

APPENDIX L

COMBINATION THERAPIES CONSIDERED.

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APPENDIX L

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A. Overview.

MRL scientists and external consultants recognized from as early as 1998 the competitive advantage to be gained from combining Vioxx with an antiplatelet agent that would provide high cardiovascular risk patients with cardiovascular prophylaxis similar to that provided by aspirin without the gastrointestinal toxicity of aspirin. In addition, MRL scientists and external consultants recognized that if Vioxx suppressed prostacyclin in the vasculature, a combination of Vioxx with certain antiplatelet agents would provide cardioprotection to those high cardiovascular risk patients who had a baseline excess of thromboxane compared to prostacyclin (such as rheumatoid arthritis patients) that might be exacerbated by Vioxx taken alone. Accordingly, several times between 1998 and the withdrawal of Vioxx from the market in 2004, external consultants proposed and/or the Company considered combination therapies that would add antiplatelet agents to Vioxx or, in one instance, provide gastrointestinal protection to support concomitant use of low-dose aspirin with Vioxx.

Section B of this Appendix introduces the various combination therapies proposed to and/or considered by Merck. Sections C through E set forth a more detailed chronological discussion of MRL's evaluation of these potential combination therapies during three time periods: (i) 1998–1999, before the VIGOR Trial data were unblinded; (ii) 2000, immediately after the VIGOR Trial unblinding; and (iii) 2001–2004. Sections

C through E also describe the rationale for and efforts made to develop each such combination.

B. Combination Therapies Considered.

Between 1998 and 2004, external consultants proposed and/or the Company considered five different types of agents to use in combination with Vioxx: (i) low-dose aspirin; (ii) a thromboxane receptor antagonist or thromboxane synthesis inhibitor; (iii) an ADP receptor antagonist; (iv) a GpIIb/IIIa receptor antagonist; and (v) a compound that releases nitric oxide. The mechanisms of these agents are described below.

1. Low-Dose Aspirin.

External consultants proposed that MRL combine Vioxx with either single-dose or slow-release low-dose aspirin in a single drug. As discussed in Appendix E, low-dose aspirin provides cardiovascular protection by inhibiting platelet Cox-1 – and therefore the production of platelet-derived thromboxane – irreversibly and nearly completely throughout the 7- to 10-day life of a platelet.¹ Even at low doses, however, aspirin is associated with increased gastrointestinal toxicity.² A form of low-dose aspirin that released aspirin at a rate of about 3 mg per hour into the intestinal tract (slow-release aspirin) was developed because, over time, it completely inhibited platelet Cox-1 with

¹ Patrono* C. Aspirin as an antiplatelet drug. *N Eng J Med.* 1994;330:1287-1294; see also Patrono* C, Collier* B, Dalen* JE, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects. *CHEST.* 1998;114:470S-488S; 3/23/00 preliminary VIGOR report to FDA, MRK-ABK0460838, at 60.

² 11/21/96 memorandum from T. Musliner to B. Friedman (later: B. Seidenberg) et al., MRK-AAX0002413, at 14-15.

only a modest reduction in systemic prostacyclin.³ Slow-release aspirin therefore theoretically provided equivalent cardioprotection to traditional low-dose aspirin, without the harmful gastrointestinal side effects.

2. Thromboxane Receptor Antagonist or
Thromboxane Synthase Inhibitor.

In April and May 2000, the Company seriously considered combining Vioxx with a thromboxane receptor antagonist or thromboxane synthase inhibitor. These types of drugs had been developed in the 1980s as alternative antiplatelet agents to aspirin because they theoretically provided cardioprotection without harmful gastrointestinal effects.

A thromboxane receptor antagonist functions by blocking the binding of thromboxane to its receptor sites, thereby decreasing platelet activation and aggregation. A thromboxane synthase inhibitor, by suppressing the formation of thromboxane, decreases the total amount of thromboxane available to bind to its receptor sites, also limiting – by a different mechanism – platelet activation and aggregation.⁴ Thromboxane receptor antagonists or synthase inhibitors provided a means by which to block thromboxane's role in platelet aggregation without (i) suppressing Cox-1, which was

³ 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 02; see also 10/23/97 Flamel press release, "Flamel Technologies S.A. Announces Initial Clinical Results on its Asacard Cardiovascular Aspirin," <http://www.flamel-technologies.fr/pressReleases/19971023.shtml>.

⁴ Schafer* AI, Aspirin and antiplatelet agents in cardiovascular disease. In: Smith* TW, ed. Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease. 1st ed. Philadelphia, PA: W.B. Saunders Company; 1996:427-442, at 435; Gresele* P, Deckmyn* H, Nenci* GG, Vermynen* J. Thromboxane synthase inhibitors, thromboxane receptor antagonists and dual blockers in thrombotic disorders. Trends Pharmacol Sci. 1991;12:158-163.

known to provide gastroprotection or (ii) decreasing prostacyclin, which was known to be a powerful platelet inhibitor and vasodilator.⁵

The clinical efficacy of these drugs to inhibit platelet aggregation remained speculative. Initial clinical trials with thromboxane synthase inhibitors had produced disappointing results, and trials involving thromboxane receptor antagonists, while promising, had not fully demonstrated efficacy equivalent to that of aspirin.⁶

3. ADP Receptor Antagonist (Clopidogrel).

Another antiplatelet therapy proposed for combination with Vioxx was an Adenosine diphosphate receptor (“ADP”) antagonist. Like thromboxane, when ADP binds to its receptor sites, it activates platelets.⁷ An ADP receptor antagonist therefore functions in a similar manner to a thromboxane receptor antagonist, blocking ADP from binding to its receptor site and thereby decreasing platelet activation and aggregation.⁸

⁵ See Gresele* P, Deckmyn* H, Nenci* GG, Vermeylen* J. Thromboxane synthase inhibitors, thromboxane receptor antagonists and dual blockers in thrombotic disorders. Trends Pharmacol Sci. 1991;12:158-163.

⁶ See Gresele* P, Deckmyn* H, Nenci* GG, Vermeylen* J. Thromboxane synthase inhibitors, thromboxane receptor antagonists and dual blockers in thrombotic disorders. Trends Pharmacol Sci. 1991;12:158-163.

⁷ See Schafer* AI, Aspirin and antiplatelet agents in cardiovascular disease. In Smith* TW, ed. Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease. 1st ed. Philadelphia, PA: W.B. Saunders Company; 1996:427-442, at 427.

⁸ See Schafer* AI, Aspirin and antiplatelet agents in cardiovascular disease. In Smith* TW, ed. Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease. 1st ed. Philadelphia, PA: W.B. Saunders Company; 1996:427-442, at 434.

ADP receptor antagonists are thought to operate only through the ADP pathway and not to have any effect on Cox-1, Cox-2, or prostacyclin.⁹

4. GpIIb/IIIa Receptor Antagonist.

A fourth antiplatelet therapy that Merck considered for possible combination with Vioxx was a GpIIb/IIIa receptor antagonist. GpIIb/IIIa receptors form on the platelet surface only after platelet activation has occurred and facilitate the final step in platelet aggregation by binding to fibrinogen and von Willenbrand factor, two ligands that operate to form the bridges between platelets during aggregation.¹⁰ A GpIIb/IIIa receptor antagonist seeks to block that final step by preventing the ligands from adhering to the GpIIb/IIIa receptors.¹¹

In contrast to ADP receptor antagonists and thromboxane receptor antagonists, which only target specific platelet receptors or platelet metabolic pathways, GpIIb/IIIa receptor antagonists were thought to block the final step in platelet aggregation no matter what the receptor or pathway. Like ADP receptor antagonists, thromboxane receptor antagonists, and thromboxane synthase inhibitors, a GpIIb/IIIa receptor antagonist would have no effect on Cox-1, Cox-2, or prostacyclin. GpIIb/IIIa receptor antagonists had

⁹ Schrör* K. Antiplatelet drugs: A comparative review. Drugs. 1995;50;7-28, at 14, MRK-ABK0453784.

¹⁰ See Schafer* AI, Aspirin and antiplatelet agents in cardiovascular disease. In Smith* TW, ed. Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease. 1st ed. Philadelphia, PA: W.B. Saunders Company; 1996:427-442.

¹¹ See Schafer* AI, Aspirin and antiplatelet agents in cardiovascular disease. In Smith* TW, ed. Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease. 1st ed. Philadelphia, PA: W.B. Saunders Company; 1996:427-442.

shown some promising clinical efficacy results,¹² but their practical usage was limited because the compounds in development required intravenous administration and were associated with an increased risk of bleeding.¹³

5. Nitric Oxide.

The Company also considered a different approach altogether: combining Vioxx with a gastroprotective agent – a nitric oxide-releasing compound¹⁴ – which would then allow Vioxx to be concomitantly administered with aspirin without adverse gastrointestinal consequences. Nitric oxide functions by:

influencing many of the biochemical and physiological reactions that are key to preventing or repairing injury to the gastrointestinal tract, such as stimulating mucus secretion from the mucus membrane lining the stomach and intestines and regulating the blood flow feeding the wall of the gastrointestinal tract and the mucus membrane.¹⁵

Nitric oxide also was theorized to provide cardiovascular and renal benefits,¹⁶ although such effects were primarily speculative since nitric oxide, when ingested, causes a highly localized reaction, typically confined to the stomach lining.¹⁷

¹² Schrör* K. Antiplatelet drugs: A comparative review. Drugs. 1995;50;7-28, MRK-ABK0453784.

¹³ See Schafer* AI, Aspirin and antiplatelet agents in cardiovascular disease. In Smith* TW, ed. Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease. 1st ed. Philadelphia, PA: W.B. Saunders Company; 1996:427-442; Schrör* K. Antiplatelet drugs: A comparative review. Drugs. 1995;50;7-28, MRK-ABK0453784.

