr. Laine\*, in response to a question about the renal results of the VIGOR Trial, said: “I don’t think you really want to go there . . . because there are no data on blood pressure . . . or edema in the [article], and the only thing it says specifically – and we were cagey about this – was related to renal failure or renal function.” Merck video news release taping session with L. Laine\* for 11/23/00 release, B2514.

<sup>150</sup> 5/26/00 email from L. Nelson to A. Reicin, MRK-AJA0119085, attaching table, MRK-AJA0119086-87. The results were not broken down by treatment group. Instead the events were listed by patient allocation number.

to Dr. Reicin (and others at MRL) tables of VIGOR cardiovascular data incorporating these additional events.<sup>151</sup> At this point, Drs. Reicin and Shapiro and the other authors of the VIGOR manuscript were in the process of preparing a first revised version of the manuscript for resubmission.<sup>152</sup> These additional events were not incorporated in the article, and the article did not state that the cardiovascular data discussed in the article were not final. Details regarding this issue are discussed in the following subsections.

a. Timeline of data availability and manuscript editing.

On April 21, 2000, the adjudication of all eligible cardiovascular events in the VIGOR Trial reported on or before February 10, 2000 was completed.<sup>153</sup> When the authors of the VIGOR article first submitted a manuscript to the New England Journal of Medicine on May 18, 2000, they used this set of cardiovascular data, which had been specified as the data set to be used for the regulatory submission planned for June 2000.<sup>154</sup> The following week, on May 26, 2000, Dr. Reicin received an email attaching a table listing the results of the adjudications of the 11 adjudication-eligible events that had been reported after February 10, 2000.<sup>155</sup> On July 5, 2000, Dr. Shapiro sent a

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<sup>151</sup> 7/5/00 memorandum from D. Shapiro to A. Reicin, E. Barr, and D. Erb, MRK-AAX0001417-29.

<sup>152</sup> The first revised version was submitted on July 17, 2000. 7/17/00 letter from C. Bombardier\* to M. Kaplan\*, MRK-AAB0009785.

<sup>153</sup> 4/21/00 email from Q. Yu to A. Reicin, MRK-NJ0249213.

<sup>154</sup> 5/18/00 draft VIGOR manuscript, MRK-AAD0019337, at 53, 60 (attached to 5/18/00 letter from C. Bombardier\* to R. Utiger\*, MRK-AAD0019325); 2/7/00 letter from A. Reicin to M. Weinblatt\*, MRK-NJ0067266, at 66; 2/10/00 "Plan for the Adjudication and Analysis of Serious Vascular Events in VIGOR," MRK-AAX0002763.

<sup>155</sup> 5/26/00 email from L. Nelson to A. Reicin attaching table, MRK-AJA0119085.

memorandum to Drs. Reicin, Barr and Erb that included updated analyses of the VIGOR Trial cardiovascular results, incorporating these additional events.<sup>156</sup> The published VIGOR article did not include the post-February 10 adjudicated cardiovascular data.

The following timeline identifies key dates in the adjudication process along with dates in the manuscript editing process:

- April 21, 2000 Adjudications completed of all cardiovascular events reported on or before February 10.
- May 18, 2000 VIGOR article manuscript submitted to the New England Journal of Medicine.
- May 26, 2000 Email to Dr. Reicin attaching table listing results of adjudications of events reported after February 10.
- June 29, 2000 Initial supplemental New Drug Application submission using all adjudicated cardiovascular event data based on the February 10 cut-off date.
- June 30, 2000 Initial comments from New England Journal of Medicine editors and peer reviewers.
- July 5, 2000 Dr. Shapiro's memorandum to Drs. Reicin, Barr and Erb with updated cardiovascular data.

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<sup>156</sup> 7/5/00 memorandum from D. Shapiro to A. Reicin, E. Barr, and D. Erb, MRK-AAX0001417-29. When the VIGOR manuscript was in page proofs, the editors of the New England Journal of Medicine had requested that Merck include a brief statement discussing the CLASS trial, recently published in the Journal of the American Medical Association, in the "Discussion" section of the VIGOR article. Page proofs of VIGOR manuscript, MRK-NJ0246698, at 709 (attached to 10/12/00 facsimile from V. Cullmann\* to A. Reicin and C. Bombardier\*, MRK-NJ0246697). The text agreed upon by Drs. Laine\* and Reicin and the editors, which was included in the final article, described the gastrointestinal results of CLASS as presented in the Journal of the American Medical Association article, but also pointed out that in the article "data were reported from the first 6 months of a study period that extended for up to 13 months." Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 26; 10/17/00 facsimile from A. Reicin and L. Laine\* to S. McLain\*, MRK-AAD0407384, at 85.

- July 17, 2000 First revised manuscript submitted to the New England Journal of Medicine.
- September 13, 2000 New England Journal of Medicine accepts the manuscript for publication.
- October 12, 2000 New England Journal of Medicine provides galley-proofs of the article.
- October 13, 2000 Merck submits updated VIGOR cardiovascular data to the FDA in a Safety Update Report.
- November 23, 2000 VIGOR article published in New England Journal of Medicine.

b. Impact of additional data on VIGOR Trial cardiovascular results.

The additional cardiovascular data from adjudicated events reported after February 10, 2000, primarily affected two aspects of the cardiovascular discussion set forth in the VIGOR article: (i) the percentage of patients on Vioxx who had myocardial infarctions in the VIGOR Trial; and (ii) the aspirin-indicated subgroup analysis.

With respect to the former, there were 21 total myocardial infarctions in the VIGOR Trial based on the February 10 cut-off: 17 in patients on Vioxx (representing 0.4% of all patients on Vioxx) and 4 in patients on naproxen (representing 0.1% of the naproxen patients) – roughly a four-to-one ratio.<sup>157</sup> These percentages (though not the raw numbers) were included in the VIGOR article.<sup>158</sup> The additional 3 myocardial infarctions changed the numbers of myocardial infarctions to 20 (0.5%) for Vioxx and

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<sup>157</sup> Table, “Summary of Adjudicated Thromboembolic Cardiovascular Serious Adverse Experiences,” MRK-NJ0249214 (attached to 4/21/00 email from Q. Yu to A. Reicin, MRK-NJ0249213).

<sup>158</sup> Bombardier\* C, Laine\* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28.

4 (0.1%) for naproxen – a five-to-one ratio.<sup>159</sup> These data are reflected in the chart

below:<sup>160</sup>

Table 9

Myocardial Infarctions in the VIGOR Trial with/without Additional Data

	Treatment	Number of Patients with Myocardial Infarctions	% of Patients in Treatment Group with Myocardial Infarctions	Relative Risk (with 95% confidence interval) – naproxen vs. Vioxx
VIGOR article (February 10 cut-off) (“Version 2”)	Vioxx	17	0.4%	0.24 (0.08, 0.74)
	Naproxen	4	0.1%	
Final VIGOR data (“Version 3”)	Vioxx	20	0.5%	0.20 (0.07, 0.58)
	Naproxen	4	0.1%	

With regard to the aspirin-indicated subgroup analysis presented in the article (and discussed above), the final data changed the numbers of myocardial infarctions in the non-aspirin-indicated subgroup from 9 (0.2%) on Vioxx versus 4 (0.1%) on naproxen to 12 (0.3%) on Vioxx versus 4 (0.1%) on naproxen. In addition, because all of the post-February 10 events occurred in non-aspirin-indicated patients, the sub-group analysis (“Version 3”) was less compelling with the additional data.<sup>161</sup> Table 10 below

<sup>159</sup> 7/5/00 memorandum from D. Shapiro to A. Reicin, E. Barr, and D. Erb, MRK-AAX0001417-29.

<sup>160</sup> Data for Table 9 taken from 10/13/00 VIGOR Safety Update Report, MRK-00420027870, Tables 19, 20 at 904, 907. The data in the “VIGOR article” row reflects the data upon which the article was based. As discussed, the raw numbers of patients with myocardial infarctions were not included in the published article.

<sup>161</sup> See Transcript of 2/8/01 FDA Arthritis Advisory Committee Meeting, MRK-AAF0003438, at 575 (Dr. Reicin stated that, “Early on, before we did the safety update report, most of the risk was in the aspirin indicated group. With the safety update report it was more evenly distributed.”); 12/16/00 email from N. Braunstein to D. Greene, MRK-ACR0011965 (“One reason the data with regard to the

compares the data on which the VIGOR article was based with the data that was  
circulated in July 2000:<sup>162</sup>

Table 10

Summary of Aspirin-indicated Subgroup Analysis with/without Additional Data  
Endpoint: Confirmed Myocardial Infarctions

	Aspirin Indication	Treatment	Number of Patients with Myocardial Infarctions	% of Patients in Subgroup with Myocardial Infarctions	Relative Risk (with 95% confidence interval) – naproxen vs. Vioxx
VIGOR article (February 10 cut-off) (“Version 2”)	Aspirin-indicated	Vioxx	8	4.7%	0.00 (0.00, 0.60)
		Naproxen	0	0%	
	Not aspirin-indicated	Vioxx	9	0.2%	0.44 (0.14, 1.44)
		Naproxen	4	0.1%	
Final VIGOR data (“Version 3”)	Aspirin-indicated	Vioxx	8	4.7%	0.00 (0.00, 0.60)
		Naproxen	0	0%	
	Not aspirin-indicated	Vioxx	12	0.3%	0.33 (0.11, 1.03)
		Naproxen	4	0.1%	

Based on the additional adjudicated data, the lack of statistical heterogeneity between the subgroups, and the opinion of their consultants (discussed in Section G of this Appendix), MRL did not highlight the aspirin-indicated subgroup analysis in future publications and presentations.<sup>163</sup>

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cohort in whom aspirin was not indicated look less impressive than when submitted in the NDA is that there were 11 cases reported after the study cut-off date.”).

<sup>162</sup> Data for Table 10 taken from 10/13/00 VIGOR Safety Update Report, MRK-00420027870, Tables 19, 20 at 904-09. The data in the “VIGOR article” row is the data upon which the article was based. As discussed, only the percentages for the non-aspirin-indicated subgroup were included in the published article.

<sup>163</sup> 1/29/01 email from L. Jordan to J. Weiner *et al.*, MRK-ADI0008060, at 60; 12/16/00 email from N. Braunstein to D. Greene, MRK-ACR0011965. Additionally, as discussed in Appendix N, in March 2001, Merck removed the analysis from the proposed revised labeling for Vioxx (it had been included in the June 2000 draft of the proposed revised labeling) and resisted the FDA’s attempts to reintroduce the analysis into the proposed labeling.

