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Study 069: A multicenter study: Vioxx Phase III: Gastrointestinal clinical event monitoring plan and case review committee procedures

The sponsor's intent in this study was to ascertain nonendoscopic safety data from the clinical experience in the drug development program to compliment the endoscopic data. While important, endoscopic ulcers are but one parameter of NSAID safety. There is little correlation between symptoms and ulcers and in the range of a log scale difference between endoscopic ulcers and clinical complications such as severe pain, bleeding perforation and obstruction. Furthermore, not all NSAID toxicity is related to discrete gastroduodenal ulcers. Esophageal and small bowel injury occurs in association with NSAID use and as noted above symptomatic UGI symptoms frequently occur without discrete gastroduodenal mucosal injury.

Serious UGI adverse events such as significant bleeding perforation or obstruction are relatively rare and any one of the studies in the submission would be too small to ascertain adequate data on clinically significant complications. Reference #1 by Silverstein et al reported on a large simple trial that studied over 8000 patients to show a 40% drop in NSAID related complications as defined by the author of the article.

The current "study" was an attempt to analyze data from eight studies that were all randomized, blinded and active controlled. Some were placebo controlled. They were studies of efficacy and safety. Two of these studies utilized scheduled endoscopic safety endpoints. Study 069 was designed and amended while investigators and sponsor were blinded to the results of the individual studies.

This study was an analysis of a composite endpoint of several adverse events called " PUB" that are associated with the use of NSAIDs. The term PUB is an acronym for perforation, ulcer and bleed. The "ulcer" in the acronym could literally refer to any ulcer of any size found and identified in any clinical context. The term is generally reserved for clinically meaningful ulcers. Most authors use this acronym to designate serious or clinically relevant adverse events. Historically, in the medical literature ascertainment of "PUBs" occurred only when patients experienced significant symptoms felt to warrant endoscopic, radiographic or even surgical evaluation. This type of ascertainment forms the basis for most of the medical literature that employs the term PUB. It is not typical of the medical literature to define an asymptomatic research protocol related endoscopic ulcer as a PUB. As the field of NSAID toxicity mushroomed in the 1980's and 1990's endoscopic studies were designed and have repeatedly shown that most NSAID ulcers are asymptomatic and most UGI symptoms in patients on NSAIDs are not due to ulcers. The new endpoint "endoscopic ulcer" was born. These facts have not yet been fully integrated into the definitions and endpoints of studies of NSAID toxicity but the designation of a PUB, as a clinically derived endpoint remains operative and distinct from "endoscopic

ulcers" that are study protocol defined. This distinction is the basis for the Merck clinical development program for Vioxx to include endoscopic studies 044 and 045 in addition to a clinically defined ulcer study 069. As will be discussed later, the actual endpoints used to ascertain this type of data are problematic.

One result of the historical development of the PUB composite endpoint is that it combines endpoints with markedly different public health implications. An ulcer causing pain is clinically relevant, associated with some morbidity and is an important safety profile endpoint. It does not however, have the magnitude of morbidity that is associated with perforation, obstruction or bleeding. These highly morbid events have driven the development of new drugs and public health warnings about NSAIDs. A composite endpoint that combines symptomatic ulcers and complicated ulcers is not ideal for defining health risk. If the data from a "PUB" study are primarily composed of symptomatic ulcers and there is little data on bleeding, perforation, obstruction or other morbid events, the results may be misleading regarding the safety profile of a drug. The sponsor dealt with this issue in a post hoc fashion with an exploratory analysis of complicated upper-GI PUBs. This reviewer considers these data to be of major and independent importance alongside the total confirmed PUB data.
An additional problem with using a symptomatic ulcer as a critical endpoint is that the definition will vary from practitioner to practitioner and the threshold for endoscopy varies from setting to setting. This is an inherent problem with subjective endpoints. Combining subjective and objective data creates a hybrid endpoint that is even more difficult to interpret. Both types are valid independently and best measured and evaluated independently. If symptomatic ulcers were surrogates for complicated ulcers, one may consider symptomatic ulcers as a valid independent indicator of risk of ulcer complications. Available medical literature indicates that this is not the case. In fact a significant proportion of NSAID ulcer complications are silent up until the associated bleed, perforation or obstruction occurs. Some authors have suggested that the analgesic effects of NSAIDs account for this phenomenon. Another theory is that patients discontinue a drug associated with symptoms and therefore prevent progression to a complication. Regardless, symptomatic ulcers cannot be accepted as precursors or surrogates for ulcer complications.

Study Objective

The sponsor's stated objective in study 069 was to ascertain clinically relevant events. This fact is clearly expressed in the original protocol synopsis approved 8/18/97 on page 8 under the section "Definitions":

"The GI clinical events of interest include two distinctly different types of events: "clinically significant upper-GI PUBs" and "NSAID-type GI symptoms". Each type of event represents a different aspect of the GI safety and tolerability of MK-0966"

In the final version of the protocol the sponsor made adjustments to the definition of a clinically significant ulcer in order to minimize the bias in including data from the two

studies (044 and 045) with 4 protocol driven endoscopies per patient. These studies represent a large portion of the patients enrolled in the study of Vioxx and the vast majority of exposure to the 50-mg. dose. As stated in the protocol section on evaluation criteria for ulcers :

> "Because surveillance endoscopy is not performed routinely in practice, many ulcers found at scheduled endoscopy would not typify "PUB" events found in practice. Therefore, ulcers were included for analysis only if they were discovered at an unscheduled endoscopy."