¹⁴ Throughout this Appendix, the term “nitric oxide/Vioxx” will be used to refer to the combination of Vioxx with a compound that releases nitric oxide into the body.

¹⁵ “Nitric Oxide’s Role in Cellular Function and Disease,” <http://www.nitromed.com/technology/no.asp>.

¹⁶ See 8/8/02 email from M. Turner to K. Metters et al., MRK-AEG0037553; Topper* JN, Jiexing* C, Falb* D, Gimbrone* MA Jr. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell

C. 1998-1999: Pre-VIGOR Trial Chronology of Combination Therapy Ideas.

In 1998 and 1999, the Company considered four different compounds for potential combination therapy with Vioxx, including a GpIIb/IIIa receptor antagonist, aspirin, an ADP receptor antagonist (clopidogrel), and a thromboxane receptor antagonist. A chronological summary of the pre-VIGOR discussions surrounding Vioxx combination therapy options is outlined below.

1. 1998: Merck Files Patent Application for a Combination Therapy.

In March 1998, Dr. Steven Nichtberger, a cardiologist in Merck's Worldwide Human Health Marketing Division, filed a Provisional Patent Application for "Combination Therapy for Treating, Preventing, or Reducing the Risks Associated with Acute Coronary Ischemic Syndrome and Related Conditions."¹⁸ The resulting patent covered "a therapeutically effective amount of an antiplatelet agent in combination with a

nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc Natl Acad Sci USA. 1996;93:10417-10422; Blann AD. How a damaged blood vessel wall contributes to thrombosis and hypertension. Pathophysiol Haemost Thromb 2003/2004;33:445-448.

¹⁷ 9/12/02 email from M. Turner to J. Lasota, MRK-AEG0037638; compare NitroMed presentation, NM08110, at 13 ("Systemically delivered NO may reduce the potential cardiovascular risk of selective COX-2 inhibitors in high risk patients.").

¹⁸ 10/24/00 United States Patent, "Combination Therapy for Treating, Preventing, or Reducing the Risks Associated with Acute Coronary Ischemic Syndrome and Related Conditions" MRK-AAK0000820, at 820. Provisional Patent Applications were "designed to provide a lower-cost first patent filing in the United States. Applicants are entitled to claim the benefit of a provisional application in a corresponding non-provisional application filed not later than 12 months after the provisional application filing date." <http://www.uspto.gov/web/offices/pac/provapp.htm>. See 35 U.S.C. §§ 111(b), 119(e) (2005).

therapeutically effective amount of a COX-2 inhibitor.”¹⁹ The stated purpose of the patent was to provide “improved treatments for inhibiting platelet aggregation” by combining a Cox-2 selective inhibitor with an antiplatelet agent, which would “provide enhanced treatment options as compared to administration of either the antiplatelet agent or the COX-2 inhibitor alone.”²⁰

According to Dr. Nichtberger, he proposed the idea of combining an antiplatelet agent with Vioxx because, as a cardiologist, he became aware of evidence that inflammation played a role in increasing cardiovascular risk. He stated that, in his view, the antiplatelet effects of aspirin were insufficient to account for the degree of reduction in cardiovascular adverse events seen in patients taking low-dose aspirin and that one theory to support explain aspirin’s efficacy in reducing cardiovascular risk was that it also served as an anti-inflammatory agent.²¹ Dr. Nichtberger therefore theorized that combining a selective Cox-2 inhibitor with a platelet blocker could provide a better alternative to aspirin for patients indicated for cardiovascular prophylaxis.

The patent, which was granted on October 24, 2000, covered the combination of a selective Cox-2 inhibitor with any antiplatelet agent, and specifically mentioned three – a

¹⁹ 10/24/00 United States Patent, “Combination Therapy for Treating, Preventing, or Reducing the Risks Associated with Acute Coronary Ischemic Syndrome and Related Conditions” MRK-AAK0000820, at 820.

²⁰ 10/24/00 United States Patent, “Combination Therapy for Treating, Preventing, or Reducing the Risks Associated with Acute Coronary Ischemic Syndrome and Related Conditions” MRK-AAK0000820, at 822.

²¹ For a more complete discussion of the theory that selective Cox-2 inhibitors might be cardioprotective because of their anti-inflammatory effects, see Appendix A.

GpIIb/IIIa receptor antagonist, clopidogrel, (an ADP receptor antagonist marketed in the United States by Bristol-Myers Squibb, and aspirin. At the time, Merck was engaged in a joint venture with DuPont to develop a GpIIb/IIIa receptor antagonist that would theoretically prove to be a more potent antiplatelet agent than aspirin. As a result, the patent application focused on the GpIIb/IIIa receptor antagonist.²²

2. 1998: The Board of Scientific Advisors
Recommends Combining Vioxx and Aspirin.

As described in Appendix A, in May 1998, Merck's Board of Scientific Advisors discussed at length the potential cardiovascular effects – both negative and positive – of selective Cox-2 inhibition and raised the possibility of combining Vioxx with low-dose aspirin.²³

Among other things, the Board of Scientific Advisors recommended that Merck evaluate the effect of selective Cox-2 suppression in certain disease states associated with platelet activation, such as “conditions associated with vessel wall disease in humans, including hypercholesterolemia, cigarette smoking, scleroderma, and ischemic limb disease.”²⁴ The Board reasoned that these diseases resulted in “sustained in vivo

²² 10/24/00 United States Patent, “Combination Therapy for Treating, Preventing, or Reducing the Risks Associated with Acute Coronary Ischemic Syndrome and Related Conditions” MRK-AAK0000820.

²³ See Appendix A for a more complete discussion of this meeting.

²⁴ 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 42. The Chairman of the Board of Scientific Advisors, Dr. Oates*, said that patients with vessel wall disease states provided a better model, compared to studying patients with a recent history of ACS, for evaluating the effects of Cox-2 inhibition on prostacyclin biosynthesis.

activation of platelets and a resulting increase in thromboxane A₂.²⁵ At the same time, the Board noted that prostacyclin levels were increased in these conditions, suggesting that Cox-2 was induced.²⁶

The Board of Scientific Advisors suggested that administering selective Cox-2 inhibitors to such patients and then measuring the levels of prostaglandin metabolites in the urine could “provide valuable information on the consequence of loss of prostacyclin in a condition of increased platelet activation.”²⁷ The Board of Scientific Advisors concluded that if administering selective Cox-2 inhibitors to such patients resulted in increased levels of urinary thromboxane metabolite and/or decreased levels of urinary prostacyclin metabolite from baseline, thus creating a greater imbalance of prostacyclin and thromboxane in patients who already had elevated levels of thromboxane and cardiovascular risk, “MRL should be the first to know, and thereby be able to take the lead in developing the obvious strategy of the combination of very low-dose aspirin (30-40 mg daily) with a COX-2 inhibitor.”²⁸

Merck did not conduct these studies nor pursue a Vioxx/aspirin combination at the time. After the VIGOR Trial, however, the idea that certain patient populations

²⁵ 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 42.

²⁶ 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 42.

²⁷ 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 42. An underlying assumption of the Board’s proposal appears to have been that prostaglandin metabolites in the urine were markers of vascular biosynthesis of those prostaglandins (and that the decreased urinary excretion of prostacyclin metabolite seen in Protocol 023 reflected decreased vascular biosynthesis of prostacyclin). See Appendix A.

²⁸ 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 42.

(those with increased platelet activation, such as patients with rheumatoid arthritis) might be more in need of antiplatelet therapy and/or more susceptible to the potential cardiovascular risk posed by depressing prostacyclin resurfaced as a rationale for combining Vioxx with a thromboxane receptor antagonist or a thromboxane synthase inhibitor (see Section E of this Appendix).

3. 1999: Dr. Oates* Proposes a Combination
with Aspirin or a Thromboxane Receptor Antagonist.

As discussed in Appendices E and F, Dr. John Oates* advised Dr. Scolnick, by letter dated August 13, 1999, that three patients with antiphospholipid syndrome had experienced thrombotic events “very soon after initiating with celecoxib [Celebrex].”²⁹ This suggested to Dr. Oates* the possibility that the thromboses might be causally linked to initiation of Celebrex therapy.³⁰ Dr. Oates* proposed a number of options available to Merck to address any potential prothrombotic effects of Vioxx, including (i) adding 30-50 mg of aspirin – administered either in a traditional single-dose formulation or in a new slow-release formulation then in development – to the formulation of Vioxx, and (ii) licensing a thromboxane receptor antagonist to create a combination product with Vioxx.³¹

With respect to low-dose aspirin, Dr. Oates* noted in his letter that Searle had licensed Asacard, “a slow release low-dose aspirin preparation being developed in

²⁹ 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 00.

³⁰ 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 01.

³¹ 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 02-03.

Europe.”³² He stated, “[o]ne may only speculate about whether Searle acquired this license to protect their enormous stake in celecoxib or whether this licensing was a coincidence.”³³ Dr. Oates* suggested that Merck develop “an alternative formulation of rofecoxib . . . [containing] 30-50 mg of aspirin, the lowest doses that effectively block platelet thromboxane biosynthesis.”³⁴

Dr. Oates* noted, however, that neither slow-release nor single-dose aspirin would have an immediate antithrombotic effect. At the low dosage, aspirin’s effects are cumulative, and the initial dose of aspirin does not fully inhibit thromboxane synthesis.³⁵ Dr. Oates* also stated that, because aspirin is a non-selective NSAID that inhibits Cox-2 as well as Cox-1, single-dose aspirin risked further depressing prostacyclin synthesis, and that even slow-release aspirin resulted in a “modest reduction in systemic prostacyclin biosynthesis.”³⁶ In Dr. Oates’s* view, the single-dose and slow-release aspirin formulations therefore might not protect against thrombotic events that occurred immediately like the ones observed in the three patients with antiphospholipid syndrome, and they could potentially further exacerbate any effect of decreased prostacyclin levels.