4. VIGOR Article Press Release.

On the same date that the VIGOR article was published, Merck issued a press release that focused on the gastrointestinal results of the VIGOR Trial. With regard to cardiovascular effects, the press release stated that there were “significantly fewer heart attacks” in the naproxen arm of the study than in the Vioxx arm, which, the press release stated, was consistent with naproxen’s ability to block platelet aggregation due to its suppression of Cox-1.<sup>164</sup> The press release did not mention the aspirin-indicated subgroup analysis.

E. Investigation of Rheumatoid Arthritis as a Factor in the VIGOR Trial Results.

As discussed in Appendix E, MRL scientists considered the possibility that there might be something special about rheumatoid arthritis patients – the study population in the VIGOR Trial – that could help explain the VIGOR Trial’s cardiovascular results. During their initial investigation, MRL scientists found studies showing that rheumatoid arthritis patients had an increased risk of cardiovascular disease compared to the general population.<sup>165</sup> They also found studies demonstrating that “anticardiolipin antibodies,” traditionally associated with lupus and known to be associated with an increased risk of

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<sup>164</sup> 11/23/00 Merck press release, “In a study of Vioxx® published in The New England Journal of Medicine, Vioxx significantly reduced the risk of serious gastrointestinal side effects by half compared to naproxen,” MRK-ABG0001775-78.

<sup>165</sup> 3/23/00 preliminary VIGOR report to FDA, MRK-ABK0460838, at 63 (citing Myllykangas-Luosujarvi\* RA, Aho\* K, Isomaki\* HA. Mortality in rheumatoid arthritis. Semin Arthritis Rheum. 1995;25:193-202; Wallberg-Jonsson\* S, Ohman\* M-L, Rantapaa-Dahlqvist\* S. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in northern Sweden. J Rheumatol. 1997;24:445-51).

thrombosis, are present in 16% to 33% of patients with rheumatoid arthritis.<sup>166</sup> Finally, Dr. Oates\* pointed MRL to studies showing that patients with such antibodies had elevated levels of thromboxane and, to a much lesser extent, prostacyclin.<sup>167</sup> Further, in August 1999, Dr. Oates\* had shared with Dr. Scolnick three case reports of patients with antiphospholipid syndrome (known to be associated with anticardiolipin antibodies) who had experienced thrombotic events soon after initiating therapy with Celebrex.<sup>168</sup>

As discussed in Appendix E, all of this information led MRL scientists to speculate that rheumatoid arthritis might have played a role in the VIGOR Trial cardiovascular results in one of two ways: (i) a drug such as naproxen, with potent, sustained inhibition of platelet Cox-1 and thromboxane, might be more likely to confer cardioprotection on these potentially sensitive patients than on others; or (ii) if a selective Cox-2 inhibitor such as Vioxx inhibited prostacyclin in the vasculature without inhibiting thromboxane, it might be more likely to trigger thrombotic events in these patients than in others.

To explore these possibilities, MRL scientists conducted three studies: (i) an observational study of the United Kingdom's General Practitioner Research Database ("GPRD") to determine whether rheumatoid arthritis patients did, in fact, suffer from

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<sup>166</sup> 3/23/00 preliminary VIGOR report to FDA, MRK-ABK0460838, at 63-64 (citing Merkel\* PA, Chang\* Y-C, Pierangeli\* SS, et al. The prevalence and clinical associations of anticardiolipin antibodies in a large inception cohort of patients with connective tissue diseases. Am J Med. 1996;101:576-83; Fort\* JG, Cowchuck\* S, Abruzzo\* JL, Smith\* JB. Anticardiolipin antibodies in patients with rheumatic diseases. Arthritis Rheum. 1987;30:752-60).

<sup>167</sup> 3/16/00 email from J. Oates\* to B. Gertz, MRK-ABH0017410.

<sup>168</sup> 8/13/99 letter from J. Oates\* to E. Scolnick, MRK-ABH0004600-04.

higher rates of cardiovascular disease than other patients; (ii) a second observational study of the General Practitioner Research Database to determine whether rheumatoid arthritis patients treated with naproxen suffered a lower rate of cardiovascular disease; and (iii) a pharmacoepidemiological study to determine whether rheumatoid arthritis patients showed an increased level of biomarkers associated with cardiovascular disease. In addition, MRL scientists conducted a review of spontaneously reported adverse events with Vioxx to determine if any patients with lupus had reported thrombotic events. This Section discusses each of these efforts.

1. Study of Mortality and Thrombotic Events among Rheumatoid Arthritis Patients in the General Practitioner Research Database.

From April 2000 through early 2001, MRL scientists, led by Dr. Douglas Watson of Merck's Epidemiology Department, conducted two epidemiological studies of rheumatoid arthritis patients utilizing the General Practitioner Research Database, a computerized database tracking as many as 7 million patients in the United Kingdom.<sup>169</sup> The hypothesis of the first of these studies was that rheumatoid arthritis patients would exhibit higher rates of all-cause mortality and certain cardiovascular events than either (i) osteoarthritis patients with no diagnosis for rheumatoid arthritis, or (ii) patients with neither osteoarthritis nor rheumatoid arthritis.<sup>170</sup>

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<sup>169</sup> 4/14/00 background material for 4/20/00 HHPAC meeting, MRK-ABI0002269, at 81.

<sup>170</sup> 9/20/00 protocol, "Estimation of Sex- and Age-Specific All-Cause Mortality, and the Incidence of Thromboembolic Events in the General Practitioner Research Database," MRK-ACT0001005, at 06.

Dr. Watson presented the results of the study to Merck's Clinical and Regulatory Review Committee<sup>171</sup> on December 6, 2000, noting that "[p]art of the explanation put forth for [the] VIGOR results is that RA patients are at higher risk of CV events than OA patients."<sup>172</sup> The study had six endpoints: all-cause mortality, myocardial infarction, sudden death, stroke, cardiovascular death (fatal myocardial infarction, fatal stroke, and sudden death), and thrombotic events (all myocardial infarctions, strokes, and sudden death).<sup>173</sup> The study showed that rheumatoid arthritis patients suffered a statistically significantly higher rate of all of these endpoints than osteoarthritis patients or non-arthritis patients.<sup>174</sup>

An article about the study was published in the Journal of Rheumatology in June 2003 and reported that patients with rheumatoid arthritis in the General Practitioner Research Database were 30% to 60% more likely to have a thrombotic event, and 60% to 70% more likely to die from any cause, compared to either osteoarthritis patients (without

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<sup>171</sup> The successor to the Clinical Development Oversight Committee, a cross-disciplinary (Research, Regulatory, and Statistics) oversight and planning committee.

<sup>172</sup> 12/6/00 slide presentation of D. Watson and T. Rhodes to CRRC, "Results of an Analysis of All-Cause Mortality and Major Acute Thromboembolic Events among Patients with RA, OA but not RA, and No Arthritis in the GPRD," MRK-ABY0063883, at 85; see also Summary of 12/6/00 CRRC Meeting, MRK-ABP0014706, at 13.

<sup>173</sup> 12/6/00 slide presentation of D. Watson and T. Rhodes to CRRC, "Results of an Analysis of All-Cause Mortality and Major Acute Thromboembolic Events among Patients with RA, OA but not RA, and No Arthritis in the GPRD," MRK-ABY0063883, at 86. In an internal slide presentation, the "thrombotic events" endpoint was labeled "thromboembolic events" and in the published article, these events were labeled "vascular events." Id.

<sup>174</sup> 12/6/00 slide presentation of D. Watson and T. Rhodes to CRRC, "Results of an Analysis of All-Cause Mortality and Major Acute Thromboembolic Events among Patients with RA, OA but not RA, and No Arthritis in the GPRD," MRK-ABY0063883, at 89-96.

rheumatoid arthritis) or those with no arthritis.<sup>175</sup> The authors reviewed the relevant scientific literature on cardiovascular mortality in rheumatoid arthritis patients, noted the consistency of their findings with those of other investigators, and concluded that the “specific risk factors for the increased risk of death and vascular disease in RA patients have not been fully explained.”<sup>176</sup>

2. Study of Naproxen Use and Thrombotic Events in Rheumatoid Arthritis Patients in the General Practitioner Research Database.

MRL’s second study in the General Practitioner Research Database explored whether rheumatoid arthritis patients who were prescribed naproxen experienced a lower incidence of cardiovascular events than those who had no such prescription within the prior year.<sup>177</sup> This study used the same endpoints as the mortality study discussed above.<sup>178</sup> The protocol for this study was finalized at the end of November 2000,<sup>179</sup> and

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<sup>175</sup> Watson DJ, Rhodes T, Guess HA. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. J Rheumatol. 2003;30:1196-1202, Table 3 at 1198, MRK-ABY0084918.

<sup>176</sup> Watson DJ, Rhodes T, Guess HA. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. J Rheumatol. 2003;30:1196-1202, Table 3 at 1198-99, MRK-ABY0084918.

<sup>177</sup> Watson, DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. Arch Int Med. 2002;162:1105-10, MRK-AEF0000847.

<sup>178</sup> 11/22/00 draft protocol, “A Case Control Study of the Risk of Acute Major Thromboembolic Events with Naproxen Among Patients with Rheumatoid Arthritis in the General Practice Research Database,” MRK-ABY0024265, at 69; Watson, DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. Arch Int Med. 2002;162:1105, at 05, MRK-AEF0000847. The draft protocol and published article referred to the “thrombotic events” endpoint as “acute thromboembolic events.” Id.

<sup>179</sup> See 11/22/00 email from D. Watson to H. Guess, B. Gertz, A. Reicin, et al., MRK-ABY0024264; 11/29/00 email from D. Watson to A. Reicin, MRK-ABY0024620.

the preliminary data became available on January 24, 2001.<sup>180</sup> The preliminary results showed that rheumatoid arthritis patients who had a current prescription for naproxen experienced statistically significantly fewer thrombotic events than those patients who had no prescription for naproxen within the prior year. As discussed in Appendix I, these preliminary results were sent to the FDA in February 2001 and were mentioned in MRL's presentation at the February 8, 2001 FDA Arthritis Advisory Committee meeting.<sup>181</sup> The results of the study appeared in The Archives of Internal Medicine on May 27, 2002.<sup>182</sup>

3. Study of Biomarkers of Inflammation and Thrombotic Risk in Patients with Rheumatoid Arthritis and Osteoarthritis ("Biomarkers Study").

In 2001 and 2002, scientists in MRL's Epidemiology Department, collaborating with clinical investigators at the University of Pittsburgh and Stanford University, conducted a clinical epidemiological study to help understand the causes of the increased thrombotic risk in rheumatoid arthritis patients versus osteoarthritis patients and the relationship, if any, of these causes to Cox inhibition.<sup>183</sup> The study, which MRL scientists had begun planning as early as April 2000, compared levels of thromboxane and prostacyclin metabolites in the urine of rheumatoid arthritis and osteoarthritis

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<sup>180</sup> 1/24/01 email from H. Guess to B. Gertz and A. Reicin, MRK-NJ0125109, at 10.

