

4. The incidence of ‘hypertension’ as an SAE occurred in three celecoxib patients, compared with no placebo or active control patients in the controlled trials (table 5.1.2.1, 5.1.2.3).

5. Hypertension as a cause of withdrawal, occurred in 6 celecoxib patients in the controlled trials (0.1%), compared with 1 active control (<0.1%) and 0 placebo (0%), (table 5.1.6.7). There were 4 discontinuations (0.1%) in the long-term open-label trial for hypertension.

Table 5.1.6.7 Patients in the controlled OA/RA trials withdrawn due to hypertension<sup>a</sup>.

Treatment Group/ Patient #	Preferred Term for AE
<b>Placebo</b>	
None	
<b>Celecoxib 50-400 mg</b>	
020-0123	Hypertension
020-0294	Hypertension
020-1147	Hypertension, Aggravated
054-0153	Hypertension
054-1396	Hypertension, Aggravated
071-2008	Hypertension, Aggravated
<b>Active Control</b>	
071-1737	Hypertension

a. Data from sponsor at reviewer’s request.

Table 5.1.6.7 Patients in the long-term OA/RA trial (024) withdrawn due to hypertension<sup>a</sup>.

Celecoxib Dose <sup>b</sup> / Patient #	Final Dose	Adverse Event	Days on Drug
<b>Celecoxib 100 mg</b> 054-0153	100	Hypertension	N/A, ongoing
<b>Celecoxib 200 mg</b> 020-0123 054-0629	200 200	Hypertension Hypertension	4, ongoing at day 465 42, ongoing at day 88
<b>Celecoxib 400 mg</b> 023-0051	400	Hypertension, Aggravated	374, ongoing

a. Data from sponsor at reviewer’s request submitted 11.3.98 .

### Conclusions regarding blood pressure

The available data are sufficient to conclude that there is an association between celecoxib and active control administration and the worsening of blood pressure in some patients. This worsening is primarily seen within 12 weeks of starting the treatment, but is of sufficient severity to lead to subject withdrawal from the study drug in both the short-term controlled and in the long-term studies.

### 5.2.2c Edema Formation

1. The incidence of edema was measured in the form of AEs and SAEs (tables 5.1.2.1, 5.1.3.1, 5.2.3.2, ). The reasons for withdrawal from the open-label trial also included edema (table 5.1.6.2 5.1.6.3, and 5.1.6.7).

2. The incidence AEs for peripheral edema, and the combination of all recorded ‘edema’ categories, were significantly higher in the celecoxib group and active control group, relative to control.

From Table 5.1.3.1 Edema as an adverse events identified in the N.A. arthritis trials from NDA 20-998<sup>a</sup>.

Edema as an AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Edema, Generalized	0 (0%)	8 (0.14%)	5 (0.1%)	10 (0.5%)
Edema, Facial	8 (0.4%)	23 (0.4%)	17 (0.4%)	5 (0.2%)
Edema, Peripheral	21 (1.1%)	124 (2.2%)	89 (2.1%)	45 (2.1%)
Edema, Peri-orbital	0 (0%)	2 (<0.1%)	2 (<0.1%)	0 (0%)
Edema, Legs	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)
Edema, All Categories	29 (1.6%)	158 (2.8%)	114 (2.7%)	60 (2.8%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

3. There were no recorded SAEs for edema, including ‘peripheral edema’, ‘generalized edema’, or ‘edema, legs’ (table 5.1.3.1).

4. The incidence of edema causing subject discontinuation was low in the North American OA/RA controlled trials, and equal among the three treatment groups. Overall, 1 placebo, 4 celecoxib and 3 active control subjects withdrew for edema of any kind.

From Table 5.1.6.7 Patients in the controlled OA/RA trials withdrawn due to edema<sup>a</sup>.

Treatment Group/ Patient #	Preferred Term for AE
<b>Placebo</b>	
021-0445	Edema, Peripheral
<b>Celecoxib 50-400 mg</b>	
054-0758	Peripheral Edema
060-0447	Peripheral Edema
087-0243	Peripheral Edema
012-0483	Generalized Edema
<b>Active Control</b>	
023-0671	Generalized Edema
023-0827	Generalized Edema
071-1310	Peripheral Edema

a. Data from sponsor at reviewer's request.

In the long-term trial there were 10 discontinuations for edema (0.2%). Note the occurrence of facial edema in the long-term trial severe enough to warrant discontinuation.

Table 5.1.6.7 Patients on celecoxib in the long-term OA/RA trial withdrawn due to renal adverse events<sup>a</sup>.

Celecoxib Dose <sup>b</sup> / Patient #	Adverse Event
<b>Celecoxib 100 mg</b>	
020-0213	Edema, ankle and peripheral
020-0313	Edema, peripheral and lower extremity
054-0589	Edema, peripheral
013-0285	Edema, generalized
<b>Celecoxib 200 mg</b>	
021-0946	Edema, peripheral and lower extremity
021-0883	Edema, peripheral and lower extremity
022-0114	Edema, facial
054-0595	Edema, peripheral and lower extremity
<b>Celecoxib 300 mg</b>	
023-1173	Edema, facial
023-0671	'Urine abnormal' & 'Urine smells' Edema, generalized

a. Data from sponsor at reviewer's request submitted 11.3.98 .

b. Dose is last recorded does taken by the patient at time of AE.

5. There was no statistically significant association between  $\geq 1$  kg weight gain and the occurrence of 'peripheral edema' in a subset of all patients with edema as an AE, although a higher % of both celecoxib and active control group patients had both.

From Table 5.1.4.2.3 Occurrence of edema and weight gain in the North American Arthritis trials<sup>a</sup>.

Syndrome	Placebo N=1864	Celecoxib N=3512	Active Control N=1099
<b>AEs</b>			
Edema, Generalized <sup>a</sup>	0 (0%)	5 (0.1%)	10 (0.5%)
Edema, Peripheral	21 (1.1%)	89 (2.1%)	45 (2.1%)
<b>Edema, Generalized<sup>b</sup></b>	0 (0%)	6 (0.2%)	9 (0.8%)
Edema, Peripheral	13 (1.1%)	83 (2.5%)	24 (2.2%)
Weight Gain $\geq 1$ kg	201 (17.7%)	879 (26.0%)	304 (27.7%)
<b>Both Edema and Weight Gain<sup>b</sup></b>	6 (0.5%)	24 (0.7%)	9 (0.8%)

a. Data from corrected tables from the ISS, table 3.1.3.6, dated 9.16.98 including only 100 and 200 mg dose groups.

b. Data from sponsor, only for those patients with both weight and edema AE data. Includes 50 to 400 mg doses.

However, the changes in weight for the trials were quite variable depending on the patient population examined. Overall, males and females that were heavier at baseline tended to gain more weight in the celecoxib and active control groups, relative to placebo. This spread may have obscured an association between weight gain and edema (edema being easier to detect in lighter individuals).

From Table 5.1.5.1 Mean changes in weights in the 12-week, controlled North American Arthritis trials of celecoxib from NDA 20-998<sup>a,b</sup>.

Vital Sign Measured (Change from baseline)	Placebo	Celecoxib 400 mg BID	Active Controls
Male Weight (Baseline ≤85 kg)	+1.43±0.9	+0.41±0.2*	0.97±0.2*
Male Weight (Baseline >85 kg)	-0.5±0.3	+1.37±0.4*	+0.56±0.2*
Female Weight (Baseline ≤70 kg)	+0.89±0.6	+0.22±0.1	+0.41±0.1
Female Weight (Baseline >70 kg)	-0.23±0.1	+0.12±0.1*	+0.24±0.1*

a. Data from NDA Integrated Safety Summary, table 30.1.2. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

b. \* represent nominal significance versus placebo.

### Conclusion regarding edema

The available data are sufficient to conclude that there is an association between either celecoxib or active control administration and the development of clinically significant edema, especially peripheral edema. This edema is of sufficient severity to lead to subject withdrawal from study drug in both the controlled and in the long-term trials. The lack of a statistical association between edema and weight gain may be attributable variability in weights both from visit to visit and within groups of patients.

### 5.2.2d Rhythm disturbances

1. Changes in mean heart rate were monitored in the controlled trials. Celecoxib administration was associated with a small, but nominally significant, slowing of the heart rate relative to control.

From Table 5.1.5.1 Mean changes in pulse rate in the controlled North American arthritis trials<sup>a,b</sup>.

	Placebo	Celecoxib 400 mg BID	Active Controls
Pulse Rate	0.8±0.3	-0.4±0.3*	0.3±0.4

a. Data from NDA Integrated Safety Summary, table 30.1.2.

b. \* indicates nominally significant difference with placebo.

2. The reported rate of AEs related to rhythm disturbances were also higher in the celecoxib and active control groups, including tachycardias, palpitations, and 'arrhythmia.'

From Table 5.1.3.1 Arrhythmias identified as adverse events in the controlled trials of celecoxib<sup>a</sup>.

Clinical AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
<b>Cardiovascular System</b>				
Arrhythmia <sup>d</sup>	2 (0.1%)	7 (0.1%)	6 (0.1%)	6 (0.3%)
Atrial fibrillation	1 (<0.1%)	1 (<0.1%)	0 (0%)	1 (<0.1%)
Bradycardia	0 (0%)	0 (0%)	0 (0%)	4 (4 (0.2%)
Tachycardia <sup>e</sup>	1 (<0.1%)	16 (0.3%)	9 (0.2%)	2 (0.1%)
Palpitations	1 (<0.1%)	22 (0.4%)	13 (0.3%)	11 (0.5%)
Ventricular arrhythmia	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

d. Includes undifferentiated arrhythmia, atrial and ventricular arrhythmia.

e. Includes undifferentiated and supraventricular tachycardia.

3. The rate of rhythm disturbances as SAEs was higher in the celecoxib and active control groups when compared with placebo. These rhythm disturbances were scattered among arrhythmias with separate pathophysiologies, including palpitations, atrial fibrillation, and supraventricular tachycardia.

From Table 5.1.2.1 Arrhythmias identified as SAEs in the U.S. Arthritis trial database<sup>a</sup>.

Cardiovascular System SAE	Placebo N=1864	Celecoxib 25-400 mg N=5083	Active Controls N=2098
<b>Rhythm Disturbances<sup>b</sup></b>	1 (<0.1%)	5 (0.1%)	2 (0.1%)

a. Data from NDA Integrated Safety Summary, Appendix Table 22.1, and electronic datasets.

b. Includes the following terms: arrhythmia; atrial arrhythmia; atrial fibrillation; heart block; palpitation; & supraventricular tachycardia.

The next table shows the incidence of relevant serious adverse events that occurred in the long-term, open-label celecoxib trials. Overall, there were few reported arrhythmic SAEs.

Table 5.1.2.2 Arrhythmias as SAEs collected in long-term, open-label database<sup>a</sup>.

Cardiovascular System SAE	Combined N=4499
<b>Cardiac Arrest</b>	1 (<0.1%)
<b>Bradycardia</b>	2 (<0.1%)
<b>Atrial Fibrillation</b>	4 (<0.1%)
<b>Ventricular Fibrillation</b>	1 (<0.1%)

a. Data from NDA Integrated Safety Summary, Table 22.2, and electronic datasets. Numbers shown as individual subjects.

Note that in some cases, a subject may have had more than one serious adverse event in the same category, which is not captured here.

b. Includes coronary thrombosis and myocardial infarction.

4. More patients in the celecoxib group (9, 0.16%), and active control group (3, 0.14%) were withdrawn due to 'Arrhythmia' as an SAEs than in the placebo group (1, <0.1%). These withdrawals were also scattered among arrhythmias with separate pathophysiologies, including palpitations, atrial fibrillation, and supraventricular tachycardia.

From Table 5.1.6.3 Arrhythmic adverse events leading to subject discontinuation in the controlled OA/RA trials<sup>a</sup>.

	Placebo N=1864	Celecoxib 50-400 mg BID N=5704	Active Control N=2098
<b>Arrhythmia<sup>c</sup></b>	1 (<0.1%)	9 (0.16%)	3 (0.14%)

a. Data from Integrated Safety Summary, Appendix table 6.4.

c. Includes 'arrhythmia', atrial arrhythmia, atrial fibrillation, palpitation, tachycardia, and supraventricular tachycardia.

There were no discontinuations for non-fatal rhythm disturbances in the long-term trials. One individual had ventricular fibrillation during a large MI.

5. The sponsor examined the time-dependence of cardiovascular events leading to withdrawal, including rhythm disturbances (table 5.1.6.4). For atrial fibrillation, palpitations, and ventricular tachycardia, there was no pattern of increased occurrence with increased exposure.

#### Conclusion regarding arrhythmias

There was a numerical excess of arrhythmias of several types in both the celecoxib and active control groups relative to placebo. In particular, supraventricular arrhythmias are more common in the celecoxib group. These arrhythmias, however, do not share a common pathophysiology, and there is no attractive mechanism for a direct effect of a COX-2 inhibitor on the entire cardiac conduction system. There is also no precedent for this adverse event from other NSAIDs, or from the pre-clinical toxicology data available. One possibility (unproven) is that this phenomenon, if real, reflects subtle effects of NSAIDs on electrolytes in susceptible patients. In conclusion, however, insufficient data exist to determine the clinical significance of this finding, or whether this observation is linked to the numerical increase in cardiac deaths in the two groups relative to control.

### 5.2.2e Heart failure

1. Cardiac failure was rarely reported as an AE in the controlled trial database.

From Table 5.1.3.1 Heart failure as an AE in the controlled trials<sup>a</sup>

Cardiac Failure as an AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Cardiac Failure <sup>b</sup>	1 (<0.1%)	5 (0.1%)	4 (0.1%)	2 (0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

b. Includes left, right, and undifferentiated cardiac failure.

2. Heart failure, as a SAE, occurred in two celecoxib patients, one placebo patient, and no active control patient. Withdrawal due to heart failure occurred in one placebo patient (<0.1%), 5 celecoxib patients (0.1%) and no active control patients (0%).

#### Conclusion regarding heart failure

There is inadequate data to assess the administration of celecoxib to the occurrence of heart failure. With the available data, there is no evidence of an adverse effect of celecoxib on CHF.

### 5.2.2f Myocardial infarction and Angina Pectoris

1. The AEs, 'MI' and 'Coronary Artery Disorder' occurred in small numbers of patients in all three treatment groups.

From Table 5.1.3.1 Cardiac AEs in the North American Arthritis trials of celecoxib from NDA 20-998<sup>3</sup>.

Myocardial, Pericardial and Valve Disorders as AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Angina Pectoris <sup>f</sup>	5 (0.3%)	18 (0.3%)	14 (0.3%)	6 (0.3%)
Coronary Artery Disorder	2 (0.1%)	6 (0.1%)	5 (0.1%)	0 (0%)
Myocardial Infarction (MI) <sup>g</sup>	2 (0.1%)	10 (0.2%)	9 (0.2%)	2 (0.1%)
MI + Coronary Artery Disorder	4 (0.2%)	16 (0.3%)	14 (0.3%)	2 (0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

c. Includes both undifferentiated hypertension and aggravated hypertension.

f. Includes 'aggravated' and 'unstable' angina pectoris.

g. Includes 'Thrombosis, coronary'.

2. MI and Angina occurred equally as SAEs, and as AEs leading to withdrawal, in the three treatment groups (table 5.1.2.1 and 5.1.6.4).

From Table 5.1.6.3 Cardiovascular adverse events leading to subject discontinuation in the controlled North American OA/RA trials<sup>a</sup>.

Cardiac AE leading to discontinuation	Placebo N=1864	Celecoxib 50-400 mg BID N=5704	Active Control N=2098
Angina <sup>d</sup>	2 (0.1%)	2 (<0.1%)	1 (<0.1%)
Myocardial infarction	2 (0.1%)	6 (0.1%)	2 (0.1%)

a. Data from Integrated Safety Summary, Appendix table 6.4.

d. Includes angina pectoris, aggravated angina pectoris and unstable angina.

In the long-term open-label trial, there were 8 individuals withdrawn due to myocardial infarction.

#### Conclusion regarding myocardial ischemic adverse events

There was no clear evidence that linked the occurrence of any specific cardiac SAE and/or AE, including those leading to withdrawal, with the administration of celecoxib. The database is inadequate to completely exclude an effect on these AEs, however.

### 5.2.3 Renal Adverse Events

The following categories of renal adverse events will be examined: clinically significant renal adverse events, and changes in renal laboratories. The renal laboratories section will be broken into the following subsections: changes in BUN, changes in creatinine, proteinuria and other urinary abnormalities, and changes in serum electrolytes (potassium, sodium, calcium, chloride and phosphate).

#### 5.2.3a Clinical Renal Adverse Events

The incidence of acute renal failure was measured in the form of AEs and SAEs both during the controlled and the long-term trials (tables 5.1.2.1, 5.1.3.1, 5.2.3.2, ). The reasons for withdrawal from the open-label trial also included 'uremia,' and 'elevated creatinine' (table 5.1.6.2 5.1.6.3, and 5.1.6.7).

1. Two individuals taking celecoxib had acute renal failure requiring dialysis in the controlled trials (versus none in the active control or placebo groups). One was due to repeated quinine use, the other associated with obstructive uropathy.

1. Patient 047-0030 was a 70-year-old female with a prior history of labile vascular hypertension, and urinary system disorders including urethral stenosis, urgency, and bladder spasms. Concomitant medications were: captopril, chlorpheniramine, docusate sodium, aspirin, estrogen, etidronate, fluconazole, dexamethasone, oxybutynin, pravastatin, quinine sulfate, and verapamil. Three weeks after starting celecoxib 400 mg BID, she experienced leg cramps for which she took quinine and subsequently experienced headache and pruritus. One week later, she repeated a single dose of quinine and again experienced headache and pruritus, but also nausea, vomiting, diarrhea, chills, and confusion. Four days later she was hospitalized with a fever and a creatinine level of 9.1  $\mu\text{mol/L}$ . She was diagnosed with hemolytic uremic syndrome presumed due to quinine sulfate. Treatment included plasmapheresis, hemodialysis, and platelet transfusion.

2. Patient 024-1490002 was a 65-year-old male with a medical history of hypertension, depression, nocturia and RA. Concurrent medications included gold sodium thiomalate, terazosin, fosinopril, metoprolol, prednisone, and combination perphenazine and amitriptyline. The patient took celecoxib 100 mg BID for 12 weeks in a double-blind clinical RA trial. After successfully completing the trial, he was admitted to the long-term open-label trial. He was instructed to take celecoxib 200 mg BID, but for unknown reasons, he took only 100 mg BID. The patient returned at week 2 and no abnormalities were noted. Four days after he was seen for his "Week 6" visit, his urine output decreased and he felt ill. This was approximately one week following an endoscopic procedure associated with anesthesia. (Laboratory results from the Week 6 Visit revealed his serum creatinine to be 8.6 mg/dL and his BUN to be 61 mg/dL, significantly higher than his Baseline values, which were 1.4 mg/dL and 21 mg/dL, respectively). Five days later, study medication was stopped when he was hospitalized with a serum creatinine level of 19.4 mg/dL and a BUN of 116 mg/dL. During his hospitalization, he required hemodialysis on two occasions. Ultrasound examination showed bilateral hydronephrosis. He was scheduled for cystoscopy and retrograde ureteroscopy and possible stent placement when he developed significant large volume diuresis with normalization of his renal function. He recovered and was discharged from the hospital five days later. One week later, his serum creatinine value was 1.8 mg/dL and his BUN was 33 mg/dL.