³² 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 02.

³³ 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 02.

³⁴ 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 02.

³⁵ 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 02; Patrignani* P, Filabozzi* P, Patrono* C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects,” J Clin Invest. 1982;69:1366-72.

³⁶ 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 02.

Accordingly, as an alternative to either a single-dose or a slow-release aspirin combination with Vioxx, Dr. Oates* proposed that a possible “winning strategy” would be to license a thromboxane receptor antagonist as a new antiplatelet regimen that could be used with Vioxx alone, or perhaps in combination with an ADP receptor antagonist such as clopidogrel.³⁷ As mentioned above, thromboxane receptor antagonists operated through the thromboxane pathway rather than through an effect on cyclooxygenase and thus were thought not to decrease prostacyclin biosynthesis nor cause gastrointestinal toxicity.³⁸ Combining a thromboxane receptor antagonist with an ADP receptor antagonist would inhibit platelet activation via two distinct mechanisms, which might therefore be more effective in decreasing thrombotic events than a thromboxane receptor antagonist alone. According to Dr. Oates*, adding either or both antiplatelet agents to Vioxx would combat a possible prothrombotic effect of Vioxx.³⁹

³⁷ 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 02-03.

³⁸ See Gresele* P, Deckmyn* H, Nenci* GG, Vermeylen* J. Thromboxane synthase inhibitors, thromboxane receptor antagonists and dual blockers in thrombotic disorders. Trends Pharmacol Sci. 1991;12:158-163.

³⁹ In his letter, Dr. Oates* also described a second potential use for a thromboxane receptor antagonist, as an effective antiangiogenic drug. Antiangiogenic drugs help prevent new blood vessel formation, and therefore were considered possible treatment options for cancer, diabetic retinopathy, and other disorders. Dr. Oates* believed that the applicability of a thromboxane receptor antagonist in the area of angiogenesis would greatly increase the potential market for a thromboxane receptor antagonist, adding to its appeal as a licensing candidate for Merck and for Merck’s competitors. 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 03.

Dr. Nies presented Dr. Oates's* suggestions to the Human Health Product Approval Committee on August 25, 1999.⁴⁰ According to Dr. Nies, the internal discussions about the possibility of combining with Vioxx one of the antiplatelet agents suggested by Dr. Oates* focused on how to make Vioxx a more desirable option for patients who needed pain relief and an antiplatelet agent without gastrointestinal toxicity, not on the possibility that Vioxx itself presented any cardiovascular risk. Dr. Nies stated that Merck did not pursue a thromboxane receptor antagonist combination therapy at that time because none of the available antiplatelet agents, including the Bristol-Myers Squibb thromboxane receptor antagonist that Dr. Oates* had mentioned in his letter, was sufficiently well developed to merit serious consideration as a licensing candidate.

4. 1999: Clopidogrel.

Following the August 25, 1999 Human Health Product Approval Committee meeting, Dr. Nies sent an email to Drs. Gertz and Seidenberg that proposed studying co-administration of Vioxx and the ADP receptor antagonist clopidogrel.⁴¹

⁴⁰ See Minutes of 8/25/99 HHPAC meeting, MRK-ABL0000709, at 710; Draft slides of A. Nies for HHPAC, MRK-ABH0016085, at 88 (attached to 8/23/99 email from A. Nies to E. Scolnick, MRK-ABH0016084).

⁴¹ 9/1/99 email from A. Nies to B. Gertz and B. Seidenberg, MRK-NJ0189371. The "discussion at pac" referenced in the email concerned the three patients with antiphospholipid syndrome who had experienced thrombotic events within days of commencing therapy with Celebrex.

To: Gertz, Barry J.; Seidenberg, Beth C.
From: Nies, Alan S.
Cc:
Bcc:
Date: 1999-09-01 20:51:59
Subject: FW: HH PAC Meeting Minutes - 8/25/99

In regards to the discussion at pac on celebrex and clotting, we should seriously consider some sort of a study with clopidogrel so that we can make a positive statement about coadministration with vioxx rather than saying that we know of no reason why they cannot be used together.
alan

If such a study demonstrated that co-administration of Vioxx and clopidogrel did not increase gastrointestinal adverse events, then the Company could advise patients at increased cardiovascular risk as to an antiplatelet regimen to use with Vioxx that did not cause increased gastrointestinal toxicity. Although Dr. Nies's suggestion did not lead to further consideration of studies with clopidogrel at that time, the combination was revisited beginning in 2001, as discussed in Section E of this Appendix.

D. 2000: After the VIGOR Trial, the Company Considers Several Combination Therapies.

In March and April of 2000, after the VIGOR Trial demonstrated a higher incidence of cardiovascular adverse events in the Vioxx arm of the study as compared to the naproxen arm, MRL scientists discussed reformulating Vioxx, or combining it with another therapy, to enhance its cardiovascular safety profile. At this time, five different antiplatelet agents were proposed for use in combination with Vioxx: aspirin, clopidogrel, a thromboxane receptor antagonist, a thromboxane synthase inhibitor, and a nitric oxide-releasing compound. The Company's efforts focused, however, on pairing Vioxx with a thromboxane receptor antagonist or synthase inhibitor.

The Sections below outline discussions about combination therapy during March and April of 2000, including: (i) a discussion initiated by Dr. FitzGerald* about combining Vioxx with either aspirin, clopidogrel, or a thromboxane receptor antagonist; (ii) the subsequent research and findings of a team of scientists from Merck Frosst regarding thromboxane receptor antagonists and synthase inhibitors; and (iii) the suggestion by an MRL scientist to couple a nitric oxide-releasing compound with Vioxx in order to counteract its hypertensive effects.

1. Dr. FitzGerald* Suggests Combining Vioxx with Aspirin, Clopidogrel, or a Thromboxane Receptor Antagonist.

Dr. FitzGerald*, the originator of the FitzGerald prostacyclin hypothesis, believed that there were three possible causes of the difference in the incidence of cardiovascular events between the Vioxx and naproxen arms of the VIGOR Trial: (i) a decrease in vascular prostacyclin in the Vioxx arm of the trial caused by Vioxx's selective suppression of Cox-2; (ii) cardioprotection in the naproxen arm brought about by naproxen's inhibition of Cox-1; or (iii) both. In the spring of 2000, he proposed to MRL three combination therapies he thought would counteract or mitigate cardiovascular risk under any of these scenarios.⁴²

On March 29, 2000, Dr. FitzGerald* proposed a Vioxx/aspirin combination in an email to Dr. Nies.⁴³ Dr. FitzGerald* described two slow-release aspirin compounds,

⁴² See 4/7/00 email from G. FitzGerald* to B. Gertz, MRK-ABC0033810; 3/29/00 email from G. FitzGerald* to A. Nies, MRK-ABH0017838.

⁴³ 3/29/00 email from G. FitzGerald* to A. Nies, MRK-ABH0017838.

Asacard⁴⁴ and one being developed by Bayer, and stated that they were “at least theoretically more attractive to conventional low dose aspirin, which, on its own, depresses PGI₂ synthesis.”⁴⁵ Dr. FitzGerald* proposed a combination of Vioxx and slow-release aspirin as a “a rational alternative”⁴⁶ to a thromboxane receptor antagonist combination, which he had proposed to Servier – a pharmaceutical company that had developed a thromboxane receptor antagonist program – prior to the release of the VIGOR Trial results (and which Dr. Oates* independently had proposed to Merck in his 1999 letter).⁴⁷

⁴⁴ As discussed above, Dr. Oates* had also suggested Asacard to Merck, noting that Searle had acquired licensing rights to it from its maker, Flamel. Merck scientists do not appear to have pursued this particular compound. In June 2004, however, Flamel approached Merck scientists about a possible Vioxx/Asacard combination. The Flamel proposal for the combination stated that they had read “that long term treatment with VIOXX could lead to cardiovascular adverse events in some patients, due to a possible lack of Thromboxane synthesis in the platelets of those patients.” 6/16/04 email from J. Chapman to N. Braunstein, MRK-AFV0307727, at 28. Dr. Reicin’s response to the proposal from Flamel was that it should be considered at the Product Development Team before going to the Core Franchise Team, and that “we dont [sic] agree with the ‘reasons’ set forth in the [Flamel] e-mail for consideration of this program.” 6/17/04 email from A. Reicin to T. Malloy, J. Chapman, N. Braunstein, and K. Grosser, MRK-AFV0307727. By mid-August 2004, MRL scientists had not yet determined which internal committee, if any, should consider the Flamel proposal. 8/9/04 email correspondence between J. Chapman, N. Braunstein, J. van Adelsberg, E. Maller, P. Heck, et al. MRK-AFV0307726-27.

⁴⁵ 3/29/00 email from G. FitzGerald* to A. Nies, MRK-ABH0017838. As discussed above, Dr. Oates* also had noted in his 1999 letter that low-dose aspirin depressed prostacyclin synthesis but, unlike Dr. FitzGerald*, Dr. Oates* had suggested that slow-release aspirin also could depress prostacyclin, albeit more modestly than low-dose aspirin. 8/13/99 letter from J. Oates* to E. Scolnick, MRK-ABH0004600, at 02.

⁴⁶ 3/29/00 email from G. FitzGerald* to A. Nies, MRK-ABH0017838; see also 3/27/00 email from G. FitzGerald* to B. Gertz, MRK-NJ0153054 (“Separately we are looking at the TP antagonist. it [sic] would be nice to look at the interaction. this [sic] is also true for the response to vascular injury where the TP antagonist is drqamatically [sic] effective . . .”).