Unscheduled endoscopy, defined solely by a date window, was specified a priori as a proxy measure of "for cause" endoscopy, based on input from expert gastroenterologists and epidemiologists. This definition may have been influenced by the desire to include data from the two endoscopic studies that comprised a large portion of the clinical data generated during the development of Vioxx. This reviewer considers this definition to significantly depart from the goal of study 069 and resulted in an endpoint that ascertained ulcers that were not clinically relevant and did not represent clinical "PUBs".

This artificial definition of the study endpoint ultimately resulted in the inclusion of many ulcers found in asymptomatic patients who had their protocol mandated procedure outside this artificial window as well as patients that had endoscopies done for indications that preceded entry into the clinical trials. A more reasonable approach may have been to model PUB ascertainment on the basis of protocol mandated unscheduled endoscopies described in study 044 and 045. "For cause" endoscopies were mandated if "a patient developed moderate to severe upper gastrointestinal symptoms for 2 days or more or other circumstances developed that would suggest the need for discontinuation". The ultimate definition chosen by the sponsor does not rely on clinical criteria. This definition shapes the data and the results are less valuable for studying the specified hypotheses. A recalculation using more appropriate endpoints was requested of the sponsor and is presented along with the sponsor generated endpoint data.

There were several other study endpoints as well that are reproduced below:

"Hypotheses
1) Primary Hypothesis
The incidence of confirmed upper-GI PUBs will be less in the group of patients treated with MK-0966 (12.5, 25, and 50 mg combined) than in those treated with NSAID comparators (nabumetone, ibuprofen, and diclofenac, combined treatment groups).
2) Secondary Hypotheses
a) The incidence of any (confirmed plus unconfirmed) upper-GI PUBs will be less in the group of patients treated with MK-0966 (doses combined) than in the group treated with NSAID comparators nabumetone, ibuprofen, and diclofenac (combined treatment groups).

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b) The incidence of any (confirmed plus unconfirmed) upper-GI PUBs will be less in the group of patients treated with placebo than in the group treated with NSAID comparators nabumetone, ibuprofen, and diclofenac (combined treatment groups).
c) The incidence of discontinuation due to GI adverse experience (AE) will be less in the group of patients treated with MK-0966 (doses combined) than in the group treated with NSAID comparators nabumetone, ibuprofen, and diclofenac (combined treatment groups).
d) The incidence of discontinuation due to GI AE will be less in the group of patients treated with placebo than in the group treated with NSAID comparators nabumetone, ibuprofen, and diclofenac (combined treatment groups).
e) The incidence of NSAID-type GI symptoms will be less in the group of patients treated with placebo than in the group treated with NSAID comparators, nabumetone, ibuprofen, and diclofenac (combined treatment groups).
f) The incidence of NSAID-type GI symptoms will be less in the group of patients treated with MK-0966 (doses combined) than in the group treated with NSAID comparators nabumetone, ibuprofen, and diclofenac (combined treatment groups)."

The statistical endpoints are reproduced below:

" **Statistical Endpoints**
1) Primary
The primary endpoint was incidence of confirmed upper-GI PUBs. Time to the first event for each patient was used for between-treatment comparisons.
2) Secondary
Confirmed or Unconfirmed Upper-GI PUBs
The incidence of confirmed plus unconfirmed upper-GI PUBs was a secondary endpoint. Time to the first event for each patient was used for between-treatment comparisons.
Discontinuation Due to GI Adverse Experiences
The incidence of discontinuation due to GI AE was a secondary endpoint. Time to the discontinuation for each patient was used for between-treatment comparisons. A GI AE was a spontaneously reported AE for which the body system was categorized as digestive. The subset of discontinuation due to NSAID-type GI AEs was also analyzed.
NSAID-type GI Symptoms
The incidence of NSAID-type GI symptoms was a secondary endpoint. Six GI AE terms (acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea or vomiting) were prespecified to comprise this endpoint. Time to the first event for each patient was used for between-treatment comparisons.

A standard analysis of drug-related NSAID-type GI AEs was also performed."

There was no set endpoint defined for statistical purposes. The sponsor did analyses at week 6, month 4, month 6, month 12 and month 24.

Study design:

Procedures for data collection, monitoring, auditing, and documentation of events were prespecified in the protocol. Investigators were instructed to report all suspected upper-GI PUBs. Investigators initiated the reporting of a suspected event using both standard AE reporting procedures and a case report form specifically for this purpose. The Clinical Monitors for each study reviewed the PUB reports and case report forms, and when necessary, requested clarification or additional information. A clinical event package (with masked protocol and treatment information) containing source documentation about each case was assembled for each investigator-reported upper-GI PUB. Spontaneous reports of AE (with a focus on the gastrointestinal tract) and early discontinuations due to GI AE were pooled from the individual clinical trials. A Case Review Committee (CRC), consisting of three independent consultants, reviewed the clinical event packages in a blinded manner. The committee adjudicated whether events were confirmed and whether they were complicated based on prospectively developed definitions of upper-GI PUBs.

