FDA Comment 2: Please provide the actual mean fecal blood loss during the study period measured in ml/day.

MRL Response: Raw data were provided in an appendix to the Clinical Study Report (Table 4.10.5 from P050 in the original NDA). A hard copy is included as Attachment 4 with this response. These data present fecal blood loss on each study day for each subject, measured in milliliters (mL).

In a subsequent teleconference, the reviewer requested an analysis of blood loss without geometric transformation. Therefore, this response provides analyses of arithmetic mean data (Tables 5-8). A limitation of this analysis is that it does not allow comparison to the comparability bound prespecified by the protocol; this comparability bound was based on geometric mean ratios, after reviewing individual patient data from a previous fecal red blood cell loss study.

As indicated by the increasing SD with increasing arithmetic mean in Tables 5 and 6, a log transformation of the data, as planned in the Protocol and reported in the CSR, is necessary in order to satisfy the homogeneity and normality assumptions for the analysis. Results based on data without log transformation are provided in Tables 7 and 8 for reference purposes only; no conclusions should be drawn from them because of departures from assumptions necessary for valid ANOVA conclusions. Results of per-protocol and intention-to-treat analyses were consistent. Rofecoxib 25 mg, rofecoxib 50 mg, and placebo are all significantly different from ibuprofen, and are not statistically different from each other.

Table 5

Intention-to-Treat Summary Statistics for Daily Fecal Blood Loss (ml/day) (Protocol 050)

Period	Treatment	N	Arithmetic Mean (SD)	84% CI
Baseline	Placebo	17	0.33(0.11)	(0.29, 0.37)
	MK-0966 25 mg qd	17	0.34(0.11)	(0.30, 0.38)
	MK-0966 50 mg qd	18	0.33(0.13)	(0.28, 0.37)
	Ibuprofen 800 mg tid	13	0.39(0.17)	(0.32, 0.46)
Week 1	Placebo	17	0.46(0.26)	(0.37, 0.56)
	MK-0966 25 mg qd	17	0.49(0.13)	(0.45, 0.54)
	MK-0966 50 mg qd	18	0.52(0.39)	(0.38, 0.65)
	Ibuprofen 800 mg tid	13	1.21(0.47)	(1.02, 1.41)
Week 2	Placebo	17	0.51(0.15)	(0.46, 0.56)
	MK-0966 25 mg qd	17	0.64(0.16)	(0.58, 0.69)
	MK-0966 50 mg qd	18	0.68(0.59)	(0.48, 0.88)
	Ibuprofen 800 mg tid	13	1.84(1.11)	(1.38, 2.30)
Week 3	Placebo	17	0.76(0.35)	(0.63, 0.88)
	MK-0966 25 mg qd	17	0.93(0.33)	(0.81, 1.05)
	MK-0966 50 mg qd	18	0.90(0.50)	(0.72, 1.07)
	Ibuprofen 800 mg tid	13	2.01(1.12)	(1.55, 2.47)
Week 4	Placebo	17	0.88(0.26)	(0.78, 0.97)
	MK-0966 25 mg qd	17	1.03(0.24)	(0.94, 1.11)
	MK-0966 50 mg qd	18	1.17(0.94)	(0.85, 1.50)
	Ibuprofen 800 mg tid	13	2.33(2.49)	(1.29, 3.36)

