Statistical Reviewer Briefing Document for the Advisory Committee

NDA20-998
Name of Drug: Celebrex (celebrex)
Applicant: G. D. Searle
Indication: Lower Upper Gastrointestinal Adverse Events Compared with NSAID
Documents Reviewed: Statistical Section of NDA20998 Dated 06/14/00 by CDER
Medical Reviewer: Lawrance Goldkind, M.D., James Witter, MD
Reviewer: Hong Laura Lu, Ph.D.
Date of Review: 6/00-

I.   Background

This NDA is submitted to support the claim that celebrex causes lower incidence of clinically significant upper gastrointestinal adverse events (CSUGIE) compared to ibuprofen and diclofenac during chronic administration (up to 12 months) in patients with osteoarthritis (OA) or rheumatoid arthritis (RA). This review focuses on the two phase III studies (Studies 035 and 102).

II.   Study Protocol (Study 035 and Study 102)

Study 035 was a randomized, double-blind, parallel group, multicenter study designed to compare the incidence of CSUGIEs associated with celebrex 400 mg BID to that associated with ibuprofen 800 mg TID in patients with OA or RA. Study 102 was identically designed as Study 035 except that the active control group was diclofenac 75 mg BID.

The treatment period for both studies was defined as the 52-week interval during which study medication was taken or until the trial was officially concluded, whichever occurred first. Patients were evaluated at Week 4, Week 13, Week 26, Week 39, Week 52 and the end of the treatment.

The primary comparison was the incidence of CSUGIEs associated with celebrex 400 mg BID to that associated with ibuprofen 800 mg TID and diclofenac 75 mg BID. Time-to-event analysis was performed to assess the difference between groups in the CSUGIE rate distribution across time. CSUGIE occurring within 2 days after first dosing or beyond 2 days after last dosing was censored and not included in these analyses. The log-rank test was used to compare the survival curves of the two treatment groups (celebrex vs. the NSAID groups) with respect to this primary outcome variable. Patients who withdrew from the study because of reasons other than incidence of CSUGIE were censored at the time of withdrawal. Patients who complete the study without a CSUGIE were censored at the final visit. Two primary treatment comparisons were performed: celebrex vs. ibuprofen and celebrex vs. diclofenac. A stepwise procedure was used to strongly control the type-I error. In this procedure, the first step was to test the overall hypothesis whether celebrex and the pooled NSAIDs were different. If the test is not significant, the null hypothesis is retained and the procedure stops. If the test is significant, the second step will be the pairwise tests between celebrex and each of the two NSAIDs. Celebrex will be claimed to be different from an NSAID if both overall and pairwise comparisons of celebrex vs. that NSAID are

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significant. Each test was performed at level α. No α adjustment was needed for each test. Two primary endpoints were analyzed. One was based on the traditional definition of CSUGIE and the other alternative one was proposed by FDA. To control the type-I error rate, a pre-specified stepwise procedure was used. The first step was to test treatment difference based on the traditional definition of endpoint. If it is significant, then test on the alternate endpoint. If both steps show significance, celebrex will be claimed to be different from the NSAID(s) on both endpoints. If only the first step shows significance, celebrex will be claimed to be different from the NSAID(s) on the traditional endpoint.

Potential risk factors such as age and history of peptic ulcer, for the development of a clinically significant UGI adverse event were identified prior to analysis and the proportional hazard model was used to assess the significance of these factors and their impact on the effect of treatment on outcome. Mean values and their confidence intervals for the Patient's Global Assessment of Arthritis, the Patient's Assessment of Arthritis Pain, and Health Assessment Questionnaire (HAQ) were tabulated. Information for Incidence of withdrawal due to lack of arthritis efficacy
was provided.

All analyses were carried out on the intent-to-treat cohort, which consisted of all randomized patients from both studies who received at least one dose of study medication.

The sample size determination was based on the assumption that the probability for experiencing a CSUGIE was 0.3% per year with celebrex and 1.2% per year with NSAIDs as a group. To detect this difference with at least 90% power at a 5% significance level (two-sided test) and assuming a withdrawal rate of 35%, a sample size of 8,000 patients (4,000 patients for the celebrex and 2000 for each NSAID group) was sufficient to obtain approximately a total of 40 clinically significant UGI adverse events.

III.   Study Report for Studies 035 and 102

III.1 Patient Disposition

A total of 8059 patients were randomized: 4031 to the celebrex 400 mg BID group, 2019 to the diclofenac 75 mg BID group, and 2009 to the ibuprofen 800 mg TID group. Ninety-one (91) patients were determined never to have taken any study medication. The majority of withdrawals in all treatment groups were due to adverse events (22.7% in celebrex group, 27.1% in diclofenac group and 23.2% in ibuprofen group), treatment failure (17.3% in celebrex group, 15.5% in diclofenac group and 23.0% in ibuprofen group), or protocol noncompliance (14.7% in celebrex group, 9.9% in diclofenac group and 18.4% in ibuprofen group). Detailed results for patient disposition are presented in Table 1 below.

Table 1. Patient Disposition

	Celebrex	Diclofenac	Ibuprofen
Overall	3987	1996	1985
Completed Study	1779(44.6%)	939(47.0%)	691(34.8%)
Complete With GI AE	401	257	187
Withdrawn	2208(55.4%)	1057(53.0%)	1294(65.2%)
Reason for Withdrawal:			
Lost to Follow-Up	0(0.0%)	0(0.0%)	0(0.0%)
Pre-Existing Violation	27(0.7%)	11(0.6%)	12(0.6%)
Protocol Noncompliance	585(14.7%)	197(9.9%)	365(18.4%)
Treatment Failure	691(17.3%)	309(15.5%)	456(23.0%)
Adverse Event	905(22.7%)	540(27.1%)	461(23.2%)

III.2 Demographics

Baseline demographic characteristics, vital signs and GI risk factors are generally balanced between treatment groups. Detailed demographic information is summarized in Tables a1-a4 in Appendix A.