2. In the long-term trial, 148 (3.3%) of the patients had the combination of proteinuria and elevated BUN/Crt. Of these, 27 (0.6%) ended the trial with proteinuria and an elevated BUN or Crt at last visit.

Seven individuals without proteinuria at the start of the trial ended with 2+ proteinuria or greater. In addition, three had markedly abnormal BUN/creatinine values at the last testing (one of these is summarized above, patient 14-90002). Follow-up information for these individuals is not available.

#### 5.1.4.2.13 Patients with marked abnormalities in final BUN/Crt from proteinuria/BUN/Crt cluster<sup>a</sup>.

Patient #	Days on Celecoxib	Baseline/ Final Crt ( $\mu\text{mol/l}$ and mg/dl)	Baseline/ Final BUN (mmol/l)
014-0002	484	168/ 239 (1.9/ 2.7)	14.3/ 26.1 (43/ 80)
013-70004	183	53/ 168 (0.6/ 1.9)	7.9/ 15.4 <sup>b</sup> (24/ 46)
014-90002	122	124/ 760 (1.4/ 8.6)	10.7/ 21.8 (32/ 65)

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.

b. BUN 23.9, Crt 194 on labs drawn 16 days earlier.

3. There were several other patients who experienced renal SAEs requiring discontinuation from the controlled and open-label trials. These are summarized below. Note in the open-label withdrawals that for many of the patients the adverse event was ongoing at time of last information. Using the patients listed below, the relative rates of withdrawal for 'renal adverse events' were 0.21%, 0.27%, and 0.24% for the placebo, celecoxib and active control groups, respectively.

From Table 5.1.6.7 Patients in the controlled OA/RA trials withdrawn due to renal adverse events<sup>a</sup>.

<b>Treatment Group/ Patient #</b>	<b>Preferred Term for AE</b>
<b><i>Placebo (n=1864)</i></b>	
020-880	Hematuria
021-0445	Edema, Peripheral
022-0345	Renal Calculus
060-0441	Renal Function, Abnormal
<b><i>Celecoxib 50-400 mg (n=5704)</i></b>	
054-0501	Creatinine Increased
020-0123	Hypertension
054-0758	Peripheral Edema
060-0447	Peripheral Edema
087-0243	Peripheral Edema
020-0294	Hypertension
020-1147	Hypertension, Aggravated
021-1340	Creatinine Increased
054-0153	Hypertension
054-1396	Hypertension, Aggravated
071-2008	Hypertension, Aggravated
071-3061	Renal Calculus
012-0483	Generalized Edema
047-0030	Uremia
047-0320	Hyperkalemia
<b><i>Active Control (n=2098)</i></b>	
023-0671	Generalized Edema
023-0827	Generalized Edema
071-1250	Creatinine Increased
071-1310	Peripheral Edema
071-1737	Hypertension

a. Data from sponsor at reviewer's request.

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Withdrawals due to renal adverse events in the long-term, open-label trial were also collected by the sponsor, and are listed below.

Table 5.1.6.7 Patients in the long-term OA/RA trial (024) withdrawn due to renal adverse events<sup>a</sup>.

Celecoxib Dose <sup>b</sup> / Patient #	Final Dose	Adverse Event	Days on Celecoxib
<b>Celecoxib 100 mg</b>			
054-0153	100	Hypertension	N/A
021-0033	100	Increased BUN	16, ongoing
021-1043	100	Increased BUN	133, ongoing at day 138
		Increased Creatinine	
		Hyperkalemia	
020-0213	100	Edema, ankle and peripheral	93
020-0313	100	Edema, peripheral and lower extremity	285, ongoing
054-0854	100	Renal insufficiency	76, ongoing
		Increased Creatinine	
054-0589	100	Edema, peripheral	51, lasted 6 days
013-0285	100	Edema, generalized	4, ongoing
<b>Celecoxib 200 mg</b>			
020-0123	200	Hypertension	4, ongoing at day 465
022-0975	200	Acute Renal Failure	127, ongoing
021-0946	200	Edema, peripheral and lower extremity	34, ongoing at day 37
021-0883	200	Edema, peripheral and lower extremity	32
022-0114	200	Edema, facial	3
020-1071	200	Proteinuria, Albuminuria	5, ongoing at day 118
023-0393	200	Hematuria	177, ongoing
054-0595	200	Edema, peripheral and lower extremity	85, ongoing
054-0629	200	Hypertension	42, ongoing
<b>Celecoxib 300 mg</b>			
023-1173	300	Edema, facial	N/A
023-0671	300	'Urine abnormal' & 'Urine smells' Edema, generalized	N/A, ongoing at day 310
<b>Celecoxib 400 mg</b>			
012-0090	400	Azotemia & Increased Creatinine	455, lasted 34 days
022-0313	400	Increased Creatinine	167, lasted 17 days
023-0051	400	Hypertension, Aggravated	374, ongoing

a. Data from sponsor at reviewer's request submitted 11.3.98 .

Time constraints have precluded the review of the individual case report forms for these individuals.

#### **Conclusion regarding clinical renal adverse events**

The NDA does not reveal a strong signal pointing towards substantial clinically serious renal disease (i.e., large number of patients with acute renal failure requiring dialysis, nephrotic syndrome) associated with celecoxib administration. There are individuals with substantial clinical AEs who received. In particular, the increased % of subjects withdrawn due to worsened hypertension and edema in both the short- and long-term trials suggest, in combination with the observed effects of celecoxib on these parameters otherwise (see below), that celecoxib is not placebo with regard to its potential clinically-relevant renal effects. A larger database would be necessary to determine the occurrence rates for rarer, more serious renal AEs such as papillary necrosis, nephrotic syndrome or interstitial nephritis.

### 5.2.3b Changes in Renal Laboratories

#### Changes in BUN

1. There was a small, but significant increase in the BUN, as measured from baseline to the final measured value in the controlled trials in the celecoxib group. This was significantly different from the placebo, where there was a small decrease in BUN over the same period (see table 5.1.4.1.3).

From Table 5.1.4.1.3 Changes in final measured BUN in the controlled N.A arthritis trials<sup>a</sup>.

Changes in Final Visit Lab Values from Baseline	Celecoxib 400 mg	Placebo	Active Controls	P-value Celecoxib vs. Placebo	P-value Celecoxib vs. Active Cntrl	P-value Active Cntrl vs. Placebo
BUN (mmol/l)	0.27±0.063	-0.57±0.061	0.55±0.071	<0.001	0.003	<0.001

a. Data from NDA Integrated Safety Summary, table 25.1.2. The database used is from studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Number of subjects in each measurement varies between 410 and 440 (see table 25.1.2 for details).

2. Significantly more patients in the celecoxib and active control groups developed high BUNs after starting with normal BUN in the controlled trials (see table 5.1.4.1.5).

From Table 5.1.4.1.5 Shift in serum BUNs in the 12-week, controlled N.A. arthritis trials<sup>a</sup>.

Maximal Change in Lab Value	Placebo	Celecoxib 400 mg	Active Controls
BUN (mmol/l) High (9.3-14.3 mmol/l)	5/420 from Normal 3/11 from High	17/409 from Normal 8/10 from High	21/423 from Normal 6/11 from High
Extreme high	None	None	0/1 from Extreme High

a. Data from NDA Integrated Safety Summary, table 5.1.2. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

3. Put another way, significantly more patients in the celecoxib and active control groups developed an elevated BUN (>6.7 mmol/l = 20 mg/dl) during the controlled trial.

From Table 5.1.4.2.5 Elevated BUNs in the controlled NA trials<sup>a</sup>.

Lab Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
BUN >6.7 mmol/l	140 (12.3%)	675 (29.9%)	482 (43.9%)

a. Data from analyses performed by sponsor, and not independently confirmed by FDA.

4. There was also an increased incidence of extreme elevations in BUN in the controlled trials, relative to placebo (>14.3 mmol/l = 40 mg/dl) (see table 5.1.4.2.3). The overall number of such patients, however, is small.

From Table 5.1.4.2.3 Incidence of elevated BUN in the North American 12-week Arthritis trials.

AE/ Lab Value	Placebo N=1136	Celecoxib 100 mg N=1131	Celecoxib 200 mg N=1125	Celecoxib 400 mg N=434	Active Control N=1099
<b>Serum Labs</b>					
BUN >6.7 mmol/l <sup>b</sup>	140 (12.3%)	296 (26.2%)	379 (33.7%)	147 (33.9%)	482 (43.9%)
BUN >14.3 mmol/l <sup>c</sup>	0 (0%)	1 (<0.1%)	4 (0.4%)	0 (0%)	2 (0.2%)

a. Data from data submitted to FDA 10.9.98 from sponsor, and not independently confirmed by FDA reviewer.

b. 20 mg/dl.

c. 40 mg/dl.

5. The incidence of AEs for renal failure depended on the specific measure. In the controlled database, there was a small increase in the incidence of 'increased BUN' in the celecoxib group relative to control. 'Nephritis' occurred in one celecoxib patient and two active control patients (no placebo patients). 'Uremia' occurred in one celecoxib patient, and in no other patients.

From Table 5.1.3.1 Adverse renal events in the controlled trials from NDA 20-998<sup>a</sup>

Renal System AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=3512	Active Controls N=2098
Uremia	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)
BUN Increased	1 (<0.1%)	11 (0.2%)	7 (0.2%)	2 (0.1%)
Nephritis	0 (0%)	1 (<0.1%)	1 (<0.1%)	2 (0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2 and 31.3.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

6. In the long-term database, the incidence of increased BUN identified as an Adverse Event was 0.3% (see table 5.1.3.2). The incidence of abnormally elevated BUN (>6.7 mmol/l = 20 mg/dl) was 44.3% in the long-term open-label trial.

Table 5.1.4.2.4 Incidence of selected adverse events and laboratory abnormalities in the North American 12-week Arthritis trials.

Serum Labs	Celecoxib N=4499
BUN >6.7 mmol/l <sup>b</sup>	1995 (44.3%)
BUN >14.3 mmol/l <sup>c</sup>	14 (0.3%)
Creatinine >132 µmol/l <sup>d</sup>	53 (1.2%)
Creatinine >159 µmol/l <sup>e</sup>	10 (0.2%)

- a. Data from data submitted to FDA 10.9.98 from sponsor.  
 b. 20 mg/dl.  
 c. 40 mg/dl.  
 d. 1.5 mg/dl.  
 e. 1.8 mg/dl.  
 f. 3.0 mg/dl.

7.-Two patients in the celecoxib groups were discontinued for elevated in BUN in the long-term trial, both within 180 days of starting celecoxib. Other renal discontinuations are also shown in the table.

From Table 5.1.6.7 Patients in the long-term trial (024) withdrawn for increased BUN or acute renal failure<sup>a</sup>.

Celecoxib Dose <sup>b</sup> / Patient #	Final Dose	Adverse Event
<b>Celecoxib 100 mg</b>		
021-0033	100	Increased BUN
021-1043	100	Increased BUN Increased Creatinine
054-0854	100	Hyperkalemia Renal insufficiency Increased Creatinine
<b>Celecoxib 200 mg</b>		
022-0975	200	Acute Renal Failure
<b>Celecoxib 400 mg</b>		
012-0090	400	Azotemia Increased Creatinine
022-0313	400	Increased Creatinine

a. Data from sponsor at reviewer's request submitted 11.3.98 .

Conclusions regarding BUN

These will be intergrated into the conclusions regarding elevations in creatinine below.

### Changes in Creatinine

1. Regardless of how it was measured, all three treatment groups had similar incidence of elevated mean serum creatinine (see table 5.1.4.1.5 and 5.1.4.2.3). This was true for both mild (>132 μmol/l = 1.5mg/dl) or marked elevation (>159 μmol/l = 1.8 mg/dl). There was a numerical and % excess of patients in the celecoxib group who had elevated creatinine at some time during the controlled trials, but the trend was not statistically significant.

Table 5.1.4.2.3 Incidence of elevated serum creatinines in the North American 12-week Arthritis trials.

Elevations in creatinine	Placebo N=1136	Celecoxib 100 mg N=1131	Celecoxib 200 mg N=1125	Celecoxib 400 mg N=434	Active Control N=1099
<b>Serum Labs</b>					
<b>Creatinine &gt;132 μmol/l<sup>d</sup></b>	6 (0.5%)	7 (0.6%)	15 (1.3%)	2 (0.5)%	14 (1.3%)
<b>Creatinine &gt;159 μmol/l<sup>e</sup></b>	0 (0%)	1 (<0.1%)	3 (0.3%)	0 (0%)	0 (0%)

a. Data from data submitted to FDA 10.9.98 from sponsor, and not independently confirmed by FDA reviewer.

d. 1.5 mg/dl.

e. 1.8 mg/dl

2. No SAEs or AEs related to increased creatinine were reported by the investigators (tables 5.1.2.3 and 5.1.3.1) in the short-term trials.

3. Regarding patients withdrawn from the controlled trials for lab abnormalities, no placebo patients, two celecoxib patients, and one active control patient withdrew for elevated creatinine (table 5.1.6.7). One patient in the placebo group was withdrawn for 'abnormal renal function.'

Table 5.1.6.7 Patients in the controlled OA/RA trials withdrawn due to renal adverse events<sup>a</sup>.

Treatment Group/ Patient #	Preferred Term for AE
<b>Placebo</b> 060-0441	Renal Function. Abnormal
<b>Celecoxib 50-400 mg</b> 054-0501 021-1340	Creatinine Increased Creatinine Increased
<b>Active Control</b> 071-1250	Creatinine Increased

a. Data from sponsor at reviewer's request.

4. Regarding patients withdrawn from the long-term trial, there were none withdrawn for elevated creatinine (table 5.1.6.6). One was discontinued for 'acute renal failure.' These patients are listed as part of the discussion regarding elevated BUN above.

### Conclusions regarding elevated BUN and Creatinine

A reasonable summary of the data presented above is the following: while there is no clear increase in clinically significant renal disease (i.e. renal failure requiring dialysis, interstitial nephritis, nephrotic syndrome), there is an increase in the number of patients who developed elevations of BUN relative to placebo. There was also a trend towards an increased incidence of elevated serum creatinine values in both the celecoxib and active control groups relative to placebo. In addition, there is a group of individuals withdrawn from the long-term trial for acute renal deterioration (marked by increased BUN, creatinine, 'azotemia', etc.). While none of these can absolutely be ascribed to celecoxib use at present, the pattern suggests that celecoxib may indeed have clinically relevant renal toxicity. The absence of examples of reported severe renal injury (i.e., nephrotic syndrome, papillary necrosis) can be expected, based on the number of patients exposed in the database and the reported incidence of these events following the use of other NSAIDs.

### 5.2.3c Proteinuria and other Urinary Abnormalities

1. Urinary abnormalities were measured during the clinic visits and the summarized. The only significant difference in this analysis was in the incidence of glycosuria (increased in celecoxib). When diabetics were removed from this analysis, there was no significant difference between the three groups.

From Table 5.1.4.1.1 Incidence of extreme urinalysis values in the controlled North American Arthritis trials of celecoxib from NDA 20-998<sup>a</sup>.

Urinary Abnormalities	Placebo N ≈1080 <sup>b</sup>	Celecoxib 400 mg N ≈3250 <sup>b</sup>	Active Controls N ≈1060 <sup>b</sup>
Urine Protein >1+	16 (1.6%)	44 (1.4%)	9 (0.9%)
Urine Glucose >1+	17 (1.7%)	88 (2.7%)	15 (1.5%)
Urine pH >8.5	0 (0%)	1 (<0.1%)	2 (0.2%)
Urine Ketones >1+	2 (0.2%)	5 (0.1%)	3 (0.3%)
Urine RBCs >10 per HPF	39 (3.9%)	142 (4.4%)	46 (4.5%)
Urine WBCs >20 per HPF	42 (4.2%)	130 (4.0%)	54 (5.3%)

a. Data from NDA Integrated Safety Summary, table 24.1. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

b. The number of available subjects varied slightly from test to test.

2. Urinary abnormalities were also examined as a shift from baseline. There was no trend towards a higher incidence of any abnormalities in the celecoxib group relative to control (see table 5.1.4.1.6 for details).

3. Urinary abnormalities that resulted in AEs included albuminuria, hematuria, and pyuria. 'Albuminuria' was reported as an AE in a higher % of the celecoxib group, relative to placebo. Hematuria and pyuria occurred in equal incidence for all three treatment groups. No SAEs related to urinary abnormalities were reported.

From Table 5.1.3.1 Urinary AEs in the North American Arthritis trials of celecoxib from NDA 20-998<sup>a</sup>.

Urinary AEs	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=3512	Active Controls N=2098
Albuminuria	2 (0.1%)	15 (0.3%)	12 (0.3%)	1 (<0.1%)
Hematuria	3 (0.2%)	11 (0.2%)	7 (0.2%)	2 (0.1%)
Pyuria	2 (0.1%)	3 (<0.1%)	2 (<0.1%)	2 (0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2 and 31.3.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

4. No SAEs related to proteinuria were recorded in the controlled trials. No cases of nephrotic syndrome were reported.

5. There was a significant association between the development of proteinuria and an increased BUN in the controlled trials.

Table 5.1.4.2.12. Association between proteinuria and elevated BUN/ Crt in controlled trials<sup>a</sup>.

Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
Urine Protein >trace	43 (3.8%)	85 (3.8%)	48 (4.4%)
Creatinine >132 mmol/l	6 (0.5%)	22 (1.0%)	13 (1.3%)
Creatinine >159 mmol/l	0 (0%)	4 (0.2%)	0 (0%)
BUN >6.7 mmol/l	140 (12.3%)	675 (29.9%)	482 (43.9%)
BUN >14.3 mmol/l	0 (0%)	5 (0.2%)	2 (0.2%)
Proteinuria and either Crt >132 or BUN >6.7 mmol/l (at least 2)	6 (0.5%)	35 (1.6%)	23 (2.1%)
Proteinuria or Crt >132 and/or BUN >6.7 mmol/l (at least 1)	142 (12.5%)	680 (30.1%)	486 (44.2%)
Proteinuria and/or Crt >159 and/or BUN >13.4 mmol/l (at least 2)	0 (0%)	1 (<0.1%)	0 (0%)
At least two abnormalities present on last available labs	2 (0.2%)	14 (0.6%) <sup>b</sup>	5 (0.45%)

a. Data from analyses performed by sponsor, and not independently confirmed by FDA.

b. P values 0.07 vs. placebo, using unadjusted chi square.

This association extended to the long-term trial, where 148 (3.3%) of the patients had the combination of proteinuria and elevated BUN/ Crt. Of these, 27 (0.6%) ended the trial with proteinuria and an elevated BUN or Crt at last visit.

Seven individuals without proteinuria at the start of the open-label trial ended with 2+ proteinuria or greater. In addition, three had markedly abnormal BUN/ creatinine values at the last testing.

From Table 5.1.4.2.13 Patients with marked abnormalities in final BUN/Crt from proteinuria/BUN/Crt cluster<sup>a</sup>.

Patient #	Days on Celecoxib	Baseline/ Final Crt (mmol/l and mg/dl)	Baseline/ Final BUN (mmol/l)
014-0002	484	168/ 239 (1.9/ 2.7)	14.3/ 26.1 (43/ 80)
013-70004	183	53/ 168 (0.6/ 1.9)	7.9/ 15.4 <sup>b</sup> (24/ 46)
14-90002	122	124/ 760 (1.4/ 8.6)	10.7/ 21.8 (32/ 65)

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.  
b. BUN 23.9, Crt 194 on labs drawn 16 days earlier.

