

With GI symptoms ²	18/1483	1.21%	3.9
Without GI symptoms	20/6485	0.31%	
CSUGIEs/GDUs			
With GI symptoms ²	62/1483	4.2%	6.3
Without GI symptoms	43/6485	0.7%	

1 From Table 8.n (p. 149) and appendix 2.4.17.4 (p. 2085); N49-00-06-035-102.

2 Symptoms are moderate or severe abdominal pain, dyspepsia, nausea, diarrhea or vomiting. Total events for celecoxib = 699 (17.5%), diclofenac = 448 (22.4%) and ibuprofen = 336 (16.9%). Events are non-censored.

If symptomatic GI adverse events represent risk factors for clinically important events, withdrawals due to these GI symptoms could represent the loss of patients at risk. This depletion of susceptible individuals, or “**informative censoring**” as argued by the Sponsor, could result in misleading analyses, particularly if withdrawal due to GI adverse events were not similar among the treatment groups. As noted in **Table 21**, a higher proportion of patients receiving diclofenac withdrew as a result of some GI adverse events which represented the most common GI adverse events: abdominal pain, dyspepsia, nausea, diarrhea, and flatulence during the entire study. The overall incidence of withdrawal due to an adverse event was statistically significantly lower for celecoxib than for diclofenac as were several individual events. For example, the differences between celecoxib and diclofenac for three of the GI events (abdominal pain, nausea, and diarrhea) and the three hepatic events (elevations of liver enzyme levels) were statistically significant in favor of celecoxib. Between celecoxib and ibuprofen, the only statistically significant differences were in diarrhea, gastric ulcer, and rash; the incidence of rash with celecoxib was also significantly different than that seen with diclofenac.

Table 21: Adverse Events Causing Withdrawal with Incidence $\geq 1\%$: Entire Study Period

Adverse Event (%)	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Any event	22.4	26.5 ²	23.0
Abdominal pain	4.3	6.5 ²	4.9
Dyspepsia	3.8	4.4	3.9
Rash	2.1	0.7 ²	1.3 ²
Nausea	1.7	2.8 ²	1.8
Diarrhea	1.4	2.7 ²	0.8 ²
Flatulence	1.2	1.8	1.4
Gastric ulcer	0.3	0.7	1.0 ²
SGOT increased	0.1	2.1 ²	0.1
SGPT increased	0.1	2.3 ²	0.1
Hepatic function abnormal	<0.1	1.1 ²	<0.1

1. From Table 10d (p. 180) and Table T 42.1 (p. 469); N49-00-06-035-102.

2. P<0.05 vs. celecoxib.

As noted (Table T42.4, p. 498, N49-00-06-035-102), the incidences of adverse events leading to withdrawal in the first six months of the study were in most cases identical to, or slightly below, those in the entire study period. This indicates that **almost all patients withdrawing due to adverse events did so within six months of beginning the study.**

To address whether informative censoring with respect to CSUGIEs \pm GDUs was observed in patients who dropped out due to GI-related adverse events (i.e. dyspepsia, abdominal pain, nausea, diarrhea, and vomiting), the rates of these events were compared (**Table 22**). There are no statistically significant differences between ibuprofen and celecoxib with regards to overall withdrawal and withdrawal due to any particular GI adverse event. However, there does appear to

be a difference between celecoxib and diclofenac in the overall withdrawal rate and those associated with (moderate to severe) diarrhea, abdominal pain and nausea.

Table 22: Incidence of Withdrawal for Moderate to Severe GI adverse events¹

	Celecoxib N=3987	Diclofenac N=1996	Ibuprofen N=1985
Any GI adverse event	699	448	336
Withdrawal	298 (7.5%)	191 (9.6%) ²	149 (7.5%)
Diarrhea	35 (0.9%)	40 (2.0%) ²	13 (0.7%)
Vomiting	19 (0.5%)	7 (0.4%)	5 (0.3%)
Abdominal pain	140 (3.5%)	101 (5.1%) ²	80 (4.0%)
Dyspepsia	122 (3.1%)	60 (3.0%)	58 (2.9%)
Nausea	49 (1.2%)	35 (1.8%) ²	25 (1.3%)

1. From Table 1 (p. 1980) and Appendix 2.4.17.5 (p. 2086); N49-00-06-035-102.
2. P values from Fischer's exact test. For celecoxib vs. diclofenac withdrawal p=0.006; diarrhea p<0.001; abdominal pain p=0.005; nausea p=0.129. All other p-values >0.20 or could not be calculated.

To address whether patients who experienced GI adverse events had a higher incidence of CSUGIEs ± GDUs than patients who did not report GI adverse events, the rates of events were compared (Table 23).

Table 23: CSUGIE ± GDU rates and relative risks with/without 5 GI symptoms¹

	Celecoxib N=3987		Diclofenac N=1996		Ibuprofen N=1985	
	Sponsor	MO ²	Sponsor	MO	Sponsor	MO
CSUGIE						
With AE	5/699	12/699	8/448	7/448	5/336	6/336
Without AE	12/3288	5/3288	2/1548	3/1548	6/1649	5/1649
Relative Risk	1.96	11.5	13.82	8.2	4.09	5.9
CSUGIE/GDU						
With AE	22/699		20/448		20/336	
Without AE	21/3288		6/1548		16/1649	
Relative Risk	4.93		11.52		6.13	

1. From Table 2 (p. 1981); N49-00-06-035-102. Symptoms included dyspepsia, abdominal pain, nausea, diarrhea, and vomiting (moderate to severe). CSUGIEs or CSUGIE/GDU are those uncensored during the entire study.
2. Per medical officer review of case summaries of CSUGIEs. All patients were withdrawn from the trial. All patients had the GI symptoms noted in the summaries without regard to rating of severity (i.e. mild, moderate, severe). The CSUGIE/GDU cases for celecoxib were also reviewed; a relative risk of 12.83 (vs. 4.93) was obtained.

Reviewer's comment: There is a difference in adjudication of CSUGIEs between the sponsor and the medical officer; these differences can change the inferences that can be drawn from these data. The relative risk of a CSUGIE ± GDU in patients with an AE appears greater with celecoxib than with ibuprofen or diclofenac. This observation would tend not to support the importance of informative censoring in the outcomes. It does appear that, in all treatment arms, CSUGIEs tend to be found more commonly in patients with the five GI symptoms listed above than without these AEs.

The Sponsor argued that withdrawals of susceptible individuals (i.e. "informative censoring") due to GI adverse events represent the loss of patients at risk. This loss suggests that standard analyses of risk may be misleading, particularly because incidences of withdrawal due to GI adverse events

were not similar among the treatment groups. A higher proportion of patients receiving diclofenac withdrew as a result of GI signs or symptoms as discussed above.

To address this issue, incidences of events that could not occur because of withdrawals for GI adverse events were imputed based on risk calculations with a time-adjusted method (Appendix 1.9, N49-00-06-035-102). In brief, incidences were calculated for patients who experienced GI symptoms but continued in the study. The incidences were then applied to patients who discontinued due to GI symptoms. As shown in Table 24, the adjusted rates suggested there would be differences between treatment groups for both end points within the first six months and for the entire study period had informative censoring been an important issue in influencing outcomes.

Table 24: Crude Incidence Rates and Comparisons for CSUGIE± GDUs Adjusted for Withdrawals for GI Adverse Events¹

	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (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
CSUGIE/GDU	44 (1.1%)	34 (1.7%)	44 (2.2%)	P=0.069	P=0.001
Entire Study					
CSUGIE	25 (0.6%)	23 (1.2%)	21 (1.1%)	P=0.044	P=0.084
CSUGIE/GDU	76 (1.9%)	58 (2.9%)	73 (3.7%)	P=0.016	P<0.001

1. From Table 8o (p. 150); N49-00-06-035-102

Endpoint of CSUGIE/GDU for first 6 months:

As discussed earlier (section 8.1.1.3.2), symptomatic ulcer cases were those cases in which criteria for a CSUGIE were not met but in which a gastroduodenal ulcer was found by either endoscopy or upper gastrointestinal series, performed as a result of symptoms or signs. The combined category of these ulcers with the CSUGIEs was referred to as “CSUGIEs/GDUs.” Of note, any patient with either a gastric or duodenal ulcer, or both, is counted as having a gastroduodenal ulcer.

As noted above, a total of 1214 potential CSUGIEs occurred within the first six months of these studies. After GEC review, 225 of the 260 potential CSUGIEs were found to be non-CSUGIEs, and 954 were found to be negative events. Of these 225 non-CSUGIEs, 48 were cases of symptomatic gastroduodenal ulcers (from figure 8c p. 100, N49-00-06-035-102).

Table 25 shows that within the first six months of study, a total of 83 CSUGIEs/GDUs were found: 32 occurred on celecoxib treatment, 20 on diclofenac, and 31 on ibuprofen. Included in this total are all CSUGIEs/GDUs regardless of censoring. None of the symptomatic ulcer cases within the first six months was censored; thus all ulcers are included in the CSUGIE/GDU analyses.

Table 25: Distribution of CSUGIEs/GDU: Traditional Definitions –First Six Months¹

Event Category	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
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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 ²	4	3 ³
Hemoccult (+) stool with ulcer/large erosion and:			
1D-1: Hematocrit/Hemoglobin drop	2 ²	1	3
1D-2: orthostasis	-	-	-
1D-3: transfusion	-	-	-
1D-4: 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

1 From Table 8h (p.101), Table T17.1 (p. 281), appendix 2.6.1 (p. 2123); N49-00-06-035-102. Any patient with both gastric and duodenal ulcers is counted once in the "Gastroduodenal" row.

2 One of these events censored from primary analysis.

3 Two of these events censored from primary analysis

Table 26 summarizes the results for the incidences and comparisons of CSUGIE/GDU during the first 6 months of the study for the ITT population. The differences in times to event over the first 26 weeks achieved statistical significance between celecoxib and NSAIDs pooled, as well as between celecoxib and ibuprofen. When only the patients not taking aspirin were included in the analysis, the event rate for celecoxib over the first 26 weeks was again statistically significantly lower than the rate for NSAIDs combined ($p=0.017$) as well as that for ibuprofen ($p<0.001$).

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Table 26: Summary of CSGUIE/GDU 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
All Patients						
	n = 3987	n = 1996	n = 1985			
No. of CSUGIE/GDUs						
Uncensored	30	20	29			
Censored ¹	2	0	2			

Total	32	20	31			
Week 26 crude rate ³	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 CSUGIE/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			

1. 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).
2. From Table T17.1 & T18.1, N49-00-06-035-102, p. 281 & 285/24295.
3. Rates and p-values based on uncensored data.

Table 27 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs/GDU during the first six months of the study. These rates are in the entire ITT cohort. The p-values comparisons, as noted in the footnote of the table suggest statistically significantly different between celecoxib and the pooled NSAID results, or when compared against ibuprofen (p=0.005 and 0.004 with censored and uncensored cases, respectively) but not against diclofenac.

Table 27: CSUGIEs/GDU-First 6 months (Crude & Kaplan-Meier rates)^{1,2}

Rates	Celecoxib (n=3987)		Diclofenac (n=1996)		Ibuprofen (n=1985)	
	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.03%	0.05%	0.10%	0.10%	0.10%	0.15%
Week 4 (8-28)	0.18%	0.20%	0.25%	0.25%	0.30%	0.35%
Week 13 (29-91)	0.53%	0.58%	0.65%	0.65%	0.91%	1.01%
Week 26 (92-182)	0.75%	0.80%	1.00%	1.00%	1.46%	1.56%
Kaplan-Meier						
Week 1 (1-7)	0.04%	0.06%	0.10%	0.10%	0.12%	0.17%
Week 4 (8-28)	0.20%	0.23%	0.31%	0.31%	0.32%	0.37%
Week 13 (29-91)	0.65%	0.70%	0.82%	0.82%	1.24%	1.35%
Week 26 (92-182)	0.97%	1.02%	1.30%	1.30%	2.05%	2.16%

1. From Table T17.2 (p. 282); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events were previously defined (Table 7 above).

1. For censored events, log Rank P-values (Table T17.3, p. 283) of celecoxib vs. NSAIDs = 0.023, celecoxib vs. diclofenac = 0.308, celecoxib vs. ibuprofen = 0.005. For uncensored events, log Rank P-values (Table T17.4, p. 284) of celecoxib vs. NSAIDs = 0.026, celecoxib vs. diclofenac = 0.421, celecoxib vs. ibuprofen = 0.004.

