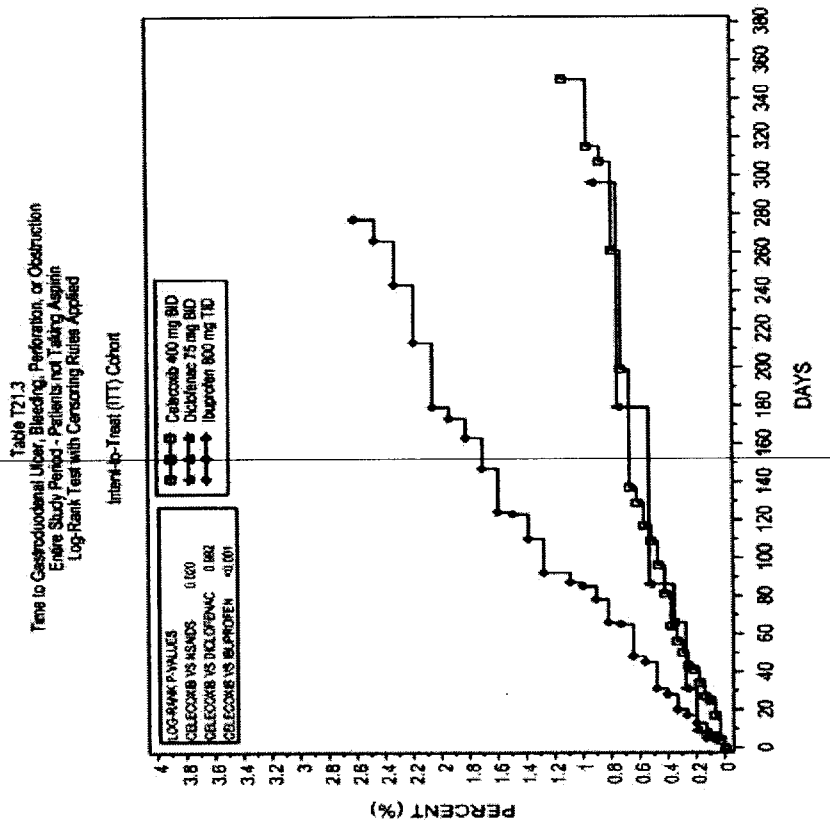

CSUGIEs in aspirin users:

Although the primary hypothesis of this study and the biologic rationale for the use of COX-2 selective agents is to avoid the GI toxicity of traditional NSAIDs, there is a lack of scientific data to guide the use of cardioprotective doses of aspirin in patients requiring NSAIDs. One may expect additive toxicity from combined use of aspirin and NSAIDs. Given the reversible platelet inhibition associated with less selective COX inhibitors, some physicians may recommend only an NSAID in subjects who require such therapy in addition to being candidates for aspirin prophylaxis. The inclusion of aspirin users in this study has generated one of the best-controlled databases with which to address this issue.

Appendix 2.5.8 indicates that the use of aspirin increases the event rate in the C group to the range of diclofenac plus aspirin. Thus, there would be no GI safety rationale to the use of low dose aspirin plus C instead of diclofenac plus an aspirin. The results in the

ibuprofen group are somewhat surprising. The event rate is substantially lower with concomitant use of ibuprofen and aspirin use compared with ibuprofen alone. This is counter intuitive. One may suggest that the small numbers of events over time yield statistically meaningless results (see appendix 2.5.11).

However, the results of CSUGIEs/GDU (PUBs) stratified by aspirin use also reveals a loss of any benefit with the concomitant use of low dose aspirin. The same pattern of greater risk in the C and diclofenac groups compared to the ibuprofen group is seen in this endpoint as well as the CSUGIE endpoint. There appears to be a higher risk of concomitant ibuprofen and aspirin use than C and aspirin use (see appendix 2.5.12) Furthermore, a secondary endpoint, rates of reported potential CSUGIEs, suggested that clinical suggestive UGI presentations were similar in all groups with concomitant aspirin use. Thus it appears that tolerability as well as clinically serious UGI events is not better in patients taking C compared to both traditional NSAIDs in aspirin users. The current label for C, based on the endoscopic studies in the original NDA database, suggests that aspirin use in conjunction with C may still be "safer" than traditional NSAIDs. This statement should be revisited in light of this new more robust data.

Appendix 2.5.8
Clinically Significant UGI Event Rates by Time Interval - Traditional Definition
Entire Study Period - Patients Taking Aspirin
Crude and Kaplan-Meier Cumulative Event Rates

Intent-to-Treat (ITT) Cohort

	Celecoxib 400 mg BID (N = 882)		Diclofenac 75 mg BID (N = 445)		Ibuprofen 800 mg TID (N = 432)	
Dosing Interval	Censoring Rule Applied	Censoring Rule Not Applied	Censoring Rule Applied	Censoring Rule Not Applied	Censoring Rule Applied	Censoring Rule Not Applied
Crude Rates						
WEEK 1 (1 - 7)	0.00%	0.00%	0.22%	0.22%	0.00%	0.24%
WEEK 4 (8 - 28)	0.11%	0.11%	0.45%	0.45%	0.00%	0.24%
WEEK 13 (29 - 91)	0.34%	0.45%	0.90%	0.90%	0.00%	0.24%
WEEK 26 (92 - 182)	0.68%	0.79%	1.12%	1.12%	0.24%	0.49%
WEEK 39 (183 - 273)	0.79%	1.02%	1.35%	1.35%	0.24%	0.49%
WEEK 52 (274 - 364)	1.02%	1.25%	1.35%	1.57%	0.24%	0.49%
Kaplan-Meier Rates						
WEEK 1 (1 - 7)	0.05%	0.05%	0.23%	0.23%	0.02%	0.26%
WEEK 4 (8 - 28)	0.15%	0.18%	0.59%	0.59%	0.07%	0.31%
WEEK 13 (29 - 91)	0.50%	0.64%	1.30%	1.30%	0.22%	0.46%
WEEK 26 (92 - 182)	1.03%	1.16%	1.60%	1.60%	0.41%	0.65%
WEEK 39 (183 - 273)	1.33%	1.66%	1.60%	2.22%	-----	-----
WEEK 52 (274 - 364)	1.60%	1.93%	-----	2.31%	-----	-----

Note: Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval.
Uncensored events were defined as those meeting either of the following two conditions: 1. Occurred after 48 hours past midnight of the first dosing day and before 48 hours following midnight of the last dosing day. 2. Occurred after 48 hours past midnight of the last dosing day and before 2 weeks following midnight of the last dosing day and were determined to be causally related to study drug by the GI events committee. Events were censored if they failed to meet either of these two conditions.

Appendix 3.5.12
Gastroduodenal Ulcer, Bleeding, Perforation, or Obstruction Rates by Time Interval
Entire Study Period - Patients Taking Aspirin
Crude and Kaplan-Meier Cumulative Event Rates

Intent-to-Treat (ITT) Cohort

Dosing Interval	Celecoxib 400 mg BID (N = 882)		Diclofenac 75 mg BID (N = 445)		Ibuprofen 800 mg TID (N = 412)	
	Censoring Rule Applied	Censoring Rule Not Applied	Censoring Rule Applied	Censoring Rule Not Applied	Censoring Rule Applied	Censoring Rule Not Applied
Crude Rates						
WEEK 1 (1 - 7)	0.00%	0.00%	0.22%	0.22%	0.00%	0.24%
WEEK 4 (8 - 28)	0.34%	0.34%	0.45%	0.45%	0.00%	0.24%
WEEK 13 (29 - 91)	1.13%	1.25%	1.35%	1.35%	0.57%	1.21%
WEEK 26 (92 - 182)	1.59%	1.70%	2.47%	2.47%	1.46%	1.70%
WEEK 39 (183 - 273)	1.70%	1.93%	3.60%	3.60%	1.46%	1.70%
WEEK 52 (274 - 364)	2.38%	2.61%	3.60%	3.82%	1.94%	2.18%
Kaplan-Meier Rates						
WEEK 1 (1 - 7)	0.05%	0.05%	0.23%	0.23%	0.08%	0.28%
WEEK 4 (8 - 28)	0.47%	0.47%	0.62%	0.62%	0.17%	0.40%
WEEK 13 (29 - 91)	1.37%	1.51%	1.87%	1.87%	1.40%	1.64%
WEEK 26 (92 - 182)	2.10%	2.24%	3.48%	3.48%	2.09%	2.33%
WEEK 39 (183 - 273)	2.41%	2.73%	5.31%	5.68%	2.48%	2.72%
WEEK 52 (274 - 364)	4.94%	5.26%	-----	5.80%	3.33%	3.56%

Note: Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval.
Uncensored events were defined as those meeting either of the following two conditions: 1. Occurred after 48 hours past midnight of the first dosing day and before 48 hours following midnight of the last dosing day. 2. Occurred after 48 hours past midnight of the last dosing day and before 2 weeks following midnight of the last dosing day and were determined to be causally related to study drug by the GI events committee. Events were censored if they failed to meet either of these two conditions.

Appendix 2.5.17
Rates of Reported Potential CSUGIES by Time Interval
First Six Months - Patients Taking Aspirin
Crude and Kaplan-Meier Cumulative Event Rates

Intent-to-Treat (ITT) Cohort

Dosing Interval	Celecoxib 400 mg BID (N = 833) Event Rate	Diclofenac 75 mg BID (N = 429) Event Rate	Ibuprofen 800 mg TID (N = 383) Event Rate
Crude Rates			
WEEK 1 (1 - 7)	3.00%	3.50%	2.87%
WEEK 4 (8 - 28)	6.60%	6.76%	8.36%
WEEK 13 (29 - 91)	13.33%	13.62%	15.93%
WEEK 26 (92 - 182)	16.65%	18.18%	18.54%
Kaplan-Meier Rates			
WEEK 1 (1 - 7)	3.04%	3.55%	3.43%
WEEK 4 (8 - 28)	6.83%	7.53%	8.56%
WEEK 13 (29 - 91)	14.81%	15.62%	17.94%
WEEK 26 (92 - 182)	19.25%	21.71%	21.89%

Note: Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval.