6. One individual in the long-term trial was discontinued for proteinuria.

Table 5.1.6.7 Patients in the long-term OA/RA trial (024) withdrawn due to renal adverse events<sup>a</sup>.

Celecoxib Dose <sup>b</sup> / Patient #	Final Dose	Adverse Event
Celecoxib 200 mg 020-1071	200	Proteinuria, Albuminuria

a. Data from sponsor at reviewer's request submitted 11.3.98 .

#### Conclusion regarding urinary abnormalities

The only urinary abnormality that needs to be discussed is the development of proteinuria. There is no data to suggest an association of celecoxib use with any of the other urinary abnormalities.

The incidence of proteinuria is low in the controlled database. While the routine measurements revealed no increased incidence of proteinuria, there is an increased number of patients in the celecoxib group identified as having proteinuria as an AE. Additionally, there is a nominally significant association between the development of proteinuria and elevated BUN in the celecoxib group. A small number of individuals also had both of these abnormalities at the time of their last clinic visit. Of particular concern are the 3 individuals who began the trial without proteinuria, but developed 2-3+ proteinuria and abnormalities of both BUN and Crt at their last clinic visit. Whether these individuals represent a nephrotoxic insult due to celecoxib is, of course, impossible to determine absolutely. It is also difficult to determine the cause of the proteinuria in the one individual withdrawn from the long-term trial. Without more data it is impossible to determine whether these individuals would have gone on to develop nephrotic syndrome or other hallmarks of NSAID nephrotoxicity.

In conclusion, the data are insufficient to determine whether celecoxib use is associated with an increased incidence of proteinuria. In the subset of patients who developed proteinuria during celecoxib use, however, there is evidence that they may be at risk for the development of decreased renal clearance function (marked by increases in BUN and/or Crt), suggesting a nephrotoxic insult. The clinical implications of this observation are not known.

#### 5.2.3d Changes in Serum Electrolytes

Serum electrolytes were collected both as lab values during clinic visits, and as abnormalities (AEs and SAEs). They will be discussed in sets, beginning with the common cations.

#### Potassium, Sodium, Calcium

1. The changes in lab values were examined as changes in the mean lab value. There were small, albeit significant, differences between celecoxib and placebo with regard to both final mean potassium (higher in celecoxib) and chloride (higher in celecoxib). During the long-term trial, mean serum K<sup>+</sup> rose 0.04±0/006 meq/L (table 5.1.4.1.4). No significant changes in either calcium or sodium were detected in any analysis (table 5.1.4.1.2).

From Table 5.1.4.1.3 Mean changes in final measured potassiums in the controlled N.A arthritis trials<sup>a</sup>.

Changes in Final Visit Lab Values from Baseline	Placebo	Celecoxib 400 mg	Active Controls	P-value Celecoxib vs. Placebo	P-value Celecoxib vs. Active Cntrl	P-value Active Cntrl vs. Placebo
Potassium (mmol/l)	-0.03±0.02	+0.05±00.02	-0.01±0.02	<0.001	0.013	NS

a. Data from NDA Integrated Safety Summary, table 25.1.2. The database used is from studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Number of subjects in each measurement varies between 410 and 440 (see table 25.1.2 for details).

2. The changes in lab values were also examined both as changes from normal (shift-table). Here again, the only significant difference in the controlled arthritis trials was that more subjects in the celecoxib and active control groups developed hyperkalemia at some point during the 12 week trials compared with placebo. Of the patients who started the trial with hyperkalemia, a significant fraction also had hyperkalemia during the trials.

From Table 5.1.4.1.5 Shift in serum potassium values in the 12-week, controlled N.A arthritis trials<sup>a</sup>.

Maximal Change in Lab Value	Celecoxib 400 mg	Placebo	Active Controls
Potassium (mmol/l) High (5-6 mmol/l)	20/399 from Normal (5.0%) 5/12 from High	8/416 from Normal (1.9%) 2/8 from High	20/419 from Normal (4.8%) 3/9 from High

a. Data from NDA Integrated Safety Summary, table 5.1.2. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

3. The incidence of AEs related to abnormalities of potassium, sodium or calcium were rare, and equal in the three treatment groups. There were no SAEs related to electrolyte abnormalities in the controlled trials.

From Table 5.1.3.1 Adverse events related to cations in the N.A arthritis trials<sup>a</sup>.

Metabolic Abnormalities AEs	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=3512	Active Controls N=2098
Hypercalcemia	1 (<0.1%)	5 (0.1%)	N/A	1 (0.1%)
Hyperkalemia	0 (0%)	5 (0.1%)	3 (<0.1%)	0 (0%)
Hypernatremia	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)
Hypocalcemia	0 (0%)	2 (<0.1%)	N/A	1 (0.1%)
Hypokalemia	8 (0.4%)	16 (0.3%)	9 (0.2%)	4 (0.2%)
Hyponatremia	4 (0.2%)	2 (<0.1%)	1 (<0.1%)	0 (0%)

a. Data from NDA Integrated Safety Summary, table 6.2 and 31.3.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

4. In the long-term trial there were two SAEs related to electrolytes: hyponatremia and hypokalemia. One of these resulted in patient discontinuation. Both patients developed hyponatremia/hypokalemia during diuretic use concurrently with celecoxib.

From Table 5.1.2.3 Changes in serum potassium identified as SAEs in the long-term celecoxib database<sup>a</sup>.

SAEs	Patient #	Age/ Sex	Treatment	Stopped Tx?
Hypokalemia	024-US0013-0130009	78/F	Celecoxib 200 mg BID	No
Hyponatremia	024-US0033-0330007	72/F	Celecoxib 300 mg BID	Yes

a. Data from Integrated Summary of Safety, Text Table 136.

1. Patient #024-US0033-0330007 was a 72-year-old female with history of hypertension, venous insufficiency, hypercholesterolemia, and hypothyroidism. Concurrent medications included hydrochlorothiazide, triamterene, verapamil, and calcium. This patient took celecoxib 300 mg BID for 14 days before discontinuing because of treatment failure. Two days after stopping celecoxib, she was hospitalized with a plasma sodium level of 122 mmol/L. She received IV fluid and her plasma sodium returned to normal. Her hospital diagnosis indicated metabolic encephalopathy secondary to hyponatremia most likely due to diuretic therapy.

2. Patient 024-US0013-0130009 was a 78-year-old female with a history of hypertension, urinary complaints, and elevated liver function tests. Concurrent medications included doxazosin, Moduretic and indapamide. The patient initiated treatment with celecoxib 200 mg BID and experienced sinusitis eight-and-one-half months later. She was treated with antibiotics but three days later she lost consciousness and was incontinent of urine. Following this syncopal episode, she vomited. She was taken to the hospital, where her serum potassium and sodium were found to be 2.9 mmol/L and 132 mmol/L, respectively. She was rehydrated with intravenous solution, treated with potassium, and indapamide was discontinued. Amoxicillin was continued to treat the sinusitis. Her hyponatremia is also presumed to be secondary to diuretic therapy

5. In the long-term trial, there was one individual who was discontinued for hyperkalemia.

**Conclusion regarding sodium, potassium, and calcium lab abnormalities**

In the short-term trials, there is a suggestion that celecoxib use may be associated with clinically significant increases in serum potassium in some individuals. These changes were of similar frequency and severity in both the celecoxib and active control groups. The long-term trial had no SAEs related to hyperkalemia, and only one individual withdrawn because of it. In conclusion, while it remains possible that there is an effect of celecoxib that can cause hyperkalemia in susceptible individuals, the database is inadequate to establish that for certain. No other effects of celecoxib on either sodium or calcium were detected.

**Chloride and Phosphate/ Disorders of Acid-Base Status**

Detection of effects on acid-base status are severely limited by the absence of long-term bicarbonate data. In its absence, one indirect marker for a decreased bicarbonate is an increase in serum chloride. Interpretation of this is limited by the other causes of an increased chloride which do not reflect the development of acidosis (i.e., infusion of anionic solutions, use of acetazolamide and other inhibitors of bicarbonate resorption). These other causes would presumably occur randomly, so that if there is a significant difference in the incidence of hyperchloremia between the three treatment groups in the controlled database this may suggest an adverse effect on acid-base balance.

First, the incidence of abnormalities related to chloride and phosphate will be examined.

1. There was also a significant increase in the mean serum chloride in the celecoxib group in the controlled OA/RA trials, and a decrease in the mean serum phosphate in the active control group, relative to placebo. There was no trend towards a decreased phosphate in the celecoxib group relative to placebo.

From Table 5.1.4.1.3 Mean changes in final measured chloride and phosphate in the controlled N.A. arthritis trials from NDA 20-998<sup>a</sup>.

Changes in Final Visit Lab Values from Baseline	Placebo	Celecoxib 400 mg	Active Controls	P-value Celecoxib vs. Placebo	P-value Celecoxib vs. Active Cntrl	P-value Active Cntrl vs. Placebo
Chloride (mmol/l)	-0.2±0.17	+0.3±0.18	+0.0±0.18	0.046	NS	NS
Phosphate (mmol/l)	+0.008±0.009	+0.010±0.009	-0.042±0.008	NS	<0.001	<0.001

a. Data from NDA Integrated Safety Summary, table 25.1.2. The database used is from studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Number of subjects in each measurement varies between 410 and 440 (see table 25.1.2 for details).

2. There were also more individuals who developed abnormally high chlorides with normal chlorides at baseline in the celecoxib and active control groups. Celecoxib and placebo had similar incidence of hypophosphatemia (both less than the active control group).

From Table 5.1.4.1.5 Shift in serum chloride and phosphate in the 12-week, controlled N.A. trials for the 400 mg dose group<sup>a</sup>.

Maximal Change in Lab Value	Placebo	Celecoxib 400 mg	Active Controls
<b>Chloride</b>			
Low (75-90 mmol/l)	0/0 from Low	0/0 from Low	0/0 from Low
High (110-130 mmol/l)	0/413 from Normal	2/408 from Normal	5/407 from Normal
Extreme High or Low	19/413 from Normal (4.6%) 4/17 from High (23%)	40/406 from Normal (9.8%) 3/13 from High (23%)	45/407 from Normal (11.0%) 12/27 from High (44%)
<b>Phosphate</b>			
Low (0.32-0.97 mmol/l) (1.0 to 3.0 mg/dl)	31/63 from Low (49%)	42/70 from Low (60%)	62/75 from Low (83%)
High (1.61-2.42 mmol/l) (5.0 to 7.5 mg/dl)	55/366 from Normal (15.0%)	61/348 from Normal (17.5%)	117/358 from Normal (32.6%)
Extreme High or Low	3/366 from Normal 2/2 from High	2/348 from Normal 0/0 from High	2/358 from Normal 0/0 from High

a. Data from NDA Integrated Safety Summary, table 5.1.2. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

3. Patients in the celecoxib group were significantly more likely to have serum chloride >110 mmol/l and PO<sub>4</sub> <0.97 mmol/l during the 12 week controlled trials, when compared with placebo.

From Table 5.1.4.2.3 Incidence of abnormal Cl and PO<sub>4</sub> the North American 12-week Arthritis trials.

AE/ Lab Value	Placebo N=1136	Celecoxib 100 mg N=1131	Celecoxib 200 mg N=1125	Celecoxib 400 mg N=434	Active Control N=1099
Chloride >110 mmol/l	48 (4.2%)	90 (8.0%)	88 (7.8%)	37 (8.5%)	82 (7.5%)
Chloride >120 mmol/l	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PO <sub>4</sub> <0.97 mmol/l <sup>f</sup>	195 (17.2%)	233 (20.6%)	237 (21.1%)	83 (19.1%)	351 (31.9%)

a. Data from data submitted to FDA 10.9.98 from sponsor, and not independently confirmed by FDA reviewer.

Overall, these differences were significant for both chloride and phosphate. There was also a trend towards patients having abnormalities in both chloride and phosphate (but not both abnormalities at the last clinic visit).

Table 5.1.4.2.11. Association between Ca<sup>2+</sup>, PO<sub>4</sub>, and Cl<sup>-</sup> abnormalities in controlled trials<sup>a</sup>.

Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
PO <sub>4</sub> <0.97 mmol/l	195 (17.2%)	470 (20.8%)	351 (31.9%)
Chloride >110 mmol/l	48 (4.2%)	178 (7.9%)	82 (7.5%)
Both low PO <sub>4</sub> and high Cl <sup>-</sup>	16 (1.4%)	51 (2.3%)	34 (3.1%)
Both low PO <sub>4</sub> and high Cl <sup>-</sup> at last clinic visit	8 (0.70%)	14 (0.62%)	8 (0.73%)

a. Data from analyses performed by sponsor, and not independently confirmed by FDA.

4. Patients in the celecoxib and active control groups were also more likely to have chlorides >113 at the time of their last visit in addition to decreased PO<sub>4</sub>.

Table 5.1.4.2.6. Patients in the N.A. OA/RA database with Cl<sup>-</sup> >113 mmol/l with one or more of the other listed abnormalities at last clinic visit<sup>a</sup>.

Patient #	Days on Study Drug	Baseline/ Final PO <sub>4</sub> <sup>-</sup> (mmol/l and mg/dl)	Baseline/ Final Cl <sup>-</sup> (mmol/l)
Placebo (n=1136) None			
Celecoxib (n=2256)			
022-0861	87	1.16/ 0.81	107/ 115
054-1137	12	0.84/ 0.74 <sup>b</sup>	109/ 115
020-0357	85	1.07/ 0.84	112/ 114 <sup>b</sup>
023-1358	43	0.97/ 0.94	109/ 116 <sup>c</sup>
Active Control (n=1099)			
023-1350	43	0.97/ 0.94	109/ 116
022-1072	81	1.13/ 0.84	110/ 116
023-0389	29	1.03/ 0.87	106/ 115

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.

b. Note that HCO<sub>3</sub> or PO<sub>4</sub> was abnormally elevated at time of entry.

c. This patient also had new, trace proteinuria at last clinic visit.

Patients with hyperchloremia, however, were more likely to also have hypophosphatemia in the celecoxib group, as shown above. The hyperchloremic individuals were not more likely to have experienced an AE related to fractures (accidental or pathological). Such Bony AEs might be expected following long-term metabolic acidosis.

From Table 5.1.4.2.14. Association between hyperchloremia and bony AEs in controlled trials<sup>a</sup>.

Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
Chloride >110 mmol/l	48 (4.2%)	178 (7.9%)	82 (7.5%)
Fractures, Accidental	3 (0.3%)	10 (0.4%)	4 (0.4%)
Fractures, Pathologic	0 (0%)	0 (0%)	0 (0%)
Myalgias	23 (2.0%)	45 (2.0%)	8 (0.7%)
Both Chloride and one AE	2 (0.2%)	6 (0.3%)	1 (<0.1%)

a. Data from analyses performed by sponsor, and not independently confirmed by FDA.

5. In the long-term trial, 13.2% of the patients had hyperchloremia during their follow-up, of which three had hyperchloremia >113 mmol/l at the last visit.

Table 5.1.4.2.8. Patients in the long-term, open-label trial with Cl<sup>-</sup> >113 mmol/l with other renal lab abnormalities at last clinic visit<sup>a</sup>.

Patient #	Days on Study Drug	Baseline/ Final PO <sub>4</sub> <sup>-</sup> (mmol/l and mg/dl)	Baseline/ Final Cl <sup>-</sup> (mmol/l)
012-0504 <sup>c</sup>	366	1.0/ 1.13	112/ 114
022-1433	83	1.10/ 0.90 (low)	109/ 114
022-0861	87	1.16/ 0.81 (low)	107/ 115

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.

c. This patient also had new, trace proteinuria at last clinic visit.

6. Two patients with notable abnormalities in renal labs the long-term trial are summarized below. One had a persistent severe hypophosphatemia with hyperchloremia. The other patient developed proteinuria associated with hypophosphatemia.

Table 5.1.4.2.9. Patients in the long-term, open-label trial with notable renal lab abnormalities<sup>a</sup>.

Patient #	Days on Study Drug	Baseline/ Final PO <sub>4</sub> <sup>-</sup> (mmol/l and mg/dl)	Baseline/ Final Cl <sup>-</sup> (mmol/l)
022-0622	92	0.55/ 0.42	109/ 113
013-0401 <sup>C</sup>	452	1.58/ 0.94	107/ 106

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.

c. This patient also had 1+ proteinuria at start of trial, which progressed to 3+ at last clinic visit. BUN/Crt were normal at all time points measured.

7. No patients developed severe hyperchloremia (>120 mmol/l) during either the controlled or open-label trials (tables 5.1.4.2.3 and 5.1.4.2.4).

8. The incidence of AEs related to serum chloride or phosphate was equal in all three treatment groups. Note that only those abnormalities identified by investigators are coded as AEs.

From Table 5.1.3.1 AEs related to PO<sub>4</sub> and Cl<sup>-</sup> in the N.A. Arthritis trials of celecoxib from NDA 20-998<sup>a</sup>.

Metabolic Abnormalities/ AE	Placebo N=1864	Celecoxib 25-400 mg	Celecoxib 100-200 mg	Active Controls
Hyperchloremia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypophosphatemia	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)

a. Data from NDA Integrated Safety Summary, table 6.2 and 31.3.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

9. There were no SAEs or withdrawals related to abnormalities in either serum chloride or phosphate in the controlled trials or in the long-term trial (tables 5.1.2.3, 5.1.6.6, and 5.1.6.7).

10. An analysis of those individuals who received bicarbonate or citrate therapy revealed no increase in their use among the celecoxib group. Where identified, patients received these products for GI reasons primarily, and none was identified as receiving them for systemic acidosis. The use of acetazolamide was also balanced between the treatment groups.

#### **Conclusion regarding chloride and phosphate lab abnormalities**

While the database contains a strong signal associating the administration of celecoxib and active control with the development of hyperchloremia, the clinical consequences of these lab abnormalities cannot be finally determined without other data (in particular, serum bicarbonates). That rare individuals develop a greater degree of hyperchloremia in the celecoxib group than is seen in the placebo is consistent with a true effect, as opposed to a statistical oddity. Unfortunately, we have no database from other NSAIDs at this time to gauge whether these effects are more or less common with celecoxib compared with other NSAIDs. If we use the active control group data, the effect of celecoxib on serum chloride is numerically similar to the active controls.

With regard to hypophosphatemia, we are again faced with a lab abnormality associated significantly with celecoxib (and especially with active control) without clear clinical consequences. There was no increase in bony fractures in those individuals with hyperchloremia or hypophosphatemia, as might be expected if there is a change in the acid-base balance. An increase in bony fractures has been seen with other drugs with prominent renal tubular toxicities resulting in renal tubular acidosis. The controlled trials were also too short to examine the rate of renal stone formation, which might also increase during renal tubular acidosis.

In conclusion then, the best evidence suggests that the observed changes in chloride reflect true effects of both celecoxib and the active controls used. The less robust association between celecoxib administration and hypophosphatemia is less more difficult to interpret, but the pattern of effects for celecoxib on phosphate can be distinguished from the placebo group. The clinical implications of these lab abnormalities, including the possibility that the changes in serum chloride may reflect some alteration in the acid-base balance in certain individuals, simply cannot be determined with the available data.