<sup>181</sup> 2/6/01 letter from R. Silverman to FDA Central Document Room, Center for Drug Evaluation and Research, MRK-AAF0003431-32.

<sup>182</sup> Watson, DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. Arch Int Med. 2002;162:1105-10, MRK-AEF0000847. A detailed summary of the published article is in Appendix P.

<sup>183</sup> 2/1/01 Protocol 141-01 study protocol, "Biomarkers of Inflammation and Thromboembolic Risk in Patients with Rheumatoid Arthritis and Osteoarthritis," MRK-ABK0323031-90.

patients, and also compared levels in certain other “biomarkers of inflammation and thromboembolic risk” such as antiphospholipid antibodies and C-reactive protein.<sup>184</sup> The study enrolled 131 rheumatoid arthritis patients and 140 osteoarthritis patients<sup>185</sup> who were required to refrain from using any NSAID for the two-week period between the initial study visit and the final visit at which blood and urine samples were taken.<sup>186</sup>

The “first goal” of the study was to compare levels of thromboxane and prostacyclin metabolites in patients with rheumatoid arthritis versus patients with osteoarthritis.<sup>187</sup> An “exploratory objective” related to this goal was to examine the ratio between thromboxane and prostacyclin metabolites in rheumatoid arthritis patients and to compare it to that of osteoarthritis patients.<sup>188</sup> A “second goal” of the study was “to assess the association between RA/OA status and prevalence or distribution of serum biomarkers that are hypothesized to reflect or influence thromboembolic risk.”<sup>189</sup>

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<sup>184</sup> 4/14/00 background material for 4/20/00 HHPAC meeting, MRK-ABI0002269, at 80-81; 2/1/01 Protocol 141-01 study protocol, “Biomarkers of Inflammation and Thromboembolic Risk in Patients with Rheumatoid Arthritis and Osteoarthritis,” MRK-ABK0323031-90.

<sup>185</sup> Wasko\* MC, Genovese\* M, DeMuro-Mercon C, *et al.* Markers of cardiovascular risk in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) [abstract 976]. *Arthritis Rheum.* 2003;48:S396.

<sup>186</sup> 2/1/01 Protocol 141-01 Protocol, “Biomarkers of Inflammation and Thromboembolic Risk in Patients with Rheumatoid Arthritis and Osteoarthritis,” MRK-ABK0323031, at 51-52.

<sup>187</sup> 2/1/01 Protocol 141-01 Protocol, “Biomarkers of Inflammation and Thromboembolic Risk in Patients with Rheumatoid Arthritis and Osteoarthritis,” MRK-ABK0323031, at 36.

<sup>188</sup> 2/1/01 Protocol 141-01 Protocol, “Biomarkers of Inflammation and Thromboembolic Risk in Patients with Rheumatoid Arthritis and Osteoarthritis,” MRK-ABK0323031, at 37.

<sup>189</sup> 2/1/01 Protocol 141-01 Protocol, “Biomarkers of Inflammation and Thromboembolic Risk in Patients with Rheumatoid Arthritis and Osteoarthritis,” MRK-ABK0323031, at 36.

As Dr. Carolyn Cannuscio, an MRL epidemiologist and one of the designers of the study, explained to Dr. Harry Guess, head of MRL's Epidemiology Department: "We are trying to understand whether certain patient populations may have a particularly prothrombotic baseline state that would be particularly vulnerable to perturbation of the thromboxane/prostacyclin axis by inhibition of COX-2."<sup>190</sup> Dr. Cannuscio also suggested that an elevated thromboxane/prostacyclin ratio would mean that "[patients] with RA have a particularly pro-thrombotic milieu."<sup>191</sup> Dr. Cannuscio's email is reproduced below:<sup>192</sup>

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<sup>190</sup> 8/22/01 email from C. Cannuscio to H. Guess, MRK-ABK0323030.

<sup>191</sup> 8/22/01 email from C. Cannuscio to H. Guess, MRK-ABK0323030.

<sup>192</sup> 8/22/01 email from C. Cannuscio to H. Guess, MRK-ABK0323030 (final paragraphs of email, discussing budget for study, omitted).

**From:** Cannuscio, Carolyn C  
**Sent:** Wednesday, August 22, 2001 5:41 PM  
**To:** Guess, Harry A  
**Subject:** RA Biomarkers protocol



complete final revised  
141-01 ...

Harry:

The attached protocol is for the RA Biomarkers Study (Protocol 141-01).

**Purpose of study:**

To understand the underlying pathophysiology of cardiovascular disease in patients with rheumatoid arthritis (systemic inflammation).

We are comparing levels of urinary prostaglandin metabolites in patients with RA and OA. Hypothesis is that thromboxane metabolite levels are higher in patients with RA than in patients with OA. (Also that thromboxane:prostacyclin metabolite ratio is elevated in RA pts--in other words, that pts with RA have a particularly pro-thrombotic milieu.)

We are also exploring the assn between these prostaglandin metabolites and markers of thromboembolic risk (like antiphospholipid antibodies, CRP, fibrinogen, Lp(a), von Willebrand factor, etc).

Authors like Crofford at Michigan have observed pts with elevated antiphospholipid antibodies who experienced thrombosis immediately following exposure to celecoxib.

We are trying to understand whether certain patient populations may have a particularly pro-thrombotic baseline state that would be particularly vulnerable to perturbation of the thromboxane/prostacyclin axis by inhibition of COX-2.

Preliminary results of the study showed borderline statistically significant elevations of thromboxane urinary metabolite and of the thromboxane/prostacyclin metabolite ratio in rheumatoid arthritis patients compared to osteoarthritis patients.<sup>193</sup>

Preliminary results also showed statistically significant elevations in the rheumatoid arthritis patients of C-reactive protein, fibrinogen, and homocysteine.<sup>194</sup>

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<sup>193</sup> 5/29/02 slide presentation, "Biomarkers of inflammation and thromboembolic risk: Preliminary results from Protocol 141-01," MRK-ACT0027789, at 91-93.

<sup>194</sup> 5/29/02 slide presentation, "Biomarkers of inflammation and thromboembolic risk: Preliminary results from Protocol 141-01," MRK-ACT0027789, at 93-95. An abstract on the study presented at the 2003 American College of Rheumatology meeting reported the elevated levels of C-Reactive protein, fibrinogen, and homocysteine, but did not report on the thromboxane metabolite or thromboxane/prostacyclin ratio data. Wasko\* MC, Genovese\* M, DeMuro-Mercon C, et al. Markers of cardiovascular risk in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) [abstract 976]. Arthritis Rheum. 2003;48:S396.

4. Investigation of Thrombotic Events  
Among Patients with Lupus Taking Vioxx.

As discussed Appendix E, Dr. John Oates\* had alerted Merck in August 1999 to three reported cases of patients with antiphospholipid syndrome who had experienced thrombotic events within days of initiating treatment with Celebrex.<sup>195</sup> These case reports were presented by Dr. Leslie Crofford\* at the Fall 1999 meeting of the American College of Rheumatology and were subsequently published.<sup>196</sup> Patients with antiphospholipid syndrome, which was traditionally associated with systemic lupus erythematosus (“SLE” or “lupus”), were known to be especially susceptible to thrombotic events. Dr. Oates’s\* letter, as well as the abstract and article by Dr. Crofford\*, raised the possibility that these thrombotic events among patients with antiphospholipid syndrome on Celebrex were related to the FitzGerald prostacyclin hypothesis.

After the cardiovascular results of the VIGOR Trial were unblinded, MRL scientists learned that 16% to 33% of patients with rheumatoid arthritis also had antiphospholipid syndrome.<sup>197</sup> Therefore, Merck’s March 23, 2000 Report to the FDA

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<sup>195</sup> 8/13/99 letter from J. Oates\* to E. Scolnick, MRK-ABH0004600.

<sup>196</sup> Gupta\* S, McCune\* WJ, Kaplan\* MJ, et al. Thrombosis and ischemia in patients with systemic lupus erythematosus treated with Celecoxib: a series of two cases [abstract 473]. Arthritis Rheum. 1999;42:S149, MRK-ABH0016221; Crofford\* LJ, Oates\* JC, McCune\* WJ, et al. Thrombosis in patients with connective tissue diseases treated with specific cyclooxygenase-2 inhibitors: a report of four cases. Arthritis Rheum. 2000;43:1891-96.

<sup>197</sup> 3/23/00 preliminary VIGOR report to FDA, MRK-ABK0460838, at 63-64.

noted the possibility that, in the VIGOR Trial, Vioxx might have had a prothrombotic effect in this highly sensitive subgroup of rheumatoid arthritis patients.<sup>198</sup>

To investigate this possibility, MRL scientists reviewed data on Vioxx usage and spontaneously reported post-marketing adverse events to see whether there was any association between use of Vioxx and thrombotic events among patients with antiphospholipid syndrome.<sup>199</sup> To estimate how many patients with the syndrome had taken Vioxx in the United States, MRL scientists reviewed a survey of prescription drug usage, conducted by IMS Health, Inc., which collected data on the disease state or symptom for which drugs are prescribed. According to this survey, approximately 30,000 patients had been prescribed Vioxx for the treatment of symptoms of lupus.<sup>200</sup> (MRL scientists used lupus as a proxy for antiphospholipid syndrome, although not all patients with lupus have the syndrome.)

Next, MRL scientists reviewed Merck's Worldwide Adverse Event System database, in which all spontaneously reported post-marketing adverse events are recorded, to find all reports regarding Vioxx that mentioned the words "lupus," "cardiolipin" (a term associated with antiphospholipid syndrome), or "Raynaud's"

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<sup>198</sup> 3/23/00 preliminary VIGOR report to FDA, MRK-ABK0460838, at 63.

<sup>199</sup> 7/13/00 memorandum from N. Braunstein to E. Scolnick and R. Perlmutter, MRK-ABO0000442-45.

<sup>200</sup> 7/13/00 memorandum from N. Braunstein to E. Scolnick and R. Perlmutter, MRK-ABO0000442, at 44-45.

(another disease associated with antiphospholipid syndrome).<sup>201</sup> Thirty-three such case reports were found, but none were “cases of acute thromboses that were thought to be related to VIOXX therapy.”<sup>202</sup> MRL scientists also searched the database for any “adverse experience[s] of ‘thrombosis’ or ‘thromboembolism’” on Vioxx. Thirty such cases were found, but none of the patients was reported to have lupus or antiphospholipid syndrome.<sup>203</sup>

Finally, Drs. Ned Braunstein and Brian Daniels contacted six academic rheumatologists “to determine if there were additional cases unknown to Merck.”<sup>204</sup> None of these rheumatologists was aware of patients with lupus or antiphospholipid syndrome who had experienced “problems similar to those reported” by Dr. Crofford\*.