Alternate definition results

The definition of the "alternate definition" may be found in Appendix I. This definition required a more serious bleeding event than the traditional definition. Given the lack of effect of C on platelet aggregation, one may expect a stronger nominal trend in favor of C in such an analysis

The trends seen in sponsor's table 8.v. and 8.u. are not supportive of the hypothesis that C is associated with a lower rate of ***bleeding*** *CSUGIEs than either ibuprofen or diclofenac.*

Table 8.v Summary of CSUGIE Incidence: Alternate Definitions - Entire Study Period

	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%

Derived from Tables T30.1 and T30.2.
† Censoring rule applied.

Table 8.u. Distributions of CSUGIEs by Category: Alternate Definitions - Entire Study Period

Event Category	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
UGI Bleeding (Category 1)			
1E: Hematemesis with ulcer/large erosion and either hemoglobin drop or hypotension	1	-	-
1F: Ulcer/large erosion with evidence of bleeding and either hemoglobin drop or hypotension	8	2	6
1G: Melena with ulcer/large erosion and either hemoglobin drop or hypotension	5 *	2	2 †
1H: Hemoccult-positive stool with ulcer/large erosion and either hemoglobin drop or hypotension	2	1	2
UGI Perforation (Category 2)	1	1 †	-
Gastric Outlet Obstruction (Category 3)	2	-	-
Total	**19**	**6**	**10**
Total Uncensored	**17**	**5**	**9**

Derived from Table T16 and Table T30.1. Entries are numbers of patients. See Section 6. 4. 3. 1. for full definitions.
* Two of these events censored from primary analysis. † One of these events censored.

Analyses not reviewed:

The sponsor has presented results of annualized rates of CSUGIEs and CSUGIE/GDU based on the first 6 months of the study. Overall no major differences in trend are seen compared to the primary analysis. If the sponsor's proposed reason for analyzing the first 6 months data were to be correct (that subjects discontinue diclofenac before CSUGIEs occur); this is relevant and important to the safety profile of the drugs under study. However it does not explain the event over time pattern for ibuprofen (table 20.3).

Sponsor's table 8.h confirms the fact that for a combined endpoint such as PUB, the majority of events will be symptomatic ulcers without major clinical outcomes such as hospitalization, bleed or mortality. Thus, the combined endpoint is not as informative as separate endpoints for symptomatic ulcers and complicated ulcers. If trends are adequately consistent for both endpoints and well correlated, a combined endpoint is potentially meaningful.

Table 8.h. Distributions of CSUGIEs/GDUs by Category: Traditional Definitions - First Six Months

Event Category	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
UGI Bleeding (Category 1)			
1A: Hematemesis with ulcer/large erosion	-	-	-
1B: Ulcer/large erosion with evidence of bleeding	7	4	7
1C: Melena with ulcer/large erosion	3 *	4	3 †
1D-1: Hemoccult-positive stool with ulcer/large erosion and hematocrit/hemoglobin drop	2 *	1	3
1D-2: Hemoccult-positive stool with ulcer/large erosion and orthostasis	-	-	-
1D-3: Hemoccult-positive stool with ulcer/large erosion and transfusion	-	-	-
1D-4: Hemoccult-positive stool with ulcer/large erosion and blood in stomach	-	-	-
UGI Perforation (Category 2)	-	-	-
Gastric Outlet Obstruction (Category 3)	1	-	-
Symptomatic Ulcers			
Gastroduodenal‡	19	11	18
Gastric	13	8	17
Duodenal	7	5	1
Total	**32**	**20**	**31**
Total Uncensored	**30**	**20**	**29**

Derived from Tables T17.1, T19, and T23.1 through T23.3 and Appendix 2.6.1. Entries are numbers of patients. See Section 6. 4. 3. 1. for full definitions.
* One of these events censored from primary analysis. † Two of these events censored.
‡ Any patient with both gastric and duodenal ulcers is counted once in the "Gastroduodenal" row.

Table 8.i. Summary of CSUGIE/GDU Incidence: Traditional Definitions - First Six Months

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celecoxib Vs: Diclo	Ibu	Both
All Patients						
	n=3987	n=1996	n=1985			
No. of CSUGIEs/GDUs						
Uncensored	30	20	29			
Censored	2	0	2			
Total	32	20	31			
Week 26 crude rate†	0.75%	1.00%	1.46%	0.308	0.005	0.023
No. per 100 pt-yrs†	2.08	2.82	4.31			
Patients not Taking Aspirin						
	n=3154	n=1567	n=1602			
No. of CSUGIEs/GDUs						
Uncensored	16	9	23			
Censored	1	0	1			
Total	17	9	24			
Week 26 crude rate†	0.51%	0.57%	1.44%	0.760	<0.001	0.017
No. per 100 pt-yrs†	1.40	1.61	4.25			

Derived from Tables T17.1 through T18.3.
† Censoring rule applied.

An alternate hypothesis to that suggested by the sponsor for why C and diclofenac results are similar in all analyses is that impending CSUGIEs in subjects on C give less warning and do not result in timely discontinuation of the drug. This interpretation is equally plausible and is more worrisome for a clinical standpoint. Both the sponsor's and this reviewer's proposed interpretations of the time to event results are conjectural. As such, the sponsor's presentations of 6-month data as well as the imputed results not presented in this review are not statistically valid or supportable.

Based on the lack of adequate rationale, these post-hoc analyses will not be further discussed or presented in this review.

Overall conclusions of analysis of GI endpoints

1. ***The sponsor has failed to demonstrate a statistically significant lower rate of CSUGIEs (traditional or alternate) compared to NSAIDs as a group or either individual comparator. In the "all subjects analysis" there is no meaningful trend among the three comparator groups.***

2. ***In subjects not taking aspirin, there is a strong trend in favor of C compared to ibuprofen for a lower rate of CSUGIEs. The statistical significance of the p value of .037 would be lost were it to be subjected to correction for multiple comparisons.***

3. ***A secondary endpoint of CSUGIE/GDU (PUB) reflects the same trends as the primary analysis of CSUGIEs. This endpoint analysis controls serves as a control or sensitivity analysis for any potential bias that may have been introduced by a higher withdrawal rate of subjects in the diclofenac group due to UGI symptoms compared to the other two groups. The differences seen between "all subjects" and "nonaspirin users" also reflect the same trends seen in the primary endpoint, CSUGIEs.***

4. ***In subjects requiring low dose aspirin, there was no superiority for C compared to either traditional NSAID at endpoints, CSUGIEs and CSUGIE/GDU (PUBs). The trends seen in event rates in relation to C for the two traditional NSAID comparators were reversed (compared with the nonaspirin population). There was a trend favoring the safety of ibuprofen over C and diclofenac (when used along with aspirin) for both endpoints. There may be an interaction between aspirin and NSAIDs that is drug rather than class specific.***

5. ***The sponsor's presentation of results of post hoc analyses at 6 months:***

a. ***does not add to the primary analysis of entire study results***

b. ***censors important data on longer duration of exposure that reflects use in practice***

c. ***does not correct for a putative bias introduced by informative censoring of subjects who withdrew due to UGI symptoms***

6. ***There appears to be a higher risk of late CSUGIEs with C compared to both ibuprofen and diclofenac. Informed censoring based on differential withdrawal rates cannot be invoked to explain the results in the ibuprofen group and therefore cannot be assumed to explain the results in the diclofenac group.***

7. ***Imputation of event rates is not supported by the evidence reviewed by this reviewer.***

a. ***The high "GI adverse event" rate noted by the sponsor in the diclofenac subjects that experienced CSUGIEs reflects the clinical presentation of the CSUGIE and cannot be used calculate a correction or imputation of an event rate in subjects who withdraw due to GI symptoms in the absence of a CSUGIE.***

b. ***The results of the analysis of CSUGIE/GDU (PUB) corrects for any putative informative censoring. The results of this analysis support the primary analysis.***

c. ***The ibuprofen and diclofenac groups experienced similar patterns over time in event rates despite the greater similarity between ibuprofen and C in withdrawals due to UGI adverse events.***

External sources of relevant data

Review of the data from the original NDA submission may inform interpretation of the current trial. The results of the ***endoscopic*** *studies submitted with the original NDA failed to show replicated superiority of C compared to diclofenac. Furthermore the nominal superiority in ulcer rates between the C groups and the diclofenac groups were smaller than with the other two NSAID comparators used in the original NDA endoscopic ulcer studies,(ibuprofen and naproxen). Thus the endoscopic studies are consistent in trend to the current outcome study in identifying less difference between C and diclofenac compared to ibuprofen. The meta-analysis of CSUGIEs presented by the sponsor in the original NDA had only 2 event in each of the databases of C and diclofenac. This database is too small to meaningfully inform this discussion.*

There is a large body of literature that supports the view that there is variability in GI toxicity within the drug class NSAID. [4-9] *This literature reflects results from uncontrolled observational studies, case controlled and epidemiological studies using various endpoints of UGI toxicity including serious bleeding, hospitalization and symptoms. There are many limitations to these studies. These limitations have restricted clinician's ability to meaningfully differentiate the safety among the various NSAIDs. The tables below are reprinted from the references noted. They are limited due to the inherent limitation of uncontrolled study.*

Overall, these studies suggest multiple-fold differences in the GI toxicity of traditional NSAIDs. The current study supports variability in traditional NSAID toxicity. The results of the current CLASS study are the best controlled study available comparing the safety of 2 NSAIDs.

Possibly the most important result of the current study is the corroboration in a large well controlled outcome study that there exists a range of toxicity among the various traditional NSAIDs. COX-2 agents may fall within the spectrum of COX inhibitors and

therefore need to be considered in relation to individual NSAIDs rather than to an entire class.

Risk factors:

Tables 24.2, and 25.2 confirm the impact of past history of GI events and cardiovascular disease on the incidence of CSUGIEs. There has been some debate in the medical literature as to the impact of H. pylori infection on the incidence of CSUGIE associated with the use of NSAIDs.

CSUGIEs: *Risk factors that appear to be different between C and the less selective COX NSAIDs include alcohol use, H.pylori infection. It is unclear whether this apparent difference is meaningful given the multiple comparisons being made and the small number of subjects in some cells.*

Tobacco use appeared protective overall. This is contrary to other literature. The meaning of this finding is unclear.