### **5.3 Recommendations of Renal/ Cardiac Consultant**

#### **General Summary**

During the development of specific inhibitors of the type 2 isoform of cyclooxygenase (COX-2), it was hoped that they would provide selective anti-inflammatory efficacy without concomitant GI and renal toxicity. This was based on animal work that suggested that the GI system and kidneys did not express the COX-2 isoform. More recent work has demonstrated the clear presence of COX-2 in the kidney, both in normal adult kidney and in patients with systemic lupus erythematosus (ref. 3). Work in animals has also suggested the up-regulation of COX-2 following volume contraction (ref. 1, 2). These data suggest, at the very least, that the target of COX-2 inhibitors is present in the kidney, and they provide a plausible mechanism for any observed clinical renal toxicity. That this target (COX-2) may be increased during times of sodium- and water-depletion suggests a role for COX-2 in protecting renal hemodynamics. Whether this observation translates into an increased risk of nephrotoxicity in clinical states associated with impaired renal perfusion, such as volume contraction, is not known at present.

Cardiac and renal safety was examined in both the short-term, controlled trials, and in the longer, open-label trial of patients with osteoarthritis/ rheumatoid arthritis (OA/ RA). Overall, 6376 patients were exposed to celecoxib during the short-term, controlled, North American trials in OA/ RA. During the open-label trials, another 9822 patients received celecoxib. Of these, the large majority received drug for <180 days. For long-term exposure, 1809 OA/ RA patients received celecoxib for periods lasting for between 12 weeks and > 1 year in an open-label trial.

As part of the safety database, the sponsor collected adverse events related to both clinical and laboratory measurements. In addition, serial laboratory measurements were obtained from a subset of patients. Significantly, no measurements of acid-base balance were performed as part of any trial in the NDA database (e.g., serum bicarbonate, arterial pH). With this exception, the database was sufficient to assess the majority of the clinically relevant renal and cardiac toxicities.

#### **Cardiac Safety**

The administration of celecoxib cannot be linked to any rare or unusual cardiac toxicities based on the available data. For some adverse events, including arrhythmias and overall cardiovascular mortality, the data are inadequate to either exclude or confirm an adverse effect of celecoxib.

With regard to cardiovascular adverse events, there is an association between celecoxib administration and worsened hypertension in susceptible individuals. This effect of celecoxib resembles that of other non-steroidal anti-inflammatory drugs (NSAIDs). There was also an association between celecoxib administration and the development of clinically significant edema, again similar to other NSAIDs.

#### **Renal Safety**

Three trials were performed on specific populations (elderly patients, patients with mild-to-moderate renal insufficiency, patients with volume contraction) to examine their renal responses to celecoxib. These trials examined the short-term effects of celecoxib on the excretion of prostaglandins, as well as a variety of other renal parameters. Given the small numbers of patients, the short trial durations, and the broad patient-patient variability, the broadest conclusion is that, under the conditions of those trials, both celecoxib and the comparator NSAIDs had significant inhibitory effects on the excretion of the urinary prostaglandins when compared with placebo. In particular, celecoxib and the comparator NSAIDs inhibit prostaglandin PGE<sub>2</sub> and 6-keto-PGF<sub>1</sub>-alpha excretion by the kidney to more or less the same extent over the duration of the individual trials.

### **Renal Safety (cont)**

With regard to the renal safety database, three outcomes were possible from the data.

1) The first was that all three treatment groups would show similar patterns of renal effects, including lab abnormalities and clinical adverse events. In this case, a reasonable conclusion would be that the database was underpowered, as it was not able to differentiate between placebo and the active control NSAIDs, which know renal toxicity. This was not the case in this database, and there was clear separation of placebo and NSAIDs, especially with regard to lab abnormalities.

2) The second possibility is that both celecoxib and the comparator NSAIDs were differentiated from placebo, and more or less resembled each other as regards renal effects. This is the pattern seen in the NDA.

3) The final possibility is that celecoxib would most closely resemble placebo, and that both would be clearly distinguished from the comparator NSAID group.

There is sufficient evidence to conclude that both celecoxib and the active controls demonstrated significant renal effects in the NDA, as reflected in the pattern of lab abnormalities associated with their administration. This pattern includes an association between celecoxib and several lab abnormalities: hyperchloremia, hypophosphatemia, and elevated BUN in association with proteinuria. These surrogates for renal toxicity suggest, but do not confirm, a link between celecoxib use and clinically relevant nephrotoxicity. Further, the incidence of the lab abnormalities occurred to a similar extent in both the celecoxib and the active control groups, suggesting that celecoxib and the other NSAIDs have similar renal effects.

There were no cases of acute renal failure in either the celecoxib or the active controls in the controlled trials. Given the known nephrotoxicity of NSAIDs, the absence of adverse clinical renal events in the controlled trials can be attributed to the low event rate, and does not mean that they do not occur. While there were no clear cases of celecoxib-induced renal failure in the controlled OA/RA trials, there were several individuals on celecoxib in the long-term, open-label trial who were withdrawn because of renal adverse events, including acute renal failure (as well as edema and worsening hypertension). While a direct link between events in open-label experience and celecoxib cannot absolutely be made with the available data, they are consistent with the patterns of clinical renal disease seen with other NSAIDs.

Within the limitations of the database there is no evidence to suggest that celecoxib has unique renal or cardiac toxicities not shared with other NSAIDs, or a toxicity also caused by NSAIDs that occurs at a significantly higher incidence rate. In the absence of bicarbonate data, an adverse effect of celecoxib on acid-base balance cannot be excluded, particularly in the context of the observed increase in hyperchloremia and hypophosphatemia.

While a through comparison of the renal effects of celecoxib and other NSAIDs has not been performed, the available data suggest that celecoxib resembles other NSAIDs in the majority of the renal effects examined in the NDA. Further, the available data suggest that the renal effects of celecoxib and the comparator NSAIDs are clearly distinguished from placebo. It remains to be determined is whether renal injury will occur following celecoxib at the same rate that is seen with other NSAIDs.

### **5.3.1 References**

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## 6.1 Appendix One: Deaths in the Celecoxib NDA Database

### 6.1.1 Deaths in patients who enrolled in a controlled arthritis trial

1. **Patient No. BE0002-0010** (Carcinoma–Gallbladder to Liver) was a 70 year old male with a past history including cardiomyopathy, pulmonary hypertension, COPD, hyperthyroidism, cholelithiasis, hypercholesterolemia, hypergammaglobulinemia, and an enlarged liver was admitted to study and randomized to the celecoxib 200 mg BID treatment group. Patient began taking study medication on 5 February 1997. Seventy nine days after the start of dosing on 26 April 1997 the patient stopped taking study medication because of nausea. On 11 May 1997 he saw his general practitioner because of sudden nausea, vomiting and intermittent diffuse abdominal pain. The patient was hospitalized on 12 May 1997 for further investigation. His bilirubin and liver enzymes were elevated. He was found to have carcinoma of the gallbladder with metastases to the liver. He also had mild macrocytic anemia with no evidence of bleeding. Laboratory work included: 21 April 1997 Hgb 10.3, Hct 31, WBC and Diff Normal, during hospitalization ECHO and CT , alpha-fetoprotein (0-12) 38, CEA (0-3) >90, Total Bilirubin 4.5, Indirect Bilirubin 2.7, SGOT 230, SGPT 111, LDH 4257, Alk Phos 360, and Gamma GT 442. The patient died on 21 May 1997 due to the carcinoma. No autopsy was performed.

2. **Patient No. US0117-46761235** (Cerebrovascular Disorder) was a 68 year old male with a history of tonsillectomy, bilateral otitis externa, herpes zoster, post-herpetic neuralgia, arteriosclerotic cardiovascular disease, bilateral claudication, hypertension, removal of abdominal aortic aneurism, appendectomy, hemorrhoidectomy, right great toe fracture, mild scoliosis, hypercholesterolemia, and OA. The patient was enrolled into the study on 14 July 1997 and randomized to receive naproxen 500 mg BID. After 63 days of treatment, the patient could not get out of bed. He had right-sided weakness and felt he would fall if he tried to stand. He felt “very funny” and had blurred vision and slurred speech. He was taken to the emergency room where his blood pressure was elevated at 192/90. Central nervous system examination revealed slurred speech, blurred vision, mild vertical nystagmus, and abnormal right upper extremity finger-to-nose. Other physical examination was normal. Initial lab data was unremarkable. A CT scan of the head did not reveal any acute hemorrhage. Chest x-ray revealed mild cardiomegaly. Brain stem evoked potential was suggestive of acute brain stem infarct. The patient was admitted to the hospital and intravenous enalapril maleate was initiated. He was also treated with metoprolol tartrate and sublingual nifedipine. His speech and coordination improved somewhat the following day, but later that day he developed focal seizures and became unresponsive. He was treated with intravenous diazepam and phenytoin but remained unresponsive. His blood pressure was 167/90 and it was felt that he had probably had an extension of his initial brain stem cerebrovascular accident. He was intubated and was started on intravenous antibiotics. Blood cultures were negative. The patient died four days later. No autopsy was performed. Concomitant medications included quinapril, metoprolol succinate SR, doxepin, and atorvastatin.

3. **Patient No. US0382-65811310** (Sudden Death) was a 78 year old male with a history of osteoarthritis, hearing loss, sinus congestion, hypertension and emphysema. The patient was enrolled into the study on 8 September 1997 and randomized to receive ibuprofen 800 mg TID. After 35 days of treatment, the patient experienced edema in his ankles and was withdrawn from the study. This subsided an unknown number of days after stopping study medication. Twenty four days later, the patient experienced severe abdominal pain. While getting into his car to go to the doctor, he collapsed and expired. The patient had previously been diagnosed with a urinary tract infection and was being treated by his primary physician. No autopsy was performed. Concomitant medications at the Early Termination Visit included nifedipine, metaproterenol sulfate and triamcinolone.

4. **Patient No. US0333-46521451** (Arteriosclerosis) was a 53 year old female with a history of hypertension, hysterectomy, allergy to codeine, and osteoarthritis. The patient was enrolled into the study on 25 August 1997 and randomized to receive diclofenac 75 mg BID. On September 9, 1997, the patient was found dead at home by her daughter. Since the patient’s family never returned the study medication containers, compliance or length of study medication cannot be determined. Her daughter stated the patient had “ probably been dead for about one hour” when she was found. She also stated that the coroner’s report listed the cause of death as “hypertensive cardiovascular disease.” Concomitant medications included fluoxetine hydrochloride, buspirone hydrochloride, and losartan.

5. **Patient No. US0021-0182** (Coronary artery disorder) was a 56 year old male with a history of seasonal allergies, corrective lenses, presbyopia, asthma, benign inflamed lymph node in the groin area, diabetes mellitus type II, obesity, allergies to dust, mold, grass and cat hair, and osteoarthritis. The patient was enrolled into the study on February 9, 1998, and randomized to celecoxib 200 mg QD. After twenty-nine days of treatment, the patient was out of town at a basketball game and collapsed and due to arteriosclerotic cardiovascular disease while getting into his car. Concomitant medications included regular insulin, NPH insulin, metformin hydrochloride, epinephrine, albuterol, beclomethasone dipropionate, albuterol sulfate, and multivitamins. Study medication was continued up until the time of death.

### 6.1.2 Deaths during the Open-Label Uncontrolled, Long-term Administration of Celecoxib

1. **Patient No. US0033-0768** (Myocardial Infarction) was an 80-year-old female with a history of OA, hypertension, borderline diet-controlled diabetes, hysterectomy, appendectomy, cholecystectomy, lumbar laminectomy, anterior cervical decompression and fusion, cataract surgery and rectal surgery for fistulas. The patient was enrolled into the study on 18 October 1996 and randomized to receive celecoxib 200 mg BID. After five days on treatment, the patient experienced severe chest pain lasting three hours which was associated with vomiting, diaphoresis and shortness of breath. She was hospitalized for an inferior wall myocardial infarction. It was noted that the patient had experienced intermittent chest pain for three days prior to hospital admission and had complained of anginal symptoms which occurred both with activity and at rest for six months prior to enrollment into the study. Treatment included aspirin, tissue plasminogen activator or a novel plasminogen activator under investigation. Additional treatment included morphine, intravenous heparin, intravenous nitroglycerin, ticlopidine and metoprolol. An ECG demonstrated ST fullness in the inferior leads with T-wave inversion and ST elevation with right-side ECG in V4-V6. A chest x-ray showed cardiomegaly and an atherosclerotic aorta with no other acute abnormalities. Emergency left heart catheterization was performed showing 100% occlusion of the mid-right coronary artery. Percutaneous transluminal coronary angioplasty was performed with suboptimum blood flow; therefore, a coronary stent was deployed which was successful. Concomitant medication included triamterene/hydrochlorothiazide, diphenoxylate/atropine and alprazolam. Study medication was discontinued and the patient was terminated early from the study. The patient was discharged from the hospital and reported feeling well. The patient was unable to schedule the Early Termination visit. Forty-five days following onset of the event, the patient expired in her sleep. No autopsy was performed. The death certificate listed immediate cause of death probable myocardial infarction due to coronary artery disease and congestive heart failure.

2. **Patient No. US0052-0683** (Pulmonary Carcinoma) was a 62-year-old female with a history of tobacco use, no taste or smell, hysterectomy, pneumonia, hypertension, arthroscopy, fibromyalgia, degenerative disc disease and OA. The patient was enrolled into the study on 19 September 1996 and randomized to receive celecoxib 100 mg BID. Eight days after treatment began, the patient was referred to a pulmonologist for increased dyspnea. Chest x-ray revealed a right upper lung nodular density. On Study Day 12, a CT scan of the patient's chest showed a 2.2 cm spiculated right upper lobe mass, consistent with a carcinoma. Bronchoscopy was performed thirteen days later and bronchoalveolar lavage cytology report showed atypical cells that were non-diagnostic. Study medication was discontinued at this time and the patient was withdrawn from the study. Thirty-four days later the patient was admitted for a right upper lobe lung mass. A thoracotomy with right upper and middle lobectomy was performed. No evidence of metastatic disease was found. The patient developed post-operative atelectasis with possible pneumonia three days later which advanced to adult respiratory distress syndrome (origin unknown) ending in death sixteen days after onset. No autopsy was performed. Other concomitant medications included nifedipine, fluoxetine, estradiol, cephalexin and minocycline.

3. **Patient No. US0191-1334** (Gallbladder Disorder, Death from Myocardial Infarction or Massive Pulmonary Embolism) was a 68 year old male with a history of OA, deep venous thrombosis following a tractor accident and pulmonary emboli. The patient has previously participated in celecoxib clinical trial #N49-96-02-047 for three days. One hundred and thirty four days later after Early Termination from this study due to treatment failure, the patient was enrolled into the current study (3 June 1997) and randomized to receive naproxen 500 mg BID. After forty six days of treatment the patient was on an out-of-town trip when he began experiencing heartburn. The heartburn progressed and became severe and was accompanied by nausea and vomiting. After returning home, he was hospitalized the following day. Physical examination revealed abdominal tenderness. He had an elevated white blood cell count. An electrocardiogram revealed some changes, including left bundle branch block, but the patient was cleared for surgery by cardiology consult who felt there were no acute changes or evidence of acute myocardial injury. Laparoscopic cholecystectomy was initially attempted but because of severe gangrenous and inflammatory changes in and around the gallbladder, it was necessary to do an open cholecystectomy. An operative cholangiogram was within normal limits. The gallbladder was found to have sludge and stones with a stone impacted in the neck of the gallbladder along with a possible common bile duct stone. The patient was maintained on intravenous fluids, intravenous antibiotics, and subcutaneous heparin postoperatively. The patient was unable to tolerate oral feedings and five days after surgery nausea and vomiting increased. An ultrasound of the abdomen showed a suspected fluid (contineud)

collection in the right upper quadrant. CT scan showed a large periduodenal hematoma. The patient's white blood cell count and amylase were elevated and some degree of pancreatitis was also suspected. A central line was placed, the patient was started on total parenteral nutrition and anticoagulant therapy was discontinued. The patient then developed some hallucinations and erratic behavior and bizarre complaints, and eight days after surgery, apparently suffered a cardiopulmonary arrest. The patient was resuscitated and was transferred to intensive care. His ECG at that time showed tachycardia with left bundle branch block. Shortly after transfer to the unit, he developed an idioventricular rhythm and was pulseless. Resuscitation attempts were unsuccessful and the patient was pronounced dead. It was the opinion of the cardiologist who attended the event that he had either suffered a massive myocardial infarction or massive pulmonary embolus. An autopsy was not done. No other concomitant medications were being taken. Study medication was interrupted during hospitalization.

**4. Patient No. US0001-0053 (Death)** was a 66 year old female with a history of cataracts, appendectomy, hemorrhoidectomy, postmenopause, fibrocystic breast disease, bilateral mastectomy, bilateral breast implant, squamous cell carcinoma, iron deficient anemia, multiple drug allergies, and RA. The patient had previously participated in the N49-96-02-022 clinical trial during which she had received placebo. After successfully completing this study, she was entered into the long-term safety study and began taking celecoxib 200 mg BID on 25 February 1997. Dosage was increased to 300 mg BID 42 days later on 8 April 1997. Nine days after that on 17 April 1997, the patient had a basal cell carcinoma removed from the right side of her nose. One hundred and thirty three days later (on 28 August 1997), dosage was increased to 400 mg BID. Approximately 12 days later, on or about 9 September 1997, the patient died of "natural causes." Concomitant medications included prednisone, methotrexate sodium, folic acid, and ferrous sulfate.

**5. Patient No. US0001-0076 (Heart Block, Hypoglycemia, Hyperglycemia)** was a 74 year old male with a history of seasonal allergies, pericarditis, prostate surgery for benign prostatic hypertrophy, bilateral ankle fusion, psoriasis, snoring, hypertension, chronic obstructive pulmonary disease, and rheumatoid arthritis. The patient previously participated in celecoxib clinical trial #N49-96-02-022, during which the patient had received either placebo, celecoxib 100 mg BID, 200 mg BID, 400mg BID or naproxen 500 mg BID. After being withdrawn early due to treatment failure, he was entered into the long-term safety study, N49-96-02-024, and began taking SC-58635200 mg BID on April 23, 1997. Dosage was adjusted to 300 mg BID 5 days later, on April 28, 1997 and to 400 mg BID 4 days later, on May 2, 1997. Three hundred and twenty-seven days later, on March 25, 1998, the patient was wheeled into the doctor's office and was cyanotic and lethargic. The patient was incubated and taken to the emergency room where he was pronounced dead. The patient was diagnosed as being in total heart block, hypoglycemic (blood sugar of 16), and hyperkalemic (potassium was 9.0). Amphetamines and antidepressants were detected in the patient's urine. The patient had gone to see his primary care physician one day prior to this event, on March 24, 1998, and the physician said the patient was "OK". Concomitant medications included prednisone, pencillamine, trinallin and amlodipine. The date of last dose is unknown at this time.