⁴⁷ Dr. FitzGerald’s* earlier proposal is referenced in the 3/9/00 email to Dr. Nies.

Dr. FitzGerald* later suggested that Merck conduct clinical pharmacology studies to explore the effect of Vioxx plus various antiplatelet agents – traditional low-dose aspirin, slow-release aspirin, clopidogrel, and a thromboxane receptor antagonist – on prostacyclin and thromboxane metabolites both in high-risk patients who were undergoing angioplasty and in low-risk patients.⁴⁸ He reasoned that “all [patients] would be getting proven antiplatelet cover” against cardiovascular risk and that measuring “the procedure related increments” in prostacyclin and thromboxane in angioplasty patients on a Vioxx/antiplatelet combination “would let you look at their [the Vioxx/antiplatelet agent combinations’] effect at baseline and in a stimulated situation in patients [sic] in the at risk category.”⁴⁹ He added: “I don’t think we would include a rofecoxib alone group, even if it is all naproxen :).”⁵⁰ Dr. FitzGerald* also offered to follow up with contacts of his at Bayer (which had developed a slow-release aspirin compound) and Servier (which had developed a thromboxane receptor antagonist).⁵¹

2. Merck Frosst Scientists Research Thromboxane
Receptor Antagonists and Thromboxane Synthase Inhibitors.

In March and April 2000, after the release of the results of the VIGOR Trial, MRL scientists researched combining a thromboxane receptor antagonist or a thromboxane synthase inhibitor with Vioxx. This effort stemmed from a theory that the

⁴⁸ 4/7/00 email from G. FitzGerald* to B. Gertz, MRK-ABC0033810.

⁴⁹ 4/7/00 email from G. FitzGerald* to B. Gertz, MRK-ABC0033810.

⁵⁰ 4/7/00 email from G. FitzGerald* to B. Gertz, MRK-ABC0033810.

⁵¹ 4/7/00 email from G. FitzGerald* to B. Gertz, MRK-ABC0033810; 4/27/00 email from G. FitzGerald* to B. Gertz, FITZG-002477.

between-treatment differential in the cardiovascular event rate in VIGOR Trial may have been due, in whole or in part, to elevated thromboxane levels as compared with prostacyclin levels in rheumatoid arthritis patients.⁵² Scientists from Merck Frosst speculated that such a preexisting imbalance, which may have been exacerbated by Vioxx's selective suppression of Cox-2, left extra thromboxane available to initiate platelet activation in the rheumatoid arthritis patients in the VIGOR Trial. A thromboxane receptor antagonist or synthase inhibitor could theoretically address such a preexisting elevation in thromboxane as well as any additional effect Vioxx might have on the balance between thromboxane and prostacyclin levels.

a. Initial research.

Merck formally considered a combination with either a thromboxane receptor antagonist or a thromboxane synthase inhibitor at the March 30, 2000 meeting of the Licensing Management Committee, a committee comprising individuals from MRL, Merck's Basic Research Laboratories, and Merck's Marketing and Public Affairs Departments.⁵³ The Licensing Management Committee met regularly to review

⁵² As discussed in Appendix E, in early March 2000, MRL scientists had raised the possibility that the rheumatoid arthritis patients population might have certain characteristics that explained the cardiovascular data. Their early research revealed that (i) rheumatoid arthritis patients had an increased risk of cardiovascular disease compared to the general population, and (ii) patients with antiphospholipid syndrome, which represent 16%-33% of the rheumatoid arthritis population, had elevated levels of thromboxane as compared with prostacyclin. See Appendix E.

⁵³ Minutes of 3/30/00 LMC meeting, MRK-JRAA0000438, at 48; see also 7/28/05 deposition of K. Metters at 78-79, 135 (*In re Vioxx Litig.*, No. 619, N.J. Sup. Ct.). The Licensing Management Committee included several senior members of MRL (including Drs. Alan Nies, Briggs Morrison, Roger Perlmutter, and Barry Gertz) and Merck's Marketing Department (including Dr. Wendy Dixon, Mr. David Anstice and Ms. Margaret McGlynn). Minutes of 3/30/00 LMC meeting, MRK-JRAA0000438, at 451.

opportunities to license products owned by outside companies, including the commercial benefit for Merck, the deal terms for a particular venture, and the science behind the potential license. The Licensing Management Committee then would make recommendations to Merck's Board of Directors about whether the Company should proceed with a particular licensing opportunity.

At its March 30, 2000 meeting, Dr. Kathleen Metters, a Director of Basic Research at Merck Frosst, presented the Committee with a number of candidates for thromboxane receptor antagonists and thromboxane synthase inhibitors, including some external compounds and some in development in-house at Merck Frosst.⁵⁴ Additionally, Dr. Michael Gresser, an Executive Director of Molecular Biology at Merck Frosst, presented an overview of "Issues relating to Thromboxane/Prostacyclin balance." In his presentation, Dr. Gresser reviewed a series of scientific articles about prostacyclin and made the following observations:

- Decrease of antiplatelet effect of prostacyclin by Cox inhibitors could be greater in arthritis patients
- If much of the prostacyclin is Cox-1 derived, more selective Cox-2 inhibitors (MK-0663 [Arcoxia] and L-791,515 [a selective Cox-2 inhibitor in development]) could inhibit prostacyclin biosynthesis less than do Celecoxib and Vioxx

⁵⁴ 7/28/05 deposition of K. Metters at 77-79, 111-13, 133-35 (In re Vioxx Litigation, No. 619, N.J. Sup. Ct.); Undated slide set presentation, "Thromboxane antagonists & Synthase Inhibitors," MRK-JRAD0000001, at 01-20.

- If much of the prostacyclin is Cox-2 derived, the thrombosis issue must be addressed by blocking the effects of prothrombotic prostanoids (Thromboxin)⁵⁵

Dr. Gresser's analysis reflected continued uncertainty as to whether prostacyclin in the vasculature was synthesized by Cox-1 or Cox-2. If vascular prostacyclin were derived from Cox-1 rather than Cox-2 (as stated in the second bullet point above), then selective suppression of Cox-2 would have no effect the balance between prostacyclin and thromboxane. If, however, vascular prostacyclin was Cox-2 derived (as stated in the third bullet point above), the Merck Frosst team stated that it might be necessary to combine Vioxx with a thromboxane receptor antagonist or a thromboxane synthase inhibitor to address "the thrombosis issue" that might arise from selective Cox-2 inhibition.⁵⁶

The minutes of the March 30 Licensing Management Committee meeting reflect that members also discussed the idea that an imbalance might exist in the prostacyclin and thromboxane levels of rheumatoid arthritis patients, and that Vioxx might further

⁵⁵ Undated slide set presentation, "Thromboxane antagonists & Synthase Inhibitors," MRK-JRAD0000001, at 21-24; 7/28/05 deposition of K. Metters at 111-13 (In re Vioxx Litigation, No. 619, N.J. Sup. Ct.). Although the presentation is undated, based upon the similarity of this presentation to the minutes of the March 30, 2000 Licensing Management Committee meeting, and based on Dr. Metters' testimony that these slides were from a Licensing Management Committee meeting in the first third of 2000, it is likely that the presentation was made at that meeting.

⁵⁶ Undated slide set presentation, "Thromboxane antagonists & Synthase Inhibitors," MRK-JRAD0000001, at 21-24. Importantly, even if the source of prostacyclin production in the vasculature were Cox-2 derived, which was part of the FitzGerald prostacyclin hypothesis, the clinical significance still was uncertain. Nevertheless, Dr. Gresser, among others, assumed that a combination therapy would be necessary if this were the case.

affect that imbalance.⁵⁷ A premise of the discussion was that, in rheumatoid arthritis patients, selective suppression of Cox-2 might have a clinical effect: “Prostacyclin is protective and lowering its levels may give [thromboxane] the upper hand causing increased platelet aggregation and thromboembolic episodes.”⁵⁸ Although participants in the meeting “did not agree on the biochemical mechanism by which Vioxx™ could be exerting its effects” on prostacyclin and thromboxane levels in rheumatoid arthritis patients, they agreed that “the end result is the same” – meaning that excess thromboxane was left available to bind to its receptor sites thereby initiating platelet activation – and suggested that it “may be necessary to co-dose” Vioxx with a thromboxane receptor antagonist or synthase inhibitor.⁵⁹ They also agreed that studies should be performed to gain a better understanding of how Vioxx might affect prostacyclin and thromboxane levels.⁶⁰

Following the Licensing Management Committee meeting, a team of scientists at the Merck Frosst basic research facility in Montreal, Canada, led by Dr. Mervyn Turner, reviewed literature on levels of prostacyclin and thromboxane in arthritis patients.⁶¹

⁵⁷ Minutes of 3/30/00 LMC meeting, MRK-JRAA0000438, at 448. Neither Dr. Turner nor Dr. Gresser recalled the precise nature of the discussions at this Licensing Management Committee meeting, beyond what is presented in the minutes.

⁵⁸ Minutes of 3/30/00 LMC meeting, MRK-JRAA0000438, at 448.

⁵⁹ Minutes of 3/30/00 LMC meeting, MRK-JRAA0000438, at 448.

⁶⁰ Minutes of 3/30/00 LMC meeting, MRK-JRAA0000438, at 448.

⁶¹ 4/3/00 “Action items” MRK-AEG0049219 (attached to 4/3/00 email from D. Riendeau to M. Turner et al., MRK-AEG0049218); 4/6/00 email from M. Gresser to M. Turner, D. Nicholson, K. Metters, D. Riendeau, R. Young, A. Nies, and B. Gertz, MRK-AEG0023601.