CSUGIEs/GDU*: The patterns were somewhat different for this composite endpoint compared to CSUGIEs alone. The meaning of this finding is not clear.*

Table T24.2
Risk Factor Analysis of Clinically Significant UGI Events (GI History)

Intent-to-Treat (ITT) Cohort

	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	P-Value (a) 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)	0.103	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		
FLEXSURE 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		

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

Table T25.2
Risk Factor Analysis of Clinically Significant UGI Events (Medication, Alcohol, and Tobacco Use)

Intent-to-Treat (ITT) Cohort

	Celecoxib 400 mg BID (N = 3987)	Diclofenac 75 mg BID (N = 1996)	Ibuprofen 800 mg TID (N = 1965)	P-Value (a) Treatment by Factor Interaction	P-Value (a) 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		

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

Table T25.4
Risk Factor Analysis of Clinically Significant UGI Events or GD Ulcer (Medication, Alcohol, and Tobacco Use)

Intent-to-Treat (ITT) Cohort

	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	P-Value (a) Factor Effect
CORTICOSTEROID USE					
ANY	10/1219 (0.8%)	6/ 568 (1.1%)	12/ 607 (2.0%)	0.709	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	33/2751 (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%)	36/1701 (2.0%)		
P-VALUE (b)	0.074	0.569	0.144		
ANTICOAGULANT USE					
ANY	1/ 43 (2.4%)	0/ 24 (0.0%)	0/ 201 (0.0%)	0.182	0.921
NONE	42/3945 (1.1%)	26/1972 (1.3%)	36/1965 (1.8%)		
P-VALUE (b)	0.453	0.994	0.994		

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

Tables 8.l and 8.m reinforce the higher risk of CSUGIEs in the elderly and those with a history of UGI complications of prior NSAID therapy and those on aspirin therapy. C did not appear to offer a unique advantage in high risk patients.

Table 8.l. Univariate Analysis of Risk Factors for CSUGIEs and CSUGIEs/GDUs

Factor	Relative Risk			
	CSUGIEs		CSUGIEs/GDUs	
	Celecoxib 400 mg BID	NSAIDs	Celecoxib 400 mg BID	NSAIDs
Age ≥75 years	5.0 (p<0.001)	5.8 (p<0.001)	3.5 (p<0.001)	3.7 (p<0.001)
Patient's Global Assessment (Baseline)	2.5 (p=0.037)	2.4 (p=0.045)	1.4 (p=0.202)	1.4 (p=0.144)
History of UGI bleeding	3.6 (p=0.144)	7.1 (p=0.006)	4.3 (p=0.006)	3.4 (p=0.019)
History of GD ulcer	1.5 (p=0.509)	3.6 (p=0.009)	2.9 (p=0.002)	2.7 (p<0.001)
History of NSAID intolerance	2.2 (p=0.183)	2.3 (p=0.105)	3.2 (p=0.001)	1.9 (p=0.037)
History of CV disease	6.9 (p=0.002)	1.6 (p=0.240)	2.5 (p=0.002)	1.6 (p=0.048)
Positive *H. pylori* serology	0.7 (p=0.460)	2.2 (p=0.072)	1.1 (p=0.423)	2.0 (p=0.005)
Aspirin use	4.0 (p=0.005)	1.8 (p=0.211)	3.7 (p<0.001)	2.3 (p=0.002)

Derived from Tables T23.1, T23.3, T24.1, T24.3, T25.1, and T25.3.

Table 8.m. Multivariate Analysis of Risk Factors for CSUGIEs/GDUs

Treatment Group	Factor	Odds Ratio (p Value)
Celecoxib	Aspirin use	2.9 (p<0.001)
	History of GD ulcer	2.5 (p=0.018)
	Age ≥75 years	2.4 (p=0.012)
NSAIDs	Age ≥75 years	3.3 (p<0.001)
	History of GD ulcer	2.6 (p=0.004)
	Aspirin use	2.1 (p=0.006)

Table 8.q. Distributions of CSUGIEs and CSUGIEs/GDUs by Number of Risk Factors and Treatment Group

Number of Risk Factors	Number of Patients	No. (%) with CSUGIE	No. (%) with CSUGIE/GDU	No. (%) Withdrawing
Celecoxib 400 mg BID				
0	2029	1 (<0.1)	7 (0.3)	1045 (52)
1	1497	8 (0.5)	20 (1.3)	856 (57)
≥2	461	8 (1.7)	16 (3.5)	307 (67)
Diclofenac 75 mg BID				
0	1019	0 (0.0)	2 (0.2)	485 (48)
1	738	4 (0.5)	13 (1.8)	416 (56)
≥2	239	6 (2.5)	11 (4.6)	156 (65)
Ibuprofen 800 mg TID				
0	1025	5 (0.5)	16 (1.6)	654 (64)
1	758	2 (0.3)	10 (1.3)	488 (64)
≥2	202	4 (2.0)	10 (5.0)	152 (75)

Derived from Appendix 1.9.

Risk associated with disease: Osteoarthritis /Rheumatoid Arthritis

Table T23.2
Risk Factor Analysis of Clinically Significant UGI Events (Demographics)

Intent-to-Treat (ITT) Cohort

	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	P-Value (a) Factor Effect
AGE (years)								
<75	30/3500	0.9%)	5/1768	0.3%)	7/1768	0.4%)	0.837	<0.001
>=75	7/ 487	1.4%)	5/ 228	2.2%)	4/ 217	1.8%)		
P-VALUE(b)	<0.001		<0.001		0.907			
GENDER								
MALE	8/1255	0.6%)	8/ 658	0.9%)	4/ 588	0.7%)	0.476	0.170
FEMALE	11/2732	0.4%)	4/1346	0.3%)	7/1465	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	0.212
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/ 929	0.2%)		
P-VALUE(b)	0.127		0.824		0.038			
DURATION (RA)								
< 5 YEARS	2/ 333	0.6%)	0/ 191	0.0%)	0/ 188	0.0%)	0.065	0.640
>= 5 YEARS	1/ 738	0.1%)	2/ 346	0.6%)	3/ 354	0.8%)		
P-VALUE(b)	0.229		0.992		0.094			
PATIENT'S GLOBAL ASSESSMENT AT BASELINE								
POOR OR VERY POOR	6/ 713	0.8%)	5/ 363	1.4%)	3/ 335	0.9%)	0.382	0.087
OTHER	11/3274	0.3%)	5/1634	0.3%)	8/1650	0.5%)		
P-VALUE(b)	0.037		0.013		0.819			

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

Tables 23.2, 23.3, and 23.4 suggest that there is no consistently higher risk for UGI toxicity in patients with RA compared to those with OA. This is in conflict with published less well-controlled studies. Co-morbid conditions more common in RA patients but not included in the current study may account for the conflicting results.

Table T23.3
Risk Factor Analysis of Clinically Significant UGI Events or GD Ulcer (Demographics) - NSAIDs Pooled

Intent-to-Treat (ITT) Cohort

	Celecoxib 400 mg BID (N = 3987)	NSAIDs (N = 3981)	-------- P-Value (a) -------- Treatment by Factor Interaction	Factor Effect
AGE (years)				
<75	29/3500(0.8%)	42/3528(1.2%)	0.739	<0.001
>=75	14/ 487(2.9%)	20/ 453(4.4%)		
P-VALUE(b)	<0.001	<0.001		
GENDER				
MALE	19/1255(1.2%)	21/1238(1.7%)	0.962	0.546
FEMALE	28/2732(1.0%)	41/2751(1.5%)		
P-VALUE(b)	0.666	0.665		
DISEASE TYPE				
OA	31/2898(1.1%)	44/2897(1.5%)	0.955	0.987
RA	12/1089(1.1%)	18/1094(1.6%)		
P-VALUE(b)	0.976	0.955		
DURATION (OA)				
< 5 YEARS	12/ 965(1.2%)	17/ 981(1.7%)	0.991	0.402
>= 5 YEARS	19/1910(1.0%)	26/1890(1.4%)		
P-VALUE(b)	0.583	0.518		
DURATION (RA)				
< 5 YEARS	4/ 333(1.2%)	3/ 359(0.8%)	0.180	0.280
>= 5 YEARS	7/ 738(0.9%)	15/ 719(2.1%)		
P-VALUE(b)	0.754	0.121		
PATIENT'S GLOBAL ASSESSMENT AT BASELINE				
POOR OR VERY POOR	10/ 713(1.4%)	14/ 697(2.0%)	0.997	0.084
OTHER	33/3274(1.0%)	48/3284(1.5%)		
P-VALUE(b)	0.202	0.144		

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

Table T23.4
Risk Factor Analysis of Clinically Significant UGI Events or GD Ulcer (Demographical)

Intent-to-Treat (ITT) Cohort

	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	P-Value (a) Factor Effect
AGE (years)					
<75	29/3500 (0.8%)	16/1760 (0.9%)	26/1768 (1.5%)	0.759	<0.001
>=75	14/ 487 (2.9%)	10/ 236 (4.2%)	10/ 217 (4.6%)		
P-VALUE(b)	<0.001	<0.001	<0.001		
GENDER					
MALE	15/1255 (1.2%)	11/ 650 (1.7%)	10/ 580 (1.7%)	0.674	0.525
FEMALE	28/2732 (1.0%)	15/1346 (1.1%)	26/1405 (1.9%)		
P-VALUE(b)	0.666	0.324	0.012		
DISEASE TYPE					
OA	31/2898 (1.1%)	21/1453 (1.4%)	23/1434 (1.6%)	0.410	0.996
RA	12/1089 (1.1%)	5/ 543 (0.9%)	13/ 551 (2.4%)		
P-VALUE(b)	0.976	0.323	0.374		
DURATION (OA)					
< 5 YEARS	12/ 965 (1.2%)	6/ 484 (1.2%)	11/ 497 (2.2%)	0.413	0.403
>= 5 YEARS	19/1910 (1.0%)	15/ 963 (1.6%)	11/ 927 (1.2%)		
P-VALUE(b)	0.583	0.608	0.169		
DURATION (RA)					
< 5 YEARS	4/ 333 (1.2%)	0/ 191 (0.0%)	3/ 168 (1.8%)	0.119	0.315
>= 5 YEARS	7/ 738 (0.9%)	5/ 345 (1.4%)	10/ 374 (2.7%)		
P-VALUE(b)	0.754	0.992	0.485		
PATIENT'S GLOBAL ASSESSMENT AT BASELINE					
POOR OR VERY POOR	10/ 713 (1.4%)	8/ 362 (2.2%)	6/ 335 (1.8%)	0.589	0.061
OTHER	33/3274 (1.0%)	18/1634 (1.1%)	30/1650 (1.8%)		
P-VALUE(b)	0.202	0.062	0.763		

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

Overall safety profile

Review of the GI adverse events, adverse events, adverse events causing withdrawal and serious adverse events are displayed in tables 10.d, e, f, g, and 10.o. There are no substantial differences between C and the NSAIDs as a group. The differences seen in GI adverse events, as well as other adverse events are drug specific rather than COX-selectively specific in incidence. Causality is not implied in the non-GI adverse events. A similar pattern is seen in overall mortality as shown in table 10.e and 10.f.