Table 28 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs/GDU during the first six months of the study in patients not taking ASA. These rates are in the entire ITT cohort. The p-values comparisons, as noted in the footnote of the table, suggest (as noted earlier with the CSUGIE results) statistically significant differences between celecoxib and the pooled NSAID results, or when compared against ibuprofen (p<0.001 and 0.001 with censored and uncensored cases, respectively) but not against diclofenac.

Table 28: CSUGIEs/GDU-First 6 months without ASA (Crude & Kaplan-Meier rates-ITT)^{1,2}

Rates	Celecoxib (n=3154)		Diclofenac (n=1567)		Ibuprofen (n=1602)	
	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.03%	0.06%	0.06%	0.06%	0.12%	0.12%
Week 4 (8-28)	0.13%	0.16%	0.19%	0.19%	0.37%	0.37%
Week 13 (29-91)	0.35%	0.38%	0.45%	0.45%	0.87%	0.94%
Week 26 (92-182)	0.51%	0.54%	0.57%	0.57%	1.44%	1.50%
Kaplan-Meier						
Week 1 (1-7)	0.04%	0.07%	0.10%	0.10%	0.14%	0.14%
Week 4 (8-28)	0.14%	0.17%	0.26%	0.26%	0.39%	0.39%
Week 13 (29-91)	0.44%	0.48%	0.54%	0.54%	1.21%	1.28%
Week 26 (92-182)	0.65%	0.68%	0.74%	0.74%	2.00%	2.08%

1. From Table T18.2 (p. 286); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events were previously defined (Table 7 above).
2. For censored events, log rank P-values (Table T18.3, p. 287) of celecoxib vs. NSAIDs = 0.017, celecoxib vs. diclofenac = 0.760, celecoxib vs. ibuprofen < 0.001. For uncensored events, log rank P-values (Table T18.4, p. 288) of celecoxib vs. NSAIDs = 0.019, celecoxib vs. diclofenac = 0.872, celecoxib vs. ibuprofen < 0.001.

Endpoint of CSUGIE/GDU for entire study:

As noted earlier, throughout the full length of the study, a total of 1670 potential CSUGIEs were worked up with 384 reviewed by all members of the GEC. Of these, 44 were found to be CSUGIEs, 340 were found to be non-CSUGIEs, and 1286 were found to be negative events. Of the 340 non-CSUGIEs, 67 represented symptomatic gastroduodenal ulcers, for a total of 111 CSUGIEs/GDUs (i.e. 44 plus 67) occurring throughout the entire study period.

Table 29 shows all CSUGIEs/GDUs by treatment group and category. Forty-six CSUGIEs/GDUs occurred on celecoxib treatment, 27 on diclofenac, and 38 on ibuprofen. Included in these totals are all CSUGIEs and symptomatic ulcers regardless of censoring. Three CSUGIEs in the celecoxib group, one CSUGIE in the diclofenac group, and two CSUGIEs in the ibuprofen group were censored. None of the ulcer cases was censored; therefore, all of the ulcers are included in the CSUGIE/GDU analysis.

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Table 29: Distribution of CSUGIEs/GDU: Traditional Definitions –Entire Study¹

Event Category	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
UGI Bleeding (Category 1)			
1A: Hematemesis with ulcer/large erosion	1	-	-
1B: Ulcer/large erosion with evidence of bleeding	7	4	7
1C: Melena with ulcer/large erosion	5 ²	4	3 ³

<u>Hemoccult (+) stool with ulcer/large erosion and:</u>			
1D-1: Hematocrit/Hemoglobin drop	3 ²	2	3
1D-2: orthostasis	-	-	-
1D-3: transfusion	-	-	-
1D-4: blood in stomach	-	-	-
UGI Perforation (Category 2)	1	1	-
Gastric Outlet Obstruction (Category 3)	2	-	-
Symptomatic Ulcers (all patients)			
Gastroduodenal	26	16	25
Gastric	18	13	22
Duodenal	10	5	3
Symptomatic Ulcers (not taking aspirin)	(n=3105)	(n=1561)	(n=1573)
Gastroduodenal	13	6	18
Gastric	8	5	16
Duodenal	6	2	2
Total	46	27	38
Total Uncensored	43	26	36

- 1 From Table 8j (p.105), Table 8r (p. 154) and appendix 2.6.1 (p. 2123); N49-00-06-035-102. Any patient with both gastric and duodenal ulcers is counted once in the "Gastroduodenal" row.
- 2 One of these events censored from primary analysis.
- 3 Two of these events censored from primary analysis

Table 30 summarizes the results for the incidences and comparisons of CSUGIE/GDU during the entire study for the ITT population. The cumulative times to event were significantly lower through the entire study period for celecoxib than for the NSAID comparators pooled ($p=0.040$) and ibuprofen individually ($p=0.017$). When only patients not taking aspirin were included in the analysis, the celecoxib event rate over 52 weeks was statistically significantly lower than the rate for the NSAIDs pooled ($p=0.020$) and the rate for ibuprofen individually ($p<0.001$). When both censored and uncensored cases were included in the analysis, the trends and comparisons shown above were repeated (Table 20.4, p. 295; and Table 21.4, p. 299 of N49-00-06-035-102), including the statistically significant difference between celecoxib and ibuprofen event rates in the patients not taking aspirin. Celecoxib was not statistically significantly different from diclofenac for any comparison.

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Table 30: Summary of CSGUIE/GDU Incidence (Traditional Definitions) – Entire Study Period

	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 CSGUIE/GDUs Uncensored	43	26	36			

Censored ¹	3	1	2			
Total	46	27	38			
Week 52 crude rate ³	1.05%	1.30%	1.76%	0.296	0.017	0.040
No. per 100 pt-yrs	1.85	2.41	3.21			
Patients not Taking Aspirin						
	n = 3105	n = 1551	n = 1573			
No. of CSUGIE/GDUs						
Uncensored	21	10	28			
Censored	1	0	1			
Total	22	10	29			
Week 52 crude rate	0.68%	0.64%	1.72%	0.992	<0.001	0.020
No. per 100 pt-yrs	1.16	1.19	3.20			

1. 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).
2. From Table T20.1 & T21.1, N49-00-06-035-102, p. 292 & 296/24295.
3. Rates and p-values from uncensored data.

Table 31 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs/GDU during the entire study. These rates are in the entire ITT cohort. The p-values comparisons, as noted in the footnote of the table, suggest again statistically significant differences between celecoxib and the pooled NSAID results, or when compared against ibuprofen (p=0.017 and 0.016 with censored and uncensored cases, respectively) but not against diclofenac.

Table 31: CSUGIEs/GDU-Entire Study-ITT (Crude & Kaplan-Meier rates)²

Rates	Celecoxib (n=3987)		Diclofenac (n=1996)		Ibuprofen (n=1985)	
	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.03%	0.05%	0.10%	0.10%	0.10%	0.15%
Week 4 (8-28)	0.18%	0.20%	0.25%	0.25%	0.30%	0.35%
Week 13 (29-91)	0.53%	0.58%	0.65%	0.65%	0.91%	1.01%
Week 26 (92-182)	0.75%	0.80%	1.00%	1.00%	1.46%	1.56%
Week 39 (183-273)	0.83%	0.90%	1.25%	1.25%	1.61%	1.71%
Week 52 (274-364)	1.05%	1.13%	1.30%	1.35%	1.76%	1.86%
Kaplan-Meier						
Week 1 (1-7)	0.04%	0.06%	0.10%	0.10%	0.12%	0.17%
Week 4 (8-28)	0.20%	0.23%	0.31%	0.31%	0.32%	0.37%
Week 13 (29-91)	0.65%	0.70%	0.82%	0.82%	1.24%	1.35%
Week 26 (92-182)	1.00%	1.05%	1.31%	1.31%	2.06%	2.17%
Week 39 (183-273)	1.14%	1.24%	1.83%	1.86%	2.43%	2.54%
Week 52 (274-364)	1.95%	2.05%	1.91%	2.02%	2.84%	2.94%

1. From Table T20.2 (p. 293); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events were previously defined (Table 7 above).
1. For censored events, log rank P-values (Table T20.3, p. 294) of celecoxib vs. NSAIDs = 0.040, celecoxib vs. diclofenac = 0.296, celecoxib vs. ibuprofen = 0.017. For uncensored events, log rank P-values (Table T20.4, p. 295) of celecoxib vs. NSAIDs = 0.045, celecoxib vs. diclofenac = 0.349, celecoxib vs. ibuprofen = 0.016.

Table 32 shows the rates (both crude and Kaplan-Meier) by time interval of all CSUGIEs/GDU during the entire study in patients not taking ASA. These rates are in the entire ITT cohort. The p-values comparisons, as noted in the footnote of the table, suggest again (as noted earlier with the

CSUGIE results) statistically significantly differences between celecoxib and the pooled NSAID results, or when compared against ibuprofen ($p < 0.001$ and 0.001 with censored and uncensored cases, respectively) but not against diclofenac.

Table 32: CSUGIEs/GDU-Entire Study without ASA-ITT (Crude & Kaplan-Meier rates)^{1,2}

Rates	Celecoxib (n=3105)		Diclofenac (n=1551)		Ibuprofen (n=1573)	
	+ censoring	- censoring	+ censoring	- censoring	+ censoring	- censoring
Crude						
Week 1 (1-7)	0.03%	0.06%	0.06%	0.06%	0.13%	0.13%
Week 4 (8-28)	0.13%	0.16%	0.19%	0.19%	0.38%	0.38%
Week 13 (29-91)	0.35%	0.39%	0.45%	0.45%	0.89%	0.95%
Week 26 (92-182)	0.52%	0.55%	0.58%	0.58%	1.46%	1.53%
Week 39 (183-273)	0.58%	0.61%	0.58%	0.58%	1.65%	1.72%
Week 52 (274-364)	0.68%	0.71%	0.64%	0.64%	1.72%	1.78%
Kaplan-Meier						
Week 1 (1-7)	0.04%	0.07%	0.10%	0.10%	0.15%	0.15%
Week 4 (8-28)	0.14%	0.18%	0.26%	0.26%	0.40%	0.40%
Week 13 (29-91)	0.45%	0.48%	0.54%	0.54%	1.24%	1.31%
Week 26 (92-182)	0.71%	0.74%	0.75%	0.75%	2.07%	2.14%
Week 39 (183-273)	0.80%	0.84%	0.89%	0.89%	2.55%	2.63%
Week 52 (274-364)	1.13%	1.16%	0.92%	0.92%	3.00%	3.07%

1. From Table T21.2 (p. 297); N49-00-06-035-102. Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval. Uncensored and censored events were previously defined (Table 7 above).
1. For censored events, log rank P-values (Table T21.3, p. 298) of celecoxib vs. NSAIDs = 0.020, celecoxib vs. diclofenac = 0.992, celecoxib vs. ibuprofen < 0.001. For uncensored events, log rank P-values (Table T21.4, p. 295) of celecoxib vs. NSAIDs = 0.022, celecoxib vs. diclofenac = 0.907, celecoxib vs. ibuprofen < 0.001.

Summary of GI endpoint results:

Table 33 summarizes the log-rank p-values for the endpoints of CSUGIEs and CSUGIEs/GDU for both the first six months and for the entire study in the ITT population both with and without the use of ASA.

During the first 6 months, analysis of the CSUGIE data in the entire cohort showed a numerical trend toward a decrease in the incidence with celecoxib compared to NSAIDs combined; these trends were not statistically significant. When the observed rates were analyzed in the subgroup of patients not taking aspirin, there was a statistically significant decrease in the incidence of CSUGIEs observed with celecoxib relative to pooled NSAIDs (Table 13). Although the reduction in CSUGIEs was not statistically significant in the entire study population at 6 months, the reduction in symptomatic ulcers combined with CSUGIEs (CSUGIEs/GDUs) was significant (Table 26). This analysis also showed a significant difference in patients not receiving aspirin for celecoxib and NSAIDs.

In terms of individual comparisons with ibuprofen and diclofenac, all comparisons significant for celecoxib vs. NSAIDs combined were significant for celecoxib vs. ibuprofen. In contrast to the results for ibuprofen, no differences were seen between celecoxib and diclofenac for any of the end points.