**6. Patient No. US0023-0020 (Myocardial Infarction, Cardiac Failure)** was a 76 year old male with a history of appendectomy, testicle cyst (removed), malaria, diabetes, sinusitis, insomnia, fractures of foot, shoulder and nose, hyperlipidemia, hypertension and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which he had received naproxen 500 mg BID. After terminating early from this study due to treatment failure, the patient entered into the long term safety study and began taking celecoxib 200 mg BID on 1 April 1997. After 23 days of treatment, on 24 April 1997, the patient was hospitalized for a previously scheduled total hip replacement. After 39 days of treatment, on 15 May 1997, the patient was hospitalized for a right deep venous thrombosis. Seven days after discharge, on 26 May 1997, the patient was seen in the emergency room for constant anterior chest pain, which had begun approximately two days earlier and was not associated with radiation, diaphoresis, or dyspnea. The patient was then hospitalized the following day, on 27 May 1997, with a myocardial infarction of the anterior wall. Treatment included intravenous nitroglycerin and heparin sodium, oxygen, and monitoring and evaluation of cardiac status. Lab work revealed glucose of 227 and CK of 52. Repeat CKs were 456, 784, and 687 with MBs of 82.6, 150.1, and 121.7. Ventilation-perfusion lung scan performed due to an episode of shortness of breath showed a low probability of a pulmonary embolus. Portable chest x-ray showed no acute cardiopulmonary disease. Echocardiogram showed normal left ventricular contractility, ejection fraction of approximately 52%, normal intracardiac chambers, and normal valvular function. Cardiac catheterization performed six days later, on 2 June 1997, showed coronary artery disease with 20% left main proximal stenosis, 100% left circumflex distal stenosis, left anterior descending with some plaquing in the midportion but no focal stenosis more than 50%, 90% mid right coronary artery stenosis, and left ventricular ejection fraction of 50-55%. The patient was then transferred to another hospital that same day, (continued)

where he underwent a percutaneous transluminal coronary angioplasty with stenting of the right coronary artery. Nine days after transfer and approximately one week after discharge, on 11 June 1997, the patient developed a sudden onset of chest pain which was not relieved by three sublingual nitroglycerin. The patient was taken to the emergency room and was intubated and cardioverted after experiencing sustained ventricular tachycardia, ventricular fibrillation, and cardiac arrest. The patient was then admitted for an acute inferior wall myocardial infarction probably due to acute closure of the right coronary stent placed two weeks prior to admission, complicated by cardiogenic shock, hypotension with systolic blood pressure 60-70, and bradycardia with heart rate in the 30's. Electrocardiogram confirmed an acute inferior infarct showing acute ST segment elevation, severe bradycardia, and third degree heart block. Despite being on warfarin sodium, his protime was only 15 and INR was 1.3. Treatment included a temporary pacemaker as well as intravenous fluids, oxygen, morphine sulfate, Levophed, thrombolytic therapy, heparin sodium, and dopamine hydrochloride. The patient expired the following day, on 12 June 1997, due to cardiogenic shock and acute myocardial infarction after an unsuccessful resuscitation attempt for pulseless ventricular fibrillation. Other concomitant medications included Centrum, multivitamins, metformin hydrochloride and nisoldipine.

**7. Patient No. US0024-0024** (Coronary Artery Disorder) was a 71 year old male with a history of hypertension, myocardial infarction, peripheral bilateral edema due to cardiovascular disease, removal of ganglion cyst on left elbow, dentures, not-fasting hyperglycemia, hypercholesterolemia, hypertriglyceridemia, hypocalcemia, macular degeneration of right eye, right inguinal hernia repair, urinary tract infection, and rheumatoid arthritis. The patient had previously participated in celecoxib clinical trial #N49-96-02-023, during which the patient had received celecoxib 100 mg BID, 200 mg BID, 400 mg BID, naproxen 500 mg or placebo BID. After the patient successfully completed this study, he was entered into the long-term safety study and began taking celecoxib 200 mg BID on February 6, 1997. Dosage was adjusted to 300 mg BID 42 days later, on March 20 1997, and again adjusted to 400 mg BID 49 days later, on May 8, 1997. Three hundred six days after last dose adjustment, on March 10, 1998, the patient expired in his home due to cardiopulmonary arrest as a consequence of coronary artery disease. Concomitant medications included methotrexate sodium, multivitamin, folic acid, diltiazem hydrochloride, inadaptamide, mononitrate, and baby aspirin. Study medication was continued until the time of death.

**8. Patient No. US0024-0004** (Myocardial Infarction) was a 59 year old male with a history of cardiomegaly, lumbar and cervical spine surgery, umbilical hernia repair, peripheral edema, hypertension, hip replacement, spinal stenosis, muscle spasm, elevated creatine phosphokinase, two pack per day smoker, obesity and RA. The patient had previously participated in the N49-96-02-012 clinical trial during which he received celecoxib 400 mg BID for four weeks. One hundred and forty days after successfully completing this study, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 31 July 1996. Dosage was increased to 300 mg BID 42 days later, on 11 September 1996, and to 400 mg BID 21 days later on 2 October 1996. Two hundred and nine days after the last adjustment, on 29 April 1997, the patient suddenly collapsed while at a horse race track. Following an unsuccessful resuscitation attempt, the patient was subsequently pronounced dead in the emergency room as a result of an acute myocardial infarction due to hypertensive heart disease. Examination on the body after death revealed distinguishable earlobe creasing and edema to the ankles. There was no indication of injury. No autopsy was performed. Concomitant medications included aurothioglucose, prednisone and lisinopril. (The Searle Medical Monitor elected to code this event as "sudden death" until more information about the evidence of M.I. was available).

**9. Patient No. US0027-0004** (Anterior Myocardial Infarction) was a 66 year old male with a history of tinnitus, hypertension, benign prostatic hypertrophy, mechanical low back pain, Baker's cyst, right knee arthroscopy, lipoma of the right shoulder, cholelithiasis, exogenous obesity, anemia, choroidal nevus, and RA. The patient had previously participated in the N49-96-02-012 clinical trial during which he had received placebo. After successfully completing this study, he was entered the long-term safety study and began taking celecoxib 200 mg BID on 18 July 1996. Dosage was increased to 300 mg BID thirteen days later on 31 July 1996, and again increased to 400 mg BID twenty eight days later on 28 August 1996. Two hundred and eighty five days after the last adjustment on 9 June 1997, the patient developed chest pressure while at rest with associated diaphoresis that persisted for one hour. He went to the emergency room where an electrocardiogram was negative. Treatment included sublingual nitroglycerin and nitroglycerin paste with relief of his pain. Subsequent electrocardiogram revealed possible non-specific anterolateral T wave change and he was admitted for further evaluation on 10 June 1997. On admission, his blood pressure was 120/80 and pulse was 76 with no abnormalities noted on physical examination. A cardiac catheterization (continued)

performed that same day revealed significant disease of the left anterior descending coronary artery, 90% discrete stenosis, followed by a large first diagonal that had a 75% stenosis (apical stenosis 70%). Left ventriculography revealed moderately severe anterolateral hypokinesis with an ejection fraction around 45 to 50% overall. One day later on 11 June 1997, the patient underwent a percutaneous transluminal coronary angioplasty with implantation of a JR II intracoronary stent in the first diagonal and a J & J intracoronary stent in the left anterior descending. There were no residual stenoses. Post procedure, when his sheath was pulled, he developed some sinus bradycardia and associated hypotension, which was treated with no further sequelae. The patient had no further complaints of chest pain or shortness of breath and was discharged two days later on 13 June 1997. Treatment included ticlopidine, acetylsalicylic acid, atenolol, and ranitidine. Study medication was discontinued, and the patient was terminated early from the study on 17 June 1997 due to taking the above medications. The patient was started on diclofenac that same day. On the night of 19 August 1997 (sixty-three days later after terminating from the study) the patient developed chest pressure. This persisted and he went to the emergency room early the following morning on 20 August 1997. Electrocardiogram showed acute anterior ST elevation. He was treated with thrombolytics. The chest pain continued and he was subsequently transferred to another hospital for further cardiac evaluation. On admission, lung sounds were diminished and heart rate and rhythm were regular with S1, S2, and S4 gallop. Peak creatine phosphokinase was 6581 with an MB of greater than 300. Potassium was 2.2, which was corrected to 4.5. Magnesium was 1.5. Following admission the patient underwent an emergency left heart catheterization with coronary angiography due to continued chest pain. This showed hazy proximal left anterior descending with subtotal occlusion of diagonal and thrombus in the distal left anterior descending. The patient was started on abciximab and an intra-aortic balloon pump was then inserted. He developed a wide complete tachycardia requiring intubation and subsequent CPR. The patient was resuscitated. In the cath lab the patient vomited approximately 200 cc of bright red blood and a gastroenterology consult was obtained. An acute GI hemorrhage was suspected either due to a Mallory-Weiss tear versus diclofenac induced surgery. It was also felt that anticoagulant therapy had contributed to the blood loss. Neurologically, the patient did not arouse post-code and developed mild clonic activity. On consultation, the neurologist felt that symptoms were indicative of a moderate to severe intracranial hypoxic event. The patient did not regain consciousness. He died the following day on 21 August 1997. Concomitant medications included folic acid, methotrexate, hydroxychloroquine, and verapamil.

**10. Patient No. US0042-0004** (Pulmonary Carcinoma) was a 77 year old female with a history of cardiomegaly, periodontal disease, hearing loss, hemorrhoids, breast cyst, myopia, chronic obstructive lung disease, smoker, pneumonia, shortness of breath and osteoarthritis. The patient had previously participated in celecoxib clinical trial #N49-96-02-022, during which she had received either placebo, celecoxib 50 mg BID, 100 mg BID, 200 mg BID or naproxen 500 mg BID. After successfully completing this study, she immediately entered into the long-term safety study and began taking celecoxib 100 mg BID on November 19, 1996. Dosage was adjusted to 200 mg BID 168 days later, on May 6, 1997. After another 288 days of treatment, on February 18, 1998, she was seen for her month 15 visit with complaints of increased shortness of breath and cough. She had completed a regimen of cefprozil on this same date. Chest x-ray was performed and showed a large infiltrate mass in the left lung. Computed tomography performed 5 days later, on February 23, 1998 confirmed a large left hilar mass which appeared to have mediastinal invasion. Nine days later, on March 4, 1998, a diagnostic bronchoscopy with endobronchial biopsy was performed and was suggestive of a bronchogenic neoplasm with secondary atelectasis. Pathology report of the left upper lobe bronchial biopsies showed non small cell carcinoma (possible large cell undifferentiated carcinoma) of the left upper lobe of her lung. Study medication was discontinued on March 10, 1998, and the patient was withdrawn from the study on March 12, 1998. Twelve days later, on March 24, 1998, the patient was admitted for an exudative pleural effusion and a new onset of atrial fibrillation. She was treated with insertion of a chest tube and warfarin sodium. She was subsequently discharged on March 31, 1998. Eleven days later, on April 11, 1998, the patient was readmitted with increasing shortness of breath. She was noted to have complete white out of her left lung. A chest tube was inserted, and 2 liters of fluid were removed. Other treatment included pain medication, antibiotics, steroids, breathing treatments, a radiation substantially, and she expired 4 days later, on April 15, 1998. Concomitant medications included triamcinolone acetonide, albuterol and calcium carbonate.

(continued)

**11. Patient No. US0052-0043** (Coronary Thrombosis) was an 84 year old female with a history of hypertension, coronary artery disease, cigarette smoking, occasional indigestion, atherosclerosis, hyperlipidemia, adult onset diabetes mellitus, anxiety attack, bronchitis, depression, and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which she received celecoxib 400 mg BID. After being withdrawn early from this study due to a nosebleed, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 10 April 1997. Dosage was increased to 300 mg BID 14 days later, on 24 April 1997. One hundred and seventy nine days later, on 20 October 1997, the patient died of a coronary thrombosis; a contributing cause of death was considered to be chronic obstructive pulmonary disease. Concomitant medications included alprazolam, ipratropium, albuterol, salmeterol xinafoate, vitamin E, baby aspirin, glipizide, Triavil, pentoxifylline, enalapril maleate, and lovastatin. The Investigator was uncertain of the association of the event with the study drug.

**12. Patient No. US0053-0001** (Ventricular Fibrillation, Myocardial Infarction, Coronary Artery Disease) was an 80 year old male with a history of cataracts, spinal stenosis, cardiomyopathy, cardiac arrhythmia, angina, mild congestive heart failure, pneumonia, colon polyps, irritable bowel syndrome, constipation, hyperlipidemia, gastroduodenal ulcer, benign prostatic hypertrophy, meniscectomy, hypothyroidism, gout, hypertension, depression and OA. The patient had previously participated in the N49-96-02-020 clinical trial during which he received celecoxib 100 mg BID. After withdrawing early from this study due to treatment failure, the patient was entered into the long-term safety study and began taking celecoxib 100 mg BID on 11 September 1996. Dosage was increased to 200 mg BID 14 days later, on 25 September 1996. One hundred and thirty days later, on 2 February 1997, the patient woke up "not feeling well". After eating breakfast, the patient left the table, collapsed and died. Death certificate reveals cause of death to be cardiorespiratory arrest due to ventricular fibrillation, acute myocardial infarction and coronary artery disease. Concomitant medications included methylcellulose, levothyroxine, allopurinol, propoxyphene, gemfibrozil, furosemide, digoxin, diltiazem, potassium chloride, losartan, sertraline and psyllium.

**13. Patient No. US0058-0018** (Coronary Artery Disorder) was a 60 year old female with a history of allergic rhinitis, nasal congestion, refraction disorder, bilateral middle finger numbness, asthma, hemorrhoids, stress incontinence, cystocele, total abdominal hysterectomy and bilateral salpingo-oophorectomy, post-menopausal, intermittent back pain, right great toe fracture, lumbar laminectomy, bilateral calcaneal spurs, intermittent eczema, hypercholesterolemia, exogenous obesity, allergies to adhesive tape and amoxicillin, inhalant allergies, and OA. The patient had previously participated in the N49-96-02-021 clinical trial during which she received celecoxib mg BID. After successfully completing this study, the patient was entered into the long-term safety study and began taking celecoxib 100 mg BID on 20 February 1997. Dosage was increased to 200 mg BID 14 days later on 6 March 1997. One hundred and forty six days later, on 30 July 1997 the patient was found dead by her son. An autopsy performed one day later, on 31 July 1997, revealed arteriosclerotic cardiovascular disease with severe narrowing of the left anterior descending coronary, right coronary artery by atherosclerosis, and severe atherosclerosis of the aorta. No evidence of a recent or old myocardial infarction was noted. Hashimoto's thyroiditis and cholesterosis of the gallbladder were also seen on autopsy. The death certificate shows the patient died of ischemic heart disease. Concomitant medications included Naldecon, pravastatin, estrogen, calcium carbonate, and allergy injection.

**14. Patient No. US0066-0004** (Respiratory Insufficiency, Pulmonary Carcinoma, Treatment Emergent Surgery) was a 60 year old male with a history of tonsillectomy, seasonal allergies, sleep apnea, hypertension, appendectomy, cholecystectomy, obesity, peripheral edema, adult onset diabetes mellitus, skin rash, proteinuria/gold therapy, excision of eyelid polyps, toe surgery, allergy to penicillin, excoriated insect bites, hyperlipidemia, hypothyroidism, chronic obstructive lung disease, tobacco use and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which he received placebo. After being withdrawn early from this study due to treatment failure, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 11 November 1996. Dosage was increased to 300 mg BID 15 days later, on 27 December 1996. Eighty three days later, on 20 March 1997, the patient complained of chest pain. The Investigator referred the patient to his primary physician, who started the patient on clarithromycin for possible pneumonia and did a chest x-ray. Twenty six days later, on 15 April 1997, the patient was hospitalized for a lung mass which was seen on the chest x-ray. Three days following hospital admission, on 18 April 1997, 4000 cc of fluid was aspirated from the patient's lungs. Cell differential of this fluid returned cancer cells. The diagnosis of adenocarcinoma of the lung was made and a scan showed metastasis of the liver. Thirteen days following admission, on 28 April 1997, a thoracotomy was performed. The patient was mechanically ventilated postoperatively. Seven days later, on 5 May 1997, the patient expired due to respiratory failure secondary to carcinoma of the left lung. Concomitant medications included diltiazem, glipizide, gemfibrozil, levothyroxine, docusate, terfenadine, methotrexate, phentermine, fenfluramine, anti-fungal cream and continuous positive airway pressure oxygen. Study drug was discontinued on 15 April 1997. The patient never recovered

**15. Patient No. US0073-0060** (Respiratory Insufficiency, Cardiac Failure) was an 85 year old female with a history of removal of benign throat tumor, hypertension, peptic ulcer disease, cholecystectomy, cigarette smoking, post-menopause, osteoporosis, right hip replacement, hypothyroidism, bilateral cataracts, lens implants, and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which she received placebo. After being withdrawn early from this study due to treatment failure, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 10 March 1997. Dosage was increased to 300 mg BID four days later, on 14 March 1997 and to 400 mg BID 11 days later, on 25 March 1997. Two hundred and twenty eight days after dose adjustment, on 8 November 1997, the patient was hospitalized for unknown reasons. The patient died 12 days later, on 20 November 1997 of respiratory secondary to congestive heart failure. Concomitant medications included sulfasalazine, levothyroxine sodium, alendronate sodium, lisinopril, furosemide, and potassium chloride. Study drug was interrupted during hospitalization.

**16. Patient No. US0073-0189** (Myocardial Infarction) was a 71 year old female with a history of sleep disturbance, hypertension, irregular heart rate, cholecystectomy, appendectomy, ovarian cyst removed, benign breast cyst removed, cataracts, post-menopausal, anemia, hyperglycemia, hypercholesterolemia, hyperuricemia, and rheumatoid arthritis. The patient had previously participated in celecoxib clinical trial #N49-96-02-022, during which the patient had received either placebo, celecoxib 100 mg BID, 200 mg BID, 400 mg BID or naproxen 500 mg BID. After terminating early due to treatment failure, she was entered into the long-term safety study and began taking celecoxib 200 mg BID on November 21, 1997. Seventeen days later, on December 8, 1997, dosage was adjusted to 400 mg BID. Seventeen days later, on December 28, 1997, the patient began experiencing jaw pain that radiated to the chest. The patient was hospitalized with a possible myocardial infarction. Initial cardiac enzymes were elevated. An electrocardiogram revealed septal and lateral wall changes. Treatment included subcutaneous heparin sodium, nitroglycerin, metoprolol tartrate, and warfarin sodium. Three days after admission, on December 31, 1997, the patient died due to complications from a myocardial infarction. Concomitant medications included methotrexate, folic acid, enalapril, calcium carbonate, vitamin E, lorazepam, multivitamin, digoxin, and prednisolone acetate.