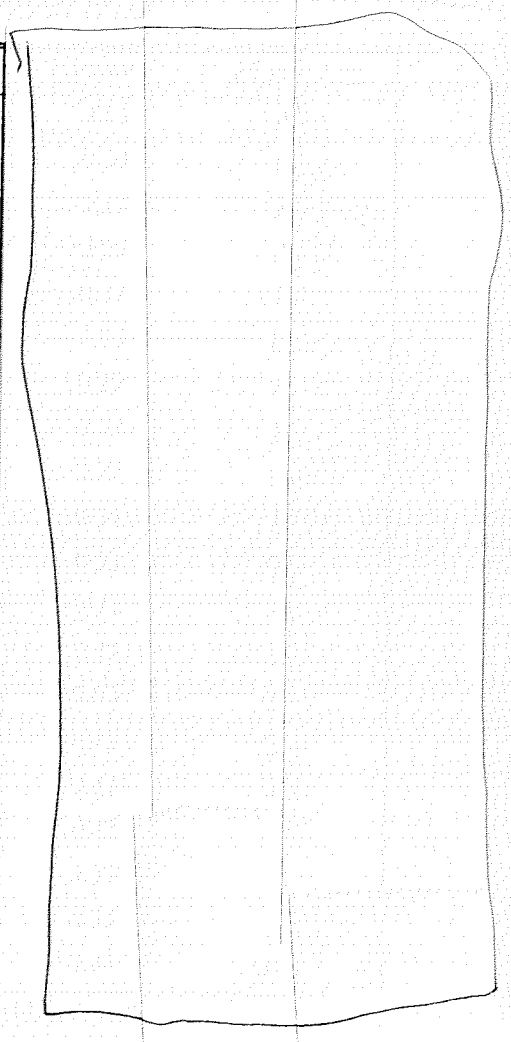


Table 6

Per-Protocol Summary Statistics for Daily Fecal Blood Loss (ml/day) (Protocol 050)

Period	Treatment	N	Arithmetic Mean (SD)	84% CI
Baseline	Placebo	15	0.34(0.11)	(0.30, 0.38)
	MK-0966 25 mg qd	16	0.34(0.11)	(0.30, 0.38)
	MK-0966 50 mg qd	17	0.33(0.13)	(0.28, 0.37)
	Ibuprofen 800 mg tid	12	0.40(0.17)	(0.32, 0.47)
Week 1	Placebo	15	0.48(0.27)	(0.37, 0.59)
	MK-0966 25 mg qd	16	0.48(0.12)	(0.44, 0.53)
	MK-0966 50 mg qd	17	0.51(0.40)	(0.36, 0.65)
	Ibuprofen 800 mg tid	12	1.22(0.49)	(1.01, 1.43)
Week 2	Placebo	15	0.52(0.15)	(0.46, 0.58)
	MK-0966 25 mg qd	16	0.63(0.16)	(0.57, 0.69)
	MK-0966 50 mg qd	17	0.69(0.61)	(0.47, 0.90)
	Ibuprofen 800 mg tid	12	1.92(1.12)	(1.43, 2.40)
Week 3	Placebo	15	0.70(0.20)	(0.62, 0.78)
	MK-0966 25 mg qd	16	0.94(0.34)	(0.82, 1.06)
	MK-0966 50 mg qd	17	0.84(0.45)	(0.68, 1.00)
	Ibuprofen 800 mg tid	12	2.09(1.13)	(1.60, 2.58)
Week 4	Placebo	15	0.91(0.26)	(0.81, 1.01)
	MK-0966 25 mg qd	16	1.02(0.24)	(0.93, 1.11)
	MK-0966 50 mg qd	17	0.99(0.53)	(0.80, 1.18)
	Ibuprofen 800 mg tid	12	2.44(2.57)	(1.33, 3.56)

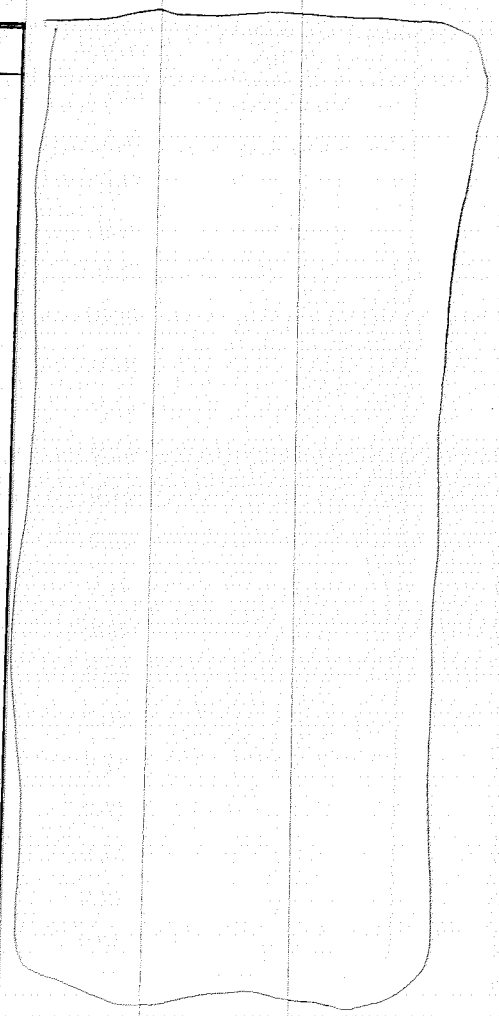


Table 7

Intention-to-Treat Analysis of Weeks 2-4 Daily Fecal Blood Loss (ml/day) (Protocol 050)