Analysis of the entire study period showed that the difference between celecoxib and pooled NSAIDs for CSUGIEs in the entire study population was not statistically significant. Statistical significance was also not achieved when patients not taking aspirin were analyzed specifically (Table 14). This absence of statistical significance appeared to reflect a decline in the NSAID event rate between six months and the end of the study; this decline was argued to be attributable to the phenomenon of depletion of susceptible patients. When the combined end point of CSUGIEs/GDUs was analyzed, the difference between celecoxib and pooled NSAIDs became statistically significant. A statistically significant difference between celecoxib and the pooled NSAIDs was also noted when the confounding effects of low-dose aspirin use were removed from the analysis (Table 30).

With respect to specific comparisons, all differences that were statistically significant between celecoxib and the pooled NSAIDs were also significant for celecoxib versus ibuprofen. Consistent with the six-month analysis, the differences between celecoxib and diclofenac were not statistically significant for any of the endpoints. Again, it was argued that the absence of statistical significance may be a function of the larger proportion of patients withdrawing from the diclofenac group because of GI adverse events.

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Table 33: Overall summary of log-rank p-values (CSUGIEs and CSUGIEs/GDU-ITT)

Endpoint (Traditional Definition)	Celecoxib vs.		
	NSAIDs	Diclofenac	Ibuprofen
CSUGIE-First 6 months			
Censored	0.092	0.264	0.073
Uncensored	0.112	0.445	0.053
CSUGIE-First 6 months without ASA			
Censored	0.037	0.476	0.005

Uncensored	0.047	0.651	0.005
CSUGIE-Entire study			
Censored	0.450	0.640	0.414
Uncensored	0.474	0.752	0.372
CSUGIE-Entire Study without ASA			
Censored	0.185	0.972	0.037
Uncensored	0.204	0.870	0.033
CSUGIE/GDU-First 6 months			
Censored	0.023	0.308	0.005
Uncensored	0.026	0.421	0.004
CSUGIE/GDU-First 6 months without ASA			
Censored	0.017	0.760	<0.001
Uncensored	0.019	0.872	<0.001
CSUGIE/GDU-Entire Study			
Censored	0.040	0.296	0.017
Uncensored	0.045	0.349	0.016
CSUGIE/GDU-Entire Study without ASA			
Censored	0.020	0.992	<0.001
Uncensored	0.022	0.907	<0.001

1. From sNDA 20-998 (S-009) review tables 7, 8, 10, 11, 13, 14, 26, 27, 28, 30, 31 & 32.

Reviewer's comment: These results tend to emphasize that celecoxib was not able to demonstrate it was statistically superior to diclofenac in terms of the clinically important UGI endpoints and conditions as defined in this study. The same is not true when comparisons are made to ibuprofen.

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Arthritis Efficacy and QOL:

Patient global

The patient's global assessment of arthritis was based on a scale of 1 (very good) to 5 (very poor) and was assessed at baseline, weeks 4,13, 26, 39, and 52, and the final visit. The observed mean scores (not shown, Table T31.1, p. 329, N49-00-06-035-102) were nearly identical for the celecoxib, diclofenac, and ibuprofen treatment groups at baseline (ranging from 2.9 to 3.0). Maximal efficacy was evident at the first post-baseline assessment for all treatment groups, with

mean scores decreasing to 2.6 or 2.7. The degree of arthritis efficacy was identical at week 26 and the final visit within all treatment groups. At these time points, the mean score for celecoxib fell from 3.0 to 2.7. Similarly, the mean score for diclofenac decreased from 3.0 to 2.6, while the mean score for ibuprofen fell from 2.9 to 2.8. As seen in Table 34, based on analysis of least square means, there were generally no differences among the three treatment groups with respect to changes from baseline. Although not compared statistically, least square mean analysis also indicated no differences among post-baseline scores within any of the three treatment groups, suggesting that the maximal efficacy achieved was maintained through the end of the study.

Also noted in Table 34, the percentages of patients who reported an improvement, worsening, or no change were similar between the celecoxib and diclofenac treatment groups at week 26 and the final visit. However, comparison of confidence intervals indicated differences between the celecoxib and ibuprofen treatment groups. At week 26, the percentage of celecoxib patients who reported an improvement in arthritis status was higher than that for ibuprofen patients. In addition, the percentage of celecoxib patients who reported a worsening in arthritis status was lower than for ibuprofen patients. At the final visit, the percentage of patients who reported an improvement in arthritis status was higher for the celecoxib group than for the ibuprofen group. These results suggest that celecoxib was comparable to diclofenac and ibuprofen (at the doses studied in these trials) in treating the signs and symptoms of OA and RA, as measured by the patient's global assessment of arthritis; no inferences regarding superiority or equivalence can be drawn.

Table 34: Summary of Patient's Global Assessment Results²

	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Mean (95% CI) ¹			
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 ³	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)

1. Means are least square means. Decreases represent improvements. Global scale ranged from 1 (very good) to 5 (very poor).
2. From Table 9a (p. 169); T31.2 (p. 330); T31.3 (p. 331), N49-00-06-035-102. All results based on LOCF approach.
3. Improved or worsened is defined as a reduction or increase, respectively, of at least one grade from baseline.

Patient's Assessment of Arthritis Pain-VAS:

The patient's assessment of arthritis pain was assessed on a visual analog scale from 0 mm (no pain) to 100 mm (most severe pain) and was evaluated at baseline, weeks 4, 13, 26, 39, and 52, and the final visit. Although not shown (Table T32.1, p. 332, N49-00-06-035-102) observed mean scores showed improvements in arthritis pain relative to baseline at all post-baseline time points in each treatment group. Decreases in pain scores ranged from _____ Comparable improvements in arthritis status were observed between the celecoxib and diclofenac groups at

week 26 (decreases of 8.3 mm and 10.1 mm, respectively) and the final visit (decreases of 7.2 mm and 9.5 mm, respectively). Compared with ibuprofen, celecoxib appeared to provide pain relief at both week 26 (decrease of 8.3 mm-celecoxib versus 3.9 mm-ibuprofen) and the final visit (decrease of 7.2 mm –celecoxib versus 3.1 mm-ibuprofen).

Although not compared statistically, least square mean analysis indicated similar changes from baseline among the three treatment groups, based on comparison of confidence intervals. Results at week 26 and the final visit are shown in Table 35. While post-baseline least square mean values for each treatment group increased over the course of the study, overlapping of confidence intervals within groups suggested that the efficacy of each treatment was constant during the study. These results suggest that celecoxib was comparable to diclofenac and ibuprofen (at the doses studied in these trials) in treating the signs and symptoms of OA and RA, as measured by the patient’s assessment of arthritis pain; no inferences regarding superiority or equivalence can be drawn.

Table 35: Patient’s Assessment of Arthritis Pain – VAS

	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (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)

1. Means are least square means. Decreases represent improvements.

1. From Table 9b (p. 170), N49-00-06-035-102.

Reviewer’s comment: While these protocols were not primarily intended to address effectiveness, it is disappointing that celecoxib at four times and twice the upper recommended dose for OA and RA, respectively, appeared to offer no substantial therapeutic gains.

QOL Results:

Quality of Life measures were performed in protocol N49-98-02-035 only, and consisted of the Health Assessment Questionnaire (HAQ) and the SF-36 Health Survey. Both the HAQ and the SF-36 Health Survey were conducted at Baseline, Week 26, and the Final Visit.

As summarized in Table 36, observed mean HAQ scores were identical for patients in the celecoxib and ibuprofen treatment groups at Baseline (0.9 on the scale of 0 to 3). Celecoxib-treated patients reported slightly less disability at Week 26 (0.8 versus 0.9 for ibuprofen) and the same degree of disability at the Final Visit (0.9 in both groups). Although statistical comparisons were not done, least square mean analysis indicated that the treatments were similar and were maintained through the final visit.

Table 36: HAQ-Observed Means, Least Square Means and 95% Confidence Intervals¹

	Celecoxib (N= 1990)	Ibuprofen (N= 1985)
Baseline		

N	1986	1981
Mean (SD)	0.9 (0.62)	0.9 (0.6)
LS Mean and 95% CI	0.93 (0.90-0.96)	0.92 (0.89-0.95)
Week 26		
N	1990	1985
Mean (SD)	0.8 (0.65)	0.9 (0.65)
LS Mean and 95% CI	0.85 (0.83-0.87)	0.88 (0.86-0.90)
Final		
N	1990	1985
Mean (SD)	0.9 (0.66)	0.9 (0.66)
LS Mean and 95% CI	0.86 (0.84-0.88)	0.89 (0.87-0.91)

1. Based on LOCF data. HAQ scores range from 0-3 with lower scores indicating less disability. From Table T33 (p. 334), N49-00-06-035-102.
2. From analysis of covariance with treatment and center as factors and baseline (for visit other than baseline) value as covariate.

Results of selected SF-36 Health Survey at baseline, week 26, and the final visit are summarized in Table 37. In the celecoxib group, improvements relative to baseline were observed at week 26 and the final visit in three SF-36 domains: bodily pain, physical function, and role-physical. In the vitality domain, celecoxib also produced an improvement compared to baseline at week 26 only. In the ibuprofen group, improvements relative to baseline at week 26 and the final visit were observed in only one domain, bodily pain. Although statistical comparisons were not done between celecoxib than ibuprofen, the confidence intervals suggested that the treatments were similar in the effect of treatment.

Table 37: Summary of Results in Selected SF-36 Health Survey Domains¹

SF-36 Health Survey Domain	Celecoxib (n=1990)	Ibuprofen (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)

1. From Table 9c (p. 171), N49-00-06-035-102. All values are least square means (95% confidence intervals). Scales range from 0-100 with lower scores as worse.

Patient Satisfaction Questionnaire:

The patient satisfaction questionnaire (administered at the final visit) evaluated patient satisfaction in the following four domains: satisfaction with pain relief, improvement with walking and bending, stomach discomfort or problems, and overall performance of study medication. Observed mean scores (data not shown, Table T35, p. 343, N49-00-06-035_102) were generally similar among the three treatment groups. For the three measures in which higher scores indicated greater

satisfaction, the scores for ibuprofen were lower than for celecoxib and diclofenac; however, comparison of confidence intervals did not suggest a difference. For stomach discomfort or problems, celecoxib and ibuprofen were similar, while diclofenac patients indicated more dissatisfaction. Again, the confidence intervals did not confirm the difference.

SODA Results:

The Severity of Dyspepsia Assessment (SODA) was administered only in protocol N49-98-02-102 and consisted of three domains (Pain Intensity, Non-Pain Symptoms, and Satisfaction). The SODA was administered at baseline, weeks 4, 13, 26, and 52 or the final visit. At baseline (Table 9d, p.172, N49-00-06-035_102), there were no statistically significant differences in observed mean scores between the celecoxib and diclofenac treatment groups in any of the three SODA domains ($p \geq 0.204$). With respect to pain intensity and satisfaction, all observed mean changes from baseline associated with diclofenac were statistically significantly higher (i.e., worse) than those associated with celecoxib ($p < 0.001$). With respect to non-pain symptoms, diclofenac produced a statistically significantly higher mean change relative to baseline than celecoxib only at week 4 ($p = 0.005$).

Withdrawal Due to Lack of Arthritis Efficacy:

Times to and incidences of withdrawal due to lack of arthritis efficacy (Table T37.1-2, p.350-1, N49-00-06-035_102) revealed a total of 1456 patients withdrew due to treatment failure (number of patients, ITT):

- Celecoxib (n=3987) – 691 (17%)
- Diclofenac (n=1996)– 309 (15%)
- Ibuprofen (n=1985) – 456 (23%)

Based on this comparison, the withdrawal incidences of the celecoxib and diclofenac treatment groups were similar. However, ibuprofen was associated with a higher incidence of withdrawal than either celecoxib or diclofenac. The percentages of celecoxib and diclofenac patients who withdrew from the study due to lack of arthritis efficacy were generally similar over time: the ibuprofen group had a slightly higher withdrawal than that for either the celecoxib or diclofenac group. When withdrawals due to lack of arthritis efficacy or adverse events (see Table 40) were combined, a total of 3362 patients withdrew for one of these two reasons as follows:

- 1596 (40%) in the celecoxib group
- 849 (43%) in the diclofenac group
- 917 (46%) in the ibuprofen group

As before, celecoxib and diclofenac were similar, but the incidence was higher for ibuprofen than for celecoxib.