One potential problem with the study was the fact that most cases were unblinded by the time the adjudication process was performed. The sponsor notes in the quote below the level of blinding that remained.

> "The protocol [3.2.1] specified that the adjudication would be performed for each patient before unblinding of the study containing that patient (with the exception of MK-0966 Protocol 029). However, this proved to be impractical because of difficulty scheduling adjudication meetings of the external Case Review Committee (CRC) and because of delays in the receipt of source documentation from sites. As a result, most cases (n=50) were adjudicated after the study containing the case had been unblinded to the statistician and clinical monitor specifically assigned to the study. Nevertheless, the PUB surveillance, data collection, and case adjudication process remained blinded. Site personnel were blinded to treatment at the time that case report forms and AE reports were completed, and while source documents were being collected. All Merck personnel involved in the adjudication process remained blinded to treatment of all PUB cases until after all cases had been adjudicated, and after a clean file containing the adjudication data was delivered for analysis. Lastly, the CRC remained blinded to treatment allocation of all cases."

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It appeared that many investigators did not deliver the prespecified type of primary source material mandated in the original protocol. This problem may have warranted the amendment to the protocol that minimized the amount of corroborating data required from the investigator. A narrative written by a Merck representative was used in many cases as substitutes for the primary source documents. The investigators were asked to sign these narratives.
The definitions used for the multiple categories of "PUBs" are shown in table 50.

Table 50

GI Clinical Event Classification, Definitions, and Criteria—Upper-GI Perforations, Ulcers, and Bleeds (Upper-GI PUBs)

Event	Criteria for Confirmed Event	Criteria for Clinically Complicated Event
Upper-GI Perforations, Ulcers, and Bleeds (Upper-GI PUBs) (cont.)		
Development of clinically significant upper-GI (esophageal, gastric, or duodenal) hemorrhage	Report of upper-GI hemorrhage fulfilling one or more of the following: 1. Physician-documented frank hematemesis (distinguished from blood tinged or streaked emesis). 2. Physician-documented frank melena (distinguished from other dark stool, e.g., that due to bismuth salts). 3. Heme-positive stool associated with a documented upper-GI lesion judged to be the source of the bleeding. 4. Active upper-GI bleeding documented by endoscopy or angiography.	Upper-GI hemorrhage having (or being associated with) one or more of the following features: 1. Significant bleeding/volume loss† 2. Transfusion of blood or packed red blood cells
† Criteria for significant bleeding/volume loss: one or more of the following is temporally related to the event: a. Decrease in hemoglobin >2 gm/dL (or >5% drop in hematocrit if hemoglobin not available) b. Evidence of orthostatic (sitting to standing, or lying to sitting) pressure changes; one or more of: 1) pulse rate increase of >20 BPM 2) decrease in SBP >20 mm Hg 3) decrease in DBP >10 mm Hg c. Other evidence of significantly reduced circulatory volume (e.g., shock, or significant hypotension corrected by volume replacement).		

Data Source: [3.2.1]

GI Clinical Event Classification, Definitions, and Criteria—Upper-GI Perforations, Ulcers, and Bleeds (Upper-GI PUBs)

Event	Criteria for Confirmed Event	Criteria for Clinically Complicated Event
Upper-GI Perforations, Ulcers, and Bleeds (Upper-GI PUBs)		
Gastric or duodenal perforation	Report of gastric or duodenal perforation confirmed by one or more of the following: 1. Endoscopy 2. Surgery 3. Unequivocal radiographic results consistent with free intraperitoneal air or extravasation of contrast media 4. Autopsy	Not applicable. All gastric or duodenal perforations are classified as complicated.
Development of active gastric ulcer (GU) or duodenal ulcer (DU)	Report of GU or DU confirmed by one or more of the following: 1. Endoscopy 2. Surgery 3. Unequivocal radiological evidence of active GU or DU on upper-GI series with contrast 4. Autopsy	GU or DU having (or being associated with) one or more of the following features: 1. Giant ulcer (≥3.0 cm diameter GU, ≥2.0 cm diameter DU) 2. Stigmata of bleeding (active bleeding or visible vessel on endoscopy) 3. Obstruction due to active GU or DU 4. Confirmed clinically significant upper-GI hemorrhage (definition follows on next page)

In order to use these definitions other pertinent definitions were required and are reproduced below.

- Melena—passage of dark-colored, tarry stools, due to the presence of blood altered by the intestinal juices;
- Hematemesis—vomiting of blood;
- Physician documented—an event directly observed by the investigator or reported to the investigator in written or oral form by a physician or other health care professional judged by the investigator to be fully credible;
- Obstruction—strong evidence of gastric outlet obstruction on a barium contrast study, nuclear medicine scan or saline load test accompanied by a gastric or duodenal ulcer (demonstrated on a barium contrast study or endoscopy) in an anatomical position consistent with mechanical outlet obstruction; or gastric outlet obstruction documented during surgery, accompanied by a gastric or duodenal ulcer.