III.3 Sponsor's Analysis and Results of UGI Safety Results (reviewer's comments and analyses are in Section IV)

III.3.1 CSUGIE results for entire study period

A total of 44 events were found to represent CSUGIE throughout the entire study. Twenty events (20) occurred on celebrex treatment, 11 on diclofenac, and 13 on ibuprofen. Among these events, a total of 6 were considered censored (3 in the celebrex group, 1 in the diclofenac group, and 2 in the ibuprofen group) due to the timing of their occurrence (occurred within 2 days after first dosing or beyond 2 days after last dosing).

As shown in Figure 1, the uncensored events were shown to continue to accrue in the celebrex group at a generally steady rate through the end of the study. In contrast, only one uncensored event occurred in the diclofenac group after 182 days, and none occurred in the ibuprofen group. The curves for the two NSAIDs therefore become essentially flat after this time, with the result that the end points of the three curves were similar by the end of the study. None of the differences in time to event among the treatment groups were statistically significant. Summary results for CSUGIE were presented in Table 2.

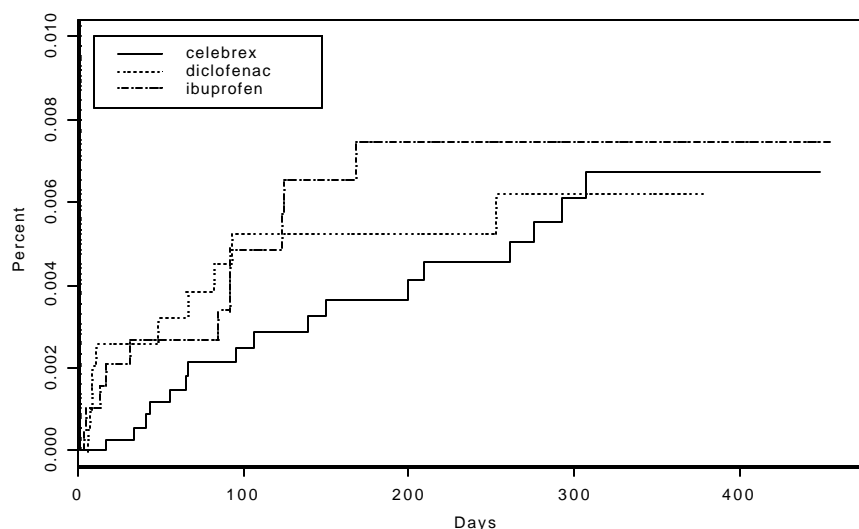Figure 1. Kaplan-Meier Estimator for CSUGIE Incidence

Table 2. Summary of CSUGIE Incidence

| | Celebrex 400 mg BID | Diclofenac 75 mg BID | Ibuprofen 800 mg TID | Log-Rank P Values for Celebrex vs. | | |
				Diclofenac	Ibuprofen	Both
No. of Patients	n=3987	n=1996	n=1985			
No. of CSUGIE						
Uncensored	17	10	11			
Censored*	3	1	2			
Total	20	11	13			
Week 52 crude rate	0.43%	0.50%	0.55%	0.640	0.414	0.450

*Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).

A total of 35 events were found to satisfy the alternate definition of CSUGIE. No statistical analysis was performed since the lack of statistical significance in the results of CSUGIE with traditional definition. However, the event rates with alternate definition followed the same trend as that with traditional definition. The results are presented in Table 3 below.

Table 3. Summary of CSUGIE Incidence: Alternate Definitions

	Celebrex 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
No. of CSUGIEs			
Uncensored	17	5	9
Censored	2	1	1
Total	19	6	10
Week 52 crude rate	0.43%	0.25%	0.45%

III.3.2 Post-Hoc Safety Analyses

III.3.2.a Analysis for the first 6 months

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The sponsor also conducted analysis for CSUGIE with only the first 6 months data based on the argument that the large dropout rate in the later stage of the study depleted high-risk patients. The 6 months' data showed that the CSUGIE rates of ibuprofen and diclofenac (0.55% and 0.45%, respectively) were numerically higher than that of celebrex (0.28%), but the difference did not reach statistical significance (p=0.092). The results are summarized in Table 5 below.

Table 5. Summary of CSUGIE Incidence - First Six Months

	Celebrex 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celebrex vs.		
				Diclofenac	Ibuprofen	Both
	n=3987	n=1996	n=1985			
No. of CSUGIEs						
Uncensored	11	9	11			
Censored*	2	0	2			
Total	13	9	13			
Week 26 crude rate	0.28%	0.45%	0.55%	0.264	0.073	0.092

*Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).

III.3.2.b Subgroup analysis

Analysis for CSUGIE was also conducted for non-aspirin users with the argument that aspirin was an independent cause for CSUGIEs. Among non-aspirin users, celebrex did not show statistically significant (p=0.185) reduction in CSUGIEs over the entire study period. However, with only the first 6 months data, the CSUGIE rate of celebrex was numerically lower than that of ibuprofen and diclofenac with a p-value less than 0.05. The detailed results for the entire study period and the first 6 months are presented in Table 6 below.

Table 6. CSUGIE Incidence in Patients not Taking Aspirin

	Celebrex 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celebrex vs.		
				Diclofenac	Ibuprofen	Both
Entire Study Period						
	n=3105	n=1551	n=1573			
No. of CSUGIEs						
Uncensored	8	4	10			
Censored*	1	0	1			
Total	9	4	11			
Week 52 crude rate	0.26%	0.26%	0.64%	0.972	0.037	0.185
First 6 Months						
	n=3154	n=1567	n=1602			
No. of CSUGIEs						
Uncensored	5	4	10			
Censored*	1	0	1			
Total	6	4	11			
Week 26 crude rate	0.16%	0.26%	0.62%	0.476	0.005	0.037

*Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).