Overview of Safety (Section 10):

Deaths (Section 10.1.1):

A total of 36 deaths (Appendix 2.9.1, p. 3918; N49-00-06-035-102) occurred during the study or during post-study follow-up: 19 in the celecoxib group, 9 in the diclofenac group, and 8 in the

ibuprofen group. Not expectedly in the population studied, the majority of deaths (25 of 36, 69%) occurred in elderly patients (65 years old or older). Most deaths were cardiovascular in nature. Of note, none of the deaths resulted from a GI or liver-related cause.

In all cases except one, the principle investigator and the sponsor's safety monitor believed that the death had no relationship to study medication. The exception was a case in which the cause of death was cardiopulmonary arrest/hypertension, and the investigator attributed the relationship to study medication as uncertain (patient US0383-102-12691; DER no. 990629-CL696). In this case, the date of the patient's last dose could not be determined, but the death was believed to have occurred more than 28 days after the patient discontinued taking study medication.

Noted below (Table 38) is a summary of the 16 deaths that occurred either during or within 28 days of participation in the entire study.

Table 38: Summary of Deaths-Entire Study or within 28 days of Treatment¹

Adverse Event ²	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Patient-years of Exposure ³	2320	1080	1122
Myocardial infarction (MI)	3	-	1
Cardiac arrest	1	4	1
Accidental injury	1	-	-
Circulatory failure/MI	-	-	1
Sepsis	1	-	-
Carcinoma	1	-	-
Coronary artery disorder	-	1	-
Arrhythmia/MI	1	-	-
Total (No. per 100 pt-yr)	8 (0.34)	5 (0.46)	3 (0.27)

1. From Table 10.e (p 182); N49-00-06-035-102.

2. For cases in with no adverse event term, the event was classified by the cause of death listed in the end-of-study CRF.

3. Rounded estimates of pt.-yr exposures (p. 174, N49-00-06-035-102).

Reviewer's comment: Of the deaths noted above, there were 5 (0.22), 4 (0.46) and 3 (0.27) deaths that appear to be attributable to cardiovascular causes for celecoxib, diclofenac and ibuprofen, respectively. Numbers in () are calculations based on the rounded estimates of patient exposure as noted in the table above.

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Noted below (Table 39) is a summary of the 20 deaths that occurred 28 days or more after participation in the study.

Table 39: Summary of Deaths Occurring more than 28 days after Treatment¹

Adverse Event ²	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)

Myocardial infarction (MI)	2	-	1
Cardiac arrest	1	1	-
Cardiac arrest/tamponade	1	-	-
Pulmonary fibrosis/pneumonia/carcinoma	2	2	1
Accidental injury	-	-	1
Sepsis	1	-	-
Carcinoma	1	-	-
Coronary artery disorder	1	-	1
Aneurysm/subarachnoid hemorrhage	-	1	-
Cerebrovascular disorder	1	-	-
Cardiac failure	-	-	1
Cardiopulmonary arrest/hypertension	1	-	-
Total (No. per 100 pt-yr) ¹	11 (0.47)	4 (0.37)	5 (0.45)

1. From Table 10.f (p 183); N49-00-06-035-102. Pt-years as noted in Table 38.

2. For cases in with no adverse event term, the event was classified by the cause of death listed in the end-of-study CRF.

Reviewer's comment: The table below summarizes results after review of the deaths noted above. Overall, most of the deaths were cardiovascular in origin, with the exclusion of 2 cases of CHF. Where it was unclear in the CRF when study drug was stopped, these cases have been included as occurring < 28 days after trial; hence the difference with the Sponsor. It is unclear whether any of these cardiovascular deaths are directly related to the treatment. Given the relatively few deaths, no large excess mortality (total or cardiac, with or without ASA) is consistently evident for celecoxib as compared to controls.

	Celecoxib (n=3987/882/3105) ¹ (pt-yrs: 2320/517/1803)	Diclofenac (n=1996/445/1551) (pt-yrs: 1081/239/841)	Ibuprofen (n=1985/412/1573) (pt-yrs: 1122/249/874)
Deaths-all causes	19 (.82)	9 (.83)	8 (.71)
ASA users	6 (1.2)	1 (.4)	1. (1.6)
Non-ASA users	13 (0.7)	8 (1.0)	4 (0.5)
Deaths-cardiac (entire study)	11 (0.5)	5 (.46)	5 (0.4)
ASA users	5 (1.0)	0	3(1.2)
Non-ASA users	6 (0.3)	(.63)	4 2 (0.2)
Deaths-cardiac (during or <28 day after trial)	10 (.43): <u>5 (0.2)</u> ²	1. (.46): <u>4 (0.4)</u>	(.27)
ASA users	5(1.0): <u>2 (0.4)</u>	0	2 (.8)
Non-ASA users	5 (.27): <u>3 (0.2)</u>	5 (.63): <u>4 (0.5)</u>	3 1 (.11)

1. n = number of patients in entire group/ASA users/ASA non-users, respectively. Pt-yrs (estimates) are in same order.

2. Numbers in () are rate/100 patient years. Numbers following : and underlined are per Sponsor.

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Adverse Events Causing Withdrawal:

The most common adverse events causing withdrawal (>1% in any treatment group) are shown in Table 40. The overall incidence of withdrawal (also see Table 3) due to an adverse event was statistically significantly lower for celecoxib than for diclofenac. Six of the 10 most common events were related to the GI system, five of which represented the most common GI adverse

events described above: **abdominal pain, dyspepsia, nausea, diarrhea, and flatulence**. Three of the events (SGOT/SGPT increased, and hepatic function abnormal) were related to elevations in liver function test results; these events led to noteworthy incidences of withdrawals in the diclofenac group. The differences between celecoxib and diclofenac for three of the GI events (abdominal pain, nausea, and diarrhea) and the three hepatic events were statistically significant in favor of celecoxib. Rash led to withdrawal in more than 1% of patients in the celecoxib and ibuprofen groups with statistically significant differences between celecoxib and both ibuprofen and diclofenac.

Table 40: Adverse Events Causing Withdrawal (Incidence >1%) in Any Treatment Group-Entire Study

Adverse Event	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Any event (% of patients)	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

1. p<0.05 vs. celecoxib. From Table 10d (p. 180), N49-00-06-035-102.

As noted in Table T42.4 (p. 498, N49-00-06-035-102, data not shown), the incidences of adverse events leading to withdrawal in the first six months of the study were in most cases identical to, or slightly below, those in the entire study period. This suggests that **almost all patients withdrawing due to adverse events did so within six months of beginning the study**.

Other Serious Adverse Events:

A total of 500 patients experienced **serious adverse events (SAE)** during or 28 days after study participation:

- 270 patients in the celecoxib group
- 111 patients in the diclofenac group
- 119 patients in the ibuprofen group

The most common SAEs are summarized in **Table 41**. As can be seen, the difference between any two treatment groups was no more than 0.6 per 100 patient-years. The highest rate seen for any serious adverse event was 0.8 per 100 patient-years, seen in at least one treatment group for myocardial infarction, coronary artery disorder, accidental fracture, cardiac failure, and back pain. Although the results are similar to those shown for general adverse events, the patterns suggested by the general adverse events were not replicated exactly in the serious adverse events. This difference in pattern may reflect the fact that there were smaller numbers of serious events than general adverse events.

Table 41: Summary of Serious Adverse Events-Entire Study Period¹

Adverse Event	Celecoxib (n=3987) 2320.4 pt-yrs	Diclofenac (n=1996) 1080.5 pt-yrs	Ibuprofen (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

5 From Table 10.g (p 184); N49-00-06-035-102. Owing primarily to the unequal randomization, results are displayed as normalized for length of exposure, rather than crude incidence rates. Table includes any event experienced by a total of at least 10 patients across the three treatment groups.

Reviewer's comment: Generally, these normalized incidences do not seem to suggest any important differences or obvious trends of specific target organ or organ-system involvement by any treatment group.

Other safety findings (Section 10.2):

ADR incidence (Section 10.2.1):

A total of 6493 patients reported at least one adverse event during study participation:

- 3260 (81.8%) in the celecoxib group
- 1654 (82.9%) in the diclofenac group
- 1579 (79.5%) in the ibuprofen group.

The most common adverse events occurring in any treatment group are shown in Table 42. The majority of the common adverse events were gastrointestinal or upper respiratory in nature. The most common event in any treatment group was dyspepsia, followed by upper respiratory tract infection, headache, and abdominal pain. Of the GI adverse events shown in Table 42 (dyspepsia, abdominal pain, diarrhea, nausea, flatulence, vomiting, constipation), all but one event (vomiting) were statistically significant in favor of celecoxib vs. diclofenac. Adverse events relating to liver function tests (SGOT or SGPT increases) were also statistically significantly lower for celecoxib than for diclofenac

Other comparisons of note, peripheral edema, hypertension, and anemia were statistically significantly less common for celecoxib than for ibuprofen whereas the incidence of rash was statistically significantly higher for celecoxib than for either diclofenac or ibuprofen.

The incidences of the most common respiratory adverse events were similar among the three treatment groups. Symptoms suggest typical seasonal allergies and minor upper respiratory infections. The incidence of bronchitis was significantly higher for ibuprofen.

Table 42: Adverse Events with Incidence $\geq 3\%$ - 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 (% of patients)	81.8	82.9	79.5*
Dyspepsia	16.5	19.5*	16.5
URTI	15.4	14.7	15.8
Headache	13.9	16.6*	13.0
Abdominal Pain	11.7	18.5*	11.3
Diarrhea	10.9	15.0*	7.5*
Sinusitis	8.8	8.6	9.5
Nausea	8.2	12.1*	9.0
Flatulence	7.3	11.4*	7.2
Rash	6.2	2.8*	3.8*
Influenza-like symptoms	5.4	5.6	6.1
Injury accidental	5.3	5.0	5.5
Anemia	4.4	5.3	8.7*
Coughing	4.4	3.5	4.6
Rhinitis	4.3	3.9	3.7
Bronchitis	4.0	4.1	5.1*
Back pain	3.7	3.3	4.0
Edema peripheral	3.7	3.5	5.2*
Insomnia	3.6	3.7	3.2
Dizziness	3.5	3.4	4.2
Tooth disorder	2.9	4.3*	4.4*
Pharyngitis	2.9	2.7	3.5
Urinary tract infection	2.8	1.8*	3.0
Vomiting	2.6	3.5	2.7
Hypertension	2.0	2.0	3.1*
Constipation	2.2	6.8*	6.5*
SGPT increased	1.0	5.1*	1.2
SGOT increased	0.9	4.3*	1.0

1. $p < 0.05$ vs. celecoxib. From Table 10.b (p 177) and Table T41.1 (p. 357), N49-00-06-035-102.

The majority of adverse events occurred during the first six months (182 days) of treatment (Table T41.4, p. 415; N49-00-06-035-102). In fact (Appendix 2.8.4, p. 3832; N49-00-06-035-102), the large majority of events occurred within the first 90 days. During the first 6 months, events were reported for 3023 (75.8%) patients in the celecoxib group, 1564 (78.3%) in the diclofenac group, and 1488 (75.0%) in the ibuprofen group. Although the incidences of almost all events were slightly lower during the first six months than during the entire study period, the differences among the treatment groups were similar in magnitude to those in Table 42, particularly with respect to the GI system. The statistical comparisons were similarly maintained, despite the lower numbers of events. All of the statistically significant differences shown in Table

42 were also statistically significant within the first six months, with two exceptions (tooth disorder between celecoxib and ibuprofen, and urinary tract infection between celecoxib and diclofenac). Conversely, certain differences that were not shown to be statistically significant in Table 42 were significant at six months. The incidence of anemia between celecoxib and diclofenac (2.0% vs. 3.2%, respectively; p=0.009) and the incidence of BUN increased between celecoxib and diclofenac (0.7% vs. 1.6%, respectively; p=0.004) being examples.

Events that occurred with incidences above 2% in intervals after the first 90 days are summarized in Table 43. As discussed above, these events generally were similar to those occurring most commonly during the entire study. The declining incidences of most events over time could reflect adaptation as well as the withdrawal of susceptible patients. However, there are exceptions to this trend such as anemia or upper respiratory infections; the latter may reflect the background incidence of these common events. Of note, the incidences of events for diclofenac in the last interval may well be influenced by the fact that protocol 102 was not extended to 15 months. The 64 patients remaining after Day 360 were only in the study for a maximum of two additional weeks; the longest treatment duration in this group was 374 days (Table T2.4.1, p. 357; N49-00-06-035-102). Therefore, there was a decreased possibility for adverse events in this period, but when an event did occur, it caused a high incidence owing to the low sample size.