The overall rate of serious outcomes (of which UGI events is but a fraction) is comparable among groups. While differences exist among the individual drugs, these tables support a conclusion that there is similarity among all three groups in overall morbidity and mortality. This may be the most important finding of the CLASS study.

Table 10.o. Summary of GI Adverse Events by Aspirin Use: Entire Study Period

Adverse Event	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Patients not Taking Aspirin			
No. of patients	3105	1551	1573
Any GI event	**43.3**	**53.8 ***	**44.5**
Dyspepsia	15.6	19.5 *	15.6
Abdominal pain	10.9	17.3 *	10.7
Diarrhea	10.5	13.9 *	7.2 *
Nausea	8.0	11.6 *	8.5
Flatulence	7.1	10.8 *	7.5
Tooth disorder	2.3	4.1 *	3.9 *
Vomiting	2.4	3.4	3.0
Constipation	1.9	6.5 *	5.9 *
Any GI event causing withdrawal	**11.5**	**15.4 ***	**13.2**
Patients Taking Aspirin			
No. of patients	882	445	412
Any GI event	**54.0**	**59.1**	**52.7**
Dyspepsia	19.7	19.8	19.9
Abdominal pain	14.5	22.7 *	13.6
Diarrhea	12.1	18.6 *	8.3 *
Nausea	9.0	13.9 *	10.7
Flatulence	7.9	13.5 *	6.1
Tooth disorder	5.0	4.7	6.1
Vomiting	3.1	3.8	1.5
Constipation	3.3	7.9 *	9.0 *
Gastroenteritis	2.8	3.1	1.7
Gastroesophageal reflux	3.5	2.2	2.2
Hemoccult positivity	2.7	3.1	3.9
Any GI event causing withdrawal	**14.9**	**20.7 ***	**14.1**

Derived from Tables T41.2, T41.3, T42.2, and T42.3. All numbers are percentages of patients.
Includes any GI adverse event with incidence ≥3% in any treatment group.
* p<0.05 vs celecoxib 400 mg BID.

Table 10.d. Adverse Events Causing Withdrawal with Incidence ≥1% in Any Treatment Group: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Any event	22.4	26.5 *	23.0
Abdominal pain	4.3	6.5 *	4.9
Dyspepsia	3.8	4.4	3.9
Rash	2.1	0.7 *	1.3 *
Nausea	1.7	2.8 *	1.8
Diarrhea	1.4	2.7 *	0.8 *
Flatulence	1.2	1.8	1.4
Gastric ulcer	0.3	0.7	1.0 *
SGOT increased	0.1	2.1 *	0.1
SGPT increased	0.1	2.3 *	0.1
Hepatic function abnormal	<0.1	1.1 *	<0.1

Derived from Table T42.1. All numbers are percentages of patients unless otherwise specified.
* p<0.05 vs celecoxib 400 mg BID.

Table 10.g. Summary of Serious Adverse Events: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (n=3987) 2320.4 pt-yrs	Diclofenac 75 mg BID (n=1996) 1080.5 pt-yrs	Ibuprofen 800 mg TID (n=1985) 1122.5 pt-yrs
Any serious event	270 (11.6)	111 (10.3)	119 (10.6)
Abdominal pain	6 (0.3)	6 (0.6)	2 (0.2)
Accidental fracture	10 (0.4)	4 (0.4)	9 (0.8)
Accidental injury	3 (0.1)	4 (0.4)	7 (0.6)
Angina pectoris	4 (0.2)	5 (0.5)	6 (0.5)
Atrial fibrillation	9 (0.4)	2 (0.2)	3 (0.3)
Back pain	15 (0.6)	3 (0.3)	9 (0.8)
Cardiac failure	9 (0.4)	2 (0.2)	9 (0.8)
Cellulitis	8 (0.3)	1 (<0.1)	1 (<0.1)
Cerebrovascular disorder	4 (0.2)	6 (0.6)	6 (0.5)
Chest pain	11 (0.5)	5 (0.5)	7 (0.6)
Coronary artery disorder	19 (0.8)	5 (0.5)	5 (0.4)
Deep thrombophlebitis	7 (0.3)	5 (0.5)	1 (<0.1)
GI hemorrhage	7 (0.3)	2 (0.2)	1 (<0.1)
Myocardial infarction	19 (0.8)	4 (0.4)	9 (0.8)
Pneumonia	14 (0.6)	5 (0.5)	5 (0.4)
Syncope	5 (0.2)	4 (0.4)	3 (0.3)
Unstable angina	8 (0.3)	4 (0.4)	0

Derived from Table T43. All numbers represent number of patients (number per 100 patient-years). Table includes any event experienced by a total of at least 10 patients across the three treatment groups.

Table 10.e. Summary of Deaths Occurring During Treatment or Within 28 Days After Discontinuation of Treatment: Entire Study Period

Adverse Event*	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Myocardial infarction	3	-	1
Cardiac arrest	1	4	1
Accidental injury	1	-	-
Circulatory failure/Myocardial infarction	-	-	1
Sepsis	1	-	-
Carcinoma	1	-	-
Coronary artery disorder	-	1	-
Arrhythmia/Myocardial infarction	1	-	-
Total (No. per 100 pt-yr)	**8 (0.34)**	**5 (0.46)**	**3 (0.27)**

Derived from Appendix 2.9.1 and Appendix 3.7. Table includes only deaths that occurred during treatment or within 28 days after last dose.
* For cases in which no adverse event preferred term is available, event is classified by cause of death listed on end-of-study CRF.

Table 10.f. Summary of Deaths Occurring More Than 28 Days After Discontinuation of Treatment: Entire Study Period

Adverse Event *	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Myocardial infarction	2	-	1
Cardiac arrest	1	1	-
Pulmonary fibrosis/Pneumonia	-	-	1
Carcinoma	1	-	-
Coronary artery disorder	1	-	1
Cardiac arrest/cardiac tamponade	1	-	-
Aneurysm/Subarachnoid hemorrhage	-	1	-
Cerebrovascular disorder	1	-	-
Accidental injury	-	-	1
Pneumonia	1	-	-
Cardiac failure	-	-	1
Pulmonary fibrosis	1	-	-
Pulmonary carcinoma	-	2	-
Sepsis	1	-	-
Cardiopulmonary arrest/hypertension	1	-	-
Total (No. per 100 pt-yr)	11 (0.47)	4 (0.37)	5 (0.45)

Derived from Appendix 2.9.1 and Appendix 3.7. Table includes only deaths that occurred more than 28 days after last dose.
* For cases in which no adverse event preferred term is available, event is classified by cause of death listed on end-of-study CRF.

Laboratory values

The mean changes in Hgb and Hct seen in sponsor table 10.l are notable. The endpoint is suggestive of a clinically relevant event (drop of 2 units in Hgb or 10% in Hct). The lack of any trend in parameters of renal function or fluid status displayed in table 10.q suggest that the lower rates of significant drops in hematological parameters may well be due to slow GI blood loss. This finding may be as meaningful as the composite endpoint of CSUGIE/GDU since large drops in Hgb and Hct. predispose to clinically relevant outcomes such as myocardial infarction, arrhythmia, congestive heart failure and syncope as well as others. In this trial, frequent monitoring likely prevented the occurrence of these events. In less well-structured follow-up such differences in a large population may result in clinically relevant differences in outcomes.

Table 10.h. Mean Changes from Baseline to Final Visit in Laboratory Values

Laboratory Test	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Hemoglobin, g/dL	-0.06 (0.013)	-0.26 (0.020) *	-0.37 (0.019) *
Hematocrit	-0.001 (0.0004)	-0.007 (0.0006) *	-0.012 (0.0007) *
Platelet count, $x10^9$/L	-2.3 (0.70)	10.0 (1.11) *	7.9 (0.94) *
WBC, $x10^9$/L	-0.09 (0.029)	0.06 (0.038) *	0.01 (0.041) *
Total bilirubin, µmol/L	0.0 (0.05)	0.1 (0.06)	-1.0 (0.07) *
Alkaline phosphatase, U/L	0.9 (0.23)	1.6 (0.38) *	-0.5 (0.31) *
AST, U/L	0.3 (0.12)	5.0 (0.57) *	0.9 (0.16)
ALT, U/L	-0.2 (0.18)	11.6 (1.10) *	1.3 (0.24)
Creatine kinase, U/L	-2.0 (1.17)	1.3 (2.18)	-0.1 (1.97)
Creatinine, µmol/L	0.8 (0.22)	2.4 (0.33) *	1.5 (0.33)
BUN, mmol/L	0.66 (0.027)	0.58 (0.041)	0.52 (0.039) *
Sodium, mmol/L	-0.1 (0.05)	-0.4 (0.07) *	0.0 (0.07)
Potassium, mmol/L	0.05 (0.007)	0.03 (0.010)	-0.03 (0.010) *
Chloride, mmol/L	0.7 (0.05)	0.4 (0.07) *	0.7 (0.07)
Bicarbonate, mmol/L	0.2 (0.04)	0.3 (0.06)	0.1 (0.06) *
Inorganic phosphorus, mmol/L	0.009 (0.0030)	-0.012 (0.0042) *	-0.003 (0.0046)

Derived from Table T44.1. All numbers are mean (SE) changes from Baseline.
* $p<0.05$ vs. celecoxib 400 mg BID.

Table 10.i. Summary of Hemoglobin/Hematocrit Contingency Tables: Entire Study Period

Patients with hemoglobin decrease >2 g/dL and/or hematocrit decrease ≥0.10	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
All patients	87/3701 (2.4)	82/1849 (4.4)	102/1802 (5.7)
Excluding CSUGIEs	83/3682 (2.3)	81/1840 (4.4)	95/1792 (5.3)
Excluding CSUGIEs/ulcers	82/3659 (2.2)	78/1824 (4.3)	93/1768 (5.3)
Excluding all adjudicated potential CSUGIEs	73/3545 (2.1)	68/1753 (3.9)	81/1693 (4.8)
Excluding all reported potential CSUGIEs	41/3068 (1.3)	41/1490 (2.8)	42/1364 (3.1)
OA patients	63/2675 (2.4)	48/1340 (3.6)	74/1299 (5.7)
RA patients	24/1026 (2.3)	34/509 (6.7)	28/503 (5.6)
Patients not taking aspirin	53/2864 (1.9)	53/1428 (3.7)	73/1414 (5.2)
Patients taking aspirin	34/837 (4.1)	29/421 (6.9)	29/388 (7.5)

Derived from Tables T46.1 through T46.9. Data are expressed as No./total and percentage of patients who meet the criterion in Column 1.