Dr. Braunstein wrote a memorandum to Dr. Scolnick and Dr. Roger Perlmutter, Executive Vice President of Basic Research at MRL, relating these efforts and results and concluding: “these data are reassuring and indicate that if these events do occur in patients taking VIOXX, they are very rare and likely at a rate indistinguishable from the

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<sup>201</sup> 7/13/00 memorandum from N. Braunstein to E. Scolnick and R. Perlmutter, MRK-ABO0000442, at 44.

<sup>202</sup> 7/13/00 memorandum from N. Braunstein to E. Scolnick and R. Perlmutter, MRK-ABO0000442, at 44.

<sup>203</sup> 7/13/00 memorandum from N. Braunstein to E. Scolnick and R. Perlmutter, MRK-ABO0000442, at 44.

<sup>204</sup> 7/13/00 memorandum from N. Braunstein to E. Scolnick and R. Perlmutter, MRK-ABO0000442, at 44. The six academic rheumatologists were: Drs. Israeli Jaffe\*, Michael Lokshin\*, Lisa Samaritano\*, Jill Buyon\*, Joan Merrill\* and Ken Kalunian\*.

background rate in these patients.”<sup>205</sup> Dr. Scolnick forwarded the memorandum to Mr. Gilmartin, Dr. Douglas Greene, Executive Vice-President, Clinical Sciences and Product Development, Ms. Margaret McGlynn, Senior Vice President, Worldwide Human Health Marketing, and Mr. David Anstice, President of U.S. Human Health, with the note: “This report has just been written. VERY reassuring.”<sup>206</sup>

F. Cardiovascular Meta-Analysis.

In April 2000, MRL scientists set in motion plans to conduct a meta-analysis<sup>207</sup> of all cardiovascular data from Phase II through V trials of at least four weeks duration,<sup>208</sup> including both adjudicated cardiovascular data from trials conducted under the Cardiovascular Adjudication SOP and unadjudicated data from earlier trials.<sup>209</sup> Minutes of a May 2000 meeting of the Clinical Development Oversight Committee, a

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<sup>205</sup> 7/13/00 memorandum from N. Braunstein to E. Scolnick and R. Perlmutter, MRK-ABO0000442, at 45.

<sup>206</sup> 7/15/00 email from E. Scolnick to D. Greene, R. Gilmartin, M. McGlynn, and D. Anstice, MRK-ABO0000441.

<sup>207</sup> Although Merck’s internal draft data analysis plans referred to this analysis as a “meta-analysis,” it is, more precisely, a pooled analysis. A “meta-analysis” is “the statistical combination of at least 2 studies . . . to produce a single estimate of the magnitude of the effect of the intervention under investigation.” Lam<sup>\*</sup> RW, Kennedy<sup>\*</sup> SH. Using metaanalysis to evaluate evidence: Practical tips and traps. Can J Psychiatry, 2005;50:167-74, at 69. A “pooled analysis” is a type of meta-analysis that “pools the data from individual patients in several studies and analyzes these data as if they were from one large study.” Id. at 70. When patient-level data is available, pooled analysis is considered a valid form of meta-analysis. Id. When this analysis was later published by Dr. Marvin Konstam<sup>\*</sup> et al. in Circulation in 2001, the authors correctly referred to it as a pooled analysis. See Appendix J. In this Appendix, we refer to this analysis as a “meta-analysis,” adopting the term Merck used at the time.

<sup>208</sup> The FDA’s classification of clinical trials does not include Phase V and considers all post-marketing trials to be part of Phase IV. Merck divided post-marketing trials between those that the FDA had requested (Phase IV) and those Merck had conducted without FDA solicitation.

<sup>209</sup> See 4/27/00 slide presentation of A. Nies to BSA, MRK-ABC0022825, at 875.

cross-disciplinary (Research, Regulatory, and Statistics) oversight and planning committee, stated that the meta-analysis would be performed “[i]n order to further explore the potential relationship between VIOXX use and the risk of CV disease.”<sup>210</sup> As discussed in Appendix A, MRL scientists had begun in 1999 to draft a data analysis plan for a meta-analysis of adjudicated cardiovascular events, but the project had been put on hold. On May 18, 2000, Merck notified the FDA that it would be conducting and planned to submit a meta-analysis in support of the VIGOR supplemental New Drug Application.<sup>211</sup>

1. The Cardiovascular Meta-Analysis Data Analysis Plan.

On August 14, 2000, MRL statistician Mr. James Bolognese circulated to fellow statisticians Drs. Leonard Oppenheimer and Deborah Shapiro a first draft of a Data Analysis Plan for the cardiovascular meta-analysis.<sup>212</sup> The draft Data Analysis Plan for the meta-analysis called for a combined analysis of all Phase II through V Vioxx and Arcoxia trials of at least four weeks duration. According to a data availability schedule in the draft, Arcoxia data would not be available until the second quarter of 2001, meaning that the first iteration of the meta-analysis would be conducted only with Vioxx data.<sup>213</sup>

The draft Data Analysis Plan listed several “endpoints for analysis,” with the primary

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<sup>210</sup> Minutes of 5/10/00 CDOC meeting, MRK-ADL0080843, at 849.

<sup>211</sup> 5/18/00 letter from D. Erb to K. Midthun\*, MRK-AAF0002836-39.

<sup>212</sup> 8/14/00 email from J. Bolognese to D. Shapiro and L. Oppenheimer attaching draft Data Analysis Plan, MRK-NJ0123054.

<sup>213</sup> 8/15/00 draft Statistical Data Analysis Plan, MRK-NJ0123055, at 60; see also 9/11/00 draft Statistical Data Analysis Plan, MRK-AJA0070486, at 93 (providing timing of planned analyses).

endpoint being “Confirmed Thrombotic Cardiovascular Serious Adverse Experiences”  
(the “confirmed thrombotic endpoint”).<sup>214</sup>

On September 1, 2000, Mr. Bolognese circulated a revised draft to a broader group that incorporated questions and comments from Drs. Reicin, Watson, Shapiro, Oppenheimer and Capizzi.<sup>215</sup> The questions and comments related to, among other things, two important aspects of the Data Analysis Plan: (i) the choice of the primary endpoint for the meta-analysis; and (ii) the manner of grouping the comparator drugs.<sup>216</sup>

With regard to the choice of the primary endpoint, the choice was between two composite endpoints: (i) the “confirmed thrombotic” endpoint mentioned in the August 14 draft and (ii) a composite endpoint known as the Antiplatelet Trialists’ Collaboration (“APTC”) composite cardiovascular endpoint.<sup>217</sup> The APTC composite cardiovascular endpoint consisted of cardiovascular death, myocardial infarction, stroke (both ischemic and hemorrhagic), and death due to unknown cause or due to bleeding.<sup>218</sup>

Dr. Carlo Patrono\*, an expert on antiplatelet agents and a member of the Antiplatelet

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<sup>214</sup> 8/15/00 draft Statistical Data Analysis Plan, MRK-NJ0123055, at 62.

<sup>215</sup> 9/1/00 email from J. Bolognese to A. Reicin attaching draft Statistical Data Analysis Plan, MRK-AFO0007496-97; see also 8/21/00 email from D. Watson to A. Reicin et al., MRK-AAD0046159; 8/18/00 email from J. Bolognese to A. Reicin et al., MRK-AAD0046159.

<sup>216</sup> 9/1/00 draft Statistical Data Analysis Plan, MRK-ACF0008675, at 76-78; see also 8/21/00 draft Statistical Data Analysis Plan, MRK-AAD0046160, at 68 (attached to 8/21/00 email from D. Watson to A. Reicin et al., MRK-AAD0046159).

<sup>217</sup> See 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 33.

<sup>218</sup> 10/5/00 Statistical Data Analysis Plan, MRK-AFO0014726, at 32.

Trialists' Collaboration, had recommended using this composite endpoint.<sup>219</sup> The APTC composite cardiovascular endpoint was well known in the scientific community, and variants of it were widely used in cardiovascular clinical studies.<sup>220</sup>

The need to analyze a mixture of adjudicated and unadjudicated cardiovascular data complicated the decision as to the primary endpoint for the analysis. Dr. Reicin acknowledged that "death due to unknown cause" (which was included in the APTC composite cardiovascular endpoint) had not been adjudicated under the Cardiovascular Adjudication SOP.<sup>221</sup> Dr. Watson stated that, given that fact, he did not "see how you can make this [the APTC composite cardiovascular endpoint] the primary endpoint."<sup>222</sup>

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<sup>219</sup> 10/11/05 transcript of Humeston v. Merck & Co., No. ATL-L-2272-03MT, N.J. Super. Ct., at 3533 (A. Reicin).

<sup>220</sup> See Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ. 1994;308:81-106. For studies using endpoints very similar to the APTC composite cardiovascular endpoint, see, e.g., CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348:1329-39; Hansson\* L, Zanchetti\* A, Carruthers\* SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet. 1998;351:1755-62; Huynh\* T, Theroux\* P, Bogaty\* P, Nasmith J\*, Solymoss\* S. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. Circulation. 2001;103:3069-74. For a later study utilizing the APTC endpoint itself, see Matchaba\* P, Gitton\* X, Krammer\* G, et al. Cardiovascular safety of lumiracoxib: a meta-analysis of all randomized controlled trials  $\geq$  1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. Clin Ther. 2005;27:1196-214.

<sup>221</sup> 9/1/00 email from D. Watson to J. Bolognese and A. Reicin, MRK-AFO0007496. The Cardiovascular Adjudication SOP was later amended to refer all deaths for adjudication. 3/17/04 email from S. Bulluck to D. Watson et al. attaching copy of revised Cardiovascular Adjudication SOP, MRK-AAC0142396, at 98 ("Attached is the revised CV adjudication SOP. . . . The major changes to the SOP primarily document policies that have already been in place (e.g., adjudication of all deaths . . .)").

<sup>222</sup> 9/1/00 email from D. Watson to J. Bolognese and A. Reicin, MRK-AFO0007496.

On the other hand, if the “confirmed thrombotic” endpoint were used, Dr. Watson raised the question of which events from the Phase IIb/III studies, which were not subject to Cardiovascular Adjudication SOP, would be included, asking: “[A]re we talking about all [serious adverse events] which are eligible for adjudication (an intentionally very long list, many of which are not thromboembolic), or a predefined subset of these?”<sup>223</sup>

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<sup>223</sup> 8/21/00 draft “Statistical Data Analysis Plan,” MRK-AAD0046160, at 68 (attached to 8/21/00 email from D. Watson to A. Reicin et al., MRK-AAD0046159).