**17. Patient No. US0087-0100** (Sepsis, Pneumonitis, Respiratory Insufficiency) was a 66 year old male with a history of hypertension, gastrointestinal upset related to anti-inflammatory medications, reflux esophagitis, gastritis, benign cyst on left hip, osteoporosis, dermatitis, heat rash, diabetes, positive *Helicobacter pylori*, right medial meniscectomy, crush injury to left hand and remote history of peptic ulcer disease, allergy to penicillin, and rheumatoid arthritis. The patient had previously participated in celecoxib clinical trial #N49-97-02-023, during which the patient had received celecoxib 100 mg BID, 200 mg BID, 400 mg BID, naproxen 500 mg BID or placebo BID. After terminating early from this study due to treatment failure, he was entered into the long-term safety study, N49-96-02-024, and began taking celecoxib 200 mg BID on May 6, 1997. Dosage was increased to 300 mg BID, 14 days later, on May 20, 1997 and increased again to 400 mg BID, 4 days after that, on May 24, 1997. One hundred and seventy-four days after dose adjustment on November 14, 1997, the patient was admitted to the intensive care unit for complaints of shortness-of-breath, dyspnea, left sided weakness and elevated blood pressure. A CAT scan of the lungs showed alveolar edema, chest x-ray revealed peripheral pulmonary fibrosis, presumably secondary to rheumatoid arthritis or long-term methotrexate therapy, and changes consistent with pulmonary edema. And electrocardiogram revealed sinus tachycardia with ST and T sagging in the lateral leads, and a suggestion of left atrial hypertrophy. A CAT scan of the head was negative. Blood cultures revealed enterococcal species. Physical exam was remarkable for crackles in bilateral lung fields almost to the scapular level and slight left arm and leg weakness with slightly diminished reflexes bilaterally. According to the study coordinator, the patient's blood pressure had been elevated to at least 176/86 at his past few visits and he had been advised to see his primary physician. The patient was started on enalapril maleate, furosemide, and digoxin. Additional treatment for this event included Humulin Insulin, multiple antibiotics, Ventolin, Atrovent, Heparin and famotidine, tracheostomy and mechanical ventilation. The patient died 29 days later, on December 2, 1997. The cause of death was determined to be respiratory failure, overwhelming sepsis and the interstitial pneumonitis. Concomitant medications included hydroxychloroquine sulfate, folic acid, glyburide, omeprazole, metformin hydrochloride, calcium and methotrexate. Study medication was interrupted during hospitalization.

**18. Patient No. US0110-0006** (Myocardial Infarction) was a 61 year old female with a history of fluid retention, hyperlipidemia, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, tobacco use, triple bypass surgery, arrhythmia, abdominal aortic aneurysm, hysterectomy, thrombocytosis and rheumatoid arthritis. The patient had previously participated in Searle study #N49-96-02-022, during which she received either placebo, celecoxib 100 mg BID, 200 mg BID, 400 mg BID or naproxen 500 mg BID. After successfully completing this study, on December 17, 1996, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID. Dosage was adjusted to 300 mg BID 17 days later, on January 3, 1997, and again to 400 mg BID 35 days after that, on February 7, 1997. Two hundred and twenty days after the last dose adjustment, on September 15, 1997, the patient underwent femoral bypass surgery due to a foot ulcer that was caused by poor circulation. The patient was discharged 3 days later, on September 18, 1997. Eleven days later, on September 29, 1997, the patient was re-hospitalized with complaints of chest pain. The patient underwent cardiac catheterization and angioplasty with stent placement. The patient was discharged 31 days later, on October 30, 1997. Seventy-seven days later, on January 13, 1998, the patient suffered a myocardial infarction and died. The patient's brother had died earlier in the week. Concomitant medications included prednisone, digoxin, pravastatin sodium, acetylsalicylic acid, furosemide, pentoxifylline, and multivitamins.

**19. Patient No. US0116-0042** (Arterial Dissection, Aneurysm) was a 78 year old female with a history of cataracts, lens implants, hypertension, supraventricular tachycardia, angioplasty, appendectomy, hiatal hernia, post-menopause, bilateral metatarsophalangeal repair, allergies to piroxicam and gold, and rheumatoid arthritis. The patient had previously participated in celecoxib clinical trial # N49-96-02- 022, during which the patient had received either placebo, celecoxib 200 mg BID on September 25, 1997. After 88 days of treatment, on December 22, 1997, the patient was hospitalized with an ascending aortic aneurysm and developed a dissection which was confirmed on repeat CT scanning. Preoperative echocardiogram revealed moderately severe aortic stenosis with a peak gradient of 42. On December 24, 1997, the patient underwent an aortic valve replacement with a 21mm St. Jude Mechanical heart valve and ascending aorta and hemi-arch replacement with 24mm Hemashield graft utilizing circulatory arrest and hypothermia. During the procedure, the patient began bleeding from the anterior portion of the proximal anastomosis and developed left ventricular aortic discontinuity from this area. Massive bleeding ensued. Attempts to repair this were unsuccessful and the patient was pronounced dead. The death certificate revealed the cause of death as type I ascending (aortic) arch dissection, arteriosclerotic coronary artery disease and critical aortic stenosis. Concomitant medications included sulfasalazine, diltiazem hydrochloride-sustained release, thyroid, Ascriptin, medroxyprogesterone acetate, conjugated estrogens, and digoxin. Study medication was interrupted one day prior to hospitalization.

**20. Patient No. US0121-0052** (Sepsis, Pneumonia, Myocardial Infarction) was a 52 year old male with a history of tinnitus, recurring sore throats, decreased hearing, sinus trouble, sores in mouth, glasses, pain behind eyes, depression, headaches, vertigo, fainting spells, occasional chest pain, influenza, cough, chronic obstructive airway disease, pneumonia, obesity, hernia repair, appendectomy, H. pylori, hemorrhoids, gastritis, pedal edema, leg cramps, bursitis, brittle nails, skin rash, hypoglycemia, diabetes mellitus, allergies to penicillamine and cyclosporin, and RA. The patient had previously participated in the N49-96-02-022 clinical trial during which he had received celecoxib 100 mg BID. After successfully completing this study, he was entered into the long-term safety study and began taking celecoxib 200 mg BID on 29 September 1997. Fourteen days later, on 13 October 1997, dosage was increased to 300 mg BID. Four days after that on 17 October 1997, the patient presented with shortness of breath which had been present for one month, and had become significantly worse, and was admitted with respiratory distress. Physical examination revealed a blood pressure of 107/50 on dopamine, respiratory rate of 15, which was decreased from 36 previously, and a temperature of 99°F. Lung auscultation revealed crackles in the left base, and a trace of bipedal pitting edema. Pleural fluid and sputum grew *Acinetobacter* "pneumoniae." White blood cell count was 10.5 on admission. Complete blood differential count revealed a left shift with 54 bands. The patient's blood urea nitrogen was 24 and creatinine was 3.3 on admission and rose to 35 and 4.7, respectively, one day after admission. Potassium rose from 4.7 to 6.9 in just a few hours. Aspartate transaminase, which was initially normal, rose to 649. Alanine transaminase rose to 309 and lactate dehydrogenase to 3,272; CK-MB index was 7.9%. Arterial blood gasses were pH 7.06, pCO<sub>2</sub> of 67, and pO<sub>2</sub> of 58 on a 7 liter oxygen mask. Pleural fluid showed 14,000 nucleated cells with neutrophilic predominance and glucose of 70 with pH of 7.2. Blood cultures grew a bacillus species. Electrocardiogram revealed sinus tachycardia with an incomplete right bundle branch block and small Q wave in lead (continued)

III with anterolateral ST changes consistent with possible ischemia. Chest x-ray showed cardiomegaly and a possible pleural effusion on the left. Treatment included intubation and subsequent ventilator support, thoracentesis, insertion of a Swan-Ganz, central venous pressure line, arterial line and Vas-Cath, dopamine in increasing doses, rescue doses of steroids, ceftriaxone, sodium, fluid replacement for dehydration and sepsis, phenylephrine hydrochloride drip, amikacin, and ofloxacin. The patient was found to have gram negative sepsis and pneumonia and subsequently expired one day later on 18 October 1997. According to the death certificate, the patient died of an acute myocardial infarction. No autopsy was done. Concomitant medications included methotrexate, prednisone, and folic acid as well as nasal continuous positive airway pressure. Study medication was continued up until the time of death.

**21. Patient No. US0139-0009** (Subarachnoid Hemorrhage) was a 57 year old female with a history of dyspepsia, hysterectomy, lumbar spinal fusion, and RA. The patient had previously participated in the N49-96-02-022 clinical trial during which she had received placebo. After successfully completing this study, she was entered into the long-term safety study and began taking celecoxib 200 mg BID on 26 August 1997. Twenty three days later on 18 September 1997, the patient was admitted with a grade V subarachnoid hemorrhage. On admission her right pupil was fixed and dilated and she had decerebrate posturing. Apparently, this had occurred at 4:30 in the morning, with onset of emesis and loss of consciousness at that time. She was subsequently intubated and received mannitol and was transferred by ambulance to the hospital. On examination her initial blood pressure was 200/80 and nitroglycerin paste was given to help lower this. Her Glasgow Coma Scale at the time of admission was 4T. A computerized tomography scan revealed diffuse subarachnoid hemorrhage with a large right sided temporal lobe clot; intraventricular hemorrhage; right to left shift; and extensive midbrain compression and swelling. The patient deteriorated and was pronounced brain dead later that same day. Concomitant medications included methotrexate, folic acid, sulfasalazine, and estrogen.

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## 7.1 Appendix Two: Serious Adverse Events related to renal function in the Celecoxib NDA Database

1) Acute Renal Failure There were two cases of acute renal failure (uremia) in celecoxib treated patients; one was due to repeated quinine use, the other associated with obstructive uropathy.

The first occurred in a 70-year-old female (047-US0033-0030) with a prior history of labile vascular hypertension, and urinary system disorders including urethral stenosis, urgency, and bladder spasms. Concomitant medications at the time of the event were: captopril, chlorpheniramine, docusate sodium, aspirin, estrogen, etidronate, fluconazole, dexamethasone, oxybutynin, pravastatin, quinine sulfate, and verapamil. Three weeks after initiating treatment with celecoxib 400 mg BID, she experienced leg cramps for which she took quinine and subsequently experienced headache and pruritus. One week later, she repeated a single dose of quinine and again experienced headache and pruritus, but also nausea, vomiting, diarrhea, chills, and confusion. Four days later she was hospitalized with a fever and a creatinine level of 9.1  $\mu\text{mol/L}$ . She was diagnosed with hemolytic uremic syndrome presumed due to quinine sulfate. Treatment included plasmapheresis, hemodialysis, and platelet transfusion.

The patient with acute renal failure associated with likely obstructive uropathy was a 65-year-old male (024-US0149-1490002), with a medical history of hypertension, depression, nocturia and RA. Concurrent medications included gold sodium thiomalate, terazosin, fosinopril, metoprolol, prednisone, and combination perphenazine and amitriptyline. The patient took celecoxib 100 mg BID for 12 weeks in a double-blind clinical RA trial. After successfully completing the trial, he was admitted to the long-term open-label trial. He was instructed to take celecoxib 200 mg BID, but for unknown reasons, he took only 100 mg BID. The patient returned for the Week 2 Visit and no abnormalities were noted. Four days after he was seen for his "Week 6" visit, his urine output decreased and he felt ill. This was approximately one week following an endoscopic procedure associated with anaesthesia. (Laboratory results from the Week 6 Visit revealed his serum creatinine to be 8.6 mg/dL and his BUN to be 61 mg/dL, significantly higher than his Baseline values, which were 1.4 mg/dL and 21 mg/dL, respectively). Five days later, study medication was stopped when he was hospitalized with a serum creatinine level of 19.4 mg/dL and a BUN of 116 mg/dL. During his hospitalization, he required hemodialysis on two occasions. Ultrasound examination showed bilateral hydronephrosis. He was scheduled for cystoscopy and retrograde ureteroscopy and possible stent placement when he developed significant large volume diuresis with normalization of his renal function. He recovered and was discharged from the hospital five days later. One week later, his serum creatinine value was 1.8 mg/dL and his BUN was 33 mg/dL. The Investigator felt there was a probable association between the event and study medication. The Searle Clinical Safety Committee considered the event not to be related to celecoxib because the radiographic evidence favored obstructive uropathy possibly secondary to prostatic enlargements.

2) Diuretic-induced hyponatremia/ hypokalemia There were two serious adverse events of diuretic-induced hyponatremia (one of which was principally coded as hypokalemia) that resulted in patients being hospitalized.

One of these patients was a 72-year-old female (024-US0033-0330007) with history of hypertension, venous insufficiency, hypercholesterolemia, and hypothyroidism. Concurrent medications included hydrochlorothiazide, triamterene, verapamil, and calcium. This patient took celecoxib 300 mg BID for 14 days before discontinuing because of treatment failure. Two days after stopping celecoxib, she was hospitalized with a plasma sodium level of 122 mmol/L. She was rehydrated with intravenous fluid and her plasma sodium returned to normal. Her hospital diagnosis indicated metabolic encephalopathy secondary to hyponatremia most likely due to diuretic therapy.

The other patient with hyponatremia (coded as hypokalemia) was a 78-year-old female (024-US0013-0130009) with a history of hypertension, urinary complaints such as nocturia and bladder suspension surgery, and elevated liver function tests. Concurrent medications included doxazosin, Moduretic and indapamide. The patient initiated treatment with celecoxib 200 mg BID and experienced sinusitis eight-and-one-half months later. She was treated with antibiotics but three days later she lost consciousness and was incontinent of urine. Following this syncopal episode, she vomited. She was taken to the hospital, where her serum potassium and sodium were found to be 2.9 mmol/L and 132 mmol/L, respectively. She was rehydrated with intravenous solution, treated with potassium, and indapamide was discontinued. Amoxicillin was continued to treat the sinusitis.

3) Renal Calculus Renal calculus occurred in 3 male and 2 female RA patients taking celecoxib 200 mg BID. The onset of occurrence ranged from 59 to 205 days. The 43-year-old male (024-US0001-0010016) had a prior history of bilateral total hip replacements. His only concurrent medication was Auranofin. He underwent a successful stenting procedure and was withdrawn from the study. The 58-year-old female (024-US0009-0090037) had a prior history of renal calculus. Concurrent medications were methotrexate and folic acid. She underwent a successful stenting procedure and continued in the study. The 27-year-old female (071-US0354-56553061) had a history of

seizure disorder, depression, and four miscarriages. Concurrent medications included prednisone and fluoxetine. She passed a kidney stone while receiving medical tx in the hospital and was withdrawn from study.

4) Cardiac Failure There were four cases of cardiac failure that were serious adverse events. Three of these patients were taking celecoxib at the time the event occurred. A 71-year-old male (024-US0006-0060001) with a history of heart disease, heart attack, pneumonia (including a recent episode), surgery for lung biopsy, hypertension, and RA experienced respiratory arrest and was hospitalized after 196 days of study medication (celecoxib 300 mg BID). He also experienced a cardiac arrest on the same day. He continued to take study medication and 76 days after this initial hospitalization, the patient experienced shortness of breath, left chest pain and was readmitted. Chest x-ray showed evidence of congestive heart failure. Treatment included supplemental oxygen, intravenous furosemide, and amlodipine. Concomitant medications included triamcinolone acetonide, potassium chloride, digoxin, and bumetanide. The patient was discharged three days later and the patient recovered.

A 76-year-old male (060-US0198-0214) with a history of atrial fibrillation, congestive heart failure, hypertension, diabetes and OA was hospitalized seven days after initiating therapy with celecoxib 100 mg BID after experiencing increasing paroxysmal nocturnal dyspnea, orthopnea, and dyspnea. Concomitant medications included digoxin, metoprolol, furosemide, flecainide acetate, potassium chloride, and aspirin. The patient was treated with nitroglycerin as needed and was discharged three days later with a final diagnosis of angina. The patient was discharged three days later and the patient recovered. An 81-year-old female (0210-US0113-0139) with a history of OA, cerebral vascular accident, angina, hypertension, arrhythmias, congestive heart failure and coronary artery disease was hospitalized 52 days after initiating therapy with celecoxib 200 mg BID for congestive heart failure. Concomitant medications included furosemide, aspirin, doxazosin mesylate, nitroglycerin and potassium chloride. The patient was treated with losartan, Prinivil, and digoxin and has recovered.

5) Aggravated Hypertension There were three cases of aggravated hypertension and one case of hypertension in patients taking celecoxib that were serious adverse events.

A 71-year-old female (024-US0005-00500022) with a history of hypertension and heart murmur was hospitalized for vertigo and nausea after taking celecoxib 200 mg BID for twelve weeks and subsequently celecoxib 100 mg BID for 10 days. Her blood pressure was found at that time to be 162/88 mm Hg, and she had a normal physical examination. She was about to be discharged when she had a similar episode of vertigo. At that time, her blood pressure was 234/99 mm Hg, with a repeat of 222/111 mm Hg. Sublingual nifedipine was given, which brought the blood pressure back to normal. Final diagnosis was calcified meningioma, which did not require surgery. Concomitant medications included verapamil and aspirin.

A 62-year-old female (071-US0016-76132005) with a history of chronic hypertension was hospitalized after 51 days of treatment with celecoxib 200 mg BID. According to the patient, her blood pressure was 180/70 mm Hg. Concomitant medications included betaxolol and doxazosin

A 40-year-old female (062-US0265-54241602) with a history of malignant hypertension, chest pain, Type II diabetes mellitus was hospitalized after 25 days of taking celecoxib 200 mg BID complaining of chest pain. Her blood pressure was 182/110 mmHg. Renal arteriogram revealed a unilateral 40% renal artery stenosis. Concomitant medications included clonidine, lisinopril and ticlopidine. Lisinopril was discontinued and she was placed on losartan and metoprolol. Forty-nine days later the patient was readmitted with a blood pressure of 196/113 mm Hg. Isosorbide was added to her treatment regimen with marked improvement noted.

A 54-year-old female (022-US0114-0345) with a history of hypertension, chest pain and type II diabetes was hospitalized after 88 days of taking celecoxib 400 mg BID. She was severely hypertensive and was diagnosed with hypertensive encephalopathy.

cc:

ORIG:

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**7. APPENDIX:**

**1. Executive CAC Recommendations and Conclusions on Carcinogenicity Studies**

**Executive CAC**  
**October 27, 1998**

**Committee:** Joseph DeGeorge, Ph.D., HFD024, Chair  
Joseph Contrera, Ph.D., HFD-900, Member  
Barry Rosloff, Ph.D., HFD-120, Alternate Member  
Josie Yang, Ph.D., HFD-550, Presenting Reviewer  
Andrea Weir, Ph.D., HFD-550, Division Team Leader

**Author of Draft:** Josie W. C. Yang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

**NDA 20-998**

**Name of Drug:** Celecoxib; Celebrex™; SC-58635  
**Sponsor:** G.D. Searle & Co

**Background:** Celecoxib (SC-58635 - C17H14F3N3O2S), a newly developed cyclooxygenase-2 (COX-2) inhibitor, is a diarylsubstituted pyrazole compound. Celecoxib is proposed for the treatment of the signs and symptoms of RA and OA, and for the management of acute and chronic pain. Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an in vivo micronucleus test in rat bone marrow.

**Mouse Carcinogenicity Study:** Groups of mice were given celecoxib at the doses shown in the following table via dietary admix.

Group	Dose (mg/kg)				
	♂		♀		
	Wk1-18	Wk 19-104	Wk1-18	Wk19-22	Wk 23-104
N	0*	0	0	0	0
1	25	12.5	50	25	25
2	50	25	100	50	50
3	75	37.5	150	75	150

The doses selected in this study were based on toxicity findings of a 13-week dietary admix (♂: 0, 75, 150 and 300 mg/kg; ♀: 0, 150, 300 and 1000 mg/kg). Due to excessive toxicity, high dose group (♂ and ♀) was terminated at Week 80. Treatment-caused histopathological changes were limited to the GI tract (erosion/ulceration with associated chronic active inflammation in the glandular stomach, duodenum, jejunum, ileum, cecum, and colon at one or more sites). Non-dose dependent pyelonephritis was only observed in drug-treated ♂ with low incidence rates. The GI injury was the most common cause of death in high-dose animals. No treatment-induced increases in the tumor incidence rates were identified.