Other potential safety concerns

Colitis

In the original GI review of C (page 47 of Division of Gastrointestinal and Coagulation Drug Products Medical officers Consult Review) concern was raised over the potential for adverse events in the lower GI tract. In the current submission the sponsor noted 1 case of colitis in the C group compared to 1 in the ibuprofen group and three in the diclofenac group. The etiology of colitis is unknown. The lack of a trend towards a higher rate of colitis in the C group is reassuring that this product and highly selective COX-2 inhibition in general are not substantially toxic to the lower GI tract. The impact of a COX–2 selective agent on healing of pre-existing colitis or inflammatory bowel disease is not addressed in the current database.

Esophagitis

C did not appear to have a meaningfully lower rate of UGI symptoms such as pain and dyspepsia, nausea and vomiting and heartburn compared to the NSAID comparators in the original NDA. This was somewhat surprising in view of the large difference in GDUs. Although is had been clear even before this NDA that UGI symptoms are not highly correlated with endoscopic ulcers, the relative lack of impact on UGI symptoms was impressive. In the current NDA, results on all subjects who underwent endoscopy were reported by organ. The tabulated results appear in reviewer table 2 below. It is possible that the UGI symptoms in the C group as well as in the NSAID comparator group are related to GERD. However, in general a significant number of subjects without symptoms will also have esophageal abnormalities on endoscopic examination. Likewise, the percentage of subjects with endoscopic abnormalities below cannot explain the bulk of UGI symptoms reported in this study. The results do strongly suggest that associated esophageal mucosal abnormalities are similar in the C group compared to the traditional NSAID groups in this study. Attribution cannot be ascribed to the drugs in the table below.

Reviewer Table 2

DRUG	*Celebrex 137*	*ibuprofen*	*diclofenac*
*Erosions**	*21/137 (15%)*	*21/105 (20%)*	*10/89 (11%)*
*Ulcers**	*8/137 (6%)*	*2/105 (2%)*	*6/89 (7%)*
*Ulcers/erosions**	*29/137 (21%)*	*23/105 (22%)*	*16/89 (18%)*
*Erosions***	*0.5%*	*1.1%*	*0.5%*
*Ulcers***	*0.2%*	*0.1%*	*0.3%*
*Ulcers/erosions***	*0.7%*	*1.2%*	*0.8%*

**represents the number of patients with the given finding on EGD/ total # of subjects undergoing endoscopy*

*** represents the % of subjects with the endoscopic finding/ITT population. Note: endoscopies performed on a small nonrandom subset of the ITT*

Overall Conclusions

Note:
All comparisons noted reflect comparisons between approved and commonly used dosages of ibuprofen and diclofenac and twice the RA dose for C. However, in the original NDA database, there did not appear to be a meaningful difference in GI tolerance or GDU incidence in subjects on 200 mg-800 mg/day. Furthermore C is currently approved for use at 800mg/day for FAP.

1. ***The sponsor has failed to demonstrate a statistically significant lower rate of CSUGIEs (traditional or alternate) compared to NSAIDs as a group or either individual comparator. In the "all subjects analysis" there is no meaningful trend among the three comparator groups.***

2. ***In subjects not taking aspirin, there is a strong trend in favor or C compared to ibuprofen for a lower rate of CSUGIEs.***

3. ***A secondary endpoint of CSUGIE/GDU (PUB) reflects the same trends as the primary analysis of CSUGIEs. This analysis controls much of any potential bias that may have been introduced by a higher withdrawal rate of subjects in the diclofenac group due to UGI symptoms compared to the other two groups. The differences seen between "all subjects" and "nonaspirin users" also reflect the same trends seen in the primary endpoint, CSUGIEs.***

4. ***In aspirin users:***

a. ***In subjects requiring low dose aspirin, there was no benefit to the use of C compared to either traditional NSAID at endpoints, CSUGIEs and CSUGIE/GDU (PUBs). The trends seen in event rates in relation to C for the two traditional NSAID comparators were reversed (compared with the nonaspirin population). There was a trend favoring the safety of ibuprofen over C and diclofenac (when used along with aspirin) for both endpoints. There may be an interaction between aspirin and NSAIDs that is drug rather than class specific.***

b. ***The potential for enhanced UGI toxicity with combined nonselective and selective COX-2 inhibition should be further explored in a prospective manner.***

5. ***The sponsor's presentation of results of post hoc analyses at 6 months:***

a. does not add to the primary analysis of entire study results

b. ***censors important data on longer duration of exposure that reflects use in practice***

c. ***does not control bias that may be introduced by informative censoring of subjects who withdrew due to UGI symptoms***

6. ***There appears to be a higher risk of late CSUGIEs with C compared to both ibuprofen and diclofenac. Informed censoring based on differential withdrawal rates cannot be invoked to explain the results in the ibuprofen group and therefore cannot be assumed to explain the results in the diclofenac group.***

7. ***Imputation of event rates is not justified.***

a. ***The high "GI adverse event" rate noted by the sponsor in the diclofenac subjects that experienced CSUGIEs reflects the clinical presentation of the CSUGIE. This rate cannot be used to calculate a correction or imputation of an event rate in subjects who withdraw due to GI symptoms prior to a CSUGIE. A factor in the excess UGI adverse events seen in the diclofenac group may be due to the excess of subjects enrolled into this group with a history of GI-related NSAID intolerance.***

b. ***The results of the analysis of CSUGIE/GDU (PUB) may be anticipated to partially or fully correct for any such informative censoring. The results of this analysis support the primary analysis.***

c. ***The ibuprofen and diclofenac groups experienced similar patterns over time in event rates despite the greater similarity between ibuprofen and C in and withdrawals due to UGI adverse events.***

8. ***In this large well-designed and controlled study, there appears to be no meaningful difference in UGI toxicity associated with NSAIDs between Osteoarthritis and Rheumatoid arthritis. In view of the multiplicity of epidemiological data suggesting otherwise, co-morbid conditions more frequently associated with RA but excluded from the current study, may account for the difference seen in previous studies.***

9. ***There may be a difference between C and both NSAID comparators at meaningful hematologic endpoints of " patients with hemoglobin decreases of >2g/dl and or hematocrit decrease ≥ 0.10. This difference may be clinically meaningful. This difference may be associated with occult GI blood loss. However, hemodilution and a primarily hematological process cannot be excluded.***

10. ***Parameters of overall toxicity are similar among the three comparators. Such parameters include; adverse events causing withdrawal, serious adverse events, and deaths occurring during treatment or within 28 days of treatment.***

Appendix 1

Relevant portions of original protocol

(Excerpted from sponsor protocol dated August 18th 1998 document number 49-98-22-035)

2.0 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the incidence of clinically significant upper gastrointestinal (UGI) adverse events, a composite safety endpoint, comprised of perforation, bleeding or gastric outlet obstruction associated with SC-58635 400 mg BID to that associated with ibuprofen 800 mg TID in patients with OA or RA. The primary analysis of this study will consist of a survival analysis of the UGI adverse events in this study pooled with those of a companion study (N49-98-02-102). The primary comparison will be the incidence of clinically significant UGI adverse events associated with SC-58635 400 mg BID to that associated with NSAID treatment consisting of ibuprofen 800 mg TID, naproxen 500 mg BID or diclofenac 75 mg BID.

2.2 Secondary Objectives

The secondary objectives of this study are to:

1. Compare the chronic overall safety and tolerability of SC-58635 versus ibuprofen;
2. Compare the effect of SC-58635 versus ibuprofen on quality of life and patient satisfaction;
3. Compare the effect of SC-58635 versus ibuprofen on indirect costs;
4. Compare the chronic arthritis efficacy of SC-58635 to that of ibuprofen; and
5. Evaluate potential risk factors (e.g., age, gender, H. pylori infection, type of arthritis, cardiovascular disease, concurrent use of oral corticosteroids, and

history of peptic ulcer and/or gastrointestinal bleeding) for their impact on the effect of treatment on outcome.

3.0 MATERIALS AND METHODS

3.1 Study Design

This is a double-blind, multicenter, parallel group trial comparing the incidence of clinically significant events associated with SC-58635 400 mg BID to that associated with ibuprofen 800 mg TID in RA and OA patients. Patients, stratified by OA and RA status, will be randomly assigned in an equalized manner to one of the following treatment arms:

- SC-58635 400 mg BID and ibuprofen placebo TID
- SC-58635 placebo BID and ibuprofen 800 mg TID

Follow-up visits will occur 4, 13, 26, 39 and 52 weeks after the first dose of study medication. The trial will continue until the anticipated number of clinically significant UGI adverse events have been observed in both studies; maximum study participation for an individual patient is 52 weeks. All patients will complete a Final Treatment visit which may coincide with the Week 52 visit, or occur at any time up to Week 52 when the trial officially concludes.

3.2 Study Population

3.2.a Subject Enrollment

Four thousand (4000) patients are expected to be enrolled and randomly assigned to either SC-58635 treatment or ibuprofen treatment. Patients will be randomly assigned in an equalized manner to one of the following treatment arms:

- SC-58635 400 mg BID and ibuprofen placebo TID
- SC-58635 placebo BID and ibuprofen 800 mg TID

3.2.b Criteria for Inclusion

To qualify for enrollment in this study, a patient must satisfy the criteria listed below:

1. The patient must be of legal age of consent or older;

2. If the patient is a female and of childbearing potential, she agrees to participate in this study by providing written informed consent, has been using adequate contraception since her last menses and will use adequate contraception during the study, is not lactating, and has had a negative serum pregnancy test within seven days before receiving the first dose of study medication;
3. The patient has a documented clinical diagnosis of OA or RA of at least three months duration;
4. The patient requires chronic NSAID therapy in the Investigator's opinion;
5. The patient is able to participate for the full duration of the study; and
6. The patient has provided written informed consent prior to admission to this study.