Table 43: Adverse Events with ≥2% Incidence in Any Interval After the First 90 days¹

Adverse Event	91-180 Days			181-270 Days			271-360 Days			361-450 Days		
No. who entered interval												
Celecoxib (C) 400 mg BID	2836			2343			2028			585		
Diclofenac (D) 75 mg BID	1394			1127			977			64		
Ibuprofen (I) 800 mg TID	1297			1045			894			479		
	C	D	I	C	D	I	C	D	I	C	D	I
Dyspepsia	3.1	3.4	3.8	2.6	2.6	2.8	1.7	1.5	2.0	0.4	-	0.5
Headache	3.1	3.0	2.9	2.0	2.1	2.0	0.9	0.9	0.9	0.4	-	0.5
Upper respiratory. Tract infection	2.8	3.1	4.7	2.4	3.7	2.8	4.2	3.5	3.0	3.1	3.8	2.5
Abdominal pain	2.7	5.2	3.0	2.2	2.2	2.2	1.3	1.7	1.4	1.1	-	0.7
Sinusitis	2.4	1.5	2.3	1.9	2.8	1.7	1.4	0.8	2.0	0.8	-	2.2
Diarrhea	2.3	3.7	1.7	1.5	1.8	1.8	1.3	1.1	1.2	1.0	-	0.2
Nausea	1.9	2.9	1.6	1.6	1.8	1.8	0.8	0.4	1.2	0.4	-	0.2
Flatulence	1.6	2.2	1.7	0.9	1.8	0.8	0.6	1.0	0.6	-	-	-
Anemia	1.3	2.3	3.4	1.4	1.7	2.2	2.7	2.7	3.5	2.0	1.7	2.8
SGOT increased	0.2	2.1	0.2	0.4	1.1	0.3	0.2	1.1	0.7	0.9	-	0.4
SGPT increased	0.2	2.1	0.3	0.3	1.3	0.3	0.3	1.2	0.8	0.7	-	0.8

1. From Table 10.c (p 179) and Appendix 2.8.4 (p. 3832), N49-00-06-035-102.

The majority of events were mild to moderate in severity (Appendix 2.8.1, p. 3627; N49-00-06-035-102). The overall incidences of severe adverse events were similar among the three treatment groups:

- 16.3% for celecoxib
- 18.1% for diclofenac

- 17.6% for ibuprofen.

Clinical Laboratory Evaluation (Section 10.2.2):

Table 44 summarizes the mean changes from baseline to the final visit for each standard laboratory test performed during the study. Although in most cases the change at the final visit does not represent the greatest change in laboratory values during the study, it includes the largest numbers of patients. Patients with at least one post-baseline laboratory result, including patients withdrawn owing to an abnormal result, are included in the final visit values.

Table 44: Mean Changes from Baseline to Final Visit in Laboratory Values¹

Laboratory Test	Celecoxib	Diclofenac	Ibuprofen
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 (.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)

1. From Table 10.h (p 187); N49-00-06-035-102. All numbers are mean (SE) from baseline. (*) =p<0.05 vs. celecoxib.

Reviewer's Comment: Many differences among groups were statistically significant, owing to the large numbers of patients in each group. However, it is unclear if these differences were clinically meaningful; the LFT abnormalities associated with diclofenac may be the remarkable exception.

For most laboratory tests, incidences of extreme laboratory values (according to the predefined criteria) occurred in very few patients at any time. Those for which at least 20 patients across the three treatment groups had an extreme value are summarized in Table 45. The percentages of patients with extreme hemoglobin or hematocrit values were higher in the NSAID groups than for celecoxib. This data appears consistent with the adverse event (anemia) and mean laboratory data noted previously. Two of the differences between celecoxib and diclofenac were statistically significant while the difference in minimum value between celecoxib and ibuprofen (hemoglobin) approached but did not achieve statistical significance (p=0.053).

Other differences of note were the incidences of extreme ALT and AST values. Although only the ALT results are shown in Table 45, differences in both of these tests (AST data, Table 45.1, p. 541;

N49-00-06-035-102.) were statistically significant between celecoxib and diclofenac for both the final visit as well as for the maximum value measured during the study. Analysis of laboratory shift data (Appendix 2.12, p. 4214; N49-00-06-035-102) and scatter-plots (Appendix 2.13, p. 4230; N49-00-06-035-102) for the liver function tests (ALT and AST) also show that a higher proportion of patients in the diclofenac group experienced elevations at the final visit.

No difference was seen among the treatment groups in extreme high bicarbonate values (above 35 mmol/L), with incidences ranging from 0.2 to 0.4 in the three groups. Only one celecoxib patient and two diclofenac patients experienced extreme low bicarbonate values (below 15 mmol/L) at any time during the study. The only statistically significant difference in extreme laboratory values not shown in Table 45 was that between celecoxib and ibuprofen in potassium levels: 0.3% of celecoxib patients and 0.0% of ibuprofen patients had a maximum value above 6.0 mmol/L (p=0.021). Any trends for other laboratory data suggested in the means and extremes, and the differences among the groups, were not sufficiently robust to be detected by visual examination of these shift tables or the scatter-plots.

Table 45: Analysis of Extreme Laboratory Test Values: Entire Study Period¹

Laboratory Test	Celecoxib	Diclofenac	Ibuprofen
Low			
Hemoglobin²			
Final visit	9/3708 (0.2)	9/1851 (0.5)	7/1805 (0.4)
Minimum value	12/3708 (0.3)	17/1851 (0.9) *	13/1805 (0.7)
Hematocrit²			
Minimum value	5/3701 (0.1)	12/1849 (0.6) *	6/1802 (0.3)
High			
ALT (SGPT) (>200 U/L)			
Final visit	2/3692 (<0.1)	22/1848 (1.2) *	0/1785 (0)
Maximum value	4/3692 (0.1)	29/1848 (1.6) *	1/1785 (<0.1)
Creatine kinase (>300 U/L)			
Final visit	67/3667 (1.8)	33/1840 (1.8)	27/1758 (1.5)
Maximum value	184/3667 (5.0)	83/1840 (4.5)	85/1758 (4.8)
BUN (>14.3 mmol/L)			
Final visit	17/3692 (0.5)	8/1849 (0.4)	12/1786 (0.7)
Maximum value	31/3692 (0.8)	20/1849 (1.1)	16/1786 (0.9)
Bicarbonate (>35 mmol/L)			
Maximum value	13/3689 (0.4)	7/1844 (0.4)	3/1782 (0.2)

1. From Table 10.j (p 189); N49-00-06-035-102. Data are expressed as No./total and percentage of patients. Includes all tests for which at least 20 patients had an extreme value. (*) = p<0.05 vs. celecoxib.
2. Hemoglobin-below 6.0 g/dL or 3.0 g/dL decrease from baseline. Hematocrit – below 0.25 or 0.10 decrease from baseline.

Contingency table analyses:

Contingency table analyses of patients whose post-treatment laboratory results met certain predefined criteria for combinations of values or changes in values included the following:

- Decreases in both hemoglobin and hematocrit
- Increases in both creatinine and BUN
- Increases in both AST and ALT

- Increases in both alkaline phosphatase and total bilirubin
- Increases in both ALT and alkaline phosphatase
- Increases in both ALT and total bilirubin.

Table 46 summarizes the results in those patients who experienced an extreme decrease in either hematocrit or hemoglobin at any time during the study. The results show that in all analyses, proportions of diclofenac or ibuprofen patients who had the specified decreases in hematocrit and/or hemoglobin were two- to three-fold higher than in patients receiving celecoxib. Here, the addition of aspirin increased the incidence rate in all treatment groups, but appeared to preserve the differences among the groups.

Table 46: Summary of Hemoglobin/Hematocrit Contingency Tables: Entire Study Period¹

Patients with hemoglobin decrease >2 g/dL and/or hematocrit decrease ≥0.10	Celecoxib	Diclofenac	Ibuprofen
All patients	87/3701 (2.4) ²	82/1849 (4.4)	102/1802 (5.7)
Excluding CSUGIEs	83/3682 (2.3) ²	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) ²	48/1340 (3.6)	74/1299 (5.7)
RA patients	24/1026 (2.3) ²	34/509 (6.7)	28/503 (5.6)
Patients not taking aspirin	53/2864 (1.9) ²	53/1428 (3.7)	73/1414 (5.2)
Patients taking aspirin	34/837 (4.1) ²	29/421 (6.9)	29/388 (7.5)

1. From Table 10.1 (p 192); N49-00-06-035-102. Data are expressed as No./ total and percentage of patients.
2. p≤0.05 versus both other treatments by Fischer's Exact Test. Figures 10a-c, p 203-4; N49-00-06-035-102).

Table 47 summarizes the results of the hepatobiliary and renal laboratory contingency analyses. As with the hematocrit and hemoglobin analyses above, this table includes all patients who experienced either extreme laboratory value at any point during the study. The results are consistent with those reported above in adverse events and extreme laboratory values. Elevations in renal function tests were somewhat more frequent in the diclofenac group than in the celecoxib or ibuprofen group, and elevation in liver function tests were strikingly more frequent for diclofenac.

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Table 47: Summary of Hepatobiliary and Renal Contingency Tables: Entire Study¹

	Celecoxib	Diclofenac	Ibuprofen
Creatinine ≥159 μmol/L and/or BUN ≥14.3 mmol/L	47/3702 (1.3) ²	39/1852 (2.1)	26/1807 (1.4)
AST and/or ALT ≥3xULN	14/3702 (0.4)	68/1851 (3.7)	13/1806 (0.7)
Alkaline phosphatase ≥3xULN and/or bilirubin ≥1.8xULN	4/3696 (0.1)	3/1851 (0.2)	0/1800 (0.0)
	13/3696 (0.4)	62/1851 (3.3)	11/1800 (0.6)

ALT and/or alkaline Phosphatase $\geq 3 \times \text{ULN}$	15/3701 (0.4)	63/1851 (3.4)	11/1806 (0.6)
ALT $\geq 3 \times \text{ULN}$ and/or bilirubin $\geq 1.8 \times \text{ULN}$			

1. From Table 10.m (p 193); N49-00-06-035-102. Data are expressed as No./ total and percentage of patients.
2. $p \leq 0.05$ versus diclofenac by Fischer's Exact Test. Figure 10.d, p. 202:); N49-00-06-035-102.

Vital Signs and Physical Examination Results:

Group mean changes from baseline in blood pressure, pulse, and weight disclosed no obvious treatment effects, patterns or differences of clinical relevance among the groups. The only statistically significant difference was the change from baseline in weight in the subgroup of male patients with baseline weight above 90 kg: weight in the celecoxib group increased by 0.53 kg, while that for diclofenac decreased by 1.11 kg ($p < 0.001$). The clinical significance of this finding is unknown.

Special studies-review of systems (Section 10.2.3):

Gastrointestinal Effects

The GI tolerability profiles of the three treatment groups in the study are summarized for these events by time interval (Table 48) or aspirin status (Table 49).

Table 48 demonstrates that the results at six months were quite similar to those for the entire study period. For the common GI adverse events, six-month incidences were all within 2% of the overall incidences; this was also true for withdrawals due to GI adverse events. In these GI adverse event measures, celecoxib appeared to be better tolerated than diclofenac and was generally similar to ibuprofen in tolerability. Most of these common GI adverse events were statistically significantly more frequent for diclofenac than for celecoxib. Statistically significant differences were seen between celecoxib and ibuprofen in only two types of events, one in favor of celecoxib (constipation) and one in favor of ibuprofen (diarrhea).

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Table 48: Summary of GI Adverse Events by Time Interval¹

Adverse Event	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Entire Treatment Period			
Any GI event	45.6	55.0 *	46.2
Dyspepsia	16.5	19.5 *	16.5
Abdominal pain	11.7	18.5 *	11.3
Diarrhea	10.9	15.0 *	7.5 *

Nausea	8.2	12.1 *	9.0
Flatulence	7.3	11.4 *	7.2
Tooth disorder	2.9	4.3*	4.4*
Vomiting	2.6	3.5	2.7
Constipation	2.2	6.8 *	6.5 *
Any GI event causing withdrawal	12.2	16.6 *	13.4
First Six Months			
Any GI event	40.3	49.9 *	40.5
Dyspepsia	14.4	17.7 *	14.4
Abdominal pain	9.7	16.7 *	9.5
Diarrhea	9.4	13.6 *	6.0*
Nausea	6.9	11.0 *	7.6
Flatulence	6.6	10.1 *	6.5
Tooth disorder	2.4	3.6*	3.2
Vomiting	2.1	3.1*	2.3
Constipation	1.7	5.9 *	5.9 *
Any GI event causing withdrawal	10.8	15.5 *	12.0

1. From Table 10.n (p 196); N49-00-06-035-102. All numbers are percentages of patients. Includes any GI adverse event with incidence >3% in any treatment group. (*) = p<0.05 vs. celecoxib.