The following chart lists many of the considerations discussed at MRL regarding the choice of a composite endpoint.<sup>224</sup>

APTC Composite Cardiovascular Endpoint	Merck “Thrombotic” Composite Endpoint
<p><b>Pros:</b></p> <ul style="list-style-type: none"> <li>• Wide acceptance in scientific community; easy to benchmark against other studies</li> <li>• “Hard” endpoint (unadjudicated investigator-reported events likely accurate, lessening problem of combining data from unadjudicated and adjudicated trials)</li> </ul> <p><b>Cons:</b></p> <ul style="list-style-type: none"> <li>• Includes non-thrombotic events such as hemorrhagic strokes, deaths due to gastrointestinal bleeding, and deaths due to unknown causes. Inclusion of non-thrombotic events may dilute power of analysis to detect a thrombotic event difference</li> <li>• Deaths due to unknown causes had not been adjudicated</li> </ul>	<p><b>Pros:</b></p> <ul style="list-style-type: none"> <li>• Includes only thrombotic events, thus directly addressing the issue of whether Vioxx is prothrombotic</li> <li>• Greater total number of events increases power of analysis</li> </ul> <p><b>Cons:</b></p> <ul style="list-style-type: none"> <li>• No pre-existing acceptance in scientific community; cannot compare to other studies</li> <li>• Includes some “soft” endpoints (unadjudicated investigator-reported events have fair chance of being mislabeled, increasing problem of combining data from unadjudicated and adjudicated trials)</li> <li>• Mixes cardiovascular and cerebrovascular thrombotic events with venous thrombotic events (venous events often considered less significant in scientific community)</li> </ul>

<sup>224</sup> See “Issues for the COXIB Cardiovascular Combined Analyses and Planned Interim PreVIGOR ACM ‘meta-analysis,’” MRK-NJ0363443, at 44-45; 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 33.

In the end, the APTC composite cardiovascular endpoint was chosen as the primary endpoint for analysis, with the “confirmed thrombotic” endpoint listed as a secondary endpoint.<sup>225</sup> In order to address the “con” that the APTC composite cardiovascular endpoint included some non-thrombotic events, the Data Analysis Plan stated:

It is recognized that inclusion of bleeds in the primary endpoint could reduce assay sensitivity to detect negative effects of COXIBs since VIOXX has been shown to reduce GI bleeds. . . . Recognizing the potential for reduction in assay sensitivity of the primary endpoint, a secondary endpoint which excludes the bleed events and hemorrhagic strokes will be provided to remove the potential for such reduction.<sup>226</sup>

When Merck submitted the meta-analysis to the FDA in January 2001, the Company advised the FDA that the APTC composite cardiovascular endpoint had been chosen for two reasons: (i) “it is the most commonly accepted endpoint used in trials evaluating antithrombotic agents;” and (ii) the terms it included (death, myocardial infarction, stroke) were “hard endpoints,” meaning that “the correlation is quite high between investigator reported events and events confirmed by the adjudication committee” and therefore use of the APTC composite endpoint “helped to ensure

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<sup>225</sup> 10/5/00 Statistical Data Analysis Plan, MRK-AFO0014726, at 32-33. The secondary “confirmed thrombotic” endpoint was defined to include “terms defined in CV adjudication SOP, Section K, with the exception of hemorrhagic cerebrovascular stroke . . . and non-thromboembolic event[s].” Id. at 33. An additional “secondary endpoint” was myocardial infarction. Id. at 32.

<sup>226</sup> 10/5/00 “Statistical Data Analysis Plan,” MRK-AFO0014726, at 32 (attached to 10/13/00 memorandum from J. Bolognese et al. to N. Braunstein et al., MRK-AFO0014724).

consistency between trials that used adjudicated data and those that used investigator reported data.”<sup>227</sup>

The second major issue discussed among the drafters of the Data Analysis Plan was whether Vioxx and Arcoxia should be compared to all non-selective NSAIDs combined, or separately compared to naproxen and to all non-naproxen NSAIDs.<sup>228</sup> In October 2000, the Clinical Development Oversight Committee approved a version of the Data Analysis Plan that listed comparisons of Vioxx to all non-selective NSAIDs and of Vioxx to placebo as the “primary objectives.”<sup>229</sup> The Data Analysis Plan also stated that “because of the VIGOR findings, [a comparison of] [Vioxx and Arcoxia] vs. naproxen will also be provided for informational purposes.”<sup>230</sup>

2. Evaluation of “Cardiovascular Death” for  
Purposes of APTC Composite Cardiovascular Endpoint.

As noted above, the APTC composite cardiovascular endpoint specified as the primary endpoint for the cardiovascular meta-analysis defined “cardiovascular deaths” to include (among other things) deaths due to unknown causes, a category that had not been adjudicated under the Cardiovascular Adjudication SOP.<sup>231</sup> To address this issue, all

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<sup>227</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 33.

<sup>228</sup> 9/1/00 draft Statistical Data Analysis Plan, MRK-ACF0008675, at 77.

<sup>229</sup> 10/5/00 Statistical Data Analysis Plan, MRK-AFO0014726, at 29 (attached to 10/13/00 memorandum from J. Bolognese et al. to N. Braunstein et al., MRK-AFO0014724).

<sup>230</sup> 10/5/00 Statistical Data Analysis Plan, MRK-AFO0014726, at 34.

<sup>231</sup> The Cardiovascular Adjudication SOP was later amended to refer all deaths for adjudication. 3/17/04 email from S. Bulluck to D. Watson et al., MRK-AAC0142396, at 98.

deaths that had not been adjudicated were reviewed by Dr. Eliav Barr, who was blinded to treatment assignment, to determine whether the deaths met the APTC composite cardiovascular endpoint criteria.<sup>232</sup>

In the course of reviewing these deaths for purposes of inclusion in the APTC composite cardiovascular endpoint, Dr. Barr came across a death in the ADVANTAGE Trial that the investigator had classified as due to “hypertensive heart disease.”<sup>233</sup> Although the ADVANTAGE Trial was conducted under the Cardiovascular Adjudication SOP, this particular event had not been sent for adjudication because the term “hypertensive heart disease” did not appear on the list of terms eligible for adjudication.<sup>234</sup> Upon reviewing the adverse event report for this death, however, Dr. Barr determined that it was most likely a case of “sudden cardiac death” or myocardial infarction which should be included in the APTC composite cardiovascular endpoint in the meta-analysis, and he so informed Dr. Reicin.<sup>235</sup>

Dr. Reicin responded that while the event would be included in the APTC composite cardiovascular endpoint if it were classified as an unknown cause of death or

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<sup>232</sup> Braunstein N, Polis A. Report of specific cardiovascular outcomes of the ADVANTAGE Trial [letter]. *Ann Intern Med.* 2005;143:158-59, at 58; 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 33.

<sup>233</sup> 11/8/00 email from E. Barr to A. Reicin, MRK-NJ0124428; 9/25/00 worksheet with handwritten notes by D. Shapiro, MRK-NJ0070140.

<sup>234</sup> Braunstein N, Polis A. Report of specific cardiovascular outcomes of the ADVANTAGE Trial [letter]. *Ann Intern Med.* 2005;143:158-59, at 59.

<sup>235</sup> 11/8/00 email from E. Barr to A. Reicin, MRK-NJ0124428 (“Common things being common, the clinical scenario is likely to be MI. Certainly, it is not definitive. I just used my clinical judgment. If it is easier to call this an unknown cause of death, I could be persuaded to say that as well.”).

as a myocardial infarction, she thought that the event should be classified as an unknown cause of death.<sup>236</sup> In the end, this event was reclassified as “unknown cause of death,” and was included in the cardiovascular meta-analysis presented to the FDA in January 2001.<sup>237</sup>

3. Results of the Meta-Analysis.

a. October 2000 meta-analysis.

On October 18, 2000, MRL presented a preliminary cardiovascular meta-analysis based on the Data Analysis Plan at a meeting of external cardiovascular consultants

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<sup>236</sup> 11/8/00 email from A. Reicin to E. Barr, MRK-NJ0124427, at 28. Drs. Barr and Reicin traded emails about the classification of this death. Dr. Reicin stated that she was concerned that if it were now classified as a myocardial infarction, it might “raise concerns.” 11/8/00 email correspondence between A. Reicin and E. Barr, MRK-NJ0124427-28, at 27. According to Dr. Reicin, the concern she wanted to avoid raising was the appearance of an inconsistency in the adjudication process. See 10/11/05 transcript of Humeston v. Merck & Co., No. ATL-L-2272-03MT, N.J. Super. Ct., at 3544 (A. Reicin). According to Dr. Reicin, if the event were changed to “myocardial infarction” or “sudden death” – terms that should have triggered adjudication under the Cardiovascular Adjudication SOP – then a reader (or FDA reviewer) might wonder why the event had not been adjudicated or counted among the confirmed thrombotic events. If the event were counted in the confirmed thrombotic events tally, Dr. Reicin stated that there would have to be an explanation that this event was not actually adjudicated. See 10/11/05 transcript of Humeston v. Merck & Co., No. ATL-L-2272-03MT, N.J. Super. Ct., at 3544 (A. Reicin). Dr. Reicin has explained that classifying the event as “unknown cause of death” would avoid these problems while still allowing the event to be included in the APTC composite cardiovascular endpoint, which was the primary endpoint of the meta-analysis. See 11/8/00 email from A. Reicin to E. Barr, MRK-NJ0124427 at 28.

<sup>237</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 44; Braunstein N, Polis A. Report of specific cardiovascular outcomes of the ADVANTAGE Trial [letter]. Ann Intern Med. 2005; 143:158-59, at 59. The event was also included as an “unknown cause of death” in the Safety Update Report for the ADVANTAGE Trial that Merck submitted to the FDA in 2001, but the underlying case report was also provided. Reviewing the case report included in the Safety Update Report, FDA medical officer Dr. Maria Lourdes Villalba\* wrote: “In the opinion of this medical reviewer, the cause of death for this patient was sudden death, which would in fact meet criteria for cardiovascular thrombotic event.” 11/28/01 FDA Medical Officer Review by M.L. Villalba\*, MRK-AFV0341732, at 52. The event was included in the tally of APTC composite cardiovascular events, but not in the tally of confirmed thrombotic events, presented in the article about the ADVANTAGE Trial published in the Annals of Internal Medicine in 2003. Lisse\* JR, Perlman\* M, Johansson\* G, et al. Gastrointestinal tolerability and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis. Ann Intern Med. 2003;139:539-546. The ADVANTAGE Trial and this article are discussed in Appendix I.