**Rat Carcinogenicity Study:** Groups of rats were given SC-58635 in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 as a suspension once daily by oral gavage at a dose schedule as shown in the following table for 104 weeks.

Group	Dose mg/kg/day				
	Wk 1-17	Wk 18-77		Wk 78-104	
	♂ & ♀	♂	♀	♂	♀
1 (Control)	0	0	0	0	0
2 (Low)	20	20	20	20	5
3 (Mid)	80	80	80	80	10
4 (High)	400	400	200	200	200

The doses selected in this study were based on the results of a 4-week oral gavage study at doses of 0, 20, 80,

400 and 600 mg/kg in which it was shown that absorption of SC-58635 attained a plateau at dosages  $\geq 400$  mg/kg/day for  $\sigma$  rats [AUC<sub>0-24</sub> ( $\mu\text{g}\cdot\text{hr}/\text{ml}$ ) for 400 and 600 mg/kg  $\sigma$ : 195.9 and 97.6 on Day 1 and 60.7 and 58.2 on Day 26, respectively] and deaths were seen at 600 mg/kg/day for  $\text{f}$  rats. Treatment-related deaths increased with dose and occurred in the mid- and high-dose  $\sigma$  and all treated female groups (Group 2: 4 $\text{f}$ ; Group 3: 4 $\sigma$  & 20 $\text{f}$ ; Group 4: 19 $\sigma$  & 31 $\text{f}$ ). Due to excessive toxicity, high dose females were sacrificed at Week 79. The major non-neoplastic findings were dose-dependent increased incidence of GI necrosis/perforation/inflammation with secondary peritonitis and pyelonephritis ( $\sigma$  only). No treatment-induced increases in the tumor incidence rates were identified.

#### Executive CAC Recommendations and Conclusions

1. The Committee found that both rat and mouse carcinogenicity studies were acceptable.
2. Based on observed GI and kidney toxicity findings as well as mortality, the MTD was reached for both mouse and rat studies.
3. Celecoxib was not carcinogenic in rats or mice.

  
Joseph DeGeorge, Ph.D.  
Chair, Executive CAC

cc:\

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/JYang  
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/ASeifried, HFD-024

I. Kalona

**Arthritis Advisory Committee**

Food and Drug Administration  
Center for Drug Evaluation and Research

**December 1, 1998**

Town Center Hotel  
8727 Colesville Road, Silver Spring, MD

**NDA 20-998, Celebrex™, (celecoxib), Searle**

**Contents**

**Agenda and Questions**

**Volume I**

**Medical Reviews**

**Primary Medical Review**

**Secondary Medical Review**

**Safety Review**

**Gastrointestinal Review**

**Renal Review**

**Volume II**

**Statistical Reviews**

**Osteoarthritis**

**Rheumatoid Arthritis**

**Pain**

**Volume III**

**Pharmacology Reviews**

**Biopharmaceutics**

**Pharmacology/Toxicology**

**Arthritis Advisory Committee**

**December 1, 1998**

**NDA 20-998 Celebrex™ (celecoxib) Searle**

**Volume I: FDA Medical Reviews**

**Osteoarthritis**

**Statistical Review**

STATISTICAL REVIEW AND EVALUATION

DRAFT

**NDA:** 20-998/1P  
**Applicant:** G.D. Searle & Co.  
**Name of Drug:** Celebra<sup>TM</sup> (Celecoxib) Capsules  
**Route of Administration:** Oral  
**Documents Reviewed:** NDA 20-998: Vol. 1.1-1.3, 1.129-1.131, 1.150-257, 1.422-441  
(Total Vol. : 1.1-1.452) (submitted June 30, 1998)  
**Indication:** Treatment of Osteoarthritis  
**Related INDs:** 48,395; 52,153; 52,613; 53,125; 53,734  
**Medical Officers:** James Witter, MD ( HFD-550 ) (Osteoarthritis)  
Lawrence Goldkind MD (HFD-180) (Gastrointestinal)

**Table of Contents:**

Background ..... 1  
Efficacy Analysis..... 8  
GI analysis.....17  
Integrated Safety Analysis.....31  
Summary and Conclusions.....38  
Appendix.....40

**1. Background**

Celecoxib (SC-58635) is a novel compound that selectively inhibits cyclooxygenase 2 (COX-2), the inducible form of the enzyme cyclooxygenase (also known as prostaglandin G/H synthase). Celecoxib is an oral anti-inflammatory and analgesic agent developed for treating the signs and symptoms of Osteoarthritis (OA) and rheumatoid arthritis (RA) and for the management of pain. All these three indications were submitted under this NDA 20-998.

OA is primarily a disease of altered cartilage metabolism of multifactorial etiology. Prevalence parallels age, with the disease being more common in women than in men. Synovial inflammation may be present in advanced disease and can occur early in variants of OA. Prominent signs and symptoms include articular pain, stiffness and functional impairment. OA of the knee and hip are associated with disability, particularly with respect to ambulation, although degenerative changes of the spine, hands and feet also lead to functional limitation. In patients with OA, mechanical stress leads to altered cartilage metabolism and eventually disruption of matrix integrity. Microfractures and erosions are the result, leading to eventual disruption and loss of articular cartilage. This loss produces a disruption of joint architecture which results in subarticular cysts, bony sclerosis, and osteophyte formation. The disruption of joint architecture typically produces pain with joint loading. Joint instability may also result. Stiffness, though common, is not prominent and may result from synovial involvement. Because mechanical stress is a principle component in the pathophysiology of OA, the disease typically occurs in weight-bearing joints.

This reviewer reviewed the indication of treatment of osteoarthritis. For this indication, the sponsor submitted eleven studies, which included five pivotal, five supportive, and one long-term safety study which were conducted in patients with OA to provide evidence of the efficacy of celecoxib for the

**Table 1.6. WOMAC Osteoarthritis Index**

<b>How much pain do you have?</b>		
-	walking on a flat surface	
-	going up or down stairs	
-	at night while in bed	
-	sitting or lying	
-	standing upright	
<b>Amount of joint stiffness</b>		
-	How severe is your stiffness after first awakening in the morning?	
-	How severe is your stiffness after sitting, lying, or resting later in the day?	
<b>Ability to move around and to look after yourself - What degree of difficulty did you have with:</b>		
-	descending stairs	- getting in/out of car
-	ascending stairs	- going shopping
-	rising from sitting	- putting on socks/stockings
-	standing	- taking off socks/stockings
-	bending to floor	- rising from bed
-	walking on flat surface	- lying in bed
		- getting in/out of bath
		- sitting
		- getting on/off toilet
		- heavy domestic duties
		- light domestic duties
<b>Score: 0=none, 1=mild, 2=moderate, 3=severe, and 4=extreme</b>		

The Incidence of and Time to Withdrawal Due to Lack of Arthritis Efficacy (treatment failure) are presented for all pivotal studies. Time to Withdrawal Due to Lack of Arthritis Efficacy was calculated as the difference between the last dose date and the first dose date plus one day. Patients who completed the study according to the protocol or withdrew for reasons other than lack of arthritis efficacy were censored at the final study visit or at the withdrawal time, respectively.

The APS Pain Measure consisted of five questions as shown in Table 1.7. The first question required a yes or no response. The remaining questions required rating the pain and its interference with daily activities on a scale of 0 (no pain) to 10 (worst pain possible). Patients completed the APS Pain Measure at Baseline and daily thereafter for the first seven days of dosing with study medication.

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**Table 1.7. APS Pain Scale**

	Question	Scale
1	Have you experienced any pain in the past 24 hours?	yes/no
2	How much pain are you having right now?	0-10
3	Indicate the worst pain you have had in the past 24 hours.	0-10
4	Indicate the average level of pain you have had in the past 24 hours	0-10
5	Indicate how pain has interfered with you in:	
	• General Activity	0-10
	• Mood	0-10
	• Walking Ability	0-10
	• Relations with other People	0-10
	• Sleep	0-10
	• Normal Work, Including Housework	0-10
	• Enjoyment of Life	0-10

The reasons for early termination are listed in Tables 1.8 and 1.9.

**Table 1.8. Reasons for Study Termination (All Randomized Patients: 12-Week Pivotal Studies 020, 021, and 054)**

Study	Number of Osteoarthritis Patients by Treatment Group				
	Placebo	Celecoxib			Naproxen
		50 mg BID	100 mg BID	200 mg BID	500 mg BID
<b>Study 020</b>	(n=204)	(n=203)	(n=197)	(n=202)	(n=198)
<b>Total Completed</b>	91 (45%)	118 (58%)	116 (59%)	129 (64%)	116 (59%)
<b>Total Withdrawn</b>	113 (55%)	85 (42%)	81 (41%)	73 (36%)	82 (41%)
Lost to Follow-up	3 ( 1%)	1 (<1%)	3 ( 2%)	1 (<1%)	3 ( 2%)
Pre-Existing Violation	3 ( 1%)	1 (<1%)	0 ( 0%)	0 ( 0%)	1 (<1%)
Protocol Non-Compliance	12 ( 6%)	4 ( 2%)	7 ( 4%)	2 (<1%)	8 ( 4%)
Treatment Failure	79 (39%)	61 (30%)	40 (20%)	49 (24%)	52 (26%)
Adverse Event	16 ( 8%)	18 ( 9%)	31 (16%)	21 (10%)	18 ( 9%)
<b>Study 021</b>	(n=242)	(n=252)	(n=240 <sup>b</sup> )	(n=233)	(n=226)
<b>Total Completed</b>	119 (49%)	168 (67%)	165 (69%)	154 (66%)	147 (65%)
<b>Total Withdrawn</b>	123 (51%)	84 (33%)	75 <sup>b</sup> (31%)	79 (34%)	79 (35%)
Lost to Follow-up	5 ( 2%)	1 (<1%)	0 ( 0%)	2 (<1%)	1 (<1%)
Pre-Existing Violation	2 (<1%)	3 ( 1%)	1 (<1%)	1 (<1%)	0 ( 0%)
Protocol Non-Compliance	13 ( 5%)	8 ( 3%)	7 ( 3%)	4 ( 2%)	8 ( 4%)
Treatment Failure	89 (37%)	56 (22%)	51 (21%)	49 (21%)	40 (18%)
Adverse Event	14 ( 6%)	16 ( 6%)	16 ( 7%)	23 (10%)	30 (13%)
<b>Study 054</b>	(n=218)	(n=216)	(n=207)	(n=213)	(n=207)
<b>Total Completed</b>	79 (36%)	111 (51%)	111 (54%)	119 (56%)	118 (57%)
<b>Total Withdrawn</b>	139 (64%)	105 (49%)	96 (46%)	94 (44%)	89 (43%)
Lost to Follow-up	2 (<1%)	4 (2%)	0 ( 0%)	2 (<1%)	1 (<1%)
Pre-Existing Violation	3 ( 1%)	2 (<1%)	0 ( 0%)	3 ( 1%)	1 (<1%)
Protocol Non-Compliance	5 ( 2%)	6 (3%)	8 ( 4%)	9 ( 4%)	7 ( 3%)
Treatment Failure	112 (52%)	76 (35%)	61 (29%)	55 (26%)	51 (25%)
Adverse Event	16 ( 7%)	17 (8%)	27 (13%)	25 (12%)	29 (14%)

**Table 1.9. Reasons for Study Termination (All Randomized Patients: 6-Week Pivotal Studies 060 and 087)**

Study	Number of Osteoarthritis Patients by Treatment Group		
	Placebo	Celecoxib	
		100 mg BID	200 mg QD
<b>Study 060</b>	(n=232)	(n=231)	(n=223)
<b>Total Completed</b>	146 (63%)	194 (84%)	182 (82%)
<b>Total Withdrawn</b>	86 (37%)	37 (16%)	41 (18%)
Lost to Follow-up	2 (<1%)	4 ( 2%)	2 (<1%)
Pre-Existing Violation	2 (<1%)	2 (<1%)	2 (<1%)
Protocol Non-Compliance	6 ( 3%)	2 (<1%)	7 ( 3%)
Treatment Failure	56 (24%)	18 ( 8%)	21 ( 9%)
Adverse Event	20 ( 9%)	11 ( 5%)	9 ( 4%)
<b>Study 087</b>	(n=244)	(n=243)	(n=231)
<b>Total Completed</b>	164 (67%)	194 (80%)	191 (83%)
<b>Total Withdrawn</b>	80 (33%)	49 (20%)	40 (17%)
Lost to Follow-up	1 (<1%)	0 ( 0%)	1 (<1%)
Pre-Existing Violation	4 ( 2%)	6 ( 2%)	4 ( 2%)
Protocol Non-Compliance	8 ( 3%)	7 ( 3%)	5 ( 2%)
Treatment Failure	55 (23%)	27 (11%)	24 (10%)
Adverse Event	12 ( 5%)	9 ( 4%)	6 ( 3%)

**Table 1.10. Number of OA Patients Who Completed or Withdrew from the GI endoscopy Studies (Randomized Patients: Supportive Studies 062, and 071)**

Study	Number of Osteoarthritis Patients by Treatment Group			
	Celecoxib	Naproxen	Diclofenac	Ibuprofen
	200 mg BID	500 mg BID	75 mg BID	800 mg TID
<b>Study 062</b>	(n=194)	(n=195)	---	---
<b>Total Completed</b>	150 (77%)	105 (54%)	---	---
<b>Total Withdrawn</b>	44 (23%)	90 (46%)	---	---
<b>Study 071</b>	(n=272)	---	(n=285)	(n=255)
<b>Total Completed</b>	220 (81%)	---	207 (73%)	167 (65%)
<b>Total Withdrawn</b>	52 (19%)	---	78 (27%)	88 (35%)

## 2. Efficacy Analysis

### 2.1 Intent-To-Treat Patients

A patient will be included in the Intent-to-Treat Cohort if he or she is randomized to treatment and has taken at least one dose of study medication.

### 2.2 Efficacy Variables:

In the study protocols for the OA studies, the endpoints originally designated primary were: Patient's Global Assessment of Arthritic Condition, Patient's Assessment of Arthritis Pain - VAS, and Physician's Global Assessment of Arthritic Condition. The per protocol secondary measures of arthritis efficacy were Functional Capacity Classification, WOMAC OA Index, Incidence of Withdrawal Due to Lack of

Arthritis Efficacy, Time to Withdrawal Due to Lack of Arthritis Efficacy, Osteoarthritis Severity Index (OASI), APS Pain Measure, Patient Assessment of Function, and SF-36 Health Survey. At the 12 February 1998 pre-NDA meeting, the Division of Anti-inflammatory, Analgesics and Ophthalmic Drug Products (HFD-550), requested modification of the primary and secondary efficacy variables. The principal change was the inclusion of the WOMAC OA Index as a primary measure of efficacy although it was not prospectively defined as a primary endpoint in the OA studies.

The final list of retrospectively defined **primary OA efficacy endpoints** included the following:

- Patient's Global Assessment of Arthritic Condition
- Patient's Assessment of Arthritis Pain - VAS
- Physician's Global Assessment of Arthritic Condition
- WOMAC OA Index (Composite score and subscores for pain, joint stiffness, and physical function)

The final list of **secondary OA efficacy endpoints** included the following:

- Incidence of Withdrawal Due to Lack of Arthritis Efficacy
- Time to Withdrawal Due to Lack of Arthritis Efficacy
- APS Pain Measure

The remaining measures,

- Functional Capacity Classification
- OASI (OA severity index)
- SF-36 Health Survey

were designated **supporting data**.

Primary treatment comparisons (celecoxib 200mg vs placebo and celecoxib 100 mg vs placebo) for primary efficacy variables were defined. Multiplicity adjustments were made for the primary treatment comparisons with Hochberg's step-up procedure to control the family-wise Type-I error at the level of 0.05. Mean change analyses (studies with a flared Baseline) or mean score analyses (studies without a flared Baseline) using analysis of covariance (ANCOVA) models were performed for Patient's Global Assessment of Arthritic Condition, Patient's Assessment of Arthritis Pain, Physician's Global Assessment of Arthritic Condition, WOMAC Osteoarthritis Index, Functional Capacity Classification, Osteoarthritis Severity Index, Quality of Life SF-36 Health Survey, APS Pain Measures, and Patient Assessment of Function. For Patient's and Physician's Global Assessments, patients were classified as 'Improved', 'No Change' or 'Worsened' based on a two-grade change criterion.

Carrying forward the last efficacy measurement will impute the efficacy measurements that are missing.

### **Multiple Comparison Adjustment**

In each study, multiplicity adjustments were made for the primary treatment comparisons with Hochberg's step-up procedure to control the family-wise Type-I error at the level of 0.05. To perform this

treatment of the signs and symptoms of OA. The pivotal studies were all double-blind, placebo-controlled trials of at least six weeks duration, in which 200 or more patients per treatment were enrolled.

### 1.1 Study Design :

**Table 1.1. Summary of Clinical Studies Conducted in Patients with OA:  
12-Week Pivotal Studies**

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-020 R: N49-98-06-020  Celecoxib Comparative Safety and Efficacy vs Naproxen in OA of the Knee	72 Investigators U.S. and Canada  5 Aug 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo
P: N49-96-02-021 R: N49-98-06-021  Celecoxib Comparative Efficacy and UGI Safety vs Naproxen in OA of the Knee	80 Investigators U.S. and Canada  26 Aug 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo
P: N49-96-02-054 R: N49-98-06-054  Celecoxib Comparative Safety and Efficacy vs Naproxen in OA of the Hip	125 Investigators U.S. and Canada  9 Jan 1997	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo

**Table 1.2. Summary of Clinical Studies Conducted in Patients with OA:  
6-Week Pivotal Studies**

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-060 R: N49-98-06-060  QD vs BID Efficacy in OA of the Knee	51 Investigators United States  29 May 1997	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Celecoxib 200mg QD or Placebo
P: N49-98-02-087 R: N49-98-06-087  QD vs BID Efficacy in OA of the Knee	101 Investigators United States  28 Jan 1998	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Celecoxib 200mg QD or Placebo

**Table 1.3. Summary of Clinical Studies Conducted in Patients with OA:  
Placebo-Controlled Supportive Studies**

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-047 R: N49-97-06-047  Dose-ranging Efficacy in OA	26 Investigators United States  9 Jan 1997	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (4 Weeks)	Celecoxib 25 mg BID, 100 mg BID or 400 mg BID or Placebo
P: N49-96-02-013 R: N49-96-16-013  Pilot Efficacy in OA	26 Investigators United States  26 Jan 1996	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (2 Weeks)	Celecoxib 40 mg BID, 100 mg BID or 200 mg BID or Placebo

**Table 1.4. Summary of Clinical Studies Conducted in Patients with OA: Active-Controlled Supportive Studies**

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: I49-96-02-042 R: I49-98-06-042  Ex-U.S. OA Trial	129 Investigators 20 countries in Australia, Europe and South Africa  2 Dec 1996	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Diclofenac 50 mg BID
P: N49-97-02-062 R: N49-98-06-062  Comparative Incidence of UGI Ulcers: Celecoxib vs Naproxen in Patients with OA and RA	75 Investigators in United States  13 May 1997	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 200 mg BID or Naproxen 500 mg BID
P: N49-97-02-071 R: N49-98-06-071  Comparative Incidence of UGI Ulcers: Celecoxib vs Diclofenac and Ibuprofen in Patients with OA and RA	121 Investigators in United States  21 Jul 1997	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 200mg BID or Diclofenac 75 mg BID or Ibuprofen 800 mg TID

## 1.2 Study Population and Design - Placebo-Controlled Studies

In order to be entered into a placebo-controlled OA trial, patients had to have been diagnosed according to the American College of Rheumatology (ACR) criteria for OA of the knee or hip. OA of the knee was defined as knee pain and radiologic evidence of OA (defined as the presence of osteophytes) plus at least one of the following three:

1. Age > 50 years;
2. Stiffness < 30 minutes;
3. Crepitus.

OA of the hip was defined as hip pain plus at least two of the following three:

1. Erythrocyte sedimentation rate (ESR, Westergren method) less than 20 mm/hour;
2. Radiographic evidence of femoral or acetabular osteophytes;
3. Radiographic evidence of joint space narrowing (superior, axial or medial).