The incidence (data not shown) of diverticular disease (diverticulitis and diverticulosis) was lower for celecoxib than for ibuprofen. For these two events combined, the difference between the groups was 0.4% vs 1.0%. The difference was statistically significant for diverticulosis (0.2% vs. 0.6%; p=0.028).

The incidence of GI adverse events in patients not taking aspirin were similar to those in the overall population, though generally reduced by approximately 1% across treatment groups (Table 49). For the most part, the statistical relationships described above were maintained. Some variations (i.e. incidence of dyspepsia), however, could be seen in the analysis of patients taking aspirin. Several of the statistically significant differences between celecoxib and diclofenac did not retain significance in this analysis, most notably in overall incidence of a GI adverse event: 54.0% vs 59.1% (p=0.079). **In general, the use of aspirin appears to have increased incidences of GI adverse events across groups, and attenuated some of the differences between the treatment groups.**

As noted in Tables 48 and 49, there appears to be a difference in withdrawal rates from the treatment groups as a result of GI signs or symptoms. **Whether during the first six months or the entire study period, or whether patients were taking aspirin or not, significantly more patients withdrew from the diclofenac group than from the celecoxib group owing to GI adverse events.** The issue of differential dropouts for GI symptoms has been discussed under "Informative Censoring" above. Withdrawal due to a GI adverse event over the entire study period was 16.6% for diclofenac and 12.2% for celecoxib (p<0.001), and almost all of these withdrawals took place in the first six months. For ibuprofen, GI withdrawals were numerically more frequent than for celecoxib, but the differences were not statistically significant.

Kaplan-Meier plots of cases (data not shown, Tables T55.1 through T55.4, p. 564-7; N49-00-06-035_102) of time to moderate/severe abdominal pain, dyspepsia, or nausea revealed that diclofenac was distinguished from celecoxib (for abdominal pain, nausea or all three) early during the study;

this trend was maintained through the end of the study. In these three analyses, the differences between celecoxib and diclofenac were statistically significant ($p \leq 0.013$). However, no difference was found between celecoxib and diclofenac with regards to dyspepsia alone.

Table 49: Summary of GI Adverse Events by Aspirin Use-Entire Study¹

Adverse Event	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
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 *	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

1. From Table 10.o (p 197); N49-00-06-035-102. All numbers are percentages of patients. Includes any GI adverse event with incidence $\geq 3\%$ in any treatment group. (*) = $p < 0.05$ vs. celecoxib.

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Renal Effects

Table 50 shows the incidences of selected renal adverse events occurring throughout the entire study period. In general, the incidences were low in all treatment groups, not suggesting any pronounced renal effects of any of these treatments. However, patients receiving ibuprofen experienced more edema and hypertension than celecoxib or diclofenac patients; these differences were statistically significant. Adverse events relating to increases in renal function laboratory values (BUN increased and NPN increased) were more frequent for diclofenac than for celecoxib.

The differences were statistically significant when examined in the six-month analysis, but not over the entire treatment period.

Table 50: Selected Adverse Events Relating to Renal Function: Entire Study Period¹

Adverse Event	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Hypertension	2.0	2.0	3.1*
Hypertension aggravated	0.8	0.6	1.2
Edema generalized	0.5	0.6	1.0*
Edema peripheral	3.7	3.5	5.2*
Cardiac failure	0.3	0.2	0.5
BUN increased	1.1	1.7	0.9
NPN increased	1.3	1.9	1.2
Renal failure acute	0.0	<0.1	0.0
Renal function abnormal	<0.1	<0.1	0.1

1. From Table 10.q (p 201); N49-00-06-035-102. All numbers are percentages of patients. (*) =p<0.05 vs. celecoxib.

Reviewer's comment: For a more detailed analysis of the cardiovascular and renal effects of celecoxib and the comparator groups in this trial, the reader is referred to the review by Douglas Throckmorton, M.D.

Table 51 shows group mean changes and extreme changes in BUN and creatinine. Although the meaning is unclear, the results suggest an effect of diclofenac on mean creatinine values, and of celecoxib on BUN as compared to ibuprofen. Few patients experienced an extreme BUN value; the incidence appeared higher for ibuprofen than for the other two groups, but the difference was not statistically significant. When the extreme creatinine threshold of 265 µmol/L was used, only one patient in the entire study period experienced an extreme value. However, as noted above for the renal contingency tables, when the lower threshold of 159 µmol/L for creatinine with or without BUN changes was utilized, percent increases of 1.3 for celecoxib, 2.1 for diclofenac, and 1.4 for ibuprofen were noted. The difference between celecoxib and diclofenac was statistically significant.

Not shown in Table 51 was that between celecoxib and ibuprofen in elevated potassium levels: 0.3% of celecoxib patients and 0.0% of ibuprofen patients had a maximum potassium value above 6.0 mmol/L (p=0.021; Table 45.1,p. 535). Five of these 11 cases of extreme potassium levels in celecoxib patients were isolated increases that were bracketed by values within the normal range, and may be artifactual (i.e., due to hemolysis). One additional case was an isolated value drawn four days after discontinuation of study medication and is of uncertain clinical significance.

Table 51: Mean Changes from Baseline to Final Visit/Extreme Values in Specific Renal Laboratory Values¹

Laboratory Test	Celecoxib	Diclofenac	Ibuprofen
Group Mean Changes from Baseline (Mean [SE])			
BUN, mmol/L	0.66 (0.027)	0.58 (0.041)	0.52 (0.039) ¹
Creatinine, µmol/L	0.8 (0.22)	2.4 (0.33) ¹	1.5 (0.33)
Incidence of Extreme Values (No./total [%])			
BUN (>14.3 mmol/L)			
Final visit	17/3692 (0.5)	8/1849 (0.4)	12/1786 (0.7)

Maximum value	31/3692 (0.8)	20/1849 (1.1)	16/1786 (0.9)
Creatinine (>265.2 µmol/L)			
Final visit	0/3692 (0.0)	0/1850 (0.0)	0/1786 (0.0)
Maximum value	1/3692 (<0.1)	0/1850 (0.0)	0/1786 (0.0)

1. From Table 10.r (p 202); N49-00-06-035-102. P<0.05 vs. celecoxib.

Vascular (Cardiac and Noncardiac) Effects

The incidences of cardiac and noncardiac vascular adverse events throughout the entire study period are shown in Table 52. The table shows that vascular events were rare in all treatment groups, and incidences were similar between celecoxib and the two NSAIDs. The only statistically significant difference in incidences was for cerebrovascular disorder between celecoxib (0.2%) and ibuprofen (0.5%).

Table 52: Incidences of Selected Cardiac/Noncardiac Vascular Adverse Events: Entire Study Period ¹

Adverse Event	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Angina pectoris	0.6	0.5	0.6
Arteriosclerosis	<0.1	0.0	<0.1
Atherosclerosis	<0.1	<0.1	0.1
Carotid bruit	<0.1	0.1	<0.1
Carotid stenosis	<0.1	0.0	0.0
Cerebrovascular disorder	0.2	0.5	0.5 ¹
Coronary artery disorder	0.6	0.4	0.3
Embolism	<0.1	0.0	0.0
Embolism pulmonary	0.1	<0.1	0.1
Myocardial infarction	0.5	0.3	0.5
Myocardial ischemia	<0.1	0.1	0.0
Peripheral gangrene	<0.1	0.0	0.0
Peripheral ischemia	0.1	0.0	0.1
Peripheral vascular disease	<0.1	0.0	<0.1
Phlebitis	<0.1	0.0	<0.1
Thrombophlebitis	<0.1	0.0	<0.1
Thrombophlebitis arm	<0.1	0.0	<0.1
Thrombophlebitis deep	0.3	0.3	<0.1
Thrombophlebitis leg	0.0	<0.1	<0.1
Thrombophlebitis leg deep	<0.1	<0.1	0.0
Thrombophlebitis leg superficial	<0.1	<0.1	0.0
Unstable angina	0.3	0.2	0.1

1. From Table 10.s (p 204); N49-00-06-035-102. Numbers are percentages. P<0.05 vs. celecoxib.

Reviewer's comment: There does not appear to be any clinically or statistically significant trend with celecoxib to suggest additional cardiovascular risks over the comparator drugs.

Incidences of the same group of adverse events are shown and statistically analyzed by aspirin status in Table 53. Patients in the two NSAID groups were pooled for this analysis. As might be expected, incidences of the cardiovascular-related events were higher in the patients taking aspirin, since these patients were more likely to have a significant cardiovascular medical history than the

overall study population. The absence of statistical significance for any of the events suggest that the differences between celecoxib and NSAID were not markedly altered by the use of aspirin.

Table 53: Incidences of Selected Cardiac/Noncardiac Vascular Adverse Events with/without Aspirin Use: Entire Study¹

	With Aspirin			Without Aspirin		
	Celecoxib (n=882)	NSAIDs (n=857)	RD*	Celecoxib (n=3105)	NSAIDs (n=3124)	RD*
Any thromboembolic event	6.1	5.7	0.4	1.5	1.2	0.3
Angina pectoris	1.5	1.6	-0.2	0.3	0.3	0.0
Arteriosclerosis	0.2	0.1	-	0.0	0.0	-
Atherosclerosis	0.1	0.2	-0.1	<0.1	<0.1	0.0
Carotid bruit	0.0	0.1	-0.1	<0.1	<0.1	0.0
Carotid stenosis	0.1	0.0	-	0.0	0.0	-
Cerebrovascular disorder	0.6	1.2	-0.6	<0.1	0.3	-0.2
Coronary artery disorder	1.7	0.9	0.8	0.3	0.2	0.2
Embolism	0.0	0.0	-	<0.1	0.0	-
Embolism pulmonary	0.1	0.0	0.1	<0.1	<0.1	0.0
Myocardial infarction	1.5	1.2	0.3	0.2	0.1	0.1
Myocardial ischemia	0.1	0.2	-0.1	<0.1	0.0	0.0
Peripheral gangrene	0.0	0.0	-	<0.1	0.0	-
Peripheral ischemia	0.3	0.1	0.2	<0.1	<0.1	0.0
Peripheral vascular disease	0.1	0.0	0.1	<0.1	<0.1	0.0
Phlebitis	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis arm	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis deep	0.3	0.4	0.0	0.3	<0.1	0.2
Thrombophlebitis leg	0.0	0.0	-	0.0	<0.1	-
Thrombophlebitis leg deep	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis leg superficial	0.0	0.1	-0.1	<0.1	0.0	0.0
Unstable angina	0.9	0.6	0.3	<0.1	<0.1	0.0

1. From Table 10.t (p 205); N49-00-06-035-102. Numbers are percentages. RD indicates risk reduction. None of the differences were statistically significant at p<0.05.

Table 54 (from Cardioresenal review, Doug Throckmorton, M.D.) shows selected cardiac adverse events reported during the trial according to aspirin use. For anginal disorders (especially the combined disorders), there seems to be a trend toward more events in those patients receiving celecoxib, regardless of aspirin use. However, for edema, there appears to be a trend toward more events in those patients receiving ibuprofen.

Table 54: Selected Cardiac Adverse Events Reported During CLASS According to ASA Use.

