

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-998/S-009

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA20-998

Name of Drug: Celecoxib

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: Larry Goldkind, M.D. and Jim Witter, M.D.

Reviewer: Hong Laura Lu, Ph.D.

Date of Review: 2/16/2001

I. Background

This NDA is submitted to support the claim that celecoxib 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, multi-center study designed to compare the incidence of CSUGIEs associated with celecoxib 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 celecoxib 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 (celecoxib 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: celecoxib vs. ibuprofen and celecoxib vs. diclofenac. A stepwise procedure was used to strongly control the type I error rate. In this procedure, the first step was to test the overall hypothesis whether celecoxib 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 celecoxib and each of the two NSAIDs. Celecoxib will be claimed to be different from an NSAID if both overall and pairwise comparisons of celecoxib vs.

that NSAID are 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, celecoxib will be claimed to be different from the NSAID(s) on both endpoints. If only the first step shows significance, celecoxib 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 celecoxib 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 celecoxib 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 celecoxib 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 celecoxib group, 27.1% in diclofenac group and 23.2% in ibuprofen group), treatment failure (17.3% in celecoxib group, 15.5% in diclofenac group and 23.0% in ibuprofen group), or protocol noncompliance (14.7% in celecoxib 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

	Celecoxib	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 celecoxib treatment, 11 on diclofenac, and 13 on ibuprofen. Among these events, a total of 6 were considered censored (3 in the celecoxib 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 celecoxib 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.

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Figure 1. Kaplan-Meier Estimator for CSUGIE Incidence

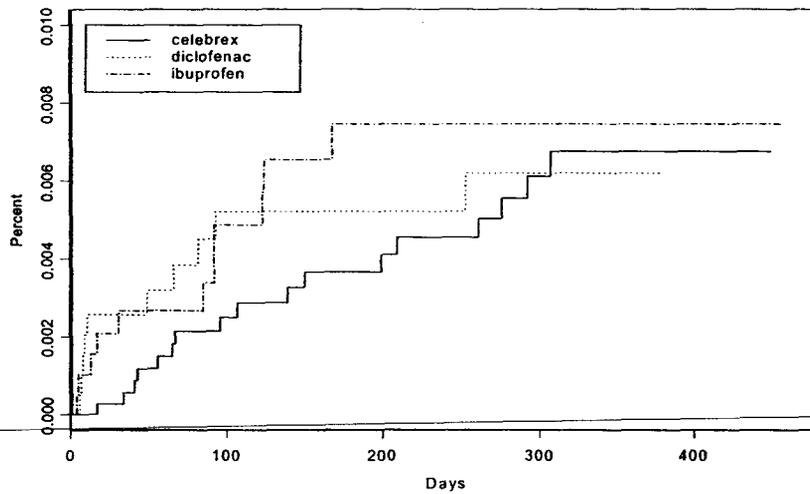


Table 2. Summary of CSUGIE Incidence

	Celecoxib 400 mg BID n=3987	Diclofenac 75 mg BID n=1996	Ibuprofen 800 mg TID n=1985	Log-Rank P Values for Celecoxib 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

	Celecoxib 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

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 celecoxib (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

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celecoxib 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 Additional 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, celecoxib 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 celecoxib 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

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celecoxib 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).

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 celecoxib group, 27 in the diclofenac group, and 38 in the ibuprofen group. The cumulative event rates were lower over the entire study period for celecoxib 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 celecoxib 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

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celecoxib 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 C.

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

	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)	Celecoxib vs. Diclofenac	Celecoxib 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 C) and 2) higher withdrawal incidence with earlier withdrawal time in the diclofenac group were observed (see Table 1 in Appendix C), 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 than 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 severe 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.

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	celecoxib	261			261

10761	celecoxib	307	307	307	307
20349	celecoxib	199	.	.	199
11159	celecoxib	43	63	63	43
10012	celecoxib	12	.	.	276
11153	celecoxib	67	67	67	67
11341	celecoxib	10	150	150	150
12176	celecoxib	139	139	.	139
20035	diclofenac	6	6	.	6
10032	diclofenac	66	66	.	66
10193	diclofenac	8	8	8	8
10294	diclofenac	7	7	7	9
20398	diclofenac	41	41	.	49
11559	diclofenac	261	261	.	253
12252	diclofenac	11	11	11	11
12815	diclofenac	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

* :Time to Mild-Moderate-Severe GI AE
 ** :Time to Moderate-Severe GI AE
 *** :Time to Severe GI AE
 ****:Time to CSUGIE

Table 10. CSUGIE Incidence in GI AE Groups and Non-GI AE Groups

	Celecoxib	Diclofenac	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

Time Point	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
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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 celecoxib 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 fashion. 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.