Dr. Gresser, one of the Merck Frosst research scientists working with Dr. Turner, noted that one article “reports that diabetics [sic] patients have increased ratios of thromboxane to prostacyclin. Might these patients be at risk when treated with Cox-2 inhibitors?”⁶²

The Merck Frosst team incorporated Dr. Gresser’s research into a background memorandum explaining the rationale for combining Vioxx with a thromboxane receptor antagonist or thromboxane synthesis inhibitor. The memorandum, which was circulated on April 14, 2000 to members of the Human Health Product Approval Committee in advance of their April 20, 2000 meeting, stated:

[A]n important factor in patients is the PGI₂/TXA₂ [prostacyclin/thromboxane] balance There are reports in the literature that diabetics have increased ratios of TXA₂ to PGI₂. This may also apply to RA patients. COX-2 inhibitors could potentially exacerbate this condition by further differentially suppressing PGI₂ versus TXA₂ synthesis. Under these conditions an alternate therapeutic approach would be to suppress TXA₂ action by combining COX-2 inhibitors with a TXA₂ (TP) receptor antagonist or TXA₂ synthase inhibitor or a dual blocker. Potentially this may have the advantage of providing cardio-protective effects similar to aspirin while avoiding the GI toxicity associated with even low dose aspirin.⁶³

The rationale therefore suggested that a combination of Vioxx with either a thromboxane receptor antagonist or a thromboxane synthase inhibitor could potentially correct a

⁶² 4/6/00 email from M. Gresser to M. Turner, D. Nicholson, K. Metters, D. Riendeau, R. Young, A. Nies, and B. Gertz, MRK-AEG0023601.

⁶³ 4/14/00 background material for 4/20/00 HHPAC meeting, MRK-ABL0000839, at 873. An earlier draft of this document concluded differently: “Under these conditions an alternate approach would be to suppress TXA₂ action by combining COX-2 inhibitors with a TXA₂ (TP) receptor antagonist or a TXA₂ synthase inhibitor or a dual blocker. This approach may not be limited to RA patients.” Draft background material for 4/20/00 HHPAC meeting, MRK-AEE0000697, at 732.

preexisting imbalance in prostacyclin and thromboxane in rheumatoid arthritis patients, and, in the process, also could correct any additional imbalance theoretically caused by Vioxx. According to Drs. Scolnick, Metters, and Turner, the primary goal of these combinations was, as stated in the last sentence of the passage quoted above, to provide cardioprotection to patients who needed it without sacrificing the gastrointestinal tolerability of Vioxx.⁶⁴

Soon after the background memorandum was circulated, the preliminary results of the CLASS trial of Celebrex were made public, revealing that Celebrex had not achieved a significant reduction in gastrointestinal problems compared to the non-selective NSAID comparators, overall, but had demonstrated a significant reduction in such events in among those patients who were not concomitantly taking aspirin.⁶⁵ This suggested to Merck scientists that aspirin had compromised the gastrointestinal tolerability of Celebrex in the trial. Based on these results, Dr. Turner wrote in an email to his team on April 17, 2000, that “aspirin is NOT the answer” for the Cox-2 inhibitor class, but that without aspirin “you are down to COX-2 [inhibition] with unopposed [thromboxane] receptors – and we have been down that path before.”⁶⁶ For these reasons, Dr. Turner

⁶⁴ 1/30/03 deposition of E. Scolnick at 170-75 (*Barlow v. Merck & Co.*, No. CV-02-2842-MC, Ala. Cir. Ct.); 7/28/05 deposition of K. Metters at 139-41 (*In re Vioxx Litig.*, No. 619, N.J. Super. Ct. Law Div.).

⁶⁵ 4/17/00 email from M. Turner to D. Riendeau, K. Metters, D. Nicholson, P. Prasit, M. Gesser, and R. Young, MRK-AEG0022420.

⁶⁶ 4/17/00 email from M. Turner to D. Riendeau, K. Metters, D. Nicholson, P. Prasit, M. Gesser, and R. Young, MRK-AEG0022420. Drs. Turner and Gesser stated that references to “unopposed thromboxane” were not references to the FitzGerald prostacyclin hypothesis, but rather to what they

noted, “[t]he Antagonist/Synthase inhibitor project becomes critical in Barry [Gertz’s] view.”⁶⁷

b. Consideration of licensing candidates.

On April 17, 2000, Dr. Turner informally reviewed possible thromboxane receptor antagonists and thromboxane synthase inhibitors in an email to Drs. Scolnick, Perlmutter, Shapiro, Gertz, and Nies.⁶⁸ Dr. Turner described a program at Servier to pursue dual thromboxane receptor antagonist/synthase inhibitor compounds, and he described two “failed” thromboxane receptor antagonists – compounds that had been studied but never went to market because of unfavorable or ambiguous results – that he thought the Company should consider as licensing candidates.⁶⁹

Although clinical studies of thromboxane synthase inhibitors to date had produced disappointing results, Dr. Turner’s review included a dual thromboxane receptor antagonist/synthase inhibitor from Servier. A theory existed that thromboxane synthase inhibitors could actually increase prostacyclin synthesis, as well as combat thrombosis by

termed the “unopposed thromboxane hypothesis.” See 4/7/00 email from M. Turner to M. Gresser et al., MRK-AEG0023611. Drs. Turner and Gresser stated that the “unopposed thromboxane hypothesis” differed from the FitzGerald prostacyclin hypothesis in two respects: (i) it concerned only the role of thromboxane – and not prostacyclin – in platelet aggregation, and (ii) it did not cede the point, argued by Dr. FitzGerald*, that the decreased levels of urinary prostacyclin metabolite seen in selective Cox-2 inhibitor users came from the vasculature and not from other places in the body.

⁶⁷ 4/17/00 email from M. Turner to D. Riendeau, K. Metters, D. Nicholson, P. Prasit, M. Gesser, and R. Young, MRK-AEG0022420.

⁶⁸ 4/16/00 email from M. Turner to E. Scolnick, R. Perlmutter, and B. Shapiro, MRK-JRAA0000179-81.

⁶⁹ 4/16/00 email from M. Turner to E. Scolnick, R. Perlmutter, and B. Shapiro, MRK-JRAA0000179-81.

acting on thromboxane.⁷⁰ As articulated by Dr. Turner, the theory held that “blocking the [thromboxane] synthase shunts PGH2 [a prostaglandin known as endoperoxide] into synthesis of vasoprotective [prostaglandins] including prostacyclin”⁷¹ He stated:

There is quite a large literature on the ability of [thromboxane synthase inhibitors] in particular to alter [thromboxane and prostacyclin] ratios (in favor of prostacyclin, obviously) in both animals . . . and man Whether we see the potential to restore that balance as an upside for a combo with [a thromboxane synthase inhibitor] is worth discussing⁷²

In response to Dr. Turner’s remarks in favor of a thromboxane synthase inhibitor, Dr. Nies pointed out certain disadvantages with that option:⁷³

From: Nies, Alan S.
Sent: Monday, April 17, 2000 1:02 PM
To: Gertz, Barry J.; Turner, Mervyn
Subject: RE: TXA antagonists etc
Importance: High

Merv,
With respect to Servier, Garret FitzGerald had said that they had an active program for CVA with a pharmaceutically good compound and that they had an IND in Canada. I don't know if it is with the compound on your list. John Oates had mentioned a BMS compound that he was impressed with, but Garret mentioned that the Servier compound is better (both antagonists). In regards to the BMS compound, I think there is literature that the potential benefits or problems. The PGH2 formed could feed the endothelium and increase [prostacyclin] production, but the endoperoxide is also a potent activator of the TP receptor. The BMS compound is an endoperoxide analog which is now used to stimulate the TP receptor. I think there is literature that synthesis inhibitors have relatively little effect on arachidonic acid induced platelet activation because of this.

Alan

In regards to synthesis inhibitors, there is more hand-waving and potential benefits or problems. The PGH2 formed could “feed” the endothelium and increase [prostacyclin] production, but the endoperoxide is also a potent activator of the TP receptor. . . . I think there is literature that the synthesis inhibitors have relatively little effect on arachidonic acid induced platelet activation because of this.

⁷⁰ See Gresele* P, Deckmyn* H, Nenci* GG, Vermuyen* J. Thromboxane synthase inhibitors, thromboxane receptor antagonists and dual blockers in thrombotic disorders. Trends Pharmacol Sci. 1991;12:158-163; Schafer* AI, Aspirin and antiplatelet agents in cardiovascular disease. In Smith* TW, ed. Cardiovascular Therapeutics: A Companion to Braunwald’s Heart Disease. 1st ed. Philadelphia, PA: W.B. Saunders Company; 1996:427-442.

⁷¹ 4/16/00 email from M. Turner to E. Scolnick, R. Perlmutter, and B. Shapiro, MRK-JRAA0000179, at 79.

⁷² 4/16/00 email from M. Turner to E. Scolnick, R. Perlmutter, and B. Shapiro, MRK-JRAA0000179, at 80.

⁷³ 4/17/00 email from A. Nies to B. Gertz and M. Turner, MRK-AEG0022430.

Both the thromboxane receptor antagonist and the thromboxane synthase inhibitor, however, remained under consideration. Merck initiated conversations with Bristol-Myers Squibb about using its thromboxane synthase inhibitors in combination with Vioxx,⁷⁴ and Dr. FitzGerald* initiated conversations between Merck and Servier about using Servier's thromboxane receptor antagonists in such a combination.⁷⁵ Through Dr. FitzGerald*, Merck continued discussions with Servier about licensing a thromboxane receptor antagonist,⁷⁶ but ultimately Servier declined the opportunity because Dr. Jacques Servier* – the founder and head of Servier – was wary of entering the U.S. drug market after his company's negative experience with fen-phen.⁷⁷

c. Patent application.