Treatment	N	Baseline Arithmetic Mean	Weeks 2-4 Arithmetic Mean	Weeks 2-4 /Baseline Ratio LS Mean	95% CI for Weeks 2-4/Baseline Ratio
Placebo	17	0.33	0.71	2.19	(0.91, 3.47)
MK-0966 25 mg qd	17	0.34	0.86	2.69	(1.41, 3.98)
MK-0966 50 mg qd	18	0.33	0.92	2.72	(1.47, 3.96)
Ibuprofen 800 mg tid	13	0.39	2.06	6.22	(4.74, 7.71)

Between-Treatment Comparison	Between-Treatment Difference of Weeks 2-4/Baseline Ratios	90% CI for Between-Treatment Difference	p-Value
MK-0966 25 mg qd vs Placebo	0.51	(-1.01, 2.02)	0.578
MK-0966 50 mg qd vs Placebo	0.53	(-0.96, 2.02)	0.557
Ibuprofen 800 mg tid vs Placebo	4.04	(2.39, 5.68)	<0.001
MK-0966 50 mg qd vs MK-0966 25 mg qd	0.02	(-1.47, 1.51)	0.981
Ibuprofen 800 mg tid vs MK-0966 25 mg qd	3.53	(1.89, 5.17)	0.001
Ibuprofen 800 mg tid vs MK-0966 50 mg qd	3.51	(1.88, 5.14)	0.001

Effect	P-value
Treatment	0.001
Baseline	0.066
Baseline by Treatment Interaction	0.484

Pooled SD for log Percent of Baseline	2.640

Table 8

Per-Protocol Analysis of Weeks 2-4 Daily Fecal Blood Loss (ml/day) (Protocol 050)

Treatment	N	Baseline Arithmetic Mean	Weeks 2-4 Arithmetic Mean	Weeks 2-4 /Baseline Ratio LS Mean	95% CI for Weeks 2-4/Baseline Ratio
Placebo	15	0.34	0.71	2.12	(0.74, 3.50)
MK-0966 25 mg qd	16	0.34	0.86	2.69	(1.35, 4.03)
MK-0966 50 mg qd	17	0.33	0.84	2.47	(1.17, 3.77)
Ibuprofen 800 mg tid	12	0.40	2.15	6.47	(4.91, 8.04)

Between-Treatment Comparison	Between-Treatment Difference of Weeks 2-4/Baseline Ratios	90% CI for Between-Treatment Difference	p-Value
MK-0966 25 mg qd vs Placebo	0.57	(-1.03, 2.18)	0.552
MK-0966 50 mg qd vs Placebo	0.35	(-1.23, 1.93)	0.713
Ibuprofen 800 mg tid vs Placebo	4.35	(2.61, 6.10)	<0.001
MK-0966 50 mg qd vs MK-0966 25 mg qd	-0.22	(-1.78, 1.33)	0.811
Ibuprofen 800 mg tid vs MK-0966 25 mg qd	3.78	(2.06, 5.51)	0.001
Ibuprofen 800 mg tid vs MK-0966 50 mg qd	4.00	(2.29, 5.72)	<0.001

Effect	P-value
Treatment	<0.001
Baseline	0.054
Baseline by Treatment Interaction	0.399

Pooled SD for log Percent of Baseline	2.666

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/shilling/ltr/606

Attachment

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Lawrence Goldkind, HFD-180, PKLN 6B-24, Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

ORIGINAL

These copies are
OFFICIAL FDA Copies
not desk copies

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

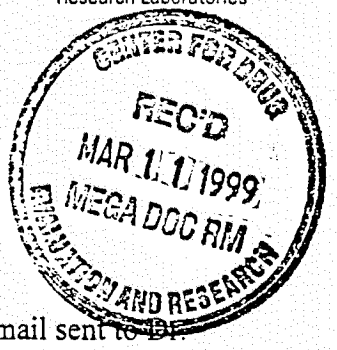
March 10, 1999

NEW CORRESP

NC

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MERCK
Research Laboratories



Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets
Response to FDA Request

Reference is made to the above New Drug application (NDA) and to an e-mail sent to Dr. R. Silverman (Merck Research Laboratories [MRL]) from Ms. S. Cook (FDA) on march 5, 1999 with a request from the PK reviewer.