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III.3.2.c Analysis for Combined CSUGIE/GDU Events

The sponsor also conducted analysis for combined CSUGIE/gastrodudenal ulcer (GDU) events. A total of 111 CSUGIEs/GDUs occurred over the entire study period: 46 in the celebrex group, 27 in the diclofenac group, and 38 in the ibuprofen group. The cumulative event rates were lower over the entire study period for celebrex than for the NSAID comparators pooled (p=0.040) and ibuprofen (p=0.017). When only patients not taking aspirin were included in the analysis, the celebrex event rate over 52 weeks was lower than the rate for the NSAIDs pooled (p=0.020) and the rate for ibuprofen (p<0.001). The detailed results are included in Table 7 below.

Table 7. Summary of CSUGIE/GDU Incidence

	Celebrex 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celebrex vs.		
				Diclofenac	Ibuprofen	Both
All Patients						
	n=3987	n=1996	n=1985			
No. of CSUGIEs						
Uncensored	43	26	36			
Censored*	3	1	2			
Total	46	27	38			
Week 52 crude rate	1.05%	1.30%	1.76%	0.296	0.017	0.040
Patients not Taking Aspirin						
	n=3105	n=1551	n=1573			
No. of CSUGIEs						
Uncensored	21	10	28			
Censored*	1	0	1			
Total	22	10	29			
Week 52 crude rate	0.68%	0.64%	1.78%	0.992	<0.001	0.020

*Occurred before 48 hours after midnight of the first dose day or more than 48 hours after midnight of the last dose day (unless occurred within two weeks after last dose and was determined by GEC to be treatment-related).

III.3.2.d Data Imputation

The sponsor argued that since GI adverse events represent risk factors for events, withdrawals due to GI adverse events represent loss of patients at risk. Based on this argument, the sponsor calculated incidences for patients who did/did not experience GI symptoms and who continued in the study, and these incidences were then applied to patients who discontinued with/without GI symptoms and the expected numbers of CSUGIE in these two patient groups were estimated. Details for imputation and calculation for CSUGIE incidence are in Appendix B.
Table 8 below shows the estimated CSUGIE numbers and rates after imputation for the withdrawal group. The p-values in Table 8 were generated by Fisher's exact test on the expected numbers of CSUGIE.

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Table 8. Crude Incidence Rates of CSUGIEs with Imputation for Withdrawals

	Celebrex 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)	Celebrex vs. Diclofenac	Celebrex vs. Ibuprofen
First six months					
CSUGIE	15 (0.4%)	16 (0.8%)	16 (0.8%)	p=0.036	p=0.035
Entire study					
CSUGIE	25 (0.6%)	23 (1.2%)	21 (1.1%)	p=0.044	p=0.084

III.3.3 Efficacy Analyses

Efficacy of the three treatment groups were assessed by patient's global, patient's assessment of arthritis pain, time to withdrawal due to lack of arthritis efficacy, and HAQ. The three treatment groups were numerically comparable in efficacy results. The means and confidence intervals are reported in Tables a5-a8 Appendix A.

IV.   Reviewer's Comments

IV.1   Imputation of CSUGIE Rates

The sponsor's rationales for imputation of CSUGIE were that 1) the patients with GI adverse events would have higher probability to develop a CSUGIE over the treatment duration (see Table 2 in Appendix B) and 2) higher withdrawal incidence with earlier withdrawal time in the diclofenac group were observed (see Table 1 in Appendix B), an estimation for the entire study period without adjustment for these informative censoring would not be appropriate for interpretation.

The above two reasons are not valid based on this reviewer's analysis. Table 9 displays the time to GI AEs (mild-moderate-severe GI AE, moderate-severe GI AE and severe GI AE) and time to CSUGIE for patients who had both GI AE and CSUGIE. A phenomenon observed in this Table is that, for most patients, the time to GI AEs and time to CSUGIE are identical. For example, among the 8 patients who had both severe GI AE and CSUGIE, 6 of them developed the GI AE and CSUGIE on the same day, one of them developed CSUGIE in two days after GI AE, and the other one had CSUGIE 20 days before GI AE. So instead of being a pre-event that predicts CSUGIE, most GI AEs were actually the sentinel symptoms of CSUGIE themselves, providing no predictive value at all (see Dr. Goldkind's review for further comments). As suggested by the medical reviewer, this reviewer recalculated the relative risk of the GI AE group vs. non-GI AE group by defining predictive GI AEs as those happened more then 48 hours before a CSUGIE, so that those GI AEs happened within 48 hours of a CSUGIE are excluded from GI AE groups. The results presented in Table 10 show that the GI AE groups (mild-moderate-severe, moderate-severe and sever GI AE) actually have lower risks than the non-GI AE group. So the sponsor's rationales for imputation of the CSUGIEs is not supported by the data.

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Table 9. Time to GI AEs and Time to CSUGIE in Patients with Both GI AE and CSUGIE

Patient #	Treatment	T_MD-MT-SV*	T_MT-SEV**	T_SEV***	T_CSUGIE****
12391	celebrex	261	.	.	261
10761	celebrex	307	307	307	307
20349	celebrex	199	.	.	199
11159	celebrex	43	63	63	43
10012	celebrex	12	.	.	276
11153	celebrex	67	67	67	67
11341	celebrex	10	150	150	150
12176	celebrex	139	139	.	139
20035	declofenac	6	6	.	6
10032	declofenac	66	66	.	66
10193	declofenac	8	8	8	8
10294	declofenac	7	7	7	9
20398	declofenac	41	41	.	49
11559	declofenac	261	261	.	253
12252	declofenac	11	11	11	11
12815	declofenac	7	7	7	7
10579	Ibuprofen	13	18	.	13
11377	Ibuprofen	4	4	.	4
11767	Ibuprofen	123	123	.	123
21191	Ibuprofen	13	13	.	17
12446	Ibuprofen	9	9	9	5
11011	Ibuprofen	112	.	.	124

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*    :Time to Mild-Moderate-Severe GI AE
**   :Time to Moderate-Severe GI AE
*** :Time to Severe GI AE
****:Time to CSUGIE
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Table 10. CSUGIE Incidence in GI AE Groups and Non-GI AE Groups