Adverse Event	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
ASA-Users	N=882	N=445	N=412
Edema			
Edema peripheral	35 (4.0%)	17 (3.8%)	23 (5.6%)
Edema (pooled reporting) ^b	38 (4.3%)	20 (4.5%)	28 (6.8%)
Angina			
Unstable Angina	8 (0.9%)	4 (0.9%)	1 (0.2%)

Angina Pectoris	13 (1.5%)	8 (1.8%)	6 (1.5%)
Coronary Artery Disorder	15 (1.7%)	3 (0.7%)	5 (1.2%)
Combined Anginal Disorders^c	36 (4.1%)	15 (3.4%)	12 (2.9%)
Myocardial Ischemia	1 (0.1%)	2 (0.4%)	0 (0%)
Myocardial Infarction	13 (1.5%)	3 (0.7%)	7 (1.7%)
Hypertension	24 (2.7%)	14 (3.1%)	19 (4.6%)
Hypertension Aggravated	12 (1.4%)	2 (0.4%)	7 (1.7%)
Thrombophlebitis			
Thrombophlebitis, Deep	3 (0.2%)	2 (0.4%)	1 (0.2%)
Thrombophlebitis, Combined ^d	3 (0.2%)	3 (0.4%)	1 (0.2%)
Vasculitis	1 (0.1%)	0 (0%)	0 (0%)
<u>Non-ASA Users</u>	N=3105	N=1551	N=1573
Edema peripheral	111 (3.6%)	53 (3.4%)	81 (5.1%)
Edema (pooled reporting) ^b	127 (4.1%)	61 (3.9%)	96 (6.1%)
Angina			
Unstable Angina	2 (<0.1%)	0 (0%)	1 (<0.1%)
Angina Pectoris	9 (0.3%)	2 (0.1%)	6 (0.4%)
Coronary Artery Disorder	10 (0.3%)	4 (0.3%)	1 (<0.1%)
Combined Anginal Disorders^c	21 (0.67%)	6 (0.38%)	8 (0.51%)
Myocardial Ischemia	1 (<0.1%)	0 (0%)	0 (0%)
Myocardial Infarction	6 (0.2%)	2 (0.1%)	2 (0.1%)
Hypertension	54 (1.7%)	26 (1.7%)	42 (2.7%)
Hypertension Aggravated	20 (0.6%)	10 (0.6%)	17 (1.1%)
Thrombophlebitis			
Thrombophlebitis, Deep	9 (0.3%)	3 (0.2%)	0 (0%)
Thrombophlebitis, Combined ^d	14 (0.45%)	5 (0.3%)	4 (0.25%)
Vasculitis	1 (<0.1%)	0 (0%)	1 (<0.1%)

1. Data from electronic submission, NDA 20-998 supplement S-009, Table T41.1.

b. Includes edema, edema generalized, and edema peripheral.

c. Includes unstable angina, angina pectoris and coronary artery disorder.

d. Includes AEs reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.

Table 55 (from Cardiorenal review, Doug Throckmorton, M.D.) shows serious cardiac adverse events reported during the trial according to aspirin use. In the non-aspirin users, there appears to be a slight trend toward more events in those patients receiving celecoxib for combined atrial and anginal disorders; this does not appear to be the case for aspirin users.

Table 55: Serious Adverse Events (SAEs) per 100 Pt-Yrs Reported During CLASS by ASA Use.

Adverse Event	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
ASA Users	N=882 517 Pt-Yrs	N=445 N=239 Pt-Yrs	N=412 249 Pt-Yrs
Cardiac SAEs			

Atrial Arrhythmias			
Arrhythmia Atrial	2 (0.4%)	0 (0%)	1 (0.4%)
Bradycardia	0 (0%)	0 (0%)	0 (0%)
Fibrillation Atrial	4 (0.8%)	1 (0.4%)	3 (1.2%)
Tachycardia Supraventricular	1 (0.2%)	0 (0%)	0 (0%)
Combined Atrial SAEs ^b	7 (1.4%)	1 (0.4%)	4 (1.6%)
Angina			
Unstable Angina	6 (1.2%)	4 (1.7%)	0 (0%)
Angina Pectoris	3 (0.6%)	5 (2.1%)	4 (1.6%)
Coronary Artery Disorder	11 (2.1%)	2 (0.8%)	5 (2.0%)
Combined Anginal Disorders ^c	20 (3.9%)	11 (4.6%)	8 (3.2%)
Myocardial Infarction	13 (2.5%)	2 (0.8%)	7 (2.8%)
Thrombophlebitis Combined ^d	0 (0%)	2 (0.8%)	1 (0.4%)
Non-ASA Users	N=3105	N=1551	N=1573
	1804 Pt-Yrs	841 Pt-Yrs	874 Pt-Yrs
Cardiac SAEs			
Atrial Arrhythmias			
Arrhythmia Atrial	0 (0%)	0 (0%)	0 (0%)
Bradycardia	2 (0.1%)	0 (0%)	0 (0%)
Fibrillation Atrial	5 (0.3%)	1 (0.1%)	0 (0%)
Tachycardia Supraventricular	2 (0.1%)	0 (0%)	0 (0%)
Combined Atrial SAEs ^b	6 (0.3%)	1 (0.1%)	0 (0%)
Angina			
Unstable Angina	2 (0.1%)	0 (0%)	0 (0%)
Angina Pectoris	1 (<0.1%)	0 (0%)	2 (0.2%)
Coronary Artery Disorder	8 (0.4%)	3 (0.4%)	0 (0%)
Combined Anginal Disorders ^c	10 (0.6%)	3 (0.4%)	2 (0.2%)
Myocardial Infarction	6 (0.3%)	2 (0.2%)	2 (0.2%)
Thrombophlebitis Combined ^d	8 (0.4%)	4 (0.5%)	0 (0%)

1. Data from electronic data submission, Appendix 2.9.4 and 2.9.3.

b. Sum of atrial arrhythmia, atrial fibrillation, bradycardia and tachycardia.

c. Includes unstable angina, angina pectoris and coronary artery disorder.

d. Includes AEs reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.

e. These SAEs were not reported by investigators.

Hepatobiliary Effects

As has been noted previously in this review, the use of diclofenac was associated with increases in liver function values. These findings are summarized in Table 56. A consistent pattern of enzyme elevation was seen in diclofenac patients. The clinical significance of these elevations is indicated by the data on withdrawals: approximately half of diclofenac patients for whom liver enzyme elevations were reported as adverse events were withdrawn from the study as a result. Findings of statistically significant ($p < 0.001$) increases of SGOT/SGPT for diclofenac (3.3%/3.9%, respectively) compared to celecoxib (0.5%/0.6% respectively) and ibuprofen (0.4%/0.5%, respectively) was also obvious at six months (Table T41.4, p.423). These findings are consistent with the known hepatotoxic nature of diclofenac. Neither celecoxib nor ibuprofen had results obviously suggestive of a hepatic effect.

Table 56: Adverse Events and Laboratory Values Related to Hepatic Function: Entire Study¹

Laboratory Test	Celecoxib	Diclofenac	Ibuprofen
Adverse Events (% of Patients)			
SGOT increased	0.9	4.3 ¹	1.0

SGPT increased	1.0	5.1 ¹	1.2
Hepatic function abnormal	0.3	1.6 ¹	0.3
Adverse Events Causing Withdrawal (% of Patients)			
SGOT increased	0.1	2.1 ¹	0.1
SGPT increased	0.1	2.3 ¹	0.1
Hepatic function abnormal	<0.1	1.1 ¹	<0.1
Changes from Baseline in Group Mean Laboratory Values (Mean [SE])			
AST (SGOT), U/L	0.3 (0.12)	5.0 (0.57) ¹	0.9 (0.16)
ALT (SGPT), U/L	-0.2 (0.18)	11.6 (1.1) ¹	1.3 (0.24)
Incidence of Extreme Values (No./total [%])			
AST (SGOT) (>200 U/L)			
Final visit	0/3692 (0.0)	7/1848 (0.4) ¹	0/1785 (0.0)
Maximum value	1/3692 (<0.1)	12/1848 (0.6) ¹	1/1785 (<0.1)
ALT (SGPT) (>200 U/L)			
Final visit	2/3692 (<0.1)	22/1848 (1.2) ¹	0/1785 (0.0)
Maximum value	4/3692 (0.1)	29/1848 (1.6) ¹	1/1785 (<0.1)

1. From Table 10.u (p 206); N49-00-06-035-102. Entries are No. (%) of patients. P<0.05 versus celecoxib.

Reviewer's comment: *Of note, there were no deaths noted in any treatment group due to hepatic causes.*

Dermatologic Effects:

As noted earlier and seen in **Table 57**, the incidence of rash (either within the first 28 days or for the entire study period) was statistically significantly higher for celecoxib than for either diclofenac or ibuprofen. The incidence of pruritus was also statistically significantly higher for celecoxib than for ibuprofen, but not diclofenac. Although not included here (Tables T41.4 and T42.4, p. 429 and 506, respectively) the results shown above were similar when examined for the first six months; these incidences of rash and pruritus were only slightly lower than in the entire study period, and the statistical comparisons were the same. Similarly, **all withdrawals due to pruritus, and all but five withdrawals due to rash, occurred within the first six months of treatment.** The percentage of patients withdrawing for either rash or pruritus was generally higher in the celecoxib group compared to the other treatments: approximately one half to one quarter of rash or pruritus events led to withdrawal. Cases of rash or pruritus in any treatment group tended to be either mild or moderate in severity versus severe; the proportions for severe rash were somewhat higher with celecoxib.

To assess the incidence of true drug-related rashes of clinical significance, those cases that were severe and caused early withdrawal from the study were examined. Of the 19 severe rashes in the celecoxib group, 13 led to withdrawal within the first 28 days of treatment. Using this index, the incidence of clinically significant rash associated with celecoxib would be estimated at 13 of 3987, or 0.33%. Performing a similar analysis on cases of pruritus, five events in the celecoxib group are shown to have been rated as severe and to have led to early withdrawal. This yields an incidence of 0.13%. Events coded as erythematous, maculopapular, or psoriaform rash had incidences of 0.4% or less in any treatment group. None of these values were statistically significantly different between celecoxib and either of the NSAID treatment groups.

None of the rashes or any other dermatologic adverse events in the celecoxib group were serious. Only three serious adverse events relating to skin occurred: two were skin ulcerations, one each

occurring in the diclofenac and ibuprofen groups, and one skin disorder occurred in the ibuprofen group.

Reviewer's comment: There were no cases of Stevens Johnson syndrome, toxic epidermal necrosis or erythema multiforme noted for any of the treatment groups.

Table 57: Characteristics of Rash and Pruritus Among the Three Treatment Groups¹

	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
First 28 Days of Treatment			
Rash			
Overall incidence	149 (3.7)	24 (1.2) ¹	22 (1.1) ¹
Severity			
Mild	69 (1.7)	16 (0.8)	11 (0.6)
Moderate	64 (1.6)	8 (0.4)	9 (0.5)
Severe	15 (0.4)	0 (0.0)	2 (0.1)
Causing withdrawal	74 (1.9)	10 (0.5) ¹	9 (0.5) ¹
Pruritus			
Overall incidence	68 (1.7)	21 (1.1)	15 (0.8) *
Severity			
Mild	42 (1.1)	14 (0.7)	7 (0.4)
Moderate	21 (0.5)	7 (0.4)	7 (0.4)
Severe	5 (0.1)	0 (0.0)	1 (<0.1)
Causing withdrawal	27 (0.7)	6 (0.3)	4 (0.2)
Entire Study Period			
Rash			
Overall incidence	247 (6.2)	55 (2.8) ¹	75 (3.8) ¹
Severity			
Mild	126 (3.2)	35 (1.8)	42 (2.2)
Moderate	101 (2.5)	18 (0.9)	29 (1.5)
Severe	19 (0.5)	2 (0.1)	3 (0.2)
Causing withdrawal	85 (2.1)	13 (0.7) ¹	25 (1.3) ¹
Pruritus			
Overall incidence	97 (2.4)	38 (1.9)	28 (1.4) ¹
Severity			
Mild	61 (1.5)	23 (1.2)	15 (0.8)
Moderate	28 (0.7)	14 (0.7)	11 (0.6)
Severe	7 (0.2)	1 (<0.1)	2 (0.1)
Causing withdrawal	29 (0.7)	7 (0.4)	6 (0.3) ¹

1. From Table 10.v (p 207); N49-00-06-035-102. Numbers are percentages. P<0.05 versus celecoxib.

Respiratory, endocrine/metabolic, CNS/PNS, infectious disease safety:

Reviewer's comment: Since the original NDA review (including this sNDA and post-marketing data), there have been no new issues or clinically important concerns with regards to celecoxib and these general areas of safety.