3.2.c Criteria for Exclusion

A patient will be excluded from this study if he or she satisfies any one of the criteria listed below:

1. The patient has an active malignancy of any type or history of a malignancy. (Patients who have a history of basal cell carcinoma that has been treated are acceptable. Patients with a history of other malignancies that have been surgically removed and who have no evidence of recurrence for at least five years before study enrollment are also acceptable.);
2. The patient has been diagnosed as having or has been treated for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to receiving the first dose of study medication;
3. The patient has active GI disease (e.g., inflammatory bowel disease);
4. The patient has a history of gastric or duodenal surgery other than simple oversew of an ulcer or perforation;
5. The patient has significant renal or hepatic dysfunction, or a significant coagulation defect considered by the Investigator to be clinically significant;
6. The patient has abnormal screening laboratory test values >1.5 x the upper limit of normal (ULN) for either AST (SGOT) or ALT (SGPT) or any other laboratory abnormality at Screening considered by the Investigator to be clinically significant;
7. The patient has a positive screening fecal occult blood test result;

8. The patient has a known hypersensitivity to COX-2 inhibitors, sulfonamides, or ibuprofen;
9. The patient has received any investigational medication within 30 days prior to the first dose of study medication or is scheduled to receive an investigational drug other than SC-58635 during the course of this study; or
10. The patient has previously been admitted to this study or a prior study with SC-58635.

4.0 STUDY PLAN

4.1 Schedule of Observation and Procedures

	Pretreatment Period -7 to 0 Days		Treatment Period Weeks + Days					Final Visit(b)	Early Term(c)
	Screening	Base-line	4±5	13±5	26±5	39±5	52± 5(a)		
Informed Consent(d)	X								
Medical History	X								
Physical Exam	X						X	X	X
Clinical Lab Tests(e)	X		X	X	X	X	X	X	X
Pregnancy Test(f)	X			X	X	X	X	X	X
Fecal Occult Blood Testing	X		X		X		X	X	X
D/C Current NSAID & anti-ulcer drugs(g)		X							
Arthritis Assessments		X	X	X	X	X	X	X	X
Signs & Symptoms		X	X	X	X	X	X	X	X
Indirect Cost Assessment		X	X	X	X	X	X	X	X
Patient Satisfaction Questionnaire							X	X	X
QOL Assessments(h)		X			X		X	X	X
Dispense Study Med		X		X	X	X			
Dispense Concurrent Meds Diary Card		X	X	X	X	X			
Retrieve Concurrent Meds Diary Card			X	X	X	X	X	X	X
Return & Count Study Med			X	X	X	X	X	X	X

(a) Use Final Treatment Visit CRFs
(b) The Final Treatment Visit coincides with the Week 52 visit or it may occur at any time up to Week 52 when the study has officially concluded
(c) Patients terminating early from this study (i.e., before Week 52 or official conclusion) must be contacted monthly for two months following their withdrawal or until the study officially concludes, whichever occurs first
(d) Informed consent must be obtained before any study-related procedures are performed
(e) Clinical laboratory tests include: **Hematology** (WBC, hemoglobin, hematocrit, platelet count); **Biochemistry** (BUN, creatinine, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), creatine kinase (CK), sodium, potassium). At Screening, serum FlexSure HP test for HP status will also be performed.
(f) For females of childbearing potential only
(g) Current NSAID and anti-ulcer drugs must be discontinued at or before the Baseline Visit
(h) SF-36 Health Survey and Health Assessment Questionnaire

4.3 Treatment Period

The Treatment Period is defined as the 52-week interval during which study medication is taken or until the trial officially concludes, whichever occurs first. The Week 4, Week 13, Week 26, Week 39, Week 52 and the Final Treatment visits occur during this interval.

4.3.b.2 Concurrent Medications

Use of any medication other than the drugs provided for this study will be avoided, if at all possible, during the Treatment period. The following drugs are specifically excluded:

1. NSAIDs, either prescription or nonprescription. (Patients taking ≤325 mg aspirin per day for reasons other than arthritis, for at least 30 days before the first dose of study medication, may continue the same dose regimen for the duration of the study.);
2. Anti-ulcer drugs (including H_2 antagonists, proton pump inhibitors, sucralfate and misoprostol), either prescription or nonprescription. Short-term use of antacids is permitted (less than seven days consecutively);
3. Antibiotics (i.e., amoxicillin, clarithromycin, azithromycin, tetracycline, metronidazole or bismuth) used alone or combined with omeprazole, lansoprazole, or ranitidine specifically as treatment for H. pylori infection; and
4. Antineoplastics (other than methotrexate ≤ 25 mg/wk or azathioprine as treatment for RA).

Acetaminophen (≤2 g/day; alone or in combination with propoxyphene hydrochloride or napsalate, hydromorphone hydrochloride, oxycodone hydrochloride or codeine phosphate) may be used as necessary throughout the study. Oral and intrarticular corticosteroids are also allowed.

4.4 Clinically Significant UGI Adverse Events

Clinically significant UGI adverse events will be classified by consensus of an independent Gastrointestinal Events Committee that will be blinded to the patient's

treatment. Nine categories of signs and symptoms have been established to classify clinically significant UGI adverse events. They are as follows.

4.4.a UGI Perforation

An opening in the wall of the stomach or duodenum requiring surgery, or laparoscopic repair but only if the evidence is unequivocal (free air, peritoneal irritation signs, etc.).

4.4.b UGI Bleeding

UGI bleeding is to be categorized as one of the following seven clinical presentations:

- Hematemesis with a gastric or duodenal ulcer or erosion proven by endoscopy or a UGI barium x-ray;
- A gastric or duodenal ulcer or erosion proven by endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or attached clot to base of an ulcer);
- Melena with a gastric or duodenal ulcer or erosion proven by endoscopy or barium UGI x-ray;
- Hemoccult positive stools with a gastric or duodenal ulcer or erosion proven by endoscopy or barium UGI x-ray and with bleeding as evidenced by a fall in hematocrit of more than 5 percentage points or a reduction of hemoglobin of more than 1.5 g/dL from baseline;
- Hemoccult positive stools with a gastric or duodenal ulcer or erosion proven by endoscopy or barium UGI x-ray and with bleeding as evidenced by orthostasis (changes to postural vital signs; increase in pulse rate of ≥20 beats/min and/or a decrease in systolic blood pressure of ≥20 mmHg and/or diastolic blood pressure of ≥10 mmHg);
- Hemoccult positive stools with a gastric or duodenal ulcer or erosion proven by endoscopy or barium UGI x-ray and with bleeding as evidenced by a need for blood transfusion of two or more units; or
- Hemoccult positive stools with a gastric or duodenal ulcer or erosion proven by endoscopy or barium UGI x-ray and with bleeding as evidenced by blood in the stomach as determined by endoscopy or nasogastric aspiration.

4.4.c Gastric Outlet Obstruction

Opinion of clinician with endoscopic or UGI barium x-ray documentation. Endoscopic evidence would include tight edematous pylorus with an ulcer in the pyloric channel, inability to pass the endoscope tip into the duodenal bulb or descending duodenum, or retained fluid/food in the stomach. UGI barium x-ray evidence of obstruction would include:

- a dilated stomach;
- a slowly emptying stomach in a patient with clinical evidence of outlet obstruction and in some instances with an ulcer in the channel or duodenal bulb; or
- severe narrowing and edema obstructing the outlet of the stomach.

In order to standardize and facilitate the evaluation of suspected GI events in this study, a chart of clinical algorithms is provided as a guide to the work-up of potential events and collection of data necessary to properly classify such events. However, clinical judgement and the administration of standard medical care should take precedence in the evaluation and treatment of all patients in the study over the algorithms detailed in Appendix 1.6.

4.5 Other GI Adverse Events

Data on lower GI adverse events including small bowel or colonic obstruction, ulceration, bleeding, perforation, stricture, colitis, etc. will also be collected and summarized.

Symptomatic UGI ulcers documented by endoscopy or UGI barium x-ray with no evidence of perforation, bleeding or obstruction will be categorized and analyzed separately. Patients with an ulcer must be withdrawn from the study and treated according to the clinical judgment of the investigator.

GI complaints will also be collected and analyzed. Patients who report symptomatic GI adverse events (e.g., abdominal pain, dypepsia, vomiting) with no endoscopic or UGI barium x-ray evidence of an ulcer may continue to participate in the study at the discretion of the investigator.

4.6 Criteria for Discontinuaton

4.6.a Treatment Failure

Patients who terminate study participation before taking 52 weeks of study medication or the trial officially concludes because their arthritis signs and symptoms have not been controlled will be reported as withdrawing due to "treatment failure".

4.6.b Non-Compliance

Patients who terminate study participation before taking 52 weeks of study medication or before the trial officially concludes due to failure to comply with the requirements of the protocol (e.g., patient fails to take at least 70% of the study medication in any 13 week dispensing interval) will be reported as withdrawing due to "non-compliance".

4.6.c Adverse Events

Patients who terminate study participation before taking 52 weeks of study medication or before the trial officially concludes due to an adverse event (including an ulcer found at an endoscopy; see further definitions in Appendix 1) will be reported as withdrawing due to an "adverse event."

4.6.d Completed Patient

A completed patient is one who takes study medication for 52 weeks or is taking study medication when the trial officially concludes.

4.7 Withdrawal of a Patient Prior to Study Completion

If for any reason a patient is withdrawn before completing the study, the reason for withdrawal must be entered on the End of Study Form and Early Termination CRFs must be completed.

All patients terminating early from the study must be contacted monthly for two months or until the official conclusion of the study, whichever occurs first, to gather pharmacoeconomic information as well as to determine if a clinically significant UGI adverse event has occurred. Reasonable attempts must be made to contact each patient.

5.0 STATISTICS

5.1 Justification of Sample Size

The null hypothesis being tested is that there is no difference in the incidence of clinically significant UGI adverse events between the SC-58635 and the NSAID group (ibuprofen, naproxen and diclofenac). The log-rank test will be used to detect this difference. The sample size determination is based on the assumption that the probability for experiencing a clinically significant UGI adverse event is 0.3% per year with SC-58635 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 each for the SC-58635 and NSAID group) will be sufficient to obtain approximately a total of 40 clinically significant UGI adverse events. One-half (4000) of the total sample size will be enrolled for this study. The other half of the sample size (4000) will go to a companion study (N49-98-02-102) with naproxen and diclofenac in the NSAID group.