	Celebrex	Declofenac	Ibuprofen	Overall
With MD-MT-SEV GI AE	2/1383 (0.14%)	1/857 (0.12%)	2/639 (0.31%)	5/2879 (0.17%)
Without MD-MT-SEV GI AE	15/2604 (0.58%)	9/1139 (0.79%)	9/1346 (0.67%)	33/5089 (0.65%)
Relative Risk	25.10%	14.77%	46.81%	26.78%
With MT-SEV GI AE	0/694 (0.00%)	1/441 (0.23%)	1/332 (0.30%)	2/1467 (0.14%)
Without MT-SEV GI AE	17/3293 (0.52%)	9/1555 (0.58%)	10/1653 (0.60%)	36/6501 (0.55%)
Relative Risk	0.00%	39.18%	49.79%	24.62%
With SEV GI AE	0/154 (0.00%)	0/125 (0.00%)	0/71 (0.00%)	0/350 (0.00%)
Without SEV GI AE	17/3833 (0.44%)	10/1871 (0.53%)	11/1914 (0.57%)	38/7618 (0.50%)
Relative Risk	0.00%	0.00%	0.00%	0.00%

IV. 2   Analysis for the First 6 Months Data

The sponsor's rationale for analyzing the first 6 months data only is that the large dropout rate in the later stage of the study depleted high-risk patients--patients who dropped out due to GI AEs. This rationale is not valid due to the following reasons.

1) Current statistical methods in survival analysis (K-M estimator, tests for time to events) can make valid statistical inference even with high proportion of censoring, unless the censoring is informative. Sponsor's argument for the existence of informative censoring was not supported by the data as discussed in Comment 1 above. Therefore, this reviewer regards the analysis for data for the entire study period as specified in the protocol, which includes most information, the appropriate analysis.

2) The 6 months analysis is not valid even with concern of informative censoring. As presented in Table 11, the drop-out rates due to GI AE were increased gradually without sudden increase at Month 6 (Week 26) in any of the treatment groups. The numerical order of the drop-out rates stayed the same across the entire study period. Therefore, there is no reason to include information only in the first 6 months.

Table 11. Drop-out Rates (%) due to GI AE

TimePoint	Celebrex (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Week1	2.85	4.25	2.80
Week4	5.08	7.46	5.09
Week13	8.20	11.05	8.94
Week26	9.90	13.66	10.54
Week39	11.09	14.65	11.59
Week52	11.41	14.95	11.71
Week65	11.41	14.95	11.99

IV.3   Subgroup Analysis for Non-Aspirin Users

As presented in Table 6 and Table 7, the sponsor conducted analysis for CSUGIE and combined CSUGIE/GDU event rates in non-aspirin users. The sponsor's analyses showed that celebrex had a numerically lower CSUGIE/GDU incidence (0.3%) than in ibuprofen group (0.6%) with a p-value 0.185 and a numerically lower CSUGIE/GDU incidence (0.7%) than in ibuprofen group (1.8%) with a p-value less than 0.05. These p-values can not be interpreted by their face values since 1) the primary endpoint did not show statistical significance, 2) numerous subgroup analyses had been conducted (at least 34, see Tables a9-a11 in Appendix A for the results of risk factor analyses) in exploratory faction with no pre-specified plan of statistical inference, and 3) subgroup analyses based on aspirin use was not even mentioned in the protocol. However, if these subgroup analyses are clinically meaningful and the results are supported by external information (see DR. Goldkind's review for further comments), the conventional frequentist's approach of adjusting α may not be appropriate. But a formal statistical inference is impossible without a pre-specified analysis plan.

It is also worth noticing that the results of CSUGIE and combined CSUGIE/GDU event rates in aspirin users were numerically inconsistent with that in the non-user group—celebrex had higher incidences (1.0% for CSUGIE and 2.5% for combined CSUGIE/GDU event) than ibuprofen group (0.2% for CSUGIE and 1.9% for combined CSUGIE/GDU event) (see Tables a11 and a12 in Appendix A).

V.   Final Conclusion

Celebrex 400 mg BID did not show significant reduction in CSUGIE incidence compared to two NSAIDs: ibuprofen 800 mg TID and diclofenac 75 mg BID in patients with OA or RA.

In a post hoc analysis of non-aspirin users, the incidence of combined CSUGIE/GDU event in the celebrex group was lower than that in ibuprofen group with p-values less than 0.05. However, this p-value can not be easily interpreted statistically by its face value due to lack of

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pre-specified analysis plan and the failure of showing statistical significance in the primary endpoint.

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NDA 20998
HFD-550/MO/Goldkind/Witter/Bullj
HFD-550/PM/Kongy
HFD-550/Div. File
HFD-725/Lu/Lin ST./Huque
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Appendix A

Table a1. Baseline Demographics

	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
AGE (yrs)			
N	3987	1996	1985
Mean	60.6	60.1	59.5
SD	11.66	11.99	11.93
Median	61.0	61.0	60.0
Range	20- 89	21- 90	18- 90
<= 34	76 (1.9%)	52 (2.6%)	49 (2.5%)
35 - 44	272 (6.8%)	166 (8.3%)	172 (8.7%)
45 - 54	881 (22.1%)	404 (20.2%)	458 (23.1%)
55 - 64	1199 (30.1%)	612 (30.7%)	582 (29.3%)
65 - 74	1072 (26.9%)	526 (26.4%)	507 (25.5%)
>= 75	487 (12.2%)	236 (11.8%)	217 (10.9%)
GENDER			
Male	1255 (31.5%)	650 (32.6%)	580 (29.2%)
Female	2732 (68.5%	1346 (67.4%)	1405 (70.8%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
RACE/ETHNIC ORIGIN			
Caucasian	3528 (88.5%)	1784 (89.4%)	1713 (86.3%)
Black	301 (7.5%)	151 (7.6%)	172 (8.7%)
Asian	29 (0.7%)	19 (1.0%)	9 (0.5%)
Hispanic	107 (2.7%)	36 (1.8%)	75 (3.8%)
Other	22 (0.6%)	6 (0.3%)	16 (0.8%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)