Merck submitted a patent application to the United States Patent and Trade Office, dated May 15, 2000, for a Vioxx/thromboxane-inhibitor drug, covering the

⁷⁴ See 5/10/00 email from E. Wyatt to B. Shapiro *et al.*, MRK-JRAA0000001 (“Julie Seawall and I spoke with Alice Leung at BMS today. The thromboxane synthesis inhibitor program was quite a large one for a number of years. However, this compound did not achieve its efficacy parameters in a Phase II trial (Ms. Leung was uncertain of the target indication) and therefore, development was halted. She indicated it is ‘very, very safe’ and is available for out-licensing.”).

⁷⁵ See 4/7/00 email from G. FitzGerald* to B. Gertz, MRK-ABC0033810; 5/3/00 email from G. FitzGerald* to B. Gertz, FITZG-002475; 5/10/2000 email from G. FitzGerald* to B. Gertz, MRK-NJ0153120.

⁷⁶ See 5/3/00 email from G. FitzGerald* to B. Gertz, FITZG-002475; 5/10/2000 email from G. FitzGerald* to B. Gertz, MRK-NJ0153120.

⁷⁷ Fen-phen refers to the combination of fenfluramine and phentermine, two diet drugs approved separately by the FDA in the 1970s. Fenfluramine (Pondimin, Wyeth-Ayerst Laboratories) and dexfenfluramine (Redux, Wyeth-Ayerst Laboratories) were withdrawn from the market in 1997 after they were identified by the FDA as “the likely cause of heart valve problems of the type that prompted FDA’s two earlier warnings concerning ‘fen-phen,’ a combination of fenfluramine and phentermine.” 9/15/97 FDA press release, “FDA Announces Withdrawal of Fenfluramine and Dexfenfluramine,” <http://www.fda.gov/cder/news/phen/fenphenpr81597.htm>.

combination of Vioxx with either a thromboxane receptor antagonist or a synthase inhibitor.⁷⁸ The patent application stated as its sole rationale the need to provide cardioprotection to high cardiovascular risk patients who were indicated both for aspirin prophylaxis and for selective Cox-2 inhibitors:

In patients who are taking COX-2 selective inhibitors, those who are at risk of developing thromboembolic event [sic] may benefit from the anti-platelet aggregation effect of traditional NSAIDs, such as aspirin. However, the chronic use of aspirin for its cardiovascular protective effect, albeit at doses lower than normally used for its antiinflammatory effect, would undesirably expose these patients to gastrointestinal side effects while they are on an otherwise GI-sparing treatment regimen. Therefore, for patients who are taking COX-2 selective inhibitors and who may benefit from the cardiovascular protective effect of aspirin, there remains a need for a cardiovascular protective treatment that does not expose them to increased risk for gastrointestinal side effects.⁷⁹

According to Drs. Scolnick and Turner, the view at the time was that the existing placebo-controlled cardiovascular data that MRL had reviewed after data from the VIGOR Trial were unblinded had reassured them that Vioxx was not prothrombotic and that adding a thromboxane receptor antagonist to the formulation was therefore not necessary for the purpose of counteracting a cardiovascular risk of Vioxx.⁸⁰

⁷⁸ 2/7/02 United States Patent Application, "Combination Therapy Using Cox-2 Selective Inhibitor and Thromboxane Inhibitor and Compositions Therefor," MRK-AAK0000233-46. The original application was filed on May 15, 2000, and a "Correction of Inventorship" was mailed on May 8, 2001, resulting in a new official filing date of May 14, 2001 for the patent. 5/8/01 "Correction of Inventorship," MRK-JRAC0000002-03.

⁷⁹ 2/7/02, United States Patent Application, "Combination Therapy Using Cox-2 Selective Inhibitor and Thromboxane Inhibitor and Compositions Therefor," MRK-AAK0000233, at 34.

⁸⁰ See generally Appendices E and F.

Merck ultimately rejected the combination of Vioxx and a thromboxane receptor antagonist because thromboxane receptor antagonists had not yet been proven to convey cardioprotection and because conducting the preclinical and clinical studies necessary to demonstrate that the combination drug was both equivalent in terms of cardioprotection and superior from a gastrointestinal safety perspective to Vioxx plus aspirin would be too expensive and time consuming. Therefore, after Merck filed for the patent covering a Vioxx/thromboxane-receptor-antagonist and a Vioxx/thromboxane-synthase-inhibitor combination, the Company did not actively investigate the development of such a compound.

The United States Patent and Trade Office issued a final rejection of Merck's patent application on September 13, 2002.⁸¹

3. Nitric Oxide/Vioxx.

Another idea proposed in April 2000 was to add to the formulation of Vioxx a compound that would release nitric oxide into the body. On April 14, 2000, MRL scientist Dr. Gerry Hickey wrote to Dr. Turner that non-selective NSAIDs coupled with nitric oxide donors did not cause or worsen hypertension – in other words, that releasing nitric oxide into the body appeared to mitigate the NSAID-class effect of increased blood

⁸¹ 9/13/02, Office Action Summary, United States Patent and Trade Office, MRK-JRAC0000078-85. The rejection was based, among other reasons, on the “obviousness doctrine.” This doctrine holds that a patent may not be obtained where “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. . . .” *Id.* at 81 (quoting 35 U.S.C. § 103(a)). Notably, the rejection did not address cardioprotection in its analysis; rather, the “obviousness” to which the rejection referred was that the existing patents for both Cox-2 inhibitors and “thromboxane A₂ inhibitors” (which included the thromboxane receptor antagonist ifetroban) had indicated that each was useful in treating inflammatory diseases such as osteoarthritis. *Id.* at 81-82.

pressure.⁸² Dr. Hickey wrote: “[g]iven that [sic] cox-2 has a physiological role in the kidney and that appear [sic] to affect water balance is there any reason for a second generation cox-2 that would couple the nitric oxide donor to a vioxx analogue?”⁸³

Dr. Turner forwarded Dr. Hickey’s suggestion to the Merck Frosst team that was researching the thromboxane receptor antagonist idea. Dr. Robert Young, a biochemical researcher at Merck Frosst and Merck’s Vice-President of Medicinal Chemistry, responded:⁸⁴

To: Gresser, Michael; Metters, Kathleen; Riendeau, Denis; Nicholson, Donald; Turner, Mervyn
From: Young, Robert
Cc: Hickey, Gerry J
Bcc:
Received Date: 2000-04-17 00:42:30
Subject: RE: cox-2

I suspect that John Wallace has a patent on that. In principle the concept could be interesting but the problem is always how do you balance the two activities and what is the right balance? The NO-NSAID camp has put forth a sustained propaganda campaign from the beginning. Much of their evidence has been contrived and crafted to show COX-2 inhibitors in the worst possible light. No obvious way to combine NO with Vioxx but we could make a nitrite ester of the metabolite of MK-663 or for that matter the metabolite of Vioxx (which is inactive but reconverted to Vioxx by reduction). What are these "models of renal disfunction?"

Bob

Drs. Hickey and Young seem to have viewed a nitric oxide combination as a means of improving Vioxx’s renal safety profile. Their exchange did not consider nitric oxide’s

⁸² 4/14/00 email from G. Hickey to M. Turner, MRK-AEG0022380.

⁸³ 4/14/00 email from G. Hickey to M. Turner, MRK-AEG0022380.

⁸⁴ 4/17/00 email from R. Young to M. Gresser, K. Metters, D. Riendeau, D. Nicholson, and M. Turner, MRK-AEG0022380.

role as a gastroprotective agent, but focused instead on the practical difficulties of combining the two agents.⁸⁵

Accordingly, and perhaps because the Merck Frosst scientists' research was already focused on the thromboxane receptor antagonist/synthase inhibitor project, nitric oxide/Vioxx was not pursued at the time.

E. 2001-2004: Post-VIGOR Chronology of Combination Therapies Considered.

MRL scientists briefly revisited, but did not pursue, potential combination therapies involving a thromboxane receptor antagonist in May 2001, and involving the ADP receptor antagonist clopidogrel in November 2001. Although these options and others arose again during mid-2002 discussions about the next generation of selective Cox-2 inhibitors, the Company at that time decided to pursue a nitric oxide/Vioxx compound and entered into an agreement for its development with an external company. A chronological summary of the post-2000 discussions surrounding Vioxx combination therapy options is outlined below.

1. May 2001: Servier Proposes a Combination
Involving a Thromboxane Receptor Antagonist.

On May 30, 2001, Dr. Bennett Shapiro, a former head of Merck Basic Research who then headed up Merck's licensing efforts for new drugs, met with the head of research at Servier to discuss potential licensing opportunities.⁸⁶ Dr. Shapiro explained in

⁸⁵ 4/17/00 email from R. Young to M. Gresser, K. Metters, D. Riendeau, D. Nicholson, and M. Turner, MRK-AEG0022380; 4/14/00 email from G. Hickey to M. Turner, MRK-AEG0022380.