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—celecoxib 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).

IV.4 GI Results Within Each Study

When comparing celecoxib against each of the NSAIDS, data for celecoxib in studies 035 and 102 were combined. Since celecoxib patients were not randomized between studies and each NSAID was only included in one study, the center effects in the study which the NSAID was absent can not be teased out from the treatment effect of celecoxib vs. each NSAID, even the designs are similar and the baseline GI risk factors are generally comparable among the two studies (See Table a13). This reviewer reanalyzed the CSUGIE incidence and combined CSUGIE/GDU event incidence within each study with the results presented in Tables 12 and 13.

Table 12 shows that, in Study 102, the crude rate of CSUGIE of celecoxib was higher than that of diclofenac (0.55% vs. 0.50%), in Study 035, the crude rate of CSUGIE of celecoxib was lower than that of ibuprofen (0.30% vs. 0.55%). No statistical significance was demonstrated in the difference of CSUGIE incidence rates between treatment groups in either study (Note that each individual study was not powered to show statistical significance). Compared with the results in Table 1 when the celecoxib data were combined from the two studies, the numerical trend of CSUGIE incidence was not preserved since celecoxib showed a higher incidence rate than diclofenac in Study 102, but there is a consistency in the sense that celecoxib was numerically close to diclofenac and further away from ibuprofen in CSUGIE incidence rate. The Kaplan-

Meier estimators for CSUGIE incidence rates for each treatment groups in each study are presented in Figures b1 and b2 in Appendix B.

Table 13 shows that the combined CSUGIE/GDU event incidence rates among treatment groups were consistent to those in Table 7 when celecoxib data were combined. The p-value for the difference between celecoxib and ibuprofen in CSUGIE/GDU event incidence rates were also less than 0.05 in Table 13. The Kaplan-Meier estimators for combined CSUGIE/GDU event incidence rates for each treatment groups in each study are presented in Figures b3 and b4 in Appendix B.

Table 12. Comparison for CSUGIE Incidences in Individual Studies

	Study 102		Study 035	
	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Celecoxib 400 mg BID	Ibuprofen 800 mg TID
No. of Patients	n=1997	n=1996	n=1990	n=1985
No. of CSUGIE				
Uncensored	11	10	6	11
Censored*	1	1	2	2
Total	12	11	8	13
Week 52 Crude Rate	0.55%	0.50%	0.30%	0.55%
P-value*	.884		.195	

*: P-values are from log-rank tests

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Table 13. Comparison for CSUGIE/GDU Event Incidences in Individual Studies

	Study 102		Study 035	
	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Celecoxib 400 mg BID	Ibuprofen 800 mg TID
No. of Patients	n=1997	n=1996	n=1990	n=1985
No. of CSUGIE/GDU				
Uncensored	21	26	22	36
Censored*	1	1	2	2
Total	22	27	24	38
Week 52 Crude Rate**	1.05%	1.30%	1.11%	1.81%
P-value*	.393		.045	

*: P-values are from log-rank tests

** : Crude rates are calculated by No. of uncensored CSUGIE/GDU over No. of Patients

V. Final Conclusion

Celecoxib 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 subgroup analysis of non-aspirin users, the incidence of combined CSUGIE/GDU event in the celecoxib 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 the failure of showing statistical significance in the primary endpoint and the fact that at 34 subgroup analyses were conducted.

Hong Laura Lu, Ph.D

Concur:

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Team Leader

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NDA 20998
HFD-550/MO/Goldkind/Witterj/Bullj
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HFD-725/Lu/Lin ST./Huque
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Appendix A. Tables

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

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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			
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			
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			
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			
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			

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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

	Celecoxib 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

	Celecoxib 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

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

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

SF-36 Health Survey Domain	Celecoxib 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		
FLEXURE 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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Table a13. GI Risk Factors By Study