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Table a2. Additional Baseline Characters

	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
HEIGHT (cm)			
N	3969	1984	1971
Mean	166.73	167.01	166.53
SD	9.999	10.171	10.042
Median	165.10	165.10	165.10
Range	118.8-203.2	106.2-203.2	135.0-210.8
WEIGHT (kg)			
N	3961	1989	1973
Mean	84.11	83.74	84.57
SD	21.227	20.663	21.212
Median	81.40	81.20	80.90
Range	36.5-204.5	40.8-190.9	36.3-179.5

Table a3. Vital Signs

	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
TEMPERATURE (C)			
N	3937	1962	1969
Mean	36.61	36.61	36.61
SD	0.438	0.436	0.407
Median	36.70	36.60	36.70
Range	32.8- 40.9	34.6- 40.2	32.9- 38.1
SITTING PULSE (beats/min)			
N	3976	1989	1982
Mean	73.8	74.1	73.8
SD	9.62	9.22	9.68
Median	73.0	72.0	72.0
Range	46-120	44-126	46-120
SITTING RESPIRATION (breaths/min)			
N	3969	1984	1978
Mean	17.0	17.1	17.0
SD	2.85	3.07	2.73
Median	16.0	16.0	16.0
Range	8- 40	8- 36	8- 36
SITTING SYSTOLIC BLOOD PRESSURE (mm Hg)			
N	3980	1989	1983
Mean	132.7	133.0	132.6
SD	17.03	17.14	16.68
Median	130.0	132.0	130.0
Range	80-200	84-238	90-202
SITTING DIASTOLIC BLOOD PRESSURE (mm Hg)			
N	3980	1989	1983
Mean	79.4	79.5	79.9
SD	9.28	9.31	9.12
Median	80.0	80.0	80.0
Range	38-120	48-130	50-118

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Table a4. GI Risk Factors

HISTORY OF:	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
UPPER GI BLEEDING			
Yes	68 (1.7%)	30 (1.5%)	28 (1.4%)
No	3919 (98.3%)	1966 (98.5%)	1957 (98.6%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
GASTRODUODENAL ULCER			
Yes	334 (8.4%)	170 (8.5%)	151 (7.6%)
No	3653 (91.6%)	1826 (91.5%)	1834 (92.4%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
GI-RELATED NSAID INTOLERANCE (b)			
Yes	347 (8.7%)	202 (10.1%)	165 (8.3%)
No	3640 (91.3%)	1794 (89.9%)	1820 (91.7%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
CARDIOVASCULAR DISEASE			
Yes	1602 (40.2%)	805 (40.3%)	794 (40.0%)
No	2384 (59.8%)	1190 (59.6%)	1190 (59.9%)
TOTAL	3986 (100.0%)	1995 (99.9%)	1984 (99.9%)
FLEXSURE FOR H. PYLORI			
Negative	2448 (61.4%)	1243 (62.3%)	1213 (61.1%)
Positive	1536 (38.5%)	752 (37.7%)	769 (38.7%)
TOTAL	3984 (99.9%)	1995 (99.9%)	1982 (99.8%)

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Table a4. GI Risk Factors (continue)

HISTORY OF:	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
ALCOHOL USE			
None	2753 (69.0%)	1184 (59.3%)	1599 (80.6%)
Yes (b)	1232 (30.9%)	812 (40.7%)	386 (19.4%)
1 or Fewer Drinks per Day	1079 (27.1%)	712 (35.7%)	326 (16.4%)
2-3 Drinks per Day	130 (3.3%)	93 (4.7%)	46 (2.3%)
4 or More Drinks per Day	11 (0.3%)	7 (0.4%)	2 (0.1%)
Yes - No Specification	12 (0.3%)	0 (0.0%)	12 (0.6%)
TOTAL	3985 (99.9%)	1996 (100.0%)	1985 (100.0%)
TOBACCO USE (c)			
None	3356 (84.2%)	1685 (84.4%)	1701 (85.7%)
Yes (b)	629 (15.8%)	311 (15.6%)	284 (14.3%)
Level I	198 (5.0%)	100 (5.0%)	62 (3.1%)
Level II	229 (5.7%)	152 (7.6%)	75 (3.8%)
Level III	85 (2.1%)	59 (3.0%)	30 (1.5%)
Yes - No Specification	116 (2.9%)	0 (0.0%)	117 (5.9%)
TOTAL	3985 (99.9%)	1996 (100.0%)	1985 (100.0%)
CORTICOSTEROID USE			
None	2768 (69.4%)	1428 (71.5%)	1378 (69.4%)
One Dose to <10% Study Days	413 (10.4%)	183 (9.2%)	214 (10.8%)
>=10% Study Days	806 (20.2%)	385 (19.3%)	393 (19.8%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
ANTICOAGULANT USE			
None	3945 (98.9%)	1972 (98.8%)	1965 (99.0%)
One Dose to <10% Study Days	24 (0.6%)	8 (0.4%)	8 (0.4%)
>=10% Study Days	18 (0.5%)	16 (0.8%)	12 (0.6%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
ASPIRIN USE			
None	3105 (77.9%)	1551 (77.7%)	1573 (79.2%)
One Dose to <10% Study Days	196 (4.9%)	104 (5.2%)	83 (4.2%)
>=10% Study Days	686 (17.2%)	341 (17.1%)	329 (16.6%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)
ASPIRIN USE DURING FIRST SIX MONTHS			
None	3154 (79.1%)	1567 (78.5%)	1602 (80.7%)
Any	833 (20.9%)	429 (21.5%)	383 (19.3%)
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)

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Table a5. Summary of Patient's Global Assessment Results