(discussed below).<sup>238</sup> As laid out in the Data Analysis Plan, the preliminary meta-analysis pooled data from all Phase II-V studies of at least four weeks duration, except those involving healthy volunteers.<sup>239</sup> The meta-analysis included cardiovascular data from studies that were completed and unblinded as of September 2000, plus unblinded data collected through September 15, 2000 in the Alzheimer's trials, which were still ongoing.<sup>240</sup> For the primary APTC composite cardiovascular endpoint, the risk of experiencing an APTC event on Vioxx was numerically lower than on placebo (relative risk 0.85; 95% confidence interval, 0.52 to 1.39), and numerically greater than on the combined group of all comparator NSAIDs, including naproxen (relative risk 1.44; 95% confidence interval, 0.98 to 2.13).<sup>241</sup> In both cases, the 95% confidence interval crossed 1.0 –the point at which Vioxx and the comparator would be equal – which means that neither comparison showed a statistically significant difference.

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<sup>238</sup> 10/18/00 slide presentation by D. Shapiro, "Vioxx Preliminary Cardiovascular Meta-Analysis," MRK-NJ0070364-416.

<sup>239</sup> 10/5/00 Statistical Data Analysis Plan, MRK-AFO0014726, at 29 (attached to 10/13/00 memorandum from J. Bolognese et al. to N. Braunstein et al., MRK-AFO0014724); 10/18/00 slide presentation by D. Shapiro, "Vioxx Preliminary Cardiovascular Meta-Analysis," MRK-NJ0070364, at 67.

<sup>240</sup> 10/18/00 slide presentation by D. Shapiro, "Vioxx Preliminary Cardiovascular Meta-Analysis," MRK-NJ0070364, at 67; see also, 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 31. As discussed in Appendix E, cardiovascular data from the Alzheimer's trials had been partially unblinded in March 2000. In September 2000, cardiovascular data from these trials were fully unblinded so that they could be incorporated into the meta-analysis. See 9/18/00 memorandum from F. Liu to L. Coffey, MRK-NJ0123681, at 81. Efficacy data (showing prevention or retardation of Alzheimer's disease) was not unblinded. See 9/12/00 memorandum from D. Shapiro to S. Reines, D. Erb and J. Arena, MRK-AAX0001301, at 01.

<sup>241</sup> 10/18/00 slide presentation by D. Shapiro, "Vioxx Preliminary Cardiovascular Meta-Analysis," MRK-NJ0070364, at 74, 82.

MRL's October 18, 2000 presentation also included pooled data of myocardial infarctions alone. The risk of experiencing a myocardial infarction on Vioxx was numerically, but not statistically significantly, greater than on placebo (relative risk 1.27; 95% confidence interval, 0.62 to 2.57) and significantly greater than on the combined group of all comparator NSAIDs, including naproxen (relative risk 2.02; 95% confidence interval, 1.14 to 3.55).<sup>242</sup> The presentation noted that with regard to the comparison of myocardial infarctions between Vioxx and all comparator NSAIDs, a statistical test for "heterogeneity" showed that the studies included in this grouping were too dissimilar to properly combine.<sup>243</sup>

b. January 2001 meta-analysis.

A few months later, on January 8, 2001, Merck submitted to the FDA a version of this meta-analysis using essentially the same dataset.<sup>244</sup> As noted above, the APTC composite cardiovascular endpoint was chosen as the primary endpoint for this

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<sup>242</sup> 10/18/00 slide presentation by D. Shapiro, "Vioxx Preliminary Cardiovascular Meta-Analysis," MRK-NJ0070364, at 90, 95.

<sup>243</sup> 10/18/00 slide presentation by D. Shapiro, "Vioxx Preliminary Cardiovascular Meta-Analysis," MRK-NJ0070364, at 96.

<sup>244</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426-86. The dataset used for the meta-analysis submitted to the FDA on January 8, 2001 included the same number of patient years at risk as the meta-analysis presented at the consultants' meeting on October 18, 2000, but included 1 additional event in the placebo comparison (in the placebo group) and 2 additional events in the comparison of Vioxx to the non-selective NSAID comparators (1 in the Vioxx group and 1 in the NSAID group). Compare 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 69-70, with 10/18/00 slide presentation by D. Shapiro, "Vioxx Preliminary Cardiovascular Meta-Analysis," MRK-NJ0070364, at 74. Appendix I discusses the submission of this meta-analysis to the FDA.

analysis.<sup>245</sup> Early drafts of the meta-analysis report being prepared for submission to the FDA included a section presenting the results of analyses based on myocardial infarctions alone.<sup>246</sup> The report submitted to the FDA on January 8, 2001, did not include this section, nor did it include analyses based on other endpoints, such as Merck's "confirmed thrombotic" composite endpoint. The submission did, however, break out the APTC composite cardiovascular events within each comparison into specific types of events, including myocardial infarctions.<sup>247</sup>

The meta-analysis submitted to the FDA compared Vioxx to naproxen separately from other non-selective NSAIDs.<sup>248</sup> The meta-analysis showed that patients on Vioxx had a significantly increased risk of APTC composite cardiovascular events compared to patients on naproxen (relative risk 1.69; 95% confidence interval, 1.07 to 2.69), but a similar (and numerically decreased) risk of APTC events compared to patients on non-naproxen NSAIDs (relative risk 0.79; 95% confidence interval, 0.40 to 1.55) as well as those on placebo (relative risk 0.84; 95% confidence interval, 0.51 to 1.38).<sup>249</sup>

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<sup>245</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 33.

<sup>246</sup> 11/7/00 draft "Cardiovascular Meta-Analysis," MRK-AAB0007792, at 793, 796, 800, 826-828, 843-846.

<sup>247</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 44, 48, 53, 58, 62.

<sup>248</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 30, 39. Several of the external consultants to whom a version of the meta-analysis was presented on 10/18/00 recommended that MRL analyze naproxen separately from other non-selective NSAIDs. 10/18/00 handwritten notes of D. Shapiro, MRK-NJ0070142, at 43; 10/18/00 handwritten notes of B. Gertz, MRK-NJ0152895, at 98.

<sup>249</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, Figure 1 at 38. The meta-analysis also showed that patients on Vioxx had a similar (but numerically decreased) risk of APTC

Merck noted that when Vioxx was compared against all comparators combined – i.e., all non-selective NSAIDs plus placebo – the analysis failed the test for homogeneity, meaning that the pooled groups of studies were too dissimilar to combine properly.<sup>250</sup> The report stated that this was “mainly due to heterogeneous results from studies with naproxen as the comparative agent versus studies with placebo or other NSAIDs as the comparative agent.”<sup>251</sup>

The results of the meta-analysis from Merck’s FDA submission are summarized in the figure below.<sup>252</sup>

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events compared to patients on non-naproxen NSAIDs or placebo combined (relative risk 0.76; 95% confidence interval, 0.50 to 1.16).

The meta-analysis of myocardial infarctions, which was not included in the FDA submission, showed that patients on Vioxx had a significantly increased risk of myocardial infarctions compared to patients on naproxen (relative risk 4.30; 95% confidence interval, 1.79 to 10.31), a similar (but numerically decreased) risk compared to both patients on non-naproxen NSAIDs (relative risk 0.67; 95% confidence interval, 0.30 to 1.54) and patients on non-naproxen NSAIDs or placebo combined (relative risk 0.98; 95% confidence interval, 0.55 to 1.73), and a similar (but numerically increased) risk of myocardial infarctions compared to patients on placebo (relative risk 1.39; 95% confidence interval, 0.67 to 2.97). 11/7/00 draft “Cardiovascular Meta-Analysis,” MRK-AAB0007792, at 843-46.

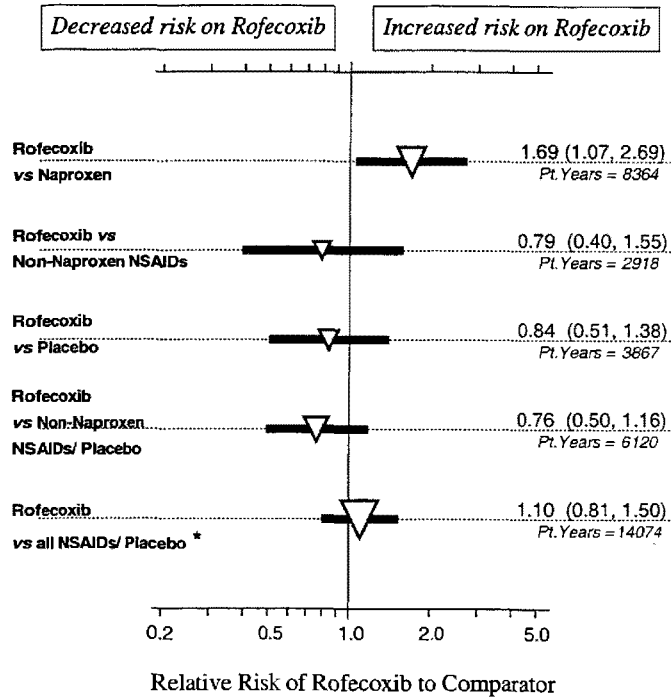
<sup>250</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 37, 59. This same lack of homogeneity was present in the meta-analysis of myocardial infarctions for the comparison of Vioxx against all comparators combined. While the validity of this comparison was limited by the heterogeneity of the included data blocks, the meta-analysis of myocardial infarctions showed that patients on Vioxx had a significantly higher risk of myocardial infarctions compared to patients on all comparators combined (relative risk 1.66; 95% confidence interval, 1.05 to 2.63). 11/7/00 draft “Cardiovascular Meta-Analysis,” MRK-AAB0007792, at 826, 846.

<sup>251</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 37.

<sup>252</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, Figure 1 at 38. The footnote to this figure refers to the “test for heterogeneity,” but in other places in Merck’s report to the FDA, this test is referred to as the “test for homogeneity.”

Figure 1

Relative Risk of an APTC with 95% CI



\* failed the test for heterogeneity

The January 2001 meta-analysis broke the results down further by patient population, specifically rheumatoid arthritis, osteoarthritis, and other (Alzheimer's and lower back pain). The results of this breakdown are shown in Table 11 below:<sup>253</sup>

<sup>253</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, Table 2 at 39.