HISTORY OF:	Celecoxib 400 mg BID (Study 035) (N=1990)	Celecoxib 400 mg BID (Study 102) (N=1997)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)	P-value (a)
UPPER GI BLEEDING					0.705
Yes	31 (1.6%)	37 (1.9%)	30 (1.5%)	28 (1.4%)	
No	1959 (98.4%)	1960 (98.1%)	1966 (98.5%)	1957 (98.6%)	
TOTAL	1990 (100.0%)	1997 (100.0%)	1996 (100.0%)	1985 (100.0%)	
GASTRODUODENAL ULCER					0.543
Yes	159 (8.0%)	175 (8.8%)	170 (8.5%)	151 (7.6%)	
No	1831 (92.0%)	1822 (91.2%)	1826 (91.5%)	1834 (92.4%)	
TOTAL	1990 (100.0%)	1997 (100.0%)	1996 (100.0%)	1985 (100.0%)	
GI-RELATED NSAID INTOLERANCE (b)					<0.001 ***
Yes	138 (6.9%)	209 (10.5%)	202 (10.1%)	165 (8.3%)	
No	1852 (93.1%)	1788 (89.5%)	1794 (89.9%)	1820 (91.7%)	
TOTAL	1990 (100.0%)	1997 (100.0%)	1996 (100.0%)	1985 (100.0%)	
CARDIOVASCULAR DISEASE					0.989
Yes	795 (39.9%)	807 (40.4%)	805 (40.3%)	794 (40.0%)	
No	1194 (60.0%)	1190 (59.6%)	1190 (59.6%)	1190 (59.9%)	
TOTAL	1989 (99.9%)	1997 (100.0%)	1995 (99.9%)	1984 (99.9%)	
FLEXSURE FOR H. PYLORI					0.722
Negative	1209 (60.8%)	1239 (62.0%)	1243 (62.3%)	1213 (61.1%)	
Positive	780 (39.2%)	756 (37.9%)	752 (37.7%)	769 (38.7%)	
TOTAL	1989 (99.9%)	1995 (99.9%)	1995 (99.9%)	1982 (99.8%)	

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Table a13. GI Risk Factors By Study (cont.)

	Celecoxib 400 mg BID (Study 035) (N=1990)	Celecoxib 400 mg BID (Study 102) (N=1997)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)	P-value (a)
CORTICOSTEROID USE					
None	1377 (69.2%)	1391 (69.7%)	1428 (71.5%)	1378 (69.4%)	0.601
One Dose to <10% Study Days	210 (10.6%)	203 (10.2%)	183 (9.2%)	214 (10.8%)	
>10% Study Days	403 (20.3%)	403 (20.2%)	385 (19.3%)	393 (19.8%)	
TOTAL	1990 (100.0%)	1997 (100.0%)	1996 (100.0%)	1985 (100.0%)	
ANTICOAGULANT USE					
None	1972 (99.1%)	1973 (98.8%)	1972 (98.8%)	1965 (99.0%)	0.502
One Dose to <10% Study Days	11 (0.6%)	13 (0.7%)	8 (0.4%)	8 (0.4%)	
>10% Study Days	7 (0.4%)	11 (0.6%)	16 (0.8%)	12 (0.6%)	
TOTAL	1990 (100.0%)	1997 (100.0%)	1996 (100.0%)	1985 (100.0%)	
ASPIRIN USE					
None	1554 (78.1%)	1551 (77.7%)	1551 (77.7%)	1573 (79.2%)	0.602
One Dose to <10% Study Days	104 (5.2%)	92 (4.6%)	104 (5.2%)	83 (4.2%)	
>10% Study Days	332 (16.7%)	354 (17.7%)	341 (17.1%)	329 (16.6%)	
TOTAL	1990 (100.0%)	1997 (100.0%)	1996 (100.0%)	1985 (100.0%)	
ASPIRIN USE DURING FIRST SIX MONTHS					
None	1580 (79.4%)	1574 (78.8%)	1567 (78.5%)	1602 (80.7%)	0.329
Any	410 (20.6%)	423 (21.2%)	429 (21.5%)	383 (19.3%)	
TOTAL	1990 (100.0%)	1997 (100.0%)	1996 (100.0%)	1985 (100.0%)	