	Celebrex 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Mean (95% CI)*			
Baseline	2.96 (2.93-2.98)	2.95 (2.91-2.99)	2.96 (2.92-3.00)
Week 26	2.68 (2.65-2.71)	2.71 (2.67-2.76)	2.73 (2.68-2.78)
Final	2.71 (2.68-2.74)	2.72 (2.67-2.77)	2.76 (2.71-2.81)
Categorical analysis, % (95% CI)			
Week 26			
Improved	38 (37-40)	40 (38-42)	32 (30-34)
No Change	46 (45-48)	43 (41-45)	48 (46-50)
Worsened	16 (15-17)	17 (15-18)	20 (18-21)
Final			
Improved	37 (35-38)	40 (38-43)	31 (29-33)
No Change	46 (44-47)	42 (40-44)	48 (46-50)
Worsened	18 (16-19)	18 (16-19)	21 (19-23)

Table a6. Summary of Patient's Assessment of Arthritis Pain (VAS) Results

	Celebrex 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Mean (95% CI)			
Baseline	50.7 (49.9-51.6)	50.8 (49.6-52.1)	50.6 (49.3-51.9)
Week 26	42.9 (42.0-43.7)	43.4 (42.0-44.8)	45.0 (43.6-46.4)
Final	44.0 (43.1-44.9)	44.2 (42.7-45.6)	45.9 (44.5-47.4)

Table a7. Incidence of Withdrawal Due to Lack of Arthritis Efficacy

	Celebrex 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Number (Percent)	691(17%)	309(15%)	456(23%)
(95% Confidence Interval)	(16% - 19%)	(14% - 17%)	(21% - 25%)

Table a8. Summary of Results in Selected SF-36 Health Survey Domains

SF-36 Health Survey Domain	Celebrex 400 mg BID (n=1990)	Ibuprofen 800 mg TID (n=1985)
Bodily Pain		
Baseline	39.5 (38.6-40.4)	39.9 (39.0-40.8)
Week 26	46.0 (45.1-46.9)	44.8 (43.9-45.8)
Final	45.9 (45.0-46.9)	44.7 (43.8-45.7)
Physical Function		
Baseline	48.3 (47.1-49.5)	48.6 (47.4-49.9)
Week 26	51.4 (50.5-52.3)	50.4 (49.4-51.3)
Final	50.8 (49.9-51.7)	50.1 (49.2-51.0)
Vitality		
Baseline	45.4 (44.3-46.4)	46.1 (45.0-47.1)
Week 26	47.6 (46.7-48.4)	46.9 (46.0-47.7)
Final	47.0 (46.1-47.8)	46.3 (45.5-47.1)
Role-Physical		
Baseline	37.9 (35.9-39.8)	38.4 (36.4-40.3)
Week 26	42.6 (40.8-44.4)	41.0 (39.2-42.8)
Final	42.1 (40.4-43.9)	41.0 (39.2-42.8)

Table a9. Risk Factor Analysis of Clinically Significant UGI Events (Demographics)

	Celecoxib 400 mg BID (N = 3987)		Diclofenac 75 mg BID (N = 1996)		Ibuprofen 800 mg TID (N = 1985)		P-Value (a) Treatment by Factor Interaction	Factor Effect
AGE (years)								
<75	10/3500(	0.3%)	5/1760(	0.3%)	7/1768(	0.4%)	0.837	<0.001
>=75	7/ 487(	1.4%)	5/ 236(	2.1%)	4/ 217(	1.8%)		
P-VALUE(b)	<0.001		<0.001		0.007			
GENDER								
MALE	6/1255(	0.5%)	6/ 650(	0.9%)	4/ 580(	0.7%)	0.476	0.170
FEMALE	11/2732(	0.4%)	4/1346(	0.3%)	7/1405(	0.5%)		
P-VALUE(b)	0.765		0.083		0.625			
DISEASE TYPE								
OA	14/2898(	0.5%)	8/1453(	0.6%)	8/1434(	0.6%)	0.855	0.312
RA	3/1089(	0.3%)	2/ 543(	0.4%)	3/ 551(	0.5%)		
P-VALUE(b)	0.341		0.597		0.928			
DURATION (OA)								
< 5 YEARS	3/ 965(	0.3%)	3/ 484(	0.6%)	6/ 497(	1.2%)	0.052	0.519
>= 5 YEARS	11/1910(	0.6%)	5/ 963(	0.5%)	2/ 927(	0.2%)		
P-VALUE(b)	0.327		0.824		0.038			
DURATION (RA)								
< 5 YEARS	2/ 333(	0.6%)	0/ 191(	0.0%)	0/ 168(	0.0%)	0.065	0.640
>= 5 YEARS	1/ 738(	0.1%)	2/ 345(	0.6%)	3/ 374(	0.8%)		
P-VALUE(b)	0.229		0.992		0.994			
PATIENT'S GLOBAL ASSESSMENT AT BASELINE								
POOR OR VERY POOR	6/ 713(	0.8%)	5/ 362(	1.4%)	2/ 335(	0.6%)	0.352	0.007
OTHER	11/3274(	0.3%)	5/1634(	0.3%)	9/1650(	0.5%)		
P-VALUE(b)	0.037		0.013		0.819			

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Table a10. Risk Factor Analysis of Clinically Significant UGI Events (GI History)