Table 11

**Meta-Analysis of APTC Endpoint  
Rofecoxib vs Comparator Agents**

Indication for Treatment	Rofecoxib		Comparator		Relative risk (95% CI) <sup>1</sup>
	N	Cases/PYR <sup>2</sup> (Rate <sup>2</sup> )	N	Cases/PYR <sup>2</sup> (Rate <sup>2</sup> )	
<b>Rofecoxib vs naproxen</b>					
RA	6057	46/ 3947 ( 1.17)	4859	20/ 3078 ( 0.65)	1.74 (1.02, 2.96)
OA	3026	11/ 675 ( 1.63)	3011	7/ 665 ( 1.05)	1.55 (0.60, 4.00)
Alz/LBP	0	-	0	-	-
<b>Total</b>	<b>9083</b>	<b>57/ 4622 ( 1.23)</b>	<b>7870</b>	<b>27/ 3742 ( 0.72)</b>	<b>1.69 (1.07, 2.69)</b>
<b>Rofecoxib vs other nonselective NSAIDs</b>					
RA	0	-	0	-	-
OA	4549	21/ 1934 ( 1.09)	2755	14/ 984 ( 1.42)	0.79 (0.40, 1.55)
Alz/LBP	0	-	0	-	-
<b>Total</b>	<b>4549</b>	<b>21/ 1934 ( 1.09)</b>	<b>2755</b>	<b>14/ 984 ( 1.42)</b>	<b>0.79 (0.40, 1.55)</b>
<b>Rofecoxib vs placebo</b>					
RA	1622	3/ 337 ( 0.89)	989	1/ 201 ( 0.50)	1.78 (0.14, 93.70)
OA	3165	12/ 655 ( 1.83)	1215	3/ 232 ( 1.30)	1.53 (0.43, 5.44)
Alz/LBP	1503	18/ 1197 ( 1.50)	1278	28/ 1246 ( 2.25)	0.68 (0.37, 1.23)
<b>Total</b>	<b>6290</b>	<b>33/ 2189 ( 1.51)</b>	<b>3482</b>	<b>32/ 1678 ( 1.91)</b>	<b>0.84 (0.51, 1.38)</b>
<b>Rofecoxib vs other nonselective NSAIDs/placebo</b>					
RA	1622	3/ 337 ( 0.89)	989	1/ 201 ( 0.50)	1.78 (0.14, 93.70)
OA	4550	21/ 1938 ( 1.08)	3750	17/ 1201 ( 1.42)	0.81 (0.42, 1.53)
Alz/LBP	1503	18/ 1197 ( 1.50)	1278	28/ 1246 ( 2.25)	0.68 (0.37, 1.23)
<b>Total</b>	<b>7675</b>	<b>42/ 3472 ( 1.21)</b>	<b>6017</b>	<b>46/ 2648 ( 1.74)</b>	<b>0.76 (0.50, 1.16)</b>
<b>Rofecoxib vs any nonselective NSAIDs/placebo</b>					
RA	6057	46/ 3947 ( 1.17)	5174	21/ 3204 ( 0.66)	1.72 (1.02, 2.90)
OA	7576	32/ 2613 ( 1.22)	6761	24/ 1866 ( 1.29)	1.00 (0.59, 1.71)
Alz/LBP	1503	18/ 1197 ( 1.50)	1278	28/ 1246 ( 2.25)	0.68 (0.37, 1.23)
<b>Total</b>	<b>15136</b>	<b>96/ 7758 ( 1.24)</b>	<b>13213</b>	<b>73/ 6316 ( 1.16)</b>	<b>1.10 (0.81, 1.50)<sup>4</sup></b>

<sup>1</sup>Patient-years at risk  
<sup>2</sup>Per 100 PYR  
<sup>3</sup>Relative risk of rofecoxib with respect to comparator from Cox model stratified by indication for totals and unstratified elsewhere when number of cases is at least 11, otherwise relative risk is ratio of rates.  
<sup>4</sup>This estimate is provided for information only since it represents pooling of heterogenous cohorts.

As shown in Table 11, the relative risk of Vioxx versus placebo was 0.68 (95% confidence interval, 0.37 to 1.23) in the Alzheimer's and lower back pain patients, but 1.78 (95% confidence interval, 0.14 to 93.70) in rheumatoid arthritis patients and 1.53 (95% confidence interval, 0.43 to 5.44) in osteoarthritis patients. Due to the small numbers of events and patient-years in the osteoarthritis and rheumatoid arthritis populations for the placebo comparison, however, the confidence intervals for these relative risks were extremely wide.<sup>254</sup>

<sup>254</sup> The relative risks, confidence intervals, and numbers of events for these comparisons are shown in the above table.

This breakdown revealed that results from the Alzheimer's studies – which favored Vioxx and provided by far the largest pool of placebo-controlled data – were driving the placebo comparison. When all the placebo-controlled data were pooled together, the overall result was a numerical (but not statistically significant) decrease in risk on Vioxx versus placebo (relative risk 0.84; 95% confidence interval, 0.51 to 1.38).

With regard to the comparison with naproxen, the relative risks for Vioxx versus naproxen were relatively consistent in rheumatoid arthritis patients (1.74; 95% confidence interval, 1.02 to 2.96) and osteoarthritis patients (1.55; 95% confidence interval, 0.60 to 4.00) – the only patient populations in the pooled trials using naproxen.<sup>255</sup>

The conclusion that MRL drew from this meta-analysis was that the risk of cardiovascular events was “similar in patients taking rofecoxib, placebo, or the nonselective NSAIDs ibuprofen, diclofenac, and nabumetone.”<sup>256</sup> MRL presented the results of this meta-analysis and repeated the above-quoted conclusion in an abstract presented at the European League Against Rheumatism conference in June 2001.<sup>257</sup> MRL submitted updates of this meta-analysis to the FDA as data from more studies

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<sup>255</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 39.

<sup>256</sup> 1/8/01 Interim Cardiovascular Meta-Analysis, MRK-01420019426, at 28.

<sup>257</sup> Shapiro DR, Barr E, Reicin AS. Cardiovascular safety profile of rofecoxib: a meta-analysis [abstract OP0133]. Ann Rheum Dis. 2001;60(Supp. 1, CD), MRK-ADY0002236; see also Shapiro E, Barr E, Reicin AS. Cardiovascular safety profile of rofecoxib: a meta-analysis [abstract 1916]. Arthritis Rheum. 2001;44(9, Supp.):S372-S372, MRK-ADY0002835.

became available.<sup>258</sup> Although the Data Analysis Plan specified that Vioxx and Arcoxia studies would be combined into one meta-analysis, as well as analyzed on their own, no combined meta-analysis was ever performed.<sup>259</sup>

G. Fall 2000 Consultants' Meetings – October 18, 30, and November 10.

In October and November 2000, MRL convened three meetings with external consultants to discuss the results of the VIGOR Trial. MRL scientists presented the complete cardiovascular data from the VIGOR Trial (including post-February 10 adjudicated cardiovascular events) at these meetings, along with the aspirin-indicated subgroup analysis and the meta-analysis of APTC events from all Vioxx trials. The purpose of these meetings was to get input on the interpretation of the cardiovascular data and to help MRL prepare for the upcoming FDA Arthritis Advisory Committee meeting regarding the post-VIGOR supplemental New Drug Application for revisions to the Vioxx label (discussed in Appendix I).

1. October 18, 2000 Cardiology Consultants' Meeting.

The first of these meetings, which involved a group of expert cardiologists, was held in New York City on October 18, 2000.<sup>260</sup> The external cardiology consultants were Dr. Marvin Konstam\* of Tufts University, Dr. Rory Collins\* of Oxford University,

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<sup>258</sup> These analyses are discussed in Appendix O.

<sup>259</sup> 10/5/00 Statistical Data Analysis Plan, MRK-AFO0014726, at 30 (attached to 10/13/00 memorandum from J. Bolognese et al. to N. Braunstein et al., MRK-AFO0014724).

<sup>260</sup> 10/18/00 VIGOR Cardiology Consultants' Meeting Participant List, MRK-NJ0272583.

Dr. Robert Califf\* of Duke University, and Dr. Myron Weisfeldt\* of Johns Hopkins University.<sup>261</sup> Numerous MRL scientists attended.<sup>262</sup>

Prior to the meeting, Merck sent the consultants a background package with a description of the Vioxx development program, the gastrointestinal results of the VIGOR Trial and prior Vioxx studies, and the cardiovascular results of the VIGOR Trial and of other completed and ongoing studies.<sup>263</sup> The consultants also received a list of questions for discussion.<sup>264</sup> At the meeting itself, Dr. Reicin presented an overview of the Vioxx development program and the VIGOR Trial results.<sup>265</sup> Dr. Shapiro then presented a “Preliminary Cardiovascular Meta-Analysis,” as described above.<sup>266</sup> Finally, there was a discussion of the questions the consultants had been sent.

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<sup>261</sup> Dr. Konstam\* was also Chief of Cardiology at the New England Medical Center. Dr. Weisfeldt\* was Chairman of the Department of Medicine at Johns Hopkins School of Medicine. Dr. Califf\* was Director of the Duke Clinical Research Institute. Dr. Collins\* was British Heart Foundation Professor of Medicine & Epidemiology at the University of Oxford and co-director, with Sir Richard Peto\*, of the Clinical Trial Services Unit.

<sup>262</sup> 10/18/00 VIGOR Cardiology Consultants’ Meeting Participant List, MRK-NJ0272583.

<sup>263</sup> 10/13/00 Consultants Background Package, MRK-AFT0011242 (attached to 10/13/00 email from L. Valdez to B. Gertz et al., MRK-AFT0011238).

<sup>264</sup> 10/13/00 Questions to the Cardiology Consultants, MRK-AFT0011240 (attached to 10/13/00 email from L. Valdez to B. Gertz et al., MRK-AFT0011238).

<sup>265</sup> 10/13/00 draft Agenda, “Rofecoxib (VIOXX) GI Outcomes Research (VIGOR™), Consultants MEETING,” MRK-AFT0011239 (attached to 10/13/00 email from L. Valdez to B. Gertz et al., MRK-AFT0011238).

<sup>266</sup> 10/18/00 slide presentation from D. Shapiro, “VIOXX Preliminary Cardiovascular Meta-Analysis,” MRK-NJ0070364-416.