By this letter, we are responding to this request.

FDA Comment: Please provide a copy of, or the location of, the case report form for Study 057-00, Patient #1. Please include the Pugh score calculation.

MRL Response: The requested case report form is attached.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/shilling/ltr/612
Attachment
Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

March 10, 1999

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MERCK
Research Laboratories

Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets
Response to FDA Request

Reference is made to the above New Drug Application (NDA) and to an e-mail sent to Dr. R. Silverman (Merck Research Laboratories [MRL]) from Ms. S. Cook (FDA) on March 1, 1999 with a request from the GI Reviewer.

By this letter, we are responding to the Agency's request.

FDA Comment 1: Please provide data on colitis, bloody diarrhea and rectal bleeding from your clinical experience data base. If these endpoints were not captured, please provide the closest AE event definition that you have.

MRL Response: All digestive system adverse event verbatim terms (those used by investigators on adverse experience worksheets) in the Integrated Summary of Safety clinical adverse experience database were reviewed by a gastroenterologist and the following dictionary terms were identified as relevant:

- **hematochezia**
- **rectal bleeding**
- **bleeding hemorrhoid**
- **bloody diarrhea**
- **colitis**

The numbers of events in each combined treatment group were small and some cases may be of uncertain clinical significance. However, a crude rate analysis of the adverse experience terms above is provided (Attachment 1), in which patients with more than one event were only counted once. Crude rates for all terms combined were 0.7%, 0.6%, and 0.6% in the combined placebo, rofecoxib and NSAID groups, respectively. There were 112, 1533, and 647 patient-years of exposure in the combined placebo, rofecoxib and NSAID groups, respectively. The rates per patient-year were therefore 4.5%, 1.4%, and 1.4% in the combined placebo, rofecoxib and NSAID groups, respectively.

A listing table of the cases identified (Attachment 2) displays treatment assignment, allocation number, protocol number, verbatim term, MRL dictionary term, relative day of treatment for the onset of the event, duration, intensity, whether the event was serious, drug relationship, action taken with the study drug (PRx), and event-related procedures and medications. Two patients had two events each; the allocation numbers of these patients are in bold.

The Clinical Comments section of Attachment 1 includes only information directly from the clinical trials databases, which were frozen prior to unblinding.

Several cases are worthy of additional comment:

- AN 8209 (diclofenac 150 mg): Rectal bleeding occurred 24 days after last dose of study medication.
- AN 447 (rofecoxib 50 mg): "Worsening colitis" reported in a patient with an active history of Irritable Bowel Syndrome (IBS) and no history of true colitis. No evidence of colonic inflammation; treatment was for IBS.
- AN 4249 (rofecoxib 5 mg): Rectal bleeding occurred while patient was in the Protocol 029 base study, assigned to rofecoxib 5 mg daily.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/shilling/ltr/603

Attachment

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

DESK COPY

March 10, 1999

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets
Response to FDA Request

Reference is made to the above New Drug Application (NDA) and a telephone conversation between Dr. Goldkind (FDA) and Dr. Silverman (Merck Research Laboratories [MRL]) on February 25, 1999 during which Dr. Goldkind requested clarification related to the blinding of the adjudication process for clinical events in Protocol 069.

By this letter, MRL is responding to the Agency' request.

FDA Comment: The clinical study report for protocol 069 states that adjudications occurred after monitoring staff were unblinded. Please document the extent to which unblinded personnel were involved in the assembly of data for adjudication packages.

MRL Response: A coordinating center was established to handle all communications with the external review committee. Coordinating Center personnel and Case Review Committee members were blinded to the treatment allocation of all cases until all final adjudications were complete, and the clinical event database was declared clean for analysis. The final adjudication data were not provided to the statistical analyst until after all final adjudications were complete and the clinical event database was declared clean for analysis. A policy was established to keep serious adverse events that were also PUB cases blinded when they were reported to FDA and in files at MRL.