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Appendix B. Figures

Figure b1. Kaplan-Meier Estimators for CSUGIE Incidence in Study 035

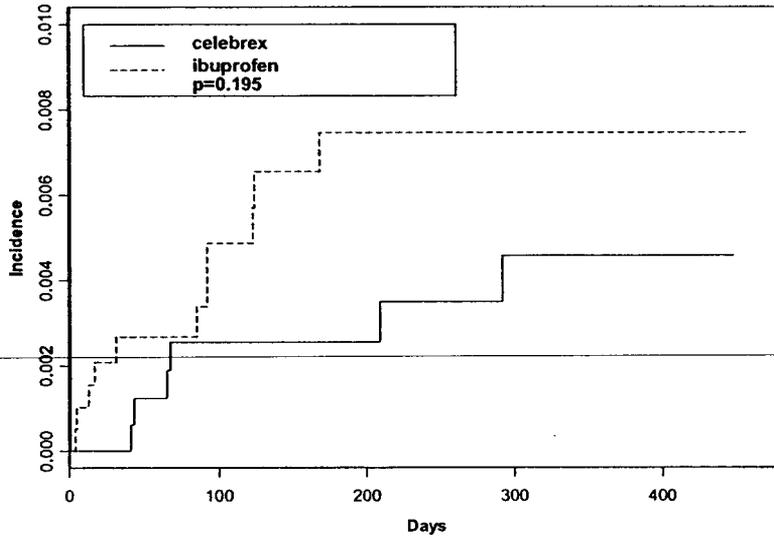
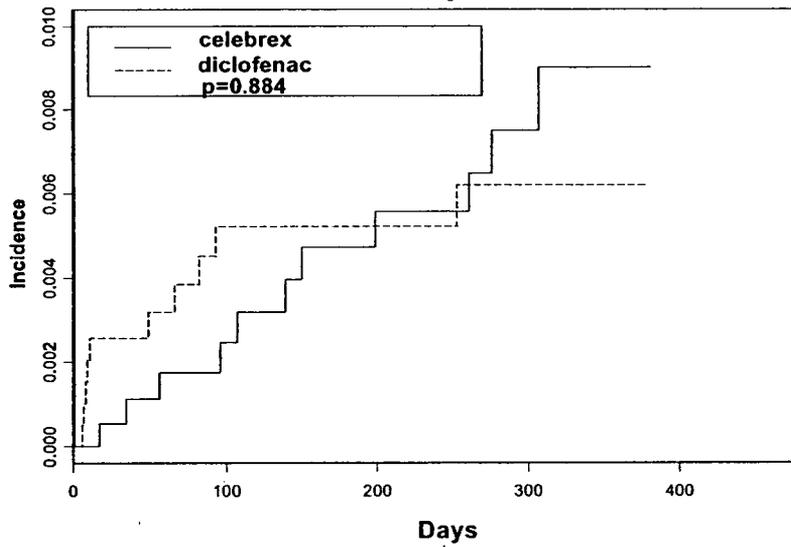


Figure b2. Kaplan-Meier Estimators for CSUGIE Incidence in Study 102



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Figure b3. Kaplan-Meier Estimators for Combined CSUGIE/GDU Incidence in Study 035

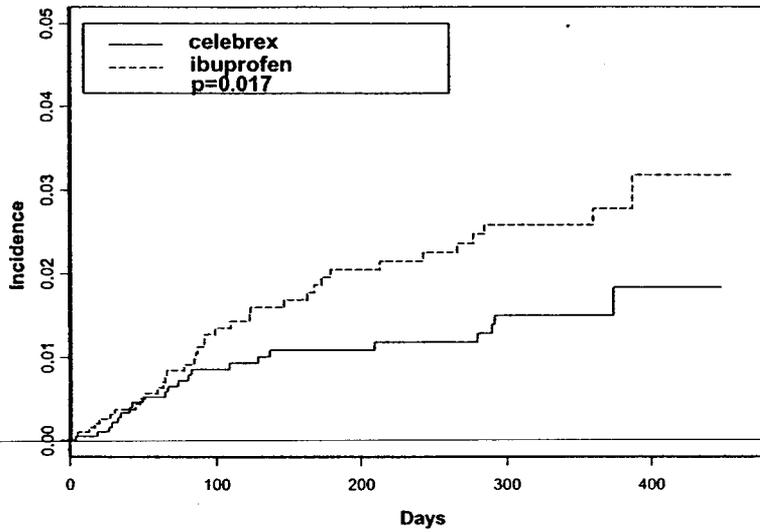
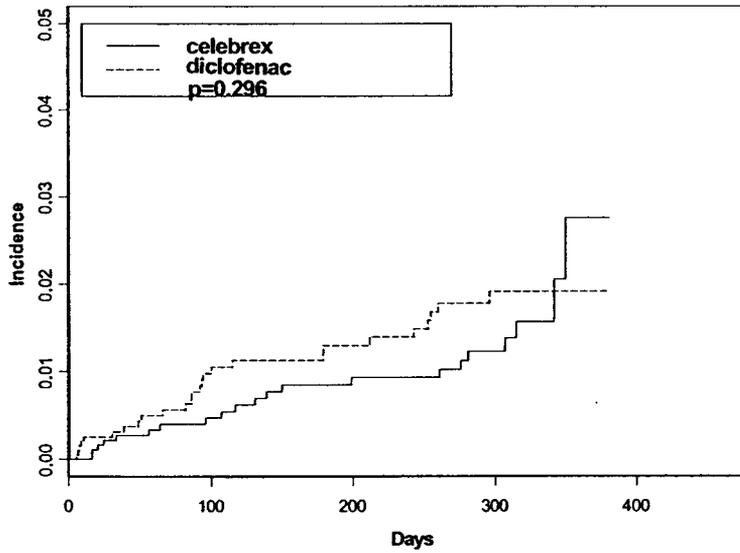