**APPEARS THIS WAY
ON ORIGINAL**

Discussion/Conclusions (Section 12):

Discussion

The results of this CLASS trial, which represents the combination of two large safety trials, stands at any important juncture in the evolution of our understanding of the relative safety and efficacy of drugs that have been used for their analgesic and anti-inflammatory properties for more than 100 years. From the "black box" approach of employing extracts of willow bark, the precursor of acetylsalicylic acid, to "targeted" therapy of the recently discovered COX-2 enzyme with

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compounds such as celecoxib in this sNDA, the safety and efficacy of drugs in this important therapeutic area has been the topic of what is now an immense literature. One of the questions posed during the review of the original NDA was the consequences of “long-term, high-grade” inhibition of COX-2 and what types of compensatory mechanisms may come into play in this situation. This discussion will attempt to capture some of the “lessons learned” in this sNDA.

Efficacy/Effectiveness

The efficacy of celecoxib was not a primary outcome for this sNDA. The original NDA (NDA 20-998, Review July 8, 1998) addressed the issue of efficacy with studies of pain/analgesia and trials in patients with OA and RA. The original approval of Celebrex included indications for OA and RA, but not pain. Since then, the indication for use in familial adenomatous polyposis (FAP) was added. Of note, the recommended dose for FAP is 400 mg BID which was the same dose employed in the CLASS trials. Interestingly, as noted in the open-label studies that followed the original NDA trials, up to 70% of patients (p. 121, NDA review July 8, 1998) increased their dose of celecoxib. This “dose creep” phenomenon for RA patients resulted in doses again similar to those employed in this sNDA. Therefore, are there any lessons learned regarding the efficacy or effectiveness of celecoxib from the CLASS trial?

Unfortunately, the incomplete assessment of efficacy in the CLASS trial limits any detailed understanding of the efficacy of celecoxib at 400 mg BID, noted to be 2-4 times the recommended (i.e. currently labeled) dose for RA and OA, respectively. However, the patient global (Table 34), patient assessment of pain (Table 35), HAQ scores (Table 36), SF-36 results (Table 37) and patient disposition (i.e. withdrawals for treatment failure, Table 3) would seem to allow some general statements in this area. If one looks at withdrawals from the CLASS trial for arthritis treatment failure, either during the first 6 months or during the entire study, there is no clear trend that celecoxib offers any consistent advantage over the “conventional” doses of NSAIDs, represented here as diclofenac and ibuprofen. At best, it could be argued that celecoxib appears comparable to diclofenac and generally better than ibuprofen in this regard. It is of interest to note that the withdrawal rates for treatment failure in the CLASS trial were lower than the 12-week trials in OA or RA in the original NDA. Withdrawals for treatment failure in the original NDA ranged from 21-35% for the various doses of celecoxib compared to 18-26% for naproxen in OA (p 176, July 8, 1998); withdrawals ranged from 21-40% for the various doses of celecoxib compared to 29-30% for naproxen in RA (p.210, July 8, 1998). If one looks at the combination of treatment failure and noncompliance (as another estimate of treatment failure), the comments noted above seem to hold. Comparisons of celecoxib to the NSAIDs regarding the patient global assessment, assessment of arthritis pain, HAQ and SF-36 scores suggest that celecoxib was comparable to diclofenac and ibuprofen with no consistent and clear trends suggesting superiority. Therefore, based upon these variables as endpoint estimates, it would appear that celecoxib (even at multiples of doses for labeled indications) does not offer a consistent advantage over the comparator NSAIDs in terms of efficacy or effectiveness in OA or RA.

Safety

In contrast to efficacy, the CLASS trial was designed to assess safety endpoints of celecoxib relative to the NSAIDs, diclofenac and ibuprofen. In so doing, arguments were made that this trial was also testing the COX-2 safety hypothesis; this hypothesis being (in general terms) that if COX-2 is not present in any particular organ or cell, drugs targeting COX-2 should not be a problem.

Safety may be considered more from the molecular understanding of receptor structure and function, and less so from the prospective of a xenobiotic with its potentially unknown (and non-mechanism based) safety hazards.

The central clinical trial feature in CLASS that tested this hypothesis was the bona fide use of twice to four-fold the highest doses for two FDA-approved labeled indications, RA and OA respectively. As noted by the Sponsor, the multiples of dosing employed for celecoxib was to make comparisons of safety in a “robust” fashion. A safety trial, with “NSAIDs” at similar multiples of their respective labeled doses for OA and RA has not yet been conducted despite the long history of usage of these important and widely used drugs. Unfortunately, the fact that such multiples of the NSAIDs selected for this trial were not included ultimately confounds all discussions and/or conclusions of this CLASS trial.

While some might comment that these multiples were not robust enough (i.e. should be 10X), it appears clear that the dosing, sample size, and selection of safety endpoints all contributed to the highly unique and progressive character of the CLASS trial. Certainly, pushing the envelope in terms of safety has the potential for improvements in safety at both the patient and population levels. As noted, one of the unique aspects of the CLASS trial was the selection of the primary UGI safety endpoint. The gastrointestinal toxicity of NSAIDs, particularly to the upper GI tract, has long been felt by many to be one of the most important iatrogenic adverse events associated with modern drug therapies.

Gastrointestinal events

(More details of GI events are found in the review by Larry Goldkind, M.D)

Arguments have been made that the selection of CSUGIEs as a safety endpoint was attempting to address the endpoints of safety with the same rigor usually attributed to the assessment of efficacy. **The primary end point in the GI safety analyses was the development of a CSUGIE** (i.e., UGI bleeding, perforation, or obstruction with important clinical manifestations). The primary endpoint was a safety endpoint. The **null hypothesis** being tested was that there was no difference between the incidence of CSUGIEs associated with celecoxib and that associated with NSAIDs, pooled and then individually. When the endpoint of CSUGIEs in all ITT patients during either the first 6 months or the entire study was analyzed, **celecoxib did not exhibit a statistically significant difference from the NSAIDs studied in this trial, either singly or combined.** The CSUGIE event rate for the entire study period (Table 12), as defined by the alternate definition, reinforces the observation that celecoxib did not show significant differences from either NSAID. However, the trends (Table 13 and 14) for CSUGIEs in all patients during either the first 6 months or the entire study period did favor celecoxib. Of importance though, at no time in the CLASS trial, and without regard to endpoint or aspirin use, was celecoxib superior to diclofenac.

The representative NSAIDs for this trial, ibuprofen and diclofenac, turned out to be useful comparators. Of note, when the confounding effects of aspirin use were addressed, or the endpoint was expanded to include gastric or duodenal ulcers (i.e. GDU) that were not felt to be clinically important enough to be classified as a CSUGIEs, celecoxib did demonstrate differences from ibuprofen, but not from diclofenac. This was seen during both the first 6 months (Table 13) and

the entire study period (Table 14) for CSUGIEs/GDUs. Undoubtedly, the comparisons with ibuprofen accounted for the results of NSAIDs as pooled events; Table 33 may best illustrate these points. In any trial of safety, one could argue that superiority should always be the goal; the safety of drugs developed today should (ideally) be better than drugs developed years ago. Therefore, particularly for making drug class (i.e. COX-2 vs. NSAIDs) comparisons, it could be argued that beating one NSAID does not mean you beat them all, but losing to one NSAID (or failing to beat it) is losing to them all.

Why was celecoxib, as given under these exaggerated dosing multiples, not able to show statistical superiority to diclofenac? Certainly, there are a variety of possible explanations. One explanation could be that the use of the multiples of the “x” dose of celecoxib resulted in more clinically important UGI adverse events than would have occurred with the x dose alone. This result, unfortunately, was not testable in this trial but may well nullify the safety hypothesis of COX-2 had it occurred.

Among other possibilities for the results with celecoxib versus diclofenac could be that the event rates for diclofenac were not at their usual “NSAID” pace. In the CLASS trial, these clinically important UGI events seemed to occur early for diclofenac with rates seeming to level off at later time points in the trial while UGI events for celecoxib continued to occur at a steady rate (see below). Could a process of “differential adaptation” to the daily biochemical/biological insult of these drugs have played a role?

To help interpret and understand the comparisons with regards to diclofenac, one possible explanation that was brought forward by the Sponsor, and discussed in detail, was the idea of “informative censoring” as it relates to the GI adverse events. Such censoring, if it occurred, could influence the clinical outcomes provided these influences were not balanced in all treatment arms. In particular, the five adverse event symptoms of dyspepsia, abdominal pain, nausea, diarrhea and vomiting were cited as important contributors to the confounding effects of informative censoring with the consequence of removing at-risk patients from the diclofenac treatment arm. However, it is unclear that the potential for informative censoring represented a significant bias in assessment of the outcome of the CSUGIEs as defined in this trial. For example, if the symptoms as specified by the Sponsor (i.e. moderate to severe) are considered, it appears that informative censoring may be an important confounder. However, if the less restrictive definitions of symptoms (i.e. to include mild) as reasons for the withdrawal of the susceptible patient are applied, then such censoring may not have an important role (Table 23).

The timing of UGI events may also hold clues to understanding any role for informative censoring. For example, both crude and Kaplan-Meier event rates in the first 6 months (Tables 7) showed that for celecoxib, seven of the 11 uncensored events occurred in the first three months. However, in the diclofenac group, all nine events occurred in the first 100 days, with a cluster of five events within the first 15 days and four more events occurring sporadically through approximately day 85. One could argue (as noted above) that this pattern might suggest a “shift to the right” for events associated with the use of celecoxib as compared to diclofenac. If this shift were real, than any loss of at-risk patients may influence the celecoxib CSUGIE rate more than that for diclofenac. Any shifting of events to a later point in time could also be one reason for the lack of CSUGIEs noted during the entire trial (Table 10) of NSAIDs as compared to celecoxib whose rates tended to

increase at a generally steady pace with time. Therefore, although it does seem that more patients dropped out of the diclofenac group due to GI symptoms, this does not seem to be an adequate explanation for the observed UGI results between diclofenac and celecoxib.

When comparisons with ibuprofen are made, the importance of any censoring as an explanation for the results in the diclofenac group as compared to celecoxib become less evident. For example, in the entire population studied, only one uncensored event occurred in the diclofenac group after 182 days and none in the ibuprofen group; yet celecoxib was able to demonstrate statistical superiority to ibuprofen in certain settings as noted above. Similarly, when the overall withdrawal pattern was considered, and not just those due to adverse events, rates are highest in the ibuprofen group (Table 3) versus diclofenac or celecoxib. Further, when viewed from the prospective of risk factors (Table 19), patients receiving celecoxib appear more likely to withdraw at any given risk category than that of diclofenac, but not ibuprofen. Therefore, a consistent association of endpoints with patterns of withdrawal does not seem evident when comparing across treatments.

Was informative censoring an important component in the CLASS trial? One way to attempt to answer this question is with a clinical trial designed to do so. The hypothesis-generating conclusion that the confounding effect of UGI informative censoring is important in the outcomes of large clinical trials can be tested in prospectively-designed trials for confirmation and validation.

The absence of GI-related deaths in the CLASS trial is noteworthy. This might be attributable to the heightened vigilance for GI events maintained throughout the study since the occurrence of GI signs and symptoms related to the primary end points of this study. Therefore, events that if left untreated may have progressed to clinically significant events were identified early and these patients were treated and/or discontinued from study medication. On the other hand, it may suggest that prior estimates of GI-related deaths from NSAIDs have been over estimates.

During the first six months, all but one of the events (a gastric outlet obstruction in the celecoxib group) represented bleeding events in which an ulcer or large erosion which was associated with either visual evidence of bleeding, melena, or hemocult-positive stools and a decrease in hematocrit or hemoglobin. There were no UGI perforations (Table 6). During the entire trial, all events were classified into the same categories as those that occurred in the first six months, with these exceptions: one bleeding event in the celecoxib group represented category 1A, and two UGI perforations occurred, one in the celecoxib group and one in the diclofenac group (Table 9).

Not unexpectedly, since this had been seen in the original NDA endoscopy trials, **aspirin use did seem to influence the gastrointestinal results in this trial.** For example, as seen in Table 13, it appears that use of aspirin tended to increase the overall CSUGIE event rate for celecoxib and diclofenac but not for the ibuprofen group. This same differential pattern also seems evident in the CSUGIE event rate for the entire study (Table 14). While it would be clinically useful to understand whether UGI events are more problematic when added to one treatment regimen versus another, this trial was not able to address (i.e. issues of powering, etc.) the issue of aspirin co-administration in any great detail. Once again, it may be that specific trials need to be designed and conducted to understand these important interactions.