The assumptions about the overall rate of clinically significant UGI adverse events and the withdrawal patterns of patients participating in the study based on the pooled data from each study (N49-98-02-035 and N49-98-02-102) will be reviewed on an ongoing basis during the enrollment period to determine whether an adjustment in the sample size is required. If the incidence rate and withdrawal rate observed are different from the estimations, an adjustment of sample size may be needed to obtain the minimum number of patients exposed to SC-58635 or NSAIDs and to obtain a total of 40 clinically significant UGI adverse events.

5.3 Analysis Cohort

All analyses will be carried out on the Intent-to-Treat cohort. The Intent-to-Treat cohort will consist of all randomized patients from this study and its companion study (N49-98-02-102) who received at least one dose of study medication. Data from this study may also be analyzed independently for exploratory purposes.

5.4 Adjudication of Clinically Significant UGI Adverse Events

A Gastrointestinal Events Committee comprised of expert gastroenterologists, blinded to treatment assignments, will review the data of each patient who is identified by study investigators or Searle as having some evidence of a potentially clinically significant UGI adverse event. The data to be reviewed will include case report forms, and medical records including endoscopy and UGI barium x-ray reports, discharge summaries, and autopsies, where appropriate. The committee will adjudicate whether a clinically significant UGI adverse event has occurred and assign the event to one of the nine classifications (see Section 4.4).

5.5 Analysis of Clinically Significant UGI Adverse Events

Clinically significant UGI adverse events will be descriptively summarized. These analyses will consist of displays of the distribution by treatment group and disease category (i.e., OA or RA) of the number of patients experiencing a clinically significant UGI adverse event (incidence table) and the total number of clinically significant UGI adverse events by classification (frequency table). The primary efficacy analysis will combine results of this study with those from study N49-98-02-102. The active control groups from the two studies will be pooled for this purpose. "Study" will be included as a stratification factor in the analyses.

Time-to-event analysis will be performed to assess the difference between groups in the clinically significant UGI adverse event rate distribution across time. Clinically significant UGI adverse events occurring within seven days after the start of double-blind treatment will be censored and not included in these analyses. The log-rank test will be used to compare the survival curves of the two treatment groups (SC-58635 vs the NSAID group) with respect to this primary outcome variable. The COX proportional hazards model will be used to estimate the corresponding hazard ratios. Patients who withdrew from the study because of reasons other than incidence of clinically significant UGI adverse events will be censored at the time of withdrawal. Patients who complete the study without a clinically significant UGI adverse event will be censored at the final visit.

The secondary analysis will be a treatment group comparison of the overall proportion of patients with a clinically significant UGI adverse event (crude incidence rate analysis). The Mantel-Haenszel test will be used for these comparisons.

Potential risk factors such as age and history of peptic ulcer, for the development of a clinically significant UGI adverse event will be identified prior to analysis and the proportional hazard model will be used to assess the significance of these factors and their impact on the effect of treatment on outcome.

Disease category (i.e., OA or RA) may be included as a factor in the above analyses.

Symptomatic UGI ulcers documented by endoscopy or UGI barium x-ray with no evidence of perforation, bleeding or obstruction will be categorized and summarized separately.

Clinically significant adverse events occurring in the lower gastrointestinal tract including small bowel or colonic obstruction, ulceration, bleeding, perforation, stricture or colitis will be descriptively summarized. These analyses will consist of displays of the distribution by treatment group and disease category, the number of patients experiencing a clinically significant event in the lower GI tract and the total number of clinically significant lower GI adverse events by classification.

1.5 CLINICALLY SIGNIFICANT UPPER GASTROINTESTINAL (UGI) ADVERSE EVENTS

If, in the Investigator's opinion, the patient experiences a sign or symptom (e.g., severe abdominal pain, hematemesis, melena, decreased hemoglobin and hematocrit, or severe and protracted nausea and vomiting) that suggests a clinically significant UGI adverse event (i.e., perforation, bleed, or obstruction), the Kendle Safety Specialist must be contacted immediately. All potential clinically significant UGI adverse events will be thoroughly investigated and reported as per following section.

1.6 ALGORITHM FOR WORK-UP OF SUSPECTED UGI EVENTS

In order to standardize and facilitate the evaluation of suspected GI events in this study, the following chart of clinical algorithms is provided as a guide to the work-up of potential events and collection of data necessary to properly classify such events. However, clinical judgement and the administration of standard medical care should take precedence in the evaluation and treatment of all patients in the study over the algorithms detailed below.

Presentation:	Initial Evaluation:	Work-up
Clinical situations requiring emergent or urgent attention **For all patients with the following presentations:** • **Obtain base data (hematocrit, stool heme, and postural vital signs) as part of initial evaluation.** • **Test for H. pylori infection as part of work-up (Meretek UBT, CLO or H&E).** • **Notify Searle medical monitor and Kendle Safety Specialist immediately. Provide contact information.** • **Complete GI event CRF.**		
Severe acute abdominal pain/acute abdomen	EMERGENT: • Evaluation for perforating ulcer including base data	• Documentation of perforation by surgery or by laparoscopy with radiographic evidence of free air in abdomen • Test for H. pylori infection
Intractable abdominal pain with nausea/vomiting	EMERGENT: • Evaluation for gastric outlet obstruction including base data	• Documentation of gastric outlet obstruction with UGI study (radiographic or endoscopic) • Test for H. pylori infection
Hematemesis or melena	EMERGENT: • Evaluation for GI bleeding source including base data	• Documentation of bleeding source by UGI endoscopy (test for H. pylori infection) • Colonoscopy at Investigator's discretion
Acute hypovolemia/hypotension	EMERGENT: • Evaluation for acute GI blood loss including base data	• If GI evaluation positive (e.g., blood in NG aspirate, heme positive stool, or hematocrit decreased by 5% or more [absolute change]), investigate source with UGI endoscopy (test for H. pylori infection) • Colonoscopy at Investigator's discretion
Current/recent (<14 days) history of: • melena (black tarry stool) or • black stool which is a change in normal pattern	IMMEDIATE: • Obtain base data	• If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for H. pylori infection) • Colonoscopy at Investigator's discretion • If work-up negative, retest stool for heme and repeat hematocrit in 1-2 weeks
Development of: • postural dizziness or lightheadedness • syncope	IMMEDIATE: • Obtain base data • If patient orthostatic, evaluate for acute GI blood loss	• If GI evaluation positive (e.g., blood in NG aspirate, heme positive stool, or hematocrit decreased by 5% or more [absolute change]), investigate source with UGI endoscopy (test for H. pylori infection) • Colonoscopy at Investigator's discretion

Presentation:	Initial Evaluation:	Work-up
Clinical situations requiring prompt attention: **For all patients with the following presentations:** • **Obtain base data (hematocrit, stool heme x3, and postural vital signs) as soon as possible.** • **Test for H. pylori infection as part of work up (Meretek UBT, CLO or H&E)** • **Notify Kendle Safety Specialist as soon as possible.** • **Complete GI event CRF.**		
History of dark stool: • >14 days previously, or • vaguely characterized, or • with concurrent iron/bismuth ingestion	ASAP: • Obtain base data	• If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for H. pylori infection) • Colonoscopy at investigator's discretion
History of : • hematochezia, or • anal/rectal bleeding after elimination	ASAP: • Obtain base data	• Perform colonoscopy • UGI endoscopy at investigator's discretion (test for H. pylori infection)
Development of: • New anemia, or • Drop in hematocrit of 5% of more (absolute change)	ASAP: • Obtain base data	• If stools heme positive, perform UGI endoscopy (test for H. pylori infection) • Colonoscopy at investigator's discretion
Development of: • Dyspepsia, or • Abdominal pain, or • Nausea/vomiting	ASAP: • Obtain base data	• If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for H. pylori infection) • Colonoscopy at investigator's discretion

Important Protocol amendments

November 9th 1998

PROTOCOL SECTION AMENDED

Abstract, 4th and 6th paragraphs, page 3 of 35

This randomized, double-blind, parallel group, multicenter study is designed to compare the incidence of clinically significant UGI adverse events associated with SC-58635 400 mg BID to that associated with ibuprofen 800 mg TID in patients with osteoarthritis (OA) or rheumatoid arthritis (RA). Clinically significant UGI adverse events is a composite safety endpoint comprised of perforation, bleeding or gastric outlet obstruction. The primary analysis of this study will consist of a survival analysis of the UGI adverse events in this study pooled with those of a companion study (N49-98-02-102). The primary

comparison will be the incidence of clinically significant UGI adverse events associated with SC-58635 400 mg BID to that associated with ~~NSAID treatment consisting of~~ ibuprofen 800 mg TID, ~~naproxen 500 mg BID~~ **and separately to that associated with** ~~or~~ diclofenac 75 mg BID.

Patients who meet all of the inclusion/exclusion criteria for the study will be randomized to receive SC-58635 400 mg BID or ibuprofen 800 mg TID. Follow-up visits will occur 4, 13, 26, 39 and 52 weeks after the first dose of study medication. The trial will continue until the anticipated number of clinically significant UGI adverse events have been observed in both studies~~;~~. **Minimum study participation for an individual patient is 26 weeks and** maximum study participation for an individual patient is 52 weeks. All patients will complete a Final Treatment visit which may coincide with the Week 52 visit or occur at any time up to Week 52 when the trial officially concludes. Patients who withdraw early from the trial will be contacted by phone monthly for two months.

PROTOCOL SECTION AMENDED

5.1 Justification of Sample Size, 1st paragraph, page 27 of 35

~~The null hypothesis being tested is that there is no difference in the incidence of clinically significant UGI adverse events between the SC-58635 and the NSAID group (ibuprofen, naproxen and diclofenac). The log-rank test will be used to detect this difference. The sample size determination is based on the assumption that the probability for experiencing a clinically significant UGI adverse event is 0.3% per year with SC-58635 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 each for the SC-58635 and NSAID group) will be sufficient to obtain approximately a total of 40 clinically significant UGI adverse events. One-half (4000) of the total sample size will be enrolled for this study. The other half of the sample size (4000) will go to a companion study (N49-98-02-102) with naproxen and diclofenac in the NSAID group.~~

2nd paragraph, page 27 of 35

~~The assumptions about the overall rate of clinically significant UGI adverse events and the withdrawal patterns of patients participating in the study based on the pooled data from each study (N49-98-02-035 and N49-98-02-102) will be reviewed on an ongoing basis during the enrollment period to determine whether an adjustment in the sample size is required. If the incidence rate and withdrawal rate observed are different from the~~

~~estimations, an adjustment of sample size may be needed to obtain the minimum number of patients exposed to SC-58635 or NSAIDs and to obtain a total of 40 clinically significant UGI adverse events.~~

The statistical analyses will be performed on the data from this study and its companion study. The patients on celecoxib will be pooled as one group (N49-98-02-035 and N49-98-02-102) while the patients on NSAIDs will remain as separate. The sample size calculation is based on the pairwise comparison of pooled celecoxib and each of the NSAIDs.