Figure b4. Kaplan-Meier Estimators for Combined CSUGIE/GDU Incidence in Study 102



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Appendix C. Sponsor’s Detailed Discussion on Informative Censoring and Data Imputation

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 endpoints, 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.

$$\begin{aligned} \text{Prob. (event occurred)} &= P(\text{event} \mid \text{no GI AE}) * P(\text{no GI AE}) \\ &+ P(\text{event} \mid \text{GI AE and continue}) * P(\text{GI AE and continue}) \\ &+ P(\text{event} \mid \text{GI AE and withdrawal}) * P(\text{GI AE and withdrawal}) \end{aligned}$$

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	p-values		
				C/N	C/D	C/I
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.

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Statistical Review: Celebrex[®] (celecoxib), Supplemental NDA 20-998, Protocol N-49-99-01-123, Bioequivalence Study of Two Formulations of Enteric Coated Diclofenac Sodium 75 mg, G.D. Searle and Corporation

This study was an open-label, randomized, two sequence, four period, replicated crossover study designed to evaluate the bioequivalence between the 75 mg diclofenac/placebo tablet formulation and the Voltaren 75 mg tablet formulation. 36 fasted healthy volunteers (27 males and 9 females) participated in the study.

Data Set Provided by Sponsor

The data set provided to us contained 36 subjects and five pharmacokinetic responses, AUC_t , AUC_{inf} , C_{max} , C_{max}/AUC_{inf} , and T_{max} . The Sponsor's own analyses included the PK parameter $T_{1/2}$, instead of T_{max} . We cannot examine the result for $T_{1/2}$ because this variable was not available to us. Other variables in the data set were subject number, sequence, treatment, period, gender, age and weight.

Study Design

Open-label, randomized, two sequences, four period, replicated crossover bioequivalence design.

Study Objectives

Primary objective: to assess the in vivo bioequivalence of diclofenac/placebo relative to Voltaren with respect to diclofenac AUC_t and AUC_{inf} .

Secondary objective: 1) to compare C_{max} , C_{max}/AUC_{inf} , and T_{max}
2) to determine intrasubject and intersubject variability for each treatment.

All parameters were statistically analyzed after natural log-transformation. This included T_{max} , for which the theoretical arguments in favor of the log-transformation for PK parameters may not apply.

Experimental Treatments

Test product: Diclofenac sodium 75 mg enteric-coated core/placebo mantle tablets orally, Lot No. RCT 11010, Manufactured by G.D. Searle & Co.

Reference Therapy: Voltaren (Diclofenac sodium) 75 mg enteric-coated tablets orally, Lot No. RCT 11011, Manufactured by Ciba Geigy (Vendor Lot No. LT5581)

Study Schematic

Sequence 1: TRRT (18 subjects)

Sequence 2: RTTR (18 subjects)

All 36 subjects were included in the assessment of bioequivalence: 33 subjects completed the study; and two subjects (17 and 27), randomized to different treatment sequences, each completed only period 1 prior to early termination and subject 19 completed only the first two periods (in Sequence 2). Hence, subjects 17 and 27 had only one observation, and subject 19 had two observations. We examined three different data sets: 1) a completed data set including all the subjects (the data set used by the Sponsor); 2) a data set without subjects 17 and 27; 3) a data set without subjects 17, 27 and 19. Subjects were distributed in two sequences as follows.

Subject numbers:

Sequence 1: 1, 3, 6, 7, 8, 9, 11, 14, 15, 20, 21, 22, 23, 25, 26, 27, 28, 32

Sequence 2: 2, 4, 5, 10, 12, 13, 16, 17, 18, 19, 24, 29, 30, 31, 33, 34, 35, 36

Statistical Analysis

The following five pharmacokinetic parameters were statistically analyzed to assess bioequivalence of the two treatments:

$$LAUC_t = \ln(AUC_t)$$

$$LAUC_{inf} = \ln(AUC_{inf})$$

$$LC_{max} = \ln(C_{max})$$

$$LT_{max} = \ln(T_{max})$$

$$LRC_AUC = \ln(C_{max}/AUC_{inf})$$

Formal statistical analyses, with confidence intervals, are not typically carried out for LT_{max} and LRC_AUC for regulatory purposes. However, these analyses have been carried out here for informational purposes. Also, we have analyzed LT_{max} even though the theoretical arguments in favor of the log-transformation for AUC_t , AUC_{inf} , and C_{max} may not apply to T_{max} .