In adjudicating events the committee did not appear to require documentation of the source of the color change associated with the term melena. While the definitions above confirm that "melena" requires more documentation than color description, adjudicators did not always appear to require this. Likewise the requirement that a health care professional directly observe melena or hematemesis was interpreted in some cases to mean that a report by a patient of "melena" was confirmed.

"An upper-GI PUB was judged "unconfirmed" if it did not meet criteria for being a "confirmed" event, and "uncomplicated" if it did not meet the criteria for a clinically complicated event. Therefore, the CRC could classify an upper-GI PUB into 1 of 4 categories: confirmed/complicated, confirmed/uncomplicated, unconfirmed/complicated, and unconfirmed/ uncomplicated."

The term unconfirmed suggests that an event may have occurred but simply lacked a piece of evidence required to meet arbitrary prespecified criteria. On review of the case reports in this study, unconfirmed cases included cases such as 1) pain without an ulcer found at endoscopy, 2)patient reports of "melena" without any confirmatory data such as signs of occult GI bleeding, drop in hemoglobin or endoscopic ulcers and 3) a patient with heartburn and gastric erosions on endoscopy (baseline endoscopy had also revealed erosions). This reviewer does not feel that analysis of unconfirmed cases will give valuable information about the sponsor defined endpoints. Confirmed PUBs are the relevant events in the database.

The analysis of NSAID type symptoms was a composite of 6 terms listed in table 51.

Table 51

GI Clinical Event Classification, Definitions, and Criteria—NSAID-type GI Symptoms

Event	Criteria for Confirmed Event	Criteria for Clinically Complicated Event
"NSAID-type" GI symptom		
"NSAID-type" GI symptom	Spontaneously reported AE mapping (in a blinded automated, or blinded manual process) to one of the following Merck broader or "preferred" dictionary terms: 1. Acid reflux 2. Dyspepsia 3. Epigastric discomfort 4. Heartburn 5. Nausea 6. Vomiting	Not applicable

Data Source: [3.2.1]

While this composite is reasonable, it may miss a significant difference in a distinct symptom such as heartburn or vomiting that may be lost in an analysis that includes a large number of cases of the more vague symptoms such as dyspepsia or epigastric discomfort. An additional analysis of the individual adverse events is therefore worthwhile. The esophageal endoscopic score data from studies 044 and 045 also raise concerns that can be further evaluated using symptomatic parameters related to the esophagus. This type of post hoc analysis cannot be confirmatory of true difference between groups. It may however give meaningful information and generate hypotheses about the safety of a new drug entity for future evaluation. Unfortunately, odynophagia and dysphagia were not terms that appeared in the dictionary of adverse events supplied by Merck to the reviewing division. Therefore, these esophagus-specific symptoms were not ascertained.

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Results:

Baseline characteristics:
5435 patients were included in the analysis. (See distribution in table 52).

Table 52

Placebo	Vioxx 12.5-mg	Vioxx 25-mg	Vioxx 50-mg	NSAID
514	1209	1603	545	1564

The NSAID category contained 127, 847 and 590 patients on nabumetone, ibuprofen and diclofenac respectively.

There were no clinically meaningful differences reported across the treatment groups in age, gender, tobacco use, race, prior serious GI adverse event history or prior NSAID use. Across studies, approximately 10% of the patients had a history of perforation, ulcer or bleeding.
The varying duration of treatment was taken into account by using a life table approach to the analysis and rates are given as incidence based on survival analysis. Results on the extent of exposure and discontinuation data are found in table 53.

Table 53

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Patients Completed and Discontinued
by Combined Treatment Group

	Number (%)			
	Placebo	MK-0966	NSAID	Total
ENTERED: Total	514	3357	1564	5435
COMPLETED:	383 (74.5)	2325 (69.3)‡	984 (62.9)	3692 (67.9)‡
DISCONTINUED: Total	131 (25.5)	1032 (30.7)‡	580 (37.1)	1743 (32.1)‡
Clinical adverse experience	24 (4.7)	317 (9.4)	168 (10.7)	509 (9.4)
Laboratory adverse experience	2 (0.0)	20 (0.6)	41 (2.6)	63 (1.2)
Lack of Efficacy	45 (8.8)	296 (8.8)	113 (7.2)	454 (8.4)
Other †	60 (11.7)	399 (11.9)‡	258 (16.5)	717 (13.2)‡

† Includes development of ulcer in endoscopic surveillance trials.

‡ One patient (AN 4289; Protocol 029) was reported as discontinuing due to a protocol deviation at Visit 9 and as completing the study at Visit 12. This table reflects the status of this patient as of Visit 12.