	Celecoxib 400 mg BID (N = 3987)		Diclofenac 75 mg BID (N = 1996)		Ibuprofen 800 mg TID (N = 1985)		P-Value (a) Treatment by Factor Interaction	Factor Effect
HISTORY OF UPPER GI BLEEDING								
YES	1/ 68(	1.5%)	0/ 30(	0.0%)	2/ 28(	7.1%)	0.207	0.017
NO	16/3919(	0.4%)	10/1966(	0.5%)	9/1957(	0.5%)		
P-VALUE(b)	0.144		0.994		<0.001			
HISTORY OF GASTRODUODENAL ULCER								
YES	2/ 334(	0.6%)	4/ 170(	2.4%)	1/ 151(	0.7%)	0.189	0.030
NO	15/3653(	0.4%)	6/1826(	0.3%)	10/1834(	0.5%)		
P-VALUE(b)	0.509		0.002		0.762			
HISTORY OF UPPER GI BLEEDING OR GASTRODUODENAL ULCER								
YES	2/ 353(	0.6%)	4/ 180(	2.2%)	2/ 162(	1.2%)	0.263	0.012
NO	15/3634(	0.4%)	6/1816(	0.3%)	9/1823(	0.5%)		
P-VALUE(b)	0.554		0.003		0.183			
HISTORY OF GI-RELATED NSAID INTOLERANCE								
YES	3/ 347(	0.9%)	2/ 202(	1.0%)	2/ 165(	1.2%)	0.993	0.055
NO	14/3640(	0.4%)	8/1794(	0.4%)	9/1820(	0.5%)		
P-VALUE(b)	0.183		0.272		0.222			
HISTORY OF CARDIOVASCULAR DISEASE								
YES	14/1602(	0.9%)	7/ 805(	0.9%)	4/ 794(	0.5%)	0.036	<0.001
NO	3/2384(	0.1%)	3/1190(	0.3%)	7/1190(	0.6%)		
P-VALUE(b)	0.002		0.064		0.793			
EXPOSURE FOR H. PYLORI								
POSITIVE	5/1536(	0.3%)	5/ 752(	0.7%)	7/ 769(	0.9%)	0.170	0.385
NEGATIVE	12/2448(	0.5%)	5/1243(	0.4%)	4/1213(	0.3%)		
P-VALUE(b)	0.460		0.417		0.092			

Table a11. Risk Factor Analysis of Clinically Significant UGI Events (Medication, Alcohol, and Tobacco Use)

	Celecoxib 400 mg BID (N = 3987)		Diclofenac 75 mg BID (N = 1996)		Ibuprofen 800 mg TID (N = 1985)		P-Value (a) Treatment by Factor Interaction	Factor Effect
CORTICOSTEROID USE								
ANY	3/1219(	0.2%)	2/ 568(	0.4%)	2/ 607(	0.3%)	0.954	0.045
NONE	14/2768(	0.5%)	8/1428(	0.6%)	9/1378(	0.7%)		
P-VALUE(b)	0.171		0.503		0.276			
ASPIRIN USE								
ANY	9/ 882(	1.0%)	6/ 445(	1.3%)	1/ 412(	0.2%)	0.020	0.006
NONE	8/3105(	0.3%)	4/1551(	0.3%)	10/1573(	0.6%)		
P-VALUE(b)	0.005		0.010		0.335			
ALCOHOL USE								
ANY	4/1232(	0.3%)	5/ 812(	0.6%)	4/ 386(	1.0%)	0.326	0.605
NONE	13/2753(	0.5%)	5/1184(	0.4%)	7/1599(	0.4%)		
P-VALUE(b)	0.506		0.574		0.166			
TOBACCO USE								
ANY	0/ 628(	0.0%)	2/ 311(	0.6%)	0/ 284(	0.0%)	0.057	0.059
NONE	17/3356(	0.5%)	8/1685(	0.5%)	11/1701(	0.6%)		
P-VALUE(b)	0.993		0.657		0.992			
ANTICOAGULANT USE								
ANY	0/ 42(	0.0%)	0/ 24(	0.0%)	0/ 20(	0.0%)	1.000	0.339
NONE	17/3945(	0.4%)	10/1972(	0.5%)	11/1965(	0.6%)		
P-VALUE(b)	0.993		0.994		0.994			

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Table a12. Risk Factor Analysis of Clinically Significant UGI Events or GD Ulcer
(Medication, Alcohol, and Tobacco Use)

	Celecoxib 400 mg BID (N = 3987)	Diclofenac 75 mg BID (N = 1996)	Ibuprofen 800 mg TID (N = 1985)	-------- P-Value (a) -------- Treatment by Factor Interaction	Factor Effect
CORTICOSTEROID USE					
ANY	10/1219(0.8%)	6/ 568(1.1%)	12/ 607(2.0%)	0.707	0.123
NONE	33/2768(1.2%)	20/1428(1.4%)	24/1378(1.7%)		
P-VALUE(b)	0.150	0.397	0.778		
ASPIRIN USE					
ANY	22/ 882(2.5%)	16/ 445(3.6%)	8/ 412(1.9%)	0.004	<0.001
NONE	21/3105(0.7%)	10/1551(0.6%)	28/1573(1.8%)		
P-VALUE(b)	<0.001	<0.001	0.960		
ALCOHOL USE					
ANY	10/1232(0.8%)	15/ 812(1.8%)	5/ 386(1.3%)	0.112	0.924
NONE	33/2753(1.2%)	11/1184(0.9%)	31/1599(1.9%)		
P-VALUE(b)	0.351	0.099	0.463		
TOBACCO USE					
ANY	2/ 628(0.3%)	5/ 311(1.6%)	2/ 284(0.7%)	0.106	0.054
NONE	41/3356(1.2%)	21/1685(1.2%)	34/1701(2.0%)		
P-VALUE(b)	0.074	0.508	0.146		
ANTICOAGULANT USE					
ANY	1/ 42(2.4%)	0/ 24(0.0%)	0/ 20(0.0%)	0.382	0.821
NONE	42/3945(1.1%)	26/1972(1.3%)	36/1965(1.8%)		
P-VALUE(b)	0.453	0.994	0.994		

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Appendix B

Discussions On Informative Censoring And Risk Factor-Related Withdrawal

In design and analysis of failure data with censoring, an important requirement is that dropouts are non-informative, that is, the failure time is independent of the reason for the individual to drop out before the event is possibly observed. However, this assumption cannot be met if the failure time is censored through withdrawal as a result of a deterioration of patient condition. This type of censoring is known as informative censoring, a special type of non-ignorable missing data. When present, informative censoring causes bias in standard analyses, and interpretation of such analyses may be misleading. In this section, we discuss the informative censoring in the present study caused by withdrawal due to GI-related symptoms, and the statistical analysis and simulation adjusted for the informative censoring. We also present the withdrawal vs. GI risk factors over time and its impact on the analysis.