For a given endpoint out of five pharmacokinetic parameters (e.g. $LAUC_t$), in the absence of carryover, the following statistical model was considered.

$$Y_{ijkl} = \mu + \alpha_i + \gamma_k + T_l + \tau_{ijl} + \epsilon_{ijkl}$$

where, Y_{ijkl} = a measurement of the endpoint for subject j in sequence i , at period k , at which time this subject received treatment l

μ = mean response

α_i = sequence effect

γ_k = period effect

T_i = treatment effect
 τ_{ijl} = random effect for subject by treatment
 ϵ_{ijkl} = unknown random error.

We assume

$$\epsilon_{ijkl} \sim N(0, \sigma_{wI}^2), \tau_{ijl} \sim N(0, \sigma_{bI}^2), \text{Cov}(\tau_{ijT}, \tau_{ijR}) = \rho\sigma_{BT}\sigma_{BR}.$$

Here “W” and “B” denote “within” and “between” respectively, and T refers to test product and R refers to reference product.

The bioequivalence of the two treatments was assessed by performing two one-sided statistical tests ($\alpha=0.05$) through constructing a 90% confidence interval for the ratio of the test mean to the reference mean. For AUC_t , AUC_{inf} , and C_{max} , the confidence interval typically needs to be within the bounds of 80% to 125% for the two treatments (test and reference) to be judged bioequivalent. We know of no established bioequivalence criteria for C_{max}/AUC_t or T_{max} , but the confidence intervals are reported for informational purposes.

Statistical analyses using this model were carried out using SAS PROC MIXED (SAS version 6.12). The SAS code was:

```
PROC MIXED;  
CLASS PERIOD SEQUENCE SUBJECT TREATMNT;  
MODEL <y> = PERIOD SEQUENCE TREATMNT/DDFM=SATTERTH;  
RANDOM TREATMNT/TYPE=FA0(2) SUBJECT=SUBJECT G;  
REPEATED/GRP=TREATMNT SUB=SUBJECT;  
ESTIMATE 'T VS. R' TREATMNT 1 -1/CL ALPHA=0.1;  
RUN;
```

Where <y> is the particular endpoint ($LAUC_t$, $LAUC_{inf}$, LC_{max} , LT_{max} , LR_CAUC) being analyzed. These SAS statements allow for possible subject-by-treatment interaction and also allow the within subject variance of test drug and reference drug to differ. The analysis provides an estimated variance-covariance matrix for the subject-specific treatment means, as well as estimates of the within-subject variance for each treatment. The intrasubject and intersubject CVs for each treatment can be estimated through the above variance-covariance parameter estimates.

Results – average bioequivalence

The results for the bioequivalence study are listed in Table 1, Table 2 and Table 3. The output in Table 1 is based on all the 36 subjects. 33 subjects completed the study and each provided 2 observations on each of the two treatments. Subject 17 had only one observation on R. Subject 27 had only one observation on T. Subject 19 provided one observation for each treatment. Among the 33 who completed the study, subject 31 had one missing value for AUC_{inf} . Therefore, there were 68 observations for each treatment with AUC_t , C_{max} , T_{max} as well as for

one treatment with AUC_{inf} and C_{max}/AUC_{inf} , and 67 observations for another treatment with AUC_{inf} and C_{max}/AUC_{inf} , in which Subject 31 had one missing value.

Similarly, Table 2 includes 34 subjects (without subjects 17 and 27) and is comprised of 67 observations for each treatment with AUC_t , C_{max} , T_{max} as well as for one treatment with AUC_{inf} and C_{max}/AUC_{inf} , and 66 observations for another treatment with AUC_{inf} and C_{max}/AUC_{inf} . Table 3 includes 33 subjects (without subjects 17, 27 and 19), and is comprised of 66 observations with AUC_t , C_{max} , T_{max} for both treatments, as well as with AUC_{inf} and C_{max}/AUC_{inf} for one treatment, and 65 observations for another treatment for AUC_{inf} and C_{max}/AUC_{inf} .

As can be seen from all the three Tables, the observed mean values for the test AUC_t , AUC_{inf} , C_{max} , T_{max} , and C_{max}/AUC_{inf} were lower than the reference values. The 90% confidence intervals for AUC_t and AUC_{inf} were within the boundary of 80% to 125%; however, 90% confidence intervals for the rest of the three parameters, namely, C_{max} , T_{max} , and C_{max}/AUC_{inf} were outside the acceptable limits of 80-125%.