Data Source: [4.3.3 to 4.3.5]

Studies 044 and 045 included scheduled endoscopic studies at baseline, 6, 12 and 24 weeks. This unique study design would clearly bias reports of "PUB"s, particularly symptomatic ulcers. In an attempt to minimize this bias the initial protocol stipulated that all ulcers found within three days of a scheduled endoscopy would not be counted. A subsequent amendment to the design of study 069 specified that all symptomatic ulcers found within 7 days of a scheduled endoscopy would not be counted while those found outside the 7 day widow period would be counted. Investigators were asked to state in writing whether protocol defined endoscopies that were performed outside the window period were for clinical reasons (that might bear on whether they were truly PUBs) or due to administrative/scheduling reasons. In the ultimate analysis, asymptomatic ulcers found outside the window period due to administrative or scheduling reasons were included as PUBs in addition to the symptomatic ulcers. This inclusion is not consistent with the sponsor's stated intent of the study objective.

There are inherent and important differences between endoscopic studies specifically intended to ascertain ulcers and dose ranging and efficacy studies. Studies other than 044 and 045 allowed proton pump inhibitors and well s H2 blockers. Investigators alertness to GI symptoms and the type of response (invasive investigation versus empiric trial of antacid or anti-ulcer therapy) may vary significantly between these two types of studies. Table 54 reveals the weight of experience and exposure that 044 and 045 represent in the database used for study 069. Although this table does not show survival rates by study, the preponderance of data originating from studies that are by design very different from the other data bases adds to concern over the validity of such data merging. The statistical reviewer noted concerns as well.

Table 54: Patient contribution and PUB contribution by study

Study #	029	034	035	033	040	044	045	058
Total patients	571	693	784	736	809	742	775	325
PUB(cases sent for adjudication)	3	11	5	1	2	20	19	1
Duration of study (weeks)	56	52	52	6	6	24	24	6

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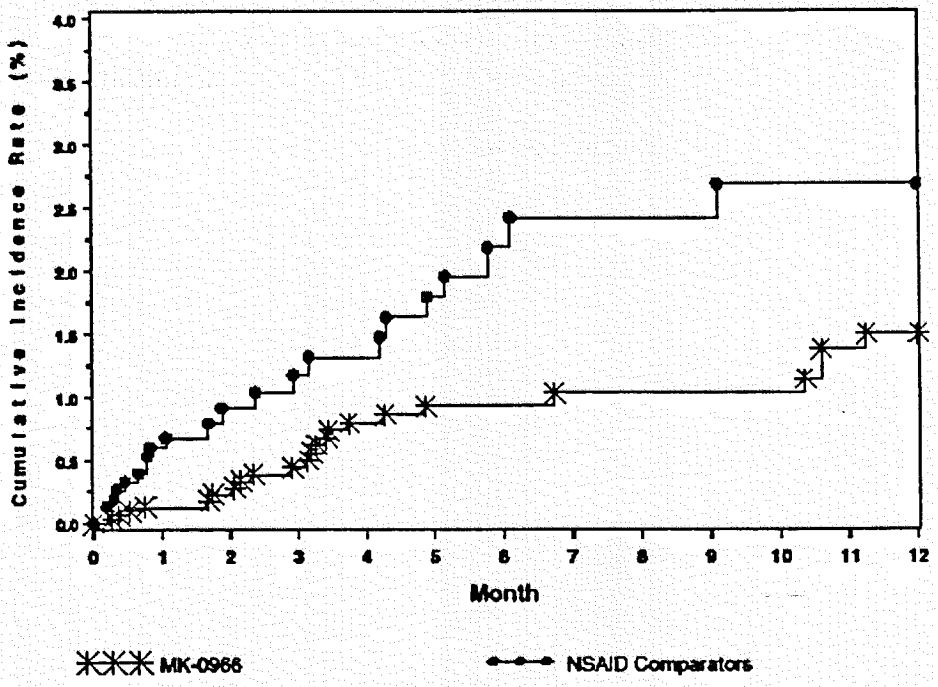
In view of the bias introduced by including endoscopy studies the sponsor provided an analysis of the data excluding studies 044 and 045. This type of analysis does give a more accurate reflection of the safety profile in practice. This analysis is presented in table 57. It shows no statistically significant difference in confirmed PUB rates between combined dosage forms of Vioxx and the group of all NSAIDs as a group. It does maintain a trend with a one-year rate of 1.00% for Vioxx groups combined and 1.39% for NSAID groups combined.

The sponsor's data will be presented followed by the agency requested recalculation of PUB data based on review of the case reports and exclusion of cases that were felt by the agency not to meet the prespecified criteria or that were asymptomatic. The endpoints to be reviewed are the confirmed PUBs and the confirmed complicated PUBs.

Sponsor's analysis: The sponsor identified 62 cases for adjudication. Seven occurred more than two weeks after study exit and were excluded. Of the remaining 55 cases, 49 were adjudicated as confirmed and 6 as unconfirmed.