Informative Censoring Caused by Withdrawal due to GI-Related Symptoms

In this study, informative censoring with respect to study end points, namely clinically significant UGI events (CSUGIEs) and CSUGIEs combined with gastroduodenal ulcers (CSUGIEs/GDUs), was observed in patients who dropped out due to GI-related adverse events, including dyspepsia, abdominal pain, nausea, diarrhea, and vomiting. First, a treatment differentiation in time to and incidence of dropout due to GI adverse events was detected. Second, the rates of CSUGIEs were different in patients without GI adverse events than in patients with GI adverse events. Patients who experienced GI adverse events had a higher incidence of CSUGIEs than patients who did not report GI adverse events. Clearly, a patient whose failure time is censored due to a GI adverse event causing withdrawal represents a higher risk for an event than those who have not had an adverse event up to that time.

Table 1. Summary of Abdominal Pain, Dyspepsia, Nausea, Diarrhea and Vomiting Incidence and Withdrawals (Moderate to Severe)

	Celecoxib n (%)	Diclofenac n (%)	Ibuprofen n (%)
Treated	3987	1996	1985
Any GI AE	699	448	336
Withdrawal	298 (7.5)	191 (9.6)	149 (7.5)

Similar summaries including mild, moderate, and severe GI adverse events and withdrawals are included in Appendix 2.4.17. Significantly higher withdrawal incidence and earlier withdrawal time in the diclofenac group were detected than in the other treatment groups (p<0.01). To assess whether the withdrawals due to GI-related adverse events affected the estimation of clinically significant UGI event rates, we examined the relative risks of CSUGIEs and CSUGIEs/GDUs in patients with and without GI symptoms.

Table 2. Summary of CSUGIE Rates and Relative Risks With and Without Five GI Adverse Events (Moderate to Severe)

	Celecoxib	Diclofenac	Ibuprofen
CSUGIEs			
With AE	5/699	8/448	5/336
Without AE	12/3288	2/1548	6/1649
Relative risk	1.96	13.82	4.09
CSUGIEs / GDUs			
With AE	22/699	20/448	20/336
Without AE	21/3288	6/1548	16/1649
Relative risk	4.93	11.52	6.13

The table indicates that the patients with GI adverse events would have higher probability to develop an event over the treatment duration. A high and early withdrawal rate due to GI-related adverse events diminished the real event rate of the patient population. A bias would have been created in favor of treatments with high withdrawal rates due to shorter exposure time to treatment, hence lower event rates. Therefore, an estimation for the entire study period without adjustment for informative dropouts would not be appropriate for interpretation.

VI.   Statistical Adjustment for Informative Censoring

Informative censoring has been widely discussed in many statistical journals over the past 20 years. There have been some proposals under certain assumptions dealing with continuous data and some other specific types of data when dropouts do not occur at random. For references, reviewers should refer to D. Rubin (1976, Biometrika, vol. 63, pp. 581-592), P. Diggle and M. Kenward (1994, Appl. Statist., Vol. 43, pp. 49-93), and J. Little (1995, JASA, vol. 90, pp. 1112-1121).

In this study, informative censoring occurred, and our primary end point is survival-type data. We will analyze the data by estimating the events missed due to informative withdrawal-based dropout incidences and times. A total probability will be calculated and simulation will be performed for Kaplan-Meier curves adjusted for the withdrawal. Fisher's exact test will be performed on the adjusted event rates.

As seen in prior discussions, treatment differentiation withdrawals due to GI adverse events and higher relative risks in the patients with GI adverse events were observed. Intuitively, early withdrawal of patients due to GI adverse events would have introduced underestimates of overall CSUGIE and ulcer rates because the probability for a patient to develop a UGI event or ulcer is higher if the patient has a GI adverse event or discontinues due to a GI adverse event. Therefore, the overall CSUGIE or ulcer rate, or the total probability of developing a CSUGIE or ulcer for the treated patient population, should be estimated by partitioning the samples into three subsets.

Prob. (event occurred) = P (event | no GI AE) * P (no GI AE)
    + P (event | GI AE and continue) * P (GI AE and continue)
    + P (event | GI AE and withdrawal) * P (GI AE and withdrawal)

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The first and second terms shall be estimated by the corresponding sample means, respectively. The third term represents the missing event rate due GI adverse event-related withdrawal. To estimate the number of CSUGIEs we would have observed had the patients not dropped out due to adverse events, we calculated the total exposure time after the GI adverse events were reported for the patients with adverse events who did not drop out as a result. The total number of the events occurring in these continuing patients with adverse events divided by this exposure would give us the estimated rate by patient exposure time after the adverse event was reported. We assume the rate in the patients who discontinued due to GI adverse events over the period between the adverse event and the end of the treatment would have been at least as high had the patients continued treatment as the rate in those who continued. The exposure times for the patients who withdrew due to adverse events were estimated by calculating the time between the dropout date and the end of the study. For the entire study period, the date of 1/10/2000 was used as the end of the study. This date is one month after the official letter of closing the study was issued, and is five days after the last withdrawal due to a GI adverse event. For the analyses of the first six months, the dates of 7/10/2000 and 9/10/2000 were used for protocols 035 and 102, respectively, due to the lag in enrollment time of 102 by approximately two months.

Table 3 summarizes the adjusted event rates and statistical tests applied. Detailed data can be found in Appendices 2.4.17.9 – 2.4.17.14.

Table 3. CSUGIE and Ulcer Rates Adjusted for Discontinuation due to Moderate and Severe GI Adverse Events

	Celecoxib	Diclofenac	Ibuprofen	C/N	C/D	C/I
				p-values		
Patients	3984	1995	1983			
First 6 Month						
CSUGIE	15	16	16	.013	.036	.035
CSUGIE/GDU	44	34	44	.002	.069	.001
Entire period						
POB	25	23	21	.022	.044	.084
PUB	76	58	73	<.01	.016	<.01

With the above rates, we simulated Kaplan-Meier curves for the three treatment groups. In each run, the estimated events were randomly assigned to the patients who discontinued due to GI adverse events. The simulations were performed 100 times; the averaged curve is presented below.