⁸⁶ 5/31/01 email from B. Shapiro to G. Wiederrecht et al., MRK-ABX0027012-13.

an email describing the meeting that two compounds in particular were of interest to him, one of which was the thromboxane receptor antagonist.⁸⁷ He noted:

We have previously considered adding such a compound to VIOXX, for obvious reasons, and are currently using low-dose aspirin in trials with VIOXX – however, as exhaustively discussed internally, there may be advantages to a [thromboxane receptor] antagonist – and Servier is exploring anti-platelet as well as pro-endothelial effects of their compounds.⁸⁸

MRL scientists expressed a negative response to the renewed suggestion of developing a combination product with a thromboxane receptor antagonist, as memorialized by Dr. Nies:⁸⁹

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

From: Nies, Alan S.
Sent: Thursday, May 31, 2001 12:04 PM
To: Shapiro, Bennett M.; Wiederrecht, Greg J.; Reines, Scott A.; Hefti, Franz; Hill, Ray; Gould, Robert J.; Schechter, Adam H; Gertz, Barry J.
Cc: Demain, Pamela R.; Kender, Richard N.; Heck, Paula Z.
Subject: RE: Servier

Ben,
I can't think of anything new to comment on in regard to the TP antagonist. I would think that it would need to be registerable on its own. Although one can make a theoretical argument that the combination with vioxx would be beneficial and one could show an effect on platelets, to develop clinical data that such a combination was useful would be difficult. We don't need to cross that hurdle with aspirin since it is already approved for cardiovascular protection. The TP antagonist would be no more effective than aspirin but it would have some potential GI advantages. For it to be labelled for CV protection would require an equivalence trial to aspirin, presumably also with a safety advantage. It would probably only be worth it if we actually do lose the GI benefit with low dose ASA as seen in our endoscopy trials. In that case, clopidogrel might be a better choice.
Alan

⁸⁷ 5/31/01 email from B. Shapiro to G. Wiederrecht et al., MRK-ABX0027012-13.

⁸⁸ 5/31/01 email from B. Shapiro to G. Wiederrecht et al., MRK-ABX0027012, at 13.

⁸⁹ 5/31/01 email from A. Nies to B. Shapiro et al., MRK-ABX0027012.

2. November 2001: The Company Considers Clopidogrel
in Connection with the Cardiovascular Outcomes Trial.⁹⁰

In November 2001, an endoscopy study of Vioxx plus aspirin, Protocol 136, demonstrated that patients taking Vioxx plus aspirin experienced a higher incidence of gastrointestinal complications than those taking aspirin alone and experienced a similar rate of gastrointestinal complications to patients taking ibuprofen.⁹¹ The results revived focus on and analysis of the use of clopidogrel as an antiplatelet agent in combination with Vioxx, as clopidogrel did not impact Cox-1 nor interfere with its gastroprotective effects.

On November 21, 2001, two days after learning the negative results of Protocol 136, Dr. Scolnick proposed looking at clopidogrel as an alternate antiplatelet agent to replace aspirin in the Vioxx cardiovascular outcomes trial then in development.⁹²

⁹⁰ In early 2001, Merck briefly considered developing its own ADP receptor antagonist as an alternative to clopidogrel, which was owned by Sanofi Research and Bristol Myers Squibb. Merck determined that designing a study that could demonstrate superiority of a new ADP receptor antagonist over clopidogrel would be a costly and time-consuming endeavor that was unlikely to demonstrate superiority in either cardiovascular or gastrointestinal results. See 2/01 email correspondence between A. Nies and D. Greene, MRK-ACR0009303-04; 2/01 email correspondence between H. Guess, A. Nies, D. Greene, L. Oppenheimer, G. Williams, and R. Bain, MRK-ACR0009305-06; 2/01-3/01 email correspondence between G. Williams, S. Snapinn, A. Nies and R. Bain, MRK-AFS0004522-24; 2/01-3/01 email correspondence between S. Snapinn, G. Williams, A. Nies and D. Greene, MRK-AFS0004531-33.

Drs. Nies and Kim have stated that this effort to develop an alternative to clopidogrel was entirely unrelated to Vioxx and arose because the mechanism of action for clopidogrel had recently been discovered. This new discovery prompted Dr. Kim's interest in exploring the possibility of Merck developing its own better version of clopidogrel.

⁹¹ See Appendix M (discussing the results of Protocol 136).

⁹² 11/21/01 email from E. Scolnick to D. Greene, P. Kim, S. Nichtberger, A. Schechter, L. Demopoulos, B. Goldmann, B. Gertz, and A. Nies, MRK-NJ0326037-38. Merck's plans to conduct a large clinical outcomes trial studying the cardiovascular safety of Vioxx are discussed in detail in Appendix M.

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

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

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

Because he already believed that Vioxx was safe from a cardiovascular perspective,⁹³

Dr. Scolnick has testified that his focus was on the question of whether, “knowing that aspirin and Vioxx elevated the rate of ulcers over aspirin alone . . . one could develop a regimen where a person who was on Vioxx and who also needed a platelet blocker could take something besides aspirin.”⁹⁴

Dr. Scolnick’s suggestion appears to refer to concomitant administration of Vioxx and clopidogrel, rather than a combination product. Drs. Douglas Greene and Steven Nichtberger, however, saw commercial advantage in creating a new drug incorporating both compounds. Dr. Greene first raised the question: “Given what we know now about the GI interaction of both valdecoxib [Searle/Pfizer’s Bextra] (from their label) and rofecoxib with low-dose aspirin, should we explore a possible approach to Sanofi with

⁹³ See Appendices E and F.

⁹⁴ 8/16/05 deposition of E. Scolnick at 1278 (In re Vioxx Litigation, No. 619, N.J. Sup. Ct.).

the idea of a combination product with clopidogrel?”⁹⁵ Dr. Nichtberger, in an email dated November 25, 2001, responded that the combination “could represent a patent extension strategy for up to 20% of the VIOXX market in my opinion (the portion of the OA market that has concomitant CV disease or risk factors).”⁹⁶

However, because clopidogrel was still under patent and was not owned by Merck, Dr. Nichtberger also pointed out that “the economics would probably not cause either party to be terribly enthusiastic about a shared product given the relatively recent launch for both molecules.”⁹⁷ Ultimately, the combination was not pursued.

3. 2002-2004: Nitric Oxide/Vioxx.
 - a. Merck’s Board of Scientific Advisors’ recommendation to pursue a nitric oxide/Vioxx combination.

The idea of combining Vioxx with a nitric oxide-releasing compound for gastroprotective purposes emerged at the May 2002 annual Board of Scientific Advisors meeting, based on a suggestion from Dr. Richard Hunt^{*}, a preeminent gastroenterologist and member of the Board of Scientific Advisors.⁹⁸ At this time, NicOx – a company specializing in nitric oxide enhanced compounds – had in development a nitric

⁹⁵ 11/25/01 email from D. Greene to D. Anstice, P. Kim, and E. Scolnick, MRK-NJ0214794.

⁹⁶ 11/25/01 email from S. Nichtberger to D. Greene, A. Schechter, D. Anstice, P. Kim, and E. Scolnick, MRK-NJ0214794.

⁹⁷ 11/25/01 email from S. Nichtberger to D. Greene, A. Schechter, D. Anstice, P. Kim, and E. Scolnick, MRK-NJ0214794.

⁹⁸ 5/3/02 email from B. Shapiro to P. Heck *et al.*, MRK-AEG0036452; 5/24/04 presentation, “HHMC Review: L-001069957: ‘A Novel Nitric Oxide Donating Cox-2 Selective Inhibitor,’” MRK-AAD0287186, at 89.

oxide/naproxen combination, and Astra-Zeneca had in development a nitric oxide/aspirin. Both companies presented favorable gastrointestinal endoscopy data for their products at the Digestive Disease Week conference held in May 2002.⁹⁹

Following the Board of Scientific Advisors meeting, Dr. Kim instructed Drs. Shapiro and Turner to “move very aggressively” to “evaluat[e] the potential for combination of [nitric oxide]-ASA with Vioxx and Arcoxia. We should also look at the potential for [nitric oxide]-Vioxx and [nitric oxide]-Arcoxia.”¹⁰⁰ Dr. Scolnick reiterated Dr. Kim’s request: “we need to aggressivley [sic] try to licesne [sic] this. If you wait for all the public data it will be pursued by everyone else.”¹⁰¹

b. Decision to pursue a nitric oxide/Vioxx compound with NitroMed.¹⁰²

In the summer of 2002, MRL representatives had several preliminary meetings with NicOx, NitroMed, and Medinox, three companies specializing in products involving

⁹⁹ 7/22/02 presentation to Coxib Task Force, “Coxib add-ons and 2nd Generation Coxibs Strategy,” MRK-ABT0083768, at 88, 90.

¹⁰⁰ 5/5/02 email from P. Kim to B. Shapiro, M. Turner, B. Gertz, A. Nies, E. Scolnick, A. Ford-Hutchinson, D. Greene, S. Nichtberger, and T. Salzmann, MRK-AAC0106654.

¹⁰¹ 5/5/02 email from E. Scolnick to B. Gertz, MRK-AEE0001244.