Figure 8

Cumulative Incidence of Confirmed Upper-GI PUBs



Data Source: [2.1.1 to 2.1.3; 2.1.5 to 2.1.12; 4.7.1; 4.7.2]

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Table 55

Summary of Survival Analysis for Incidence of Confirmed Upper-GI PUBs—Primary Endpoint

Overall Summary Statistics for Between-Treatment Comparison				
		Relative Risk*	95% CI for Relative Risk	p-Value** for the Primary Analysis
Primary Results:	MK-0966 vs. NSAIDs (across first 12 months)	0.45	(0.25, 0.81)	0.006
Other Results:	MK-0966 vs. NSAIDs (across first 6 weeks)	0.19	(0.06, 0.59)	0.001
	MK-0966 vs. NSAIDs (across first 4 months)	0.46	(0.23, 0.94)	0.029
	MK-0966 vs. NSAIDs (across first 6 months)	0.39	(0.20, 0.73)	0.002
Placebo Results:	NSAIDs vs. placebo (across first 4 months)	1.31	(0.43, 3.94)	0.634
	MK-0966 vs. placebo (across first 4 months)	0.60	(0.20, 1.82)	0.365

* From the Cox Proportional Hazards Model.
** From the log rank test for the comparison of the cumulative incidence curves.

Data Source: [2.1.1 to 2.1.3; 2.1.5 to 2.1.12; 4.7.1; 4.7.2]

Table 55 (continued)

Survival Analysis for Incidence of Confirmed Upper-GI PUBs—Primary Endpoint

Time Point	Number of Patients With Events			Rate Per 100 Patient-Years			Cumulative Incidence† (%) at Each Time Point		
	Placebo (N=514)	MK-0966 (N=3357)	NSAIDs (N=1564)	Placebo	MK-0966	NSAIDs	Placebo	MK-0966	NSAIDs
6 weeks	1	4	10	1.76	1.05	5.68	0.22	0.12	0.67
4 months	4	16	15	3.58	2.10	4.49	1.23	0.79	1.32
6 months	n/a	18	20	n/a	1.80	4.66	n/a	0.92	2.18
12 months	n/a	23	22	n/a	1.61	3.58	n/a	1.50	2.68

Overall Summary Statistics for Between-Treatment Comparison

		Cumulative Incidence Difference (%)	95% CI for Cumulative Incidence Diff. (%)	Relative Risk*	95% CI for Relative Risk	p-Value** for the Primary Analysis
Primary Results:	MK-0966 vs. NSAIDs (across first 12 months)	-1.18	(-2.59, 0.23)	0.45	(0.25, 0.81)	0.006
Other Results:	MK-0966 vs. NSAIDs (across first 6 weeks)	-0.55	(-0.98, -0.12)	0.19	(0.06, 0.59)	0.001
	MK-0966 vs. NSAIDs (across first 4 months)	-0.53	(-1.33, 0.27)	0.46	(0.23, 0.94)	0.029
	MK-0966 vs. NSAIDs (across first 6 months)	-1.26	(-2.38, -0.14)	0.39	(0.20, 0.73)	0.002
Placebo Results:	NSAIDs vs. placebo (across first 4 months)	0.09	(-1.31, 1.49)	1.31	(0.43, 3.94)	0.634
	MK-0966 vs. placebo (across first 4 months)	-0.44	(-1.72, 0.84)	0.60	(0.20, 1.82)	0.365

† Cumulative incidence from the survival analysis, it may not equal (number of patients with events/N) x 100.
* From the Cox Proportional Hazards Model.
** From the log rank test for the comparison of the cumulative incidence curves.

Data Source: [2.1.1 to 2.1.3; 2.1.5 to 2.1.12; 4.7.1; 4.7.2]

Figure 9

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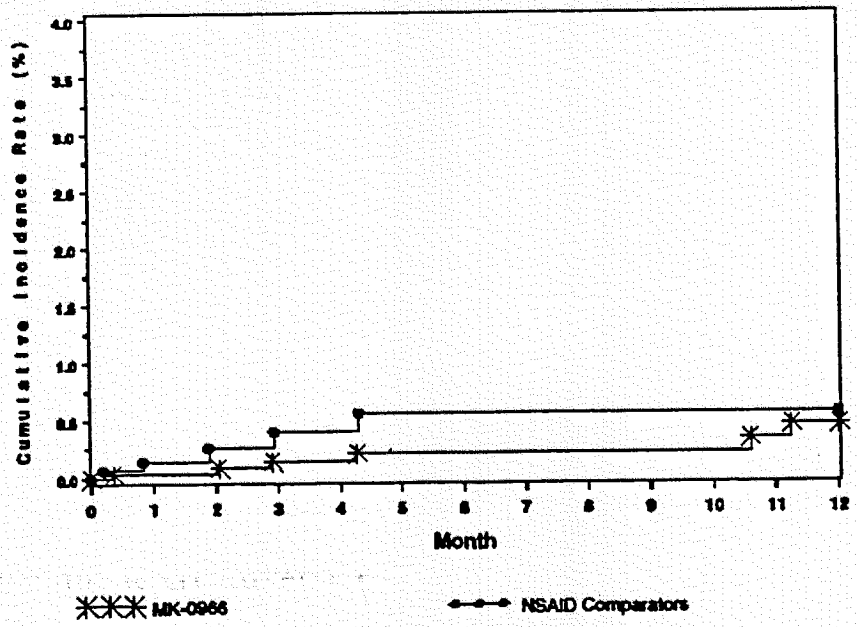
Cumulative Incidence of Confirmed Upper-GI PUBs That Were Complicated