Clinical monitors were blinded to treatment assignment for all PUB cases while information was being provided to the Coordinating Center, with two exceptions:

Case number 15 was mistakenly unblinded in the department responsible for adverse experience reporting (Worldwide Product Safety and Epidemiology); the clinical monitor and investigator became aware of the treatment assignment, and the package was subsequently prepared for adjudication. This case was adjudicated as a confirmed, complicated case.

In another case (case number 37), the Coordinating Center requested a specific endoscopy report from a medical program coordinator (an assistant to the clinical monitor) after the study was unblinded to MRL clinical personnel. This individual contacted the site, obtained the report, and provided it unaltered to the Coordinating Center. The requested endoscopy report was created prior to unblinding. The case was adjudicated as a confirmed, uncomplicated case.

Except for the two cases described above, no clinical monitor was unblinded to the treatment assignment for a PUB case until after all data had been provided to the Coordinating Center for that case.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/shilling/ltr615

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317
Dr. Lawrence Goldkind, HFD-180, PKLN 6B-24, Federal Express #2

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

DESK COPY

March 10, 1999

MERCK
Research Laboratories

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets
Response to FDA Request

Reference is made to the above New Drug Application (NDA) and to a fax sent on February 26, 1999, to Dr. R. Silverman (Merck Research Laboratories [MRL]) from Mr. A. Zecolla (FDA) requesting information for the Medical Officer.

By this letter, we are responding to this request.

FDA Comments: Please provide an analysis of abdominal pain on the study 069 data base. Please provide an analysis of heartburn alone and of nausea and vomiting (considered together) for study 069 database.

MRL Response: The requested analyses are provided in this response.

By way of introduction, we note that the MK-0966 Protocol 069 data analysis plan prespecified the following secondary hypothesis: "The incidence of NSAID-type GI symptoms will be less in the group of patients treated with MK-0966 than in that treated with NSAID comparators nabumetone, ibuprofen, and diclofenac." NSAID-type GI symptoms were predefined, and included spontaneously reported AEs that coded to the Merck AE broader Dictionary terms of acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea, or vomiting. This grouping was based in part on published analyses of Meloxicam [1, reference listed in Attachment]. Because the Merck AE Dictionary structure codes a variety of spontaneously reported AEs to the term "abdominal pain", many of which are non-specific or include symptoms that are clearly not of interest to the analysis, the term abdominal pain was not included in the list of predefined NSAID-type GI symptoms.

In Protocol 069 we based symptom comparisons on the combined incidence of a predefined set of GI symptoms. Because of the variability in how different patients and physicians report GI symptoms, we did not believe that distinctions among the many different individual terms would be meaningful.

Although analyses of abdominal pain were not pre-specified, post hoc analyses of this AE were performed and reported in the MK-0966 Protocol 069 clinical study report in the original NDA [see page 107: Section II.C.3.c.3) - Abdominal Pain And Diarrhea, and Appendices 4.1.93 through 4.1.96]. These analyses showed that compared to NSAIDs, MK-0966 was associated with a statistically significantly lower incidence of all reported abdominal pain over 12 months (relative risk 0.71, 95% CI 0.54, 0.93; p=0.012). These results were corroborated by analyses of abdominal pain AEs that were considered by the investigator to be drug-related. For convenience, these analyses are attached to this response (Tables 2, 4, 5 and 7 below are identical to Appendices 4.1.93, 4.1.94, 4.1.95, and 4.1.96, respectively, in the MK-0966 Protocol 069 clinical study report).

The MK-0966 Protocol 069 analyses of NSAID-type GI AEs and abdominal pain were performed both with and without stratification by type of study. Analyses with type of study as a stratification factor showed very similar results to those of the unstratified analyses, indicating there was no confounding by type of protocol.

In response to the Agency's request, MRL performed survival analyses for incidence of heartburn alone, and for the incidence of nausea and vomiting considered together in the population of MK-0966 Protocol 069. These were done using the same approaches to the analysis as for the incidence of NSAID-type GI AEs in the Protocol 069 clinical study report. The detailed summary and analysis results are attached.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

Attachment

q/shilling/ltr/599a

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Lawrence Goldkind, HFD-180, PKLN 6B-24, Federal Express #2