Table 1 (A complete date set)

Diclofenac PK Parameters	AUC_t (obs=68)	AUC_{inf} (obs=68-67)	C_{max} (obs=68)	C_{max}/AUC_{inf} (obs=68-67)	T_{max} (obs=68)
Observed Test Product Mean	2304.00	2343.22	1586.34	0.68	1.44
Observed Reference Product Mean	2398.55	2460.64	2167.09	0.88	2.25
Ratio (%) (Test/Reference) of Observed Means	96.06	95.23	73.20	77.65	63.98
90% CI (%)	(90.81, 101.76)	(90.88, 98.91)	(66.68, 82.78)	(70.93, 83.85)	(60.89, 70.03)

Table 2 (Without subjects 17 and 27, but subject 19 was included in the study)

Diclofenac PK Parameters	AUC_t (obs=67)	AUC_{inf} (obs=67-66)	C_{max} (obs=67)	C_{max}/AUC_{inf} (obs=67-66)	T_{max} (obs=67)
Observed Test Product Mean	2296.33	2335.78	1595.64	0.69	1.43
Observed Reference Product Mean	2383.58	2445.63	2162.42	0.88	2.26
Ratio (%) (Test/Reference) of Observed Means	96.33	95.51	73.79	78.41	63.27
90% CI (%)	(90.88, 101.88)	(90.79, 98.85)	(67.16, 83.55)	(71.62, 84.42)	(50.13, 69.14)

Table 3 (Without Subjects 17, 27 and 19)

Diclofenac PK Parameters	AUC _t (obs=66)	AUC _{inf} (obs=66-65)	C _{max} (obs=66)	C _{max} /AUC _{inf} (obs=66-65)	T _{max} (obs=66)
Observed Test Product Mean	2306.64	2345.962	1596.64	0.69	1.42
Observed Reference Product Mean	2398.25	2460.65	2174.73	0.88	2.27
Ratio (%) (Test/Reference) of Observed Means	96.18	95.34	73.42	77.67	62.80
90% CI (%)	(90.51, 101.65)	(90.43, 98.53)	(66.50, 82.95)	(71.18, 84.11)	(49.69, 68.91)

Results – variability estimates

Confusion may arise due to a lack of standard terminology regarding variability in a crossover bioequivalence study. Generally, the variability of responses within a given subject, around that subject's subject-specific mean, is termed within-subject, or intrasubject, variability. The term between-subject, or intersubject, variability sometimes refers to the variability of the subject-specific means from one individual to another. The sum of the within-subject variance and the between-subject variance may be termed the total variance. The total variance represents the variability of randomly observed observations from randomly chosen subjects. This terminology is used, for example, in the recently issued CDER Guidance "Statistical Approaches to Establishing Bioequivalence". However, what we have just termed the total variance is also called the between-subject variance by some.

Using the Guidance definitions, suppose the estimated within-subject (intrasubject) and between-subject (intersubject) variances in a log-transformed diclofenac pharmacokinetic parameter are s_{WT}^2 and s_{BT}^2 for the test product, and s_{WR}^2 and s_{BR}^2 for the reference product. Then, under the lognormal distribution assumption (which, once again, may not be a good assumption for T_{max}), the estimated within-subject and between-subject CVs in untransformed scales are $\sqrt{e^{s_{WT}^2} - 1}$ and $\sqrt{e^{s_{BT}^2} - 1}$ for the test product, and $\sqrt{e^{s_{WR}^2} - 1}$ and $\sqrt{e^{s_{BR}^2} - 1}$ for the reference product. The estimated total CVs in original scale are $\sqrt{e^{s_{WT}^2 + s_{BT}^2} - 1}$ for the test product, and $\sqrt{e^{s_{WR}^2 + s_{BR}^2} - 1}$ for the reference product, respectively.

Our analysis of intrasubject variability used data from 33 subjects (the same as the Sponsor's analyses) who received replicate treatment and the intersubject variability study was based on the 36 subjects (the same as the Sponsor's analyses). Estimated intrasubject CVs in AUC_t, AUC_{inf}, C_{max}, C_{max}/AUC_{inf} and T_{max} were 11.62%, 11.62%, 28.09%, 22.70% and 61.08%, respectively, for the test product, and 16.84%, 11.79%, 31.83%, 24.44% and 41.52%, respectively, for the

reference product. Estimated intersubject CVs of the subject-specific means in AUC_t , AUC_{inf} , C_{max} , C_{max}/AUC_{inf} and T_{max} were 24.94%, 24.80%, 23.37%, 14.60% and 36.03%, respectively, for the test product, and 23.28%, 21.28%, 28.87%, 11.79% and 35.63%, respectively, for the reference product. We also estimated total variabilities. The estimated total CVs in AUC_t , AUC_{inf} , C_{max} , C_{max}/AUC_{inf} and T_{max} were 27.67%, 27.53%, 37.13%, 27.19% and 74.25%, respectively, for the test product, and 29%, 24.46%, 43.94%, 27.28% and 56.67%, respectively, for the reference product. As one can see later in this review, our reported total variabilities (CV%) are compatible with what the Sponsor called intersubject variabilities (CV%).