Data Source: [2.1.1 to 2.1.3; 2.1.5 to 2.1.12; 4.7.1; 4.7.2]

The results of analyses of complicated PUBs were quite different than for total PUBs. There was no statistical difference between groups at 12 months, the prespecified endpoint. The rate for Vioxx groups combined was only 18% lower than the NSAID group. At earlier time points the difference between the two groups was larger. It is impossible to state whether the shrinking difference between the groups is due to a real rise in risk over time in the Vioxx group. This apparent effect may simply be due to the small number of events and the much smaller number of NSAID patients enrolled at one year compared to the Vioxx group (238 versus 580). The analysis by specific NSAID shown in table 59 reveals a smaller point estimate for PUBs associated with diclofenac than ibuprofen. This may account for the fall in the difference between the two groups over the later time interval. Exposure to ibuprofen was minimal after 6 months. The results may have been significantly different if ibuprofen exposure continued. This effect points out a flaw related to the design of study 069. The Vioxx dose specific rates and NSAID specific rates may not be similar enough to warrant combining the three doses of Vioxx together and the three NSAIDs together.

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Table 56

Survival Analysis for Incidence of Confirmed Upper-GI PUBs That Were Complicated

	Number of Patients With Events			Rate Per 100 Patient-Years			Cumulative Incidence† (%) at Each Time Point		
Time Point	Placebo (N=514)	MK-0966 (N=3357)	NSAIDs (N=1564)	Placebo	MK-0966	NSAIDs	Placebo	MK-0966	NSAIDs
6 weeks	0	1	2	0.00	0.26	1.14	0.00	0.03	0.14
4 months	1	3	4	0.89	0.39	1.20	0.33	0.14	0.39
6 months	n/a	4	5	n/a	0.40	1.16	n/a	0.20	0.55
12 months	n/a	6	5	n/a	0.42	0.81	n/a	0.45	0.55

Overall Summary Statistics for Between-Treatment Comparison

		Cumulative Incidence Difference (%)	95% CI for Cumulative Incidence Diff. (%)	Relative Risk‡	95% CI for Relative Risk	p-Value* for the Primary Analysis
Primary Results:	MK-0966 vs. NSAIDs (across first 12 months)	-0.11	(-0.75, 0.54)	0.51	(0.16, 1.69)	0.263
Other Results:	MK-0966 vs. NSAIDs (across first 6 weeks)	-0.10	(-0.30, 0.09)	0.23	(0.02, 2.56)	0.193
	MK-0966 vs. NSAIDs (across first 4 months)	-0.25	(-0.69, 0.18)	0.33	(0.07, 1.46)	0.124
	MK-0966 vs. NSAIDs (across first 6 months)	-0.35	(-0.90, 0.20)	0.34	(0.09, 1.27)	0.094
Placebo Results:	NSAIDs vs. placebo (across first 4 months)	0.06	(-0.71, 0.83)	1.44	(0.16, 12.88)	0.744
	MK-0966 vs. placebo (across first 4 months)	-0.19	(-0.87, 0.48)	0.48	(0.05, 4.59)	0.512

† Cumulative incidence from the survival analysis, it may not equal (number of patients with events/N) x 100.
‡ From the Cox Proportional Hazards Model.
* From the log rank test for the comparison of the cumulative incidence curves.

Data Source: [2.1.1 to 2.1.3; 2.1.5 to 2.1.12; 4.7.1; 4.7.2]

Table 57

Survival Analysis for Incidence of Confirmed Upper-GI PUBs
Excluding Protocols 044 and 045

Time Point	Number of Patients With Events			Rate Per 100 Patient-Years			Cumulative Incidence† (%) at Each Time Point		
	Placebo (N=143)	MK-0966 (N=2588)	NSAIDs (N=1187)	Placebo	MK-0966	NSAIDs	Placebo	MK-0966	NSAIDs
6 weeks	0	0	3	0.00	0.00	2.25	0.00	0.00	0.27
4 months	0	4	4	0.00	0.73	1.62	0.00	0.32	0.44
6 months	n/a	5	6	n/a	0.70	1.87	n/a	0.41	0.88
12 months	n/a	10	8	n/a	0.87	1.58	n/a	1.00	1.39

Overall Summary Statistics for Between-Treatment Comparison

		Cumulative Incidence Difference (%)	95% CI for Cumulative Incidence Diff. (%)	Relative Risk‡	95% CI for Relative Risk	p-Value** for the Primary Analysis
Primary Results:	MK-0966 vs. NSAIDs (across first 12 months)	-0.39	(-1.60, 0.81)	0.55	(0.22, 1.39)	0.201
Other Results:	MK-0966 vs. NSAIDs (across first 6 weeks)	-0.27	(-0.57, 0.03)	.	(. , .)	0.011
	MK-0966 vs. NSAIDs (across first 4 months)	-0.12	(-0.67, 0.43)	0.45	(0.11, 1.81)	0.249
	MK-0966 vs. NSAIDs (across first 6 months)	-0.47	(-1.30, 0.37)	0.37	(0.11, 1.22)	0.089
Placebo Results:	NSAIDs vs. placebo (across first 4 months)	0.44	(-0.01, 0.89)	.	(. , .)	0.562
	MK-0966 vs. placebo (across first 4 months)	0.32	(0.01, 0.63)	.	(. , .)	.