¹⁰² In the months following the May 2002 Board of Scientific Advisors meeting, the Coxib Task Force met to review more generally “Coxib add-ons and 2nd Generation Coxibs Strategy.” See 7/22/02 slide presentation to Coxib Task Force, MRK-ABT0083768-95. One option that the Task Force considered was to develop a PGE synthase inhibitor. *Id.* at 91-94; 7/4/02 email from M. Turner to K. Grosser *et al.*, MRK-AEG0037354, at 55. MRL scientists theorized that inhibition of PGE2 synthesis could “achieve anti-inflammatory, analgesic and antipyretic effects without inhibition of the prostacyclin and thromboxane pathways.” 11/20/02 “RPRC Review: Arthritis/Immunology,” MRK-ABX0074353, at 390. MRL scientists therefore reasoned that PGE synthase inhibitors would not implicate the externally-raised concerns about selective Cox-2 inhibitors’ possible prothrombotic effects. *Id.* Although the PGE synthase inhibitor remained under consideration, it was characterized as a “backup” to the nitric oxide/Vioxx program. “Arthritis & Immunology Franchise Background Document: 2003 Princeton Annual MRL Review Meeting,” MRK-AAD0327302, at 04.

nitric oxide releasing compounds, and began considering not only a nitric oxide/Vioxx compound, but also a nitric oxide/aspirin or nitric oxide/NSAID compound.¹⁰³ On June 27, 2002, several MRL scientists, including Drs. Reicin, Nies, Turner, and DiBattiste, met with NicOx to review its nitric oxide/aspirin product.¹⁰⁴ MRL decided to decline the NicOx opportunity “since there appear to be several obstacles, including the need to administer the drug bid [twice daily] and the fundamentally different kinetics of platelet inactivation compared with aspirin.”¹⁰⁵

Three weeks later, on July 18, 2002, a similar group of MRL representatives met with both Medinox, which had developed nitric oxide blocking technology, and NitroMed, which had several different nitric oxide combination products in development.¹⁰⁶ The MRL team decided against pursuing the nitric oxide blocking technology held by Medinox, but continued communications with NitroMed about developing either a nitric oxide/Vioxx, nitric oxide/aspirin, or nitric oxide/naproxen combination drug.¹⁰⁷

¹⁰³ See 5/28/02 email from B. Shapiro to B. Gertz et al., MRK-AAC0107721; 5/30/02 email from M. Turner to T. Baille et al., MRK-ACD0119976.

¹⁰⁴ 8/23/02 memorandum from J. Lasota to P. Demain et al., MRK-AAD0238749, at 50.

¹⁰⁵ 8/23/02 memorandum from J. Lasota to P. Demain et al., MRK-AAD0238749, at 49. The Company later opted to pursue a research collaboration with NicOx, whereby NicOx provided Merck with “proprietary nitric oxide-donating compounds for evaluation in a preclinical testing program in an undisclosed therapeutic area.” 8/19/03 NicOx press release, “Merck & Co., Inc. and NicOx form research collaboration on Nitric Oxide-donating drugs,” NM01537.

¹⁰⁶ 8/23/02 memorandum from J. Lasota to P. Demain et al., MRK-AAD0238749, at 52-56.

¹⁰⁷ 8/23/02 memorandum from J. Lasota to P. Demain et al., MRK-AAD0238749, at 49-50.

NitroMed's initial proposal, prepared in March 2002, to develop a nitric-oxide enhanced selective Cox-2 inhibitor described as one rationale for the product: "there is evidence that COX-2 selective inhibitors limit endothelial prostacyclin (PGI₂) formation, potentially inciting a prothrombotic environment in the vasculature."¹⁰⁸ NitroMed suggested that, because it believed nitric oxide to be vasoprotective and inhibitory of platelet aggregation, its nitric oxide enhanced selective Cox-2 inhibitor "should mitigate the observed COX-2 related increases in adverse cardiovascular events."¹⁰⁹ MRL scientists' considerations of a nitric oxide/Vioxx combination, however, focused on the possibility of providing gastroprotection for patients taking Vioxx concomitantly with aspirin.¹¹⁰

¹⁰⁸ 3/02 document, "Vasoprotective Cyclooxygenase-2 Inhibitors: Second-Generation Medicines to Treat Pain and Inflammation with Beneficial Gastrointestinal and Cardiovascular Profiles," MRK-ABC0052007, at 09.

¹⁰⁹ 3/02 document, "Vasoprotective Cyclooxygenase-2 Inhibitors: Second-Generation Medicines to Treat Pain and Inflammation with Beneficial Gastrointestinal and Cardiovascular Profiles," MRK-ABC0052007, at 08-09. Even after Merck and NitroMed officially entered a collaboration to develop a nitric oxide/Vioxx, NitroMed made a presentation to Merck that included both a gastrointestinal and a cardiovascular rationale for the combination. 1/14/03 NitroMed slide presentation, "NO-COX-2 Selective Inhibitors (Merck Frosst/NitroMed Meeting)," NM05435, at 44 ("Systemically delivered NO may reduce the potential adverse cardiovascular risk of selective COX-2 inhibitors Locally delivered (gastric) NO may prevent the GI discomfort associated with selective COX-2 inhibitors and further reduce GI complications, particularly with aspirin usage. . . .").

¹¹⁰ A review of internal Merck documents indicates that MRL scientists viewed the combination as one that would allow co-administration of a selective Cox-2 inhibitor with aspirin, without harmful gastrointestinal side effects, not as a hedge against a possible prothrombotic effect of Vioxx. 8/8/02 email from M. Turner to Z. Wang *et al.*, MRK-AEG0037553; 9/12/02 email from M. Turner to J. Lasota, MRK-AEG0037638; *see* 7/7/22/02 presentation to Coxib Task Force, "Coxib add-ons and 2nd Generation Coxibs Strategy," MRK-ABT0083768, at 84; 9/6/05 email from C. Chan to J. Ellis, MRK-ALE0059022.

In October of 2003, on the basis of his review of a document prepared by NitroMed in connection with a potential initial public offering, a member of Merck's Marketing Department became concerned that NitroMed might express the view that the nitric oxide/Vioxx combination therapy was being developed to address a hypothetical cardiovascular risk of Vioxx. 10/1/03 email from

In a September 12, 2002 email to Ms. Joan Lasota – a member of Merck’s licensing organization who was working with NitroMed – Dr. Turner reviewed the purpose behind pursuing a nitric oxide/Vioxx license. He summarized four “issues surrounding coxibs,” the last of which addressed CV safety:¹¹¹

To: Lasota, Joan A
From: Turner, Mervyn
Cc: Nicholson, Donald; Demain, Pamela R.; Shapiro, Bennett M.; Young, Robert; Metters, Kathleen; Riendeau, Denis; Roy, Sophie
Bcc:
Received Date: 2002-09-12 21:20:43
Subject: RE: NitroMed

Joan,

Our goal is to identify an NO-coxib with a developable advantage. The primary issues surrounding coxibs are:

- 1) ability to co-dose with ASA and preserve GI-sparing properties
- 2) impairment of renal function, and associated edema
- 3) elevations in blood pressure -- perceived to be associated with effects on renal prostaglandin production, but unproven
- 4) concerns about cv safety, originally based on alterations in thromboxane/prostacyclin balances, but subsequently by the outcome of the VIGOR study. We do not believe that the VIGOR study represents a true prothrombotic property of coxibs.

Dr. Turner had earlier emphasized that Merck’s “first goal was a form of Vioxx which can be codosed with ASA without risking any of the excellent GI tolerability of Vioxx [and its] second goal was to determine whether there are any other advantages in the form of beneficial effects on the kidney, hypertension (linked?) or [cardiovascular] systems.”¹¹² Put differently, Merck’s primary aim was to design a

M. Stejbach to P. Demain et al., MRK-ACW0051261-62 (“We can’t be in a position of having [NitroMed] (even if inadvertently) creating the impression (or allowing an opposing attorney to create the impression) that we are pursuing NO-enhancement to ‘fix the CV issue.’”).

Additionally, in September 2005, one year after Merck and NitroMed had terminated the development of a nitric oxide/Vioxx combination, an MRL scientist expressed the concern that an abstract prepared by NitroMed “inappropriately ties development of NO-Coxibs with cardiovascular risk. . . . This is not consistent with Merck’s hypothesis for an NO-coxib combination.” 9/6/05 email from C. Chan to J. Ellis*, MRK-ALE0059022.

¹¹¹ 9/12/02 email from M. Turner to J. Lasota, MRK-AEG0037638, at 38.

¹¹² 8/8/02 email from M. Turner to Z. Wang et al., MRK-AEG0037553.

nitric oxide/Vioxx combination product that would provide additional gastrointestinal protection so that it could be safely co-administered with aspirin. Any potential cardiovascular benefit derived from the nitric oxide/Vioxx combination alone, without concomitant administration of aspirin, was highly theoretical.

The collaboration between NitroMed and MRL was presented to Merck's Board of Directors for approval on November 21, 2002,¹¹³ and Merck entered into an agreement with NitroMed on December 12, 2002.¹¹⁴ Thereafter, the Company began conducting preliminary trials on the nitric oxide/Vioxx combination, including animal studies and endoscopy studies.¹¹⁵ On June 21, 2004, Merck and NitroMed announced the initiation of Phase II studies on their nitric oxide/coxib combination.¹¹⁶ The preliminary endoscopy study results were released on September 29, 2004, and showed increased gastrointestinal erosion for patients taking nitric oxide/Vioxx plus aspirin as compared with patients taking conventional Vioxx plus aspirin.¹¹⁷ Shortly thereafter, Merck

¹¹³ 11/21/02 memorandum from P. Kim to Board of Directors, MRK-AIC0001594-96.

¹¹⁴ 12/13/02 email from P. Demain to J. Lasota, "NitroMed Deal Signed!," MRK-ABX0068813.

¹¹⁵ 7/21/04 slide presentation, "NO-Rofecoxib plus Aspirin 12-week Endoscopy Study," MRK-ACM0006314-18; 2/24/04 memorandum from K. Grosser and A. Plump to EDRC, MRK-ABP0028703-34.

¹¹⁶ 6/18/04 email from J. Skidmore to M. Turner, A. Reicin *et al.*, MRK-AAD0404604.

¹¹⁷ 9/28/04 memorandum from Y. Wan to E. Maller, MRK-AAD0326727, at 28.

withdrew Vioxx from the market and halted its testing of a nitric oxide/Vioxx
combination therapy.¹¹⁸

* * *

¹¹⁸ 9/30/04 NitroMed press release, "Merck and NitroMed Halt Phase II Testing of Nitric Oxide-Enhancing COX-2 Inhibitor," NM06324; 10/1/2004 email from P. Huang to L. Hostelley, MRK-AIU0177474.