The null hypothesis being tested is that there is no difference in the incidence of clinically significant UGI adverse events between the SC-58635 group and each of the NSAID groups (ibuprofen and diclofenac). The log-rank test will be used to detect the difference by pairwise comparisons. The sample size determination is based on the assumption that the probability for experiencing a clinically significant UGI adverse events is 0.3% per year with SC-58635 and 1.2% per year with each NSAID group. With approximately 85% power at a 5% significance level (two-sided test) and assuming a withdrawal rate of 35%, a sample size of 4,000 patients (combining the two studies) for the SC-58635 group and 2,000 for each of the NSAID groups would be needed. A total number of 40 events will be expected (8 from the combined SC-58635 group and 16 from each NSAID group). The enrollment is designed to take about three months and the follow-up will be at least six months. The studies will be concluded with at least 20 events from each of the studies or a total of 45 events from the two studies.

1.6 ALGORITHM FOR WORK-UP OF SUSPECTED UGI EVENTS, pages 5 and 6 of 6

Presentation:	Initial Evaluation:	Work-up
Clinical situations requiring emergent or urgent attention For all patients with the following presentations: • Obtain base data (hematocrit, stool heme, and postural vital signs) as part of initial evaluation. • Test for H. pylori infection as part of work-up (Meretek UBT, CLO or H&E). • Notify Searle medical monitor and Kendle Safety Specialist immediately. Provide contact information. • Complete GI event CRF.		
Severe acute abdominal pain/acute abdomen	EMERGENT: Evaluation for perforating ulcer including base data	Documentation of perforation by surgery or by laparoscopy with radiographic evidence of free air in abdomen Test for H. pylori infection
Intractable abdominal pain with nausea/vomiting	EMERGENT: Evaluation for gastric outlet obstruction including base data	Documentation of gastric outlet obstruction with UGI study (radiographic or endoscopic) Test for H. pylori infection
Hematemesis or melena	EMERGENT: Evaluation for GI bleeding source including base data	Documentation of bleeding source by UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Lower GI workup if bleeding source uncertain**
Acute hypovolemia/hypotension	EMERGENT: Evaluation for acute GI blood loss including base data	If GI evaluation positive (e.g., blood in NG aspirate, heme positive stool, or hematocrit decreased by 5% or more [absolute change]), investigate source with UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Lower GI workup if bleeding source uncertain**
Current/recent (<14 days) history of: melena (black tarry stool) or black stool which is a change in normal pattern	IMMEDIATE: Obtain base data	If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Lower GI workup if bleeding source uncertain** If work-up negative, retest stool for heme and repeat hematocrit in 1-2 weeks
Development of: postural dizziness or lightheadedness syncope	IMMEDIATE: Obtain base data If patient orthostatic, evaluate for acute GI blood loss	If GI evaluation positive (e.g., blood in NG aspirate, heme positive stool, or hematocrit decreased by 5% or more [absolute change]), investigate source with UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Lower GI workup if bleeding source uncertain**

Two primary treatment comparisons will be performed: celecoxib vs. ibuprofen and celecoxib vs. diclofenac. A stepwise procedure will be used to strongly control the type-I error. In this procedure, the first step is to test the overall hypothesis whether celecoxib and the pooled NSAIDs are 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 said to be different from an NSAID if both overall and pairwise comparisons of celecoxib vs that NSAID are significant. Each test will be performed at level alpha. No alpha adjustment is needed for each test. (See Appendix 6 for a statistical proof)

Two endpoints will be analyzed. One is based on the traditional definition and the

1.6 ALGORITHM FOR WORK-UP OF SUSPECTED UGI EVENTS, pages 5 and 6 of 6

Presentation:	Initial Evaluation:	Work-up
Clinical situations requiring emergent or urgent attention For all patients with the following presentations: • Obtain base data (hematocrit, stool heme, and postural vital signs) as part of initial evaluation. • Test for H. pylori infection as part of work-up (Meretek UBT, CLO or H&E). • Notify Searle medical monitor and Kendle Safety Specialist immediately. Provide contact information. • Complete GI event CRF.		
Severe acute abdominal pain/acute abdomen	EMERGENT: Evaluation for perforating ulcer including base data	Documentation of perforation by surgery or by laparoscopy with radiographic evidence of free air in abdomen Test for H. pylori infection
Intractable abdominal pain with nausea/vomiting	EMERGENT: Evaluation for gastric outlet obstruction including base data	Documentation of gastric outlet obstruction with UGI study (radiographic or endoscopic) Test for H. pylori infection
Hematemesis or melena	EMERGENT: Evaluation for GI bleeding source including base data	Documentation of bleeding source by UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Lower GI workup if bleeding source uncertain**
Acute hypovolemia/hypotension	EMERGENT: Evaluation for acute GI blood loss including base data	If GI evaluation positive (e.g., blood in NG aspirate, heme positive stool, or hematocrit decreased by 5% or more [absolute change]), investigate source with UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Lower GI workup if bleeding source uncertain**
Current/recent (<14 days) history of: melena (black tarry stool) or black stool which is a change in normal pattern	IMMEDIATE: Obtain base data	If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Lower GI workup if bleeding source uncertain** If work-up negative, retest stool for heme and repeat hematocrit in 1-2 weeks
Development of: postural dizziness or lightheadedness syncope	IMMEDIATE: Obtain base data If patient orthostatic, evaluate for acute GI blood loss	If GI evaluation positive (e.g., blood in NG aspirate, heme positive stool, or hematocrit decreased by 5% or more [absolute change]), investigate source with UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Lower GI workup if bleeding source uncertain**

Presentation:	Initial Evaluation:	Work-up
Clinical situations requiring prompt attention: For all patients with the following presentations: • Obtain base data (hematocrit, stool heme x3, and postural vital signs) as soon as possible. • Test for H. pylori infection as part of work up (Meretek UBT, CLO or H&E) • Notify Kendle Safety Specialist as soon as possible. • Complete GI event CRF.		
History of dark stool: >14 days previously, or vaguely characterized, or with concurrent iron/bismuth ingestion	ASAP: Obtain base data	If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Lower GI workup if bleeding source uncertain**
History of : ~~hematochezia, or~~ anal/rectal bleeding after elimination	ASAP: ~~Obtain base data~~	Perform colonoscopy ~~UGI endoscopy at investigator's~~ discretion (test for H. pylori infection)
Development of: New anemia, or Drop in hematocrit of 5% or more (absolute change)	ASAP: Obtain base data **including ferritin, iron, iron binding capacity, MCV, MCHC**	If stools heme positive or **studies indicate iron deficiency**, perform UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Lower GI workup if bleeding source uncertain**
Development of: Dyspepsia, or Abdominal pain, or Nausea/vomiting	ASAP: Obtain base data	If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for H. pylori infection) ~~Colonoscopy at investigator's discretion~~ **Additional studies as indicated by "ordinary care"**
Development of: **Heme-positive stools**	**ASAP:** **Obtain base data**	**Perform UGI endoscopy (test for H. pylori infection)** **Lower GI workup if bleeding source uncertain**

NEW APPENDIX ADDED

Appendix 6. Additional Statistical Procedures

Justification of the Stepwise Procedure:

The strong control of type-I error using this method can be proved by closed testing procedure setup or by direct calculation as following:

H_0: H_{01} rate of celecoxib = rate of ibuprofen,
H_{02} rate of celecoxib = rate of diclofenac.

By definition, we need to prove that the type-I error is controlled under any configuration of the null hypothesis. In our case, we need to prove that for each H_{01}, H_{02} and H_0. The demonstration for the cases of H_{01} and H_{02} are straightforward. The probability of rejecting H_{01} or H_{02} when H_0 is true can be seen by the following expression:

P(reject H_{01} or reject H_{02} | H_{01} and H_{02} true) =
P(reject overall first and (reject H_{01} or reject H_{02} pairwise) | H_{01} and H_{02} true) =
P(reject overall | H_{01} and H_{02} true) x
P(reject H_{01} or H_{02} pairwise) | H_{01} and H_{02} true and overall rejected) $\leq$
P(reject overall | H_{01} and H_{02} true)
= 0.05

Hence the result.

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Amendment November 24th 1999

REASON FOR ADMINISTRATIVE CHANGE

1. To change and further clarify the censoring rules for clinically significant UGI adverse events.

Protocol section(s) corrected and details of the changes are as follows:

PROTOCOL SECTION CORRECTED:
5.5 Analysis of Clinically Significant UGI Adverse Events, 2nd Paragraph, page 29 of 35

Time-to-event analysis will be performed to assess the difference between groups in the clinically significant UGI adverse event rate distribution across time. ~~Clinically significant UGI adverse events occurring within seven days after the start of double-blind treatment will be censored and not included in these analyses.~~ **All clinically significant UGI adverse events which occur after 48 hours following the first dosing day and before 48 hours following the last dosing day will be included in the analysis. In addition, the Gastrointestinal Events Committee will review potential clinically significant UGI adverse events which occur after the back-end censoring cut-off date. If such adverse events are deemed to be clinically significant UGI adverse events, occur within 2 weeks of the last study drug dose, and are felt to be study drug related, they will also be included. These rules thus exclude only clinically significant adverse events which occur within 48-72 hours after initiation of study drug (which are not reasonably attributable to study drug) or clinically significant adverse events which occur after the cessation of study drug where another cause of the clinically significant adverse event is evident (e.g., resumption of NSAID use) or where sufficient time has elapsed to call causality into question (2 weeks).** The log-rank test will be used to compare the survival curves of the two treatment groups (celecoxib vs ibuprofen and celecoxib vs diclofenac) with respect to this primary outcome variable. The COX proportional hazards model will be used to estimate the corresponding hazard ratios. Patients who withdrew from the study because of reasons other than incidence of clinically significant UGI adverse events will be censored at the time of withdrawal. Patients who complete the study without a clinically significant UGI adverse event will be censored at the final visit.

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