† Cumulative incidence from the survival analysis, it may not equal (number of patients with events/N) x 100.
‡ From the Cox Proportional Hazards Model.
** From the log rank test for the comparison of the cumulative incidence curves.

Data Source: [2.1.1 to 2.1.3; 2.1.5 to 2.1.10; 4.7.1; 4.7.2]

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The sponsor listed relevant protocol violation data related to concomitant NSAID usage that may have affected the outcome but did not reanalyze the PUB data. A reanalysis would have lowered the number of events. The data as provided however, with the protocol violators included are more informative of what may happen in post-marketing practice and are therefore the more relevant for analysis.

An analysis of confirmed PUBs stratified by history of PUB showed a strong correlation with prior history of PUB. This was true for all groups. The rise in all groups including placebo highlights the importance of this risk factor. In those patients at most risk of PUBs and most in need of a safer option to nonselective cyclooxygenase inhibitors, there was no statistically significant difference between NSAID and Vioxx groups. The cumulative incidence rate over 12 months was 6.57 for the Vioxx group and 5.67 for the NSAID group. When evaluated per100 patient-years, the trend shows a lower rate in the Vioxx group than the NSAID group (7.79 versus 10.75). The differences between the two types of analysis (cumulative incidence and rate per 100 patient-years) are possibly a reflection of the duration of exposure to the various NSAIDs. The ibuprofen group was larger and had a higher incidence for a shorter duration while the diclofenac group had a longer duration at a lower incidence rate. This phenomenon again points to the difficulties in grouping both NSAIDs together.

It is of note that the steepest rise in PUB rate when comparing the entire population to the subpopulation with a history of PUBs was seen in the Vioxx group (See table 58).

Patients with a history of PUBs may not lower their risk of PUBs as dramatically as the ulcer data from the endoscopic studies may suggest by using Vioxx compared to ibuprofen (if one were to accept endoscopic ulcers as a surrogate). Comparisons to other NSAIDs and firm conclusions related to diclofenac and ibuprofen cannot be made based on this subanalysis. As much medical literature indicates, factors beyond NSAID exposure remain critical to risks of PUBs.

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Table 58

Survival Analysis for 12-Month Incidence of Confirmed Upper-GI PUBs Stratified by History of PUB†

Group	Treatment‡	N	Number of Patients With Events	Total Patient-Years	Mean Patient-Years	Rate Per 100 Patient-Years	Cumulative Incidence§ (%)	95% CI for Cumulative Incidence (%)
Absent	Placebo	464	3	99.19	0.21	3.02	1.16	(0.00, 2.48)
	MK-0966	2582	13	1048.40	0.41	1.24	1.10	(0.46, 1.75)
	NSAIDs	1325	17	501.89	0.38	3.39	2.72	(1.28, 4.16)
Present	Placebo	50	1	12.58	0.25	7.95	2.17	(0.00, 6.39)
	MK-0966	296	8	102.68	0.35	7.79	6.57	(0.77, 12.37)
	NSAIDs	147	5	46.53	0.32	10.75	5.67	(0.34, 11.01)

† Protocol 029 was excluded because GI history data were not collected.
‡ Maximum duration of placebo treatment was 4 months. Maximum duration for MK-0966 and NSAIDs was 24 months.
§ Cumulative incidence from the survival analysis, it may not equal (number of patients with events/N) x 100.

Data Source: [2.1.5 to 2.1.12; 4.7.1; 4.7.2]

The sponsor's analysis reviewed above shows:

1. A statistically significantly lower confirmed PUB rate over 12 months for Vioxx in a combined analysis of 12.5, 25 and 50mg of Vioxx compared to the entire group of NSAIDs combined. Relative risk of .45
2. Excluding protocols 044 and 045, there was no statistical difference between Vioxx and NSAID groups over the 12 months of the study. There was a trend in favor of Vioxx with a relative risk of .55 (Vioxx group compared to NSAID group).
3. No statistical difference between placebo verses Vioxx or NSAID at 4 months. (note small number of cases 4, 15 and 16 respectively)
4. No statistically significant difference in the incidence of complicated PUBs between Vioxx and NSAID groups (.45 verses .55%) at one year.
5. History of prior PUB was a strong risk factor for PUBs across all groups.

An analysis of the various dosage forms would be of value in characterizing the risks associated with Vioxx. Comparisons to specific NSAIDs is needed before a valid analysis of relative safety of Vioxx compared to "NSAIDs" as a group can be made. The sponsor's choice of combining all three doses of Vioxx and all comparators for their prespecified analysis resulted in a larger number of events for statistical analysis. It did not, however allow adequate analysis of safety issues related to this new molecular entity with major new safety claims. Data suggesting increased efficacy at the 50-mg dose and the phenomenon of dose creep seen with analgesics reinforces the importance of reviewing dose related adverse event data.

The different NSAIDs are not necessarily a homogeneous group. Comparisons by NSAID are also of value. A post hoc and stratified analysis will limit the ability to assign