Sponsor's Results

The Sponsor assessed bioequivalence by using a mixed linear model for parameters AUC_t , AUC_{inf} , C_{max} , C_{max}/AUC_{inf} and $T_{1/2}$. The analysis of bioequivalence used data from 36 subjects. Analysis of intrasubject variability used data from 33 subjects who completed the study and the analysis of intersubject variability used the complete data set. The Sponsor's results are summarized in Table 4.

The ratios in Table 4 are the ratios of the test product observed mean and the reference product observed mean for AUC_t , AUC_{inf} , C_{max} . However, it is not clear how the ratios for C_{max}/AUC_{inf} and $T_{1/2}$ were calculated.

Table 4 (Sponsor's results)

Diclofenac PK Parameters	AUC_t (obs=68)	AUC_{inf} (obs=68-67)	C_{max} (obs=68)	C_{max}/AUC_{inf} (obs=68-67)	$T_{1/2}$ (obs=67-68) *
Test Product Mean	2233.14	2271.13	1483.60	0.66	1.81
Reference Product Mean	2323.42	2399.58	1996.90	0.85	1.73
Ratio (%) (Test/Reference of Observed)	96.114	94.647	74.295	77.176	105.078
90% CI (%)	(91.7, 100.7)	(91.2, 98.2)	(67.8, 81.4)	(71.8, 83.0)	(98.0, 112.7)

*Note: $T_{1/2}$ was used instead of T_{max} .

The Sponsor's estimated intrasubject variabilities in diclofenac AUC_t , AUC_{inf} , C_{max} , and C_{max}/AUC_{inf} were 11.04%, 10.91%, 27.02%, and 21.99%, respectively, for the test product, and 12.78%, 10.60%, 26.04% and 20.54%, respectively, for the reference product. The intrasubject variability was not reported for either T_{max} or $T_{1/2}$. Intersubject CVs were only reported for AUC_t , AUC_{inf} , and C_{max} . Estimated intersubject CVs for diclofenac AUC_t and AUC_{inf} were 27% for the test product and 23-25% for the reference product. For diclofenac C_{max} , intersubject CVs were 37% for the test product and 38% for the reference product. Unlike our own variability estimates, the Sponsor's variability estimates were based on analysis of untransformed PK responses.

Conclusion and Comments

1. Even though the Sponsor's results cannot be replicated exactly (even using the same data set, See Table 1 and Table 4), our conclusions are the same for the usual PK parameters AUC_t , AUC_{inf} , and C_{max} . Namely, our analyses support a conclusion of bioequivalence for AUC_t and AUC_{inf} , but not for C_{max} .
2. According to the Sponsor's analysis, the confidence interval for $T_{1/2}$ was within the standard bioequivalence limits of 80% to 125%. However, we cannot examine this result since $T_{1/2}$ is not available to us.
3. The Sponsor calculated the intra and intersubject variabilities (%CV) based on the original data without log-transformation and their results can be replicated using the SAS PROC UNIVARIATE procedure. For comparison purpose, Table 5 lists both the Sponsor's and our results, a total variance (%CV) in the last column is also reported.

In general, our intrasubject variabilities are compatible with the results provided by the Sponsor except for a few cases. For instance, our intrasubject variabilities for AUC_t and C_{max} are 23.8% and 18.24% higher than the Sponsor's numbers for the reference product. However, our between-subject variabilities are very different from the values reported by the Sponsor. We discovered that intersubject variabilities in the Sponsor's report were the total variances and one can check this argument by using PROC UNIVARIATE procedure.

Table 5 (Intra and intersubject variabilities (%CV) and Total subject variability (%CV))

		Intrasubject		Intersubject		Total	
		Sponsor	Us	Sponsor	Us	Sponsor	Us
AUC_t	Test	11.0	11.6	27.3	24.94	NA	27.7
	Reference	12.8	16.8	25.1	23.28	NA	29.0
AUC_{inf}	Test	10.9	11.6	27.0	24.80	NA	27.5
	Reference	10.6	11.8	23.3	21.28	NA	24.5
C_{max}	Test	27.0	28.1	37.0	23.37	NA	37.1
	Reference	26.0	31.8	37.6	28.87	NA	43.9

4. The Sponsor also mentioned analyses including carryover effects, and no statistically significant results were detected ($p > 0.10$ in all cases). In our analyses, carryover effect was not considered.

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