According to notes taken by Drs. Shapiro and Gertz, consultants asked questions about Vioxx's effects on blood pressure, hypertension and edema.<sup>267</sup> They noted that although both Vioxx and non-selective NSAIDs affect blood pressure, there was a greater increase in blood pressure in the Vioxx 50 mg arm than in the naproxen arm in the VIGOR Trial. Dr. Collins\* noted that blood pressure reductions of similar magnitude to the blood pressure increases seen in the Vioxx arm of the VIGOR Trial had been shown to reduce cardiovascular events, but only over several years, a time span much longer than the VIGOR Trial.<sup>268</sup> In the end, Dr. Collins\* did not believe that blood pressure effects could explain the VIGOR Trial cardiovascular results, but felt that attention should be paid to this issue in the long term.<sup>269</sup>

Asked their reactions to the aspirin-indicated subgroup analysis (described above in Section A of this Appendix), all consultants felt that there was not a meaningfully different relative risk for cardiovascular events between the aspirin-indicated and non-indicated subgroups.<sup>270</sup> According to Dr. Gertz's notes, Dr. Collins\* stated that it was

misleading to provide estimate of effects in ASA-indicated group as there is heterogeneity of effect, therefore he feels the best estimate of effect is the overall estimate for all groups and can't say that the absence of significant effect in

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<sup>267</sup> 10/18/00 handwritten notes of D. Shapiro, MRK-NJ0070142; 10/18/00 handwritten notes of B. Gertz, MRK-NJ0152895.

<sup>268</sup> 10/18/00 handwritten notes of D. Shapiro, MRK-NJ0070142, at 42-44.

<sup>269</sup> 10/18/00 handwritten notes of D. Shapiro, MRK-NJ0070142, at 44.

<sup>270</sup> 10/18/00 handwritten notes of B. Gertz, MRK-NJ0152895, at 96; see also 10/18/00 handwritten notes of D. Shapiro, MRK-NJ0070142; see also 1/29/01 email from L. Jordan to J. Weiner et al., MRK-ADI0008060, at 60; 12/16/00 email from N. Braunstein to D. Greene, MRK-ACR0011965.

the ASA-not indicated group should imply a reduced  
relative risk in the ASA-non indicated group.<sup>271</sup>

Dr. Collins\* had made nearly identical comments to Dr. Guess in June 2000 after  
reviewing cardiovascular data from the VIGOR Trial and other Vioxx trials.<sup>272</sup>

Based on the VIGOR Trial cardiovascular data and the results of the Vioxx  
cardiovascular meta-analysis of the APTC combined endpoint, the consultants all stated  
that while naproxen might have conferred cardioprotection in the VIGOR Trial, it was  
also possible that the VIGOR Trial cardiovascular results were partially due to a  
prothrombotic effect of Vioxx, perhaps limited to the rheumatoid arthritis patient  
population.<sup>273</sup>

2. October 30, 2000 “Prostaglandins Group” Consultants’ Meeting.

The second consultants’ meeting, involving an international group of experts in  
the field of prostanoids (e.g., prostacyclin and thromboxane), was held in Philadelphia on  
October 30, 2000.<sup>274</sup> The consultants were Dr. Garret FitzGerald\* of the University of  
Pennsylvania, Dr. Desmond Fitzgerald\* of the Royal College of Surgeons in Dublin,

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<sup>271</sup> 10/18/00 handwritten notes of B. Gertz, MRK-NJ0152895, at 96; see also 10/18/00 handwritten notes  
of D. Shapiro, MRK-NJ0070142.

<sup>272</sup> 6/28/00 letter from R. Collins\* to H. Guess, MRK-ACF0000564-66.

<sup>273</sup> 10/18/00 handwritten notes of B. Gertz, MRK-NJ0152895, at 97-102; see also 10/18/00 handwritten  
notes of D. Shapiro, MRK-NJ0070142. According to Dr. Shapiro’s and Dr. Gertz’s notes of the  
meeting, Drs. Califf\* and Collins\* assigned rough percentages to the potential explanations.  
Dr. Shapiro’s notes stated: “Answer not known but 50% protective naprx, 35% chance, 15% harm.”  
10/18/00 handwritten notes of D. Shapiro, MRK-NJ0070142, at 43. Dr. Gertz’s notes reflected  
similar percentages. 10/18/00 handwritten notes of B. Gertz, MRK-NJ0152895, at 900.

<sup>274</sup> 10/30/00 VIGOR Consultants’ Meeting – Prostaglandins Group, Participant List,  
MRK-YAD0000004.

Ireland, Dr. John Oates\* of Vanderbilt University, and Dr. Carlo Patrono\* of the Institute for Excellence on Aging, Chieti, Italy. Numerous MRL scientists attended this meeting as well.<sup>275</sup>

MRL scientists had previously spoken to several of these experts regarding cardiovascular data from the VIGOR Trial. As described in Appendix E, MRL scientists had solicited input from Drs. Oates\* and FitzGerald\* in March 2000 when they were initially interpreting cardiovascular data from the VIGOR Trial. In addition, Dr. Patrono\* had shared his thoughts on the VIGOR Trial results with Dr. Martino Laurenzi, an Italian Merck representative, in March 2000. According to Dr. Laurenzi, Dr. Patrono\* “[did] not think that the CV effect that we observed [in the VIGOR Trial] can be attributed to naproxen for a couple of good reasons.”<sup>276</sup> First, according to Dr. Laurenzi, Dr. Patrono\* felt that there was a “weak pharmacological basis and no epidemiological evidence . . . for CV protection associated with conventional NSAIDs” such as naproxen.”<sup>277</sup> Second, according to Dr. Laurenzi, Dr. Patrono\* felt that “the magnitude of the [cardioprotective] effect [seen in the VIGOR Trial] would not be plausible even if the comparator had been aspirin itself.”<sup>278</sup> Dr. Patrono\* did not, however, think that the FitzGerald prostacyclin

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<sup>275</sup> 10/30/00 VIGOR Consultants’ Meeting – Prostaglandins Group, Participant List, MRK-YAD0000004.

<sup>276</sup> 3/28/00 email from M. Laurenzi to B. Daniels et al., MRK-ABD0001992.

<sup>277</sup> 3/28/00 email from M. Laurenzi to B. Daniels et al., MRK-ABD0001992.

<sup>278</sup> 3/28/00 email from M. Laurenzi to B. Daniels et al., MRK-ABD0001992.

hypothesis explained the VIGOR Trial cardiovascular results. Instead, Dr. Patrono\* concluded that “what we saw in VIGOR is to be attributed to a large extent to chance.”<sup>279</sup>

Dr. Patrono\* reiterated this opinion at the October 30, 2000 consultants’ meeting, describing the VIGOR Trial cardiovascular results as an “uneven distribution of events in a very low risk patient population followed for a short period of time.”<sup>280</sup> As recorded in two sets of notes from the meeting, Dr. Patrono\*, a co-author of the seminal Antiplatelet Trialists’ Collaboration meta-analysis of the cardioprotective effects of aspirin and other antiplatelet drugs, was not willing to take the “leap of faith” that he felt both the naproxen cardioprotection hypothesis and the FitzGerald prostacyclin hypothesis required.<sup>281</sup>

According to notes of the meeting, the other consultants agreed that the number of cardiovascular events was low and that chance likely played a role in the results, but they did not believe that chance was the sole explanation. Dr. Desmond Fitzgerald\*, for example, stated that a cardioprotective effect of naproxen was a plausible explanation because he had performed a study showing that naproxen had similar antiplatelet effects

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<sup>279</sup> 3/28/00 email from M. Laurenzi to B. Daniels et al., MRK-ABD0001992.

<sup>280</sup> 10/30/00 notes, “Clinical Pharmacology/ Prostaglandin Consultant Meeting,” MRK-ACF0009163, at 65.

<sup>281</sup> 10/30/00 notes, “Clinical Pharmacology/ Prostaglandin Consultant Meeting,” MRK-ACF0009163, at 65; see also 10/30/00 notes “VIGOR Consultants’ Meeting,” MRK-NJ0085505, at 05. Dr. Patrono\* later changed his view on naproxen cardioprotection and agreed that naproxen could, if regularly dosed, confer cardioprotection and may have done so in the VIGOR Trial. See Capone\* ML, Tacconelli\* S, Sciulli\* MG, Grana\* M, Ricciotti\* E, Minuz\* P, Di Gregorio\* P, Merciaro\* G, Patrono\* C, Patrignani\* P. Clinical pharmacology of platelet, monocyte, and vascular cyclooxygenase inhibition by naproxen and low-dose aspirin in healthy subjects. *Circulation*. 2004;109:1468-71, at 68, 70.

to aspirin when dosed regularly. He was not willing, however, to rule out a prothrombotic effect.<sup>282</sup>

Similarly, Dr. Garret FitzGerald\*, the originator of the FitzGerald prostacyclin hypothesis, and Dr. Oates\* felt that the data were compatible with either explanation – naproxen cardioprotection or the FitzGerald prostacyclin hypothesis – or both.<sup>283</sup>

Dr. Oates\* stated that 50 mg of Vioxx is “not a safe dose” and felt that “no patients should see 50 mg in a clinical trial,” but he also stated that the meta-analysis data for Vioxx against placebo mitigated against the possibility that Vioxx was prothrombotic.<sup>284</sup>

Dr. Patrono\* argued that the meta-analysis only confirmed that there was little definitive evidence one way or the other.<sup>285</sup> As with the prior group of consultants, these consultants were concerned about the increases in blood pressure in the VIGOR Trial and requested more information.<sup>286</sup>

### 3. November 10, 2000 Consultants’ Meeting.

The third consultants’ meeting was held in Short Hills, New Jersey on November 10, 2000 and involved a mixed group of experts, including rheumatologists, statisticians

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<sup>282</sup> 10/30/00 notes, “VIGOR Consultants’ Meeting,” MRK-NJ0085505, at 05.

<sup>283</sup> 10/30/00 notes, “Clinical Pharmacology/ Prostaglandin Consultant Meeting,” MRK-ACF0009163, at 65-66; 10/30/00 notes, “VIGOR Consultants’ Meeting,” MRK-NJ0085505, at 05.

<sup>284</sup> 10/30/00 notes, “Clinical Pharmacology/ Prostaglandin Consultant Meeting,” MRK-ACF0009163, at 65.

<sup>285</sup> 10/30/00 notes, “Clinical Pharmacology/ Prostaglandin Consultant Meeting,” MRK-ACF0009163, at 66.

<sup>286</sup> 10/30/00 notes, “Clinical Pharmacology/ Prostaglandin Consultant Meeting,” MRK-ACF0009163, at 63-64.

and nephrologists.<sup>287</sup> The consultants were: Dr. Claire Bombardier\* of the University of Toronto, Dr. Craig Brater\* of the University of Indiana, Dr. Leslie Crofford\* of the University of Michigan, Dr. Barry Davis\* of the University of Texas, Dr. James O'Dell\* of the University of Nebraska, Dr. Harold Paulus\* of the University of California at Los Angeles, Dr. Alexander Walker\* of the Harvard School of Public Health, Dr. Michael Weinblatt\* of Harvard Medical School, and Dr. Scott Zeger\* of Johns Hopkins University. No substantive notes of this meeting have been located.

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<sup>287</sup> 11/10/00 VIGOR Consultants' Meeting, Attendee List, MRK-AAX0001173.