Patients were to be in an OA flare at the Baseline Visit. The criteria for demonstrating OA flare depended on whether the patient was in Category 1 (i.e., currently receiving NSAID or analgesic therapy for his/her OA) or Category 2 (i.e., not receiving NSAID or analgesic therapy and had uncontrolled OA).

For patients in Category 1, an OA flare was demonstrated if both the Baseline Patient's and the Physician's Global Assessment of Arthritic Condition were rated as "fair," "poor" or "very poor" and the Baseline arthritis assessments met at least three of the following four criteria:

1. Patient's Assessment of Arthritis Pain (VAS) measurement of at least 40 mm;
2. An increase of two or more points in the OA Severity Index from the screening assessment;

3. An increase from the screening visit of one or more grades in the Patient's Global Assessment of Arthritic Condition;
4. An increase from the screening visit of one or more grades in the Physician's Global Assessment of Arthritic Condition.

For patients in Category 2, an OA flare was demonstrated if they met at least three of the following four criteria during the Baseline arthritis assessments:

1. Patient's Assessment of Arthritis Pain (VAS) measurement of at least 40 mm;
2. The OA Severity Index was  $\geq 7$ ;
3. The Patient's Global Assessment of Arthritic Condition was "poor" or "very poor";
4. The Physician's Global Assessment of Arthritic Condition was "poor" or "very poor."

In addition, patients in these studies were to have a Functional Capacity Classification (46) of I-III at Baseline as described by the following criteria:

<b>Class</b>	<b>Description</b>
I	Complete functional capacity with ability to carry on all usual duties without handicaps
II	Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints
III	Functional capacity adequate to perform only few or none of the duties of usual occupation or of self care
IV	Largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self care

Each of the three 12-week pivotal studies (Studies 020, 021, and 054) was a randomized, multicenter, double-blind, active- and placebo-controlled comparison study of the efficacy and safety of celecoxib 50 mg BID, 100 mg BID, and 200 mg BID and naproxen 500 mg BID in patients with OA of the knee (Studies 020 and 021) or hip (Study 054). Each study was comprised of a Screening Period, a Baseline Visit, and a 12-week Treatment Period. The Screening Visit occurred 2 to 14 days prior to the administration of the first dose of study medication, at which time each patient gave a medical history, underwent a physical examination, and had clinical laboratory tests performed. Following completion of the Screening Assessments, patients taking NSAIDs or analgesics were instructed to discontinue current NSAID or analgesic use and notify the Investigator when flare symptoms began. In Study 021, Baseline and Week 12 endoscopies were also performed.

Patients satisfying the arthritis flare criteria returned to the study site for a Baseline Visit where the SF-36 Health Survey and WOMAC Osteoarthritis Index were completed and the following Baseline arthritis assessments were performed: Patient's and Physician's Global Assessment of Arthritic Condition, OA Severity Index, and Functional Capacity Classification. In addition, patients were asked to identify the joint with the most severe OA symptoms, either right knee or left knee (Studies 020 and 021) or right hip or left hip (Study 054). This joint was identified as the "Index Joint." Patients assessed the amount of arthritis pain in the "Index Joint" using a 100 mm VAS between 0 (no pain) and 100 (very severe pain). Patients were issued American Pain Society (APS) Pain Measure and Patient Assessment of Function

questionnaires to be completed at Baseline and every evening for the first seven days of the study. Patients were instructed to return the questionnaires to the study site at the Week 2 Visit.

The arthritis assessments were repeated at the Week 2, Week 6, and Week 12 Visits. The SF-36 Health Survey and WOMAC Osteoarthritis Index were repeated at the Week 2 and Week 12 Visits. In addition, at each of the follow-up visits, adverse effects were assessed, selected clinical laboratory tests were performed, and information on concomitant medications was collected. Patients who withdrew before the end of the study had all final assessments performed at the time of withdrawal (Early Termination Visit).

The two 6-week pivotal studies (Studies 060 and 087) were conducted to confirm whether a once-a-day dose regimen was appropriate and were both randomized, parallel group, multicenter, double-blind, placebo-controlled studies comparing the efficacy of celecoxib 200 mg QD to celecoxib 100 mg BID in patients with OA of the knee. These studies were each comprised of a Screening Period, a Baseline Visit, and a six-week Treatment Period. The Screening Visit occurred 2 to 14 days prior to the administration of the first dose of study medication and was identical to the Screening Visit performed in the 12-week pivotal studies. Patients satisfying the arthritis flare criteria returned to the study site for a Baseline Visit. With the exception of the APS Pain Measure and Patient Assessment of Function, arthritis assessments performed were identical to those in the 12-week pivotal studies. The arthritis assessments were repeated at Week 2 and Week 6 Visits. The SF-36 Health Survey (Study 060 only) and WOMAC Osteoarthritis Index were repeated at the Week 6 Visit. In addition, at each of the follow-up visits, adverse effects were assessed, selected clinical laboratory tests were performed, and information on concomitant medications was collected. Patients who withdrew before the end of the study had all final assessments performed at the time of withdrawal (Early Termination Visit).

### 1.3 Description of the Scales Used for Measurement of OA Efficacy

The Patient's and Physician's Global Assessments of Arthritic Condition were made independently and were graded according to the scale in Table 1.5.

**Table 1.5. Scale for Patient's and Physician's Global Assessments of Arthritic Condition**

<b>Grade</b>	<b>Assessment</b>
1	Very good, asymptomatic and no limitation of normal activities
2	Good, mild symptoms and no limitation of normal activities
3	Fair, moderate symptoms and limitation of some normal activities
4	Poor, severe symptoms and inability to carry out most normal activities
5	Very poor, very severe symptoms that are intolerable; inability to carry out all normal activities

The Patient's Assessment of Arthritis Pain (VAS) was used for patient-identified "Index Joints". Patients assessed the amount of arthritis pain in the "Index Joint" on a 100 mm line (Visual Analog Scale) with the 0 mm point indicating no pain and 100 mm point indicating very severe pain.

The WOMAC Osteoarthritis Index is a tri-dimensional, self-administered questionnaire. The patient responded to 24 component items: five regarding pain, two regarding stiffness, and 17 regarding physical function. The questionnaire is listed in Table 1.6.

procedure, the p-values for the two primary treatment comparisons were ordered. First, the largest p-value was compared with the value of 0.05. If this value is  $\leq 0.05$ , then both treatment groups were claimed to be significant, or else, the smaller p-value was compared with the value of 0.025. If the smaller p-value is  $\leq 0.025$ , the treatment corresponding to this p-values was claimed to be significant, or else, no treatment was claimed to significant.

Four primary variables were defined in each Phase III pivotal study. To claim a celecoxib treatment group to be significantly better than placebo, WOMAC and two of the three remaining primary variables must be statistically significant against placebo with Hochberg's step-up procedure applied to the primary comparisons for each variable.

### 2.3 Study N49-96-02-020

#### **STUDY OBJECTIVES**

##### **Primary Objectives**

The primary objectives of this study were to:

1. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks with placebo in treating the signs and symptoms of OA of the knee; and
2. Evaluate the safety of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks in patients with OA of the knee.

##### **Secondary Objectives**

The secondary objectives of this study were to:

1. Compare the efficacy of naproxen 500 mg BID and placebo in treating the signs and symptoms of OA of the knee; and
2. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID with naproxen 500 mg BID in treating the signs and symptoms of OA of the knee.

##### **Study Design**

This randomized, double-blind, placebo-controlled, parallel group, multicenter study is designed to compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID versus naproxen 500 mg BID in treating the signs and symptoms of osteoarthritis (OA) of the knee. In addition, the safety of SC-58635 50 mg, 100 mg, and 200 mg administered BID will be evaluated. Patients with OA of the knee that is in a flare state and with a Functional Capacity Classification of I-III, who have not received any non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics within two days (within four days for patients receiving oxaprozin or piroxicam) before the Baseline Arthritis Assessments, are eligible for study participation.

Patients were randomized to receive either SC-58635 50 mg BID, SC-58635 100 mg BID, SC-58635 200 mg BID, naproxen 500 mg BID, or placebo. The duration of treatment was 12 weeks with follow-up visits two, six and 12 weeks after the first dose of study medication. The planned sample size for this trial was 200 patients per treatment group.

## **Analysis results**

The tables of the analysis results are presented in the appendix.

The patient disposition is listed in Table A.1.

### **Primary variables:**

For the primary efficacy variables: the mean and categorical change from baseline of the scores of Patient's Global Assessment of Arthritic Condition, (Tables A.2, A.9) and Physician's Global Assessment of Arthritic Condition (Tables A.3, A.10), the mean change from baseline of Patient's Assessment of Pain (VAS) (Table A.4), WOMAC scores (Tables A.5-A.8), SC-58635 100 mg BID and SC-58635 200 mg BID were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. There were no statistically significant differences between SC-58635 100 mg BID, SC-58635 200 mg BID and naproxen 500 mg BID for each primary efficacy assessment at most visits.

### **Secondary variables:**

The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, SC-58635 200 mg BID doses compared to placebo (Table A.11). The SC-58635 100 mg BID, and SC-58635 200 mg BID groups were statistically significantly different from placebo with regard to time to withdrawal due to lack of arthritis efficacy (Table A.12). The differences between the SC-58635 100 mg BID and SC-58635 200 mg BID groups and the naproxan group were mostly not statistically significant ( $p>0.05$ ).

For the mean change in APS pain score from baseline, the SC-58635 100 mg BID and SC-58635 200 mg BID groups were statistically superior to placebo on day 2-7 ( $p<0.05$ ) (Table A.13). The differences between the SC-58635 100 mg BID and SC-58635 200 mg BID groups and the naproxan group were not statistically significant ( $p>0.05$ ) (Table A.13).

### **Supportive variables:**

The mean changes from Baseline in the Functional Capacity Classification were statistically significantly greater ( $p<0.05$ ) for SC-58635 100 mg BID at Weeks 2 and 12 and for SC-58635 200 mg BID at all timepoints as compared to placebo (Table A.14). Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for SC-58635 100 mg BID and SC-58635 200 mg BID groups compared to placebo at Weeks 2, 6, and 12 (Table A.15). There were no statistically significant differences between the two SC-58635 treatment groups for this variable.

Study N49-96-02-021

## **STUDY OBJECTIVES**

### **Primary Objectives**

The primary objectives of this study were to:

1. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID with placebo in treating the signs and symptoms of OA of the knee;
2. Evaluate the UGI safety of SC-58635 50 mg, 100 mg, and 200 mg BID versus naproxen 500 mg BID and placebo in patients with OA of the knee; and
3. Evaluate the safety of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks in patients with OA of the knee.

### **Secondary Objectives**

The secondary objectives of this study were to:

1. Compare the efficacy of naproxen 500 mg BID and placebo in treating the signs and symptoms of OA of the knee; and
2. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID with naproxen 500 mg BID in treating the signs and symptoms of OA of the knee.

### **Study Design**

This was a double-blind, placebo-controlled, multicenter, parallel group comparison of the efficacy and UGI safety of SC-58635 versus placebo and naproxen in patients with OA of the knee. The study consisted of Arthritis Assessments at pretreatment screening, at Baseline prior to dosing with study drug, and at Week 2, Week 6, and Week 12 following the first dose of study drug. The UGI safety of SC-58635 was assessed with endoscopies performed at Baseline and Week 12 (or Early Termination) and testing was done for *Helicobacter pylori* (*H. pylori*) at Baseline and Week 12 (or Early Termination) Visit. Patients who met the inclusion criteria (see below) were randomly assigned to receive SC-58635 50 mg BID, SC-58635 100 mg BID, SC-58635 200 mg BID, naproxen 500 mg BID, or placebo. The duration of treatment was 12 weeks.

The planned sample size for this trial was 200 patients per treatment group.

### **Analysis results**

The tables of the analysis results are presented in the appendix.

The patient disposition is listed in Table A.16.

### **Primary variables:**

For the primary efficacy variables: the mean and categorical change from baseline of the scores of Patient's Global Assessment of Arthritic Condition, (Tables A.17, A.24) and Physician's Global Assessment of Arthritic Condition (Tables A.18, A.25), the mean change from baseline of Patient's Assessment of Pain (VAS) (Table A.19), WOMAC scores (Tables A.20-A.23), SC-58635 100 mg BID and SC-58635 200 mg BID were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. There were no statistically significant differences between SC-58635 100 mg BID, SC-58635 200 mg BID and naproxen 500 mg BID for each primary efficacy assessment at most visits.

### **Secondary variables:**

The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, and SC-58635 200 mg BID, compared to placebo (Table A.26). The SC-58635 100 mg BID, and SC-58635 200 mg BID groups were statistically significantly different from placebo with regard to time to withdrawal due to lack of arthritis efficacy (Table A.27). The differences between the SC-58635 100 mg BID and SC-58635 200 mg BID groups and the naproxan group were not statistically significant ( $p>0.05$ ).

For the mean change in APS pain score from baseline, the SC-58635 100 mg BID and SC-58635 200 mg BID groups were statistically superior to placebo on day 2-7 ( $p<0.05$ ) (Table A.28). The differences between the SC-58635 100 mg BID and SC-58635 200 mg BID groups and the naproxan group were not statistically significant ( $p>0.05$ ) (Table A.28).

### **Supportive variables:**

The mean changes from Baseline in the Functional Capacity Classification were statistically significantly greater ( $p<0.05$ ) for SC-58635 100 mg BID and SC-58635 200 mg BID at all timepoints as compared to placebo (Table A.29). Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for SC-58635 100 mg BID and SC-58635 200 mg BID groups compared to placebo at Weeks 2, 6, and 12 (Table A.30). There were no statistically significant differences between the two SC-58635 treatment groups for this variable.

Study N49-98-06-054

## **STUDY OBJECTIVES**

### **Primary Objectives**

The primary objectives of this study were to:

1. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks with placebo in treating the signs and symptoms of OA of the hip; and
2. Evaluate the safety of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks in patients with OA of the hip.

### **Secondary Objectives**

The secondary objectives of this study were to:

1. Compare the efficacy of naproxen 500 mg BID and placebo in treating the signs and symptoms of OA of the hip; and
2. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID with naproxen 500 mg BID in treating the signs and symptoms of OA of the hip.

### **Study Design**

This is a double-blind, randomized, placebo-controlled, multicenter, parallel group study comparing the efficacy of SC-58635 versus naproxen in patients with OA of the hip. The planned sample size for this trial was 200 patients per treatment group.

### **Analysis results**

The tables of the analysis results are presented in the appendix.

The patient disposition is listed in Table A.31.

**Primary variables:**

For the primary efficacy variables: the mean and categorical change from baseline of the scores of Patient's Global Assessment of Arthritic Condition, (Tables A.32, A.38) and Physician's Global Assessment of Arthritic Condition (Tables A.33, A.39), the mean change from baseline of Patient's Assessment of Pain (VAS) (Table A.34), WOMAC scores (Tables A.35-A.37), SC-58635 100 mg BID and SC-58635 200 mg BID were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. There were no statistically significant differences between SC-58635 100 mg BID, SC-58635 200 mg BID and naproxen 500 mg BID for each primary efficacy assessment at most visits.

**Secondary variables:**

The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, and SC-58635 200 mg BID, compared to placebo (Table A.40). The SC-58635 100 mg BID, and SC-58635 200 mg BID groups were statistically significantly different from placebo with regard to time to withdrawal due to lack of arthritis efficacy (Table A.41). The differences between the SC-58635 100 mg BID and SC-58635 200 mg BID groups and the naproxan group were not statistically significant ( $p>0.05$ ).

For the mean change in APS pain score from baseline, the SC-58635 100 mg BID and SC-58635 200 mg BID groups were statistically superior to placebo on days 1-7 ( $p<0.05$ ) (Table A.42). The differences between the SC-58635 200 mg BID group and the naproxan group were not statistically significant ( $p>0.05$ ). The naproxan group was statistically superior to the SC-58635 100 mg BID group on days 4-7 (Table A.42).

**Supportive variables:**

The mean changes from Baseline in the Functional Capacity Classification were statistically significantly greater ( $p<0.05$ ) for SC-58635 100 mg BID and SC-58635 200 mg BID at weeks 6 and 12 as compared to placebo (Table A.43). Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for SC-58635 100 mg BID and SC-58635 200 mg BID groups compared to placebo at Weeks 2, 6, and 12 (Table A.44). There were no statistically significant differences between the two SC-58635 treatment groups for this variable.

**Reviewer's Comment:** In Studies N49-96-02-020, N49-96-02-021 and N49-98-06-054, the SC-58635 100 mg BID, and SC-58635 200 mg BID groups were demonstrated to be statistically superior to the placebo group in the treatment of OA of the knee, in terms of the primary efficacy variables. There were no statistically significant differences between the SC-58635 100 mg BID, SC-58635 200 mg BID groups, and the naproxan group. These results were supported by the analyses of the secondary and the supportive variables.

**Study N49-98-06-060****STUDY OBJECTIVES****Primary Objective**

The primary objective of this study was to compare the efficacy of SC-58635 200 mg QD and SC-58635 100 mg BID with placebo in treating the signs and symptoms of OA of the knee.

**Secondary Objectives**

The secondary objectives of this study were to:

1. Compare the efficacy of SC-58635 200 mg QD with SC-58635 100 mg BID in treating the signs and symptoms of OA of the knee; and
2. Assess the safety of SC-58635 200 mg taken QD for six weeks and SC-58635 100 mg taken BID for six weeks in patients with OA of the knee.

**Study Design**

This is a double-blind, randomized, placebo-controlled, multicenter, parallel group study comparing the efficacy of SC-58635 versus placebo in treating the signs and symptoms of OA of the knee.

**Intent-to-Treat Patients**

A patient will be included in the Intent-to-Treat Cohort if he or she has OA of the knee and the knee is identified as the index joint, is randomized to treatment and has taken at least one dose of study medication.

**Analysis results**

The tables of the analysis results are presented in the appendix.

The patient disposition is listed in Table A.45.

**Primary variables:**

For the primary efficacy variables: the mean and categorical change from baseline of the scores of Patient's Global Assessment of Arthritic Condition, (Tables A.46, A.50) and Physician's Global Assessment of Arthritic Condition (Tables A.47, A.51), the mean change from baseline of Patient's Assessment of Pain (VAS) (Table A.48), WOMAC scores (Tables A.49), SC-58635 100 mg BID and SC-58635 200 mg QD were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. There were no statistically significant differences between SC-58635 100 mg BID and SC-58635 200 mg QD for each primary efficacy assessment.

**Secondary variables:**

The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, and SC-58635 200 mg QD, compared to placebo (Table A.52). The SC-58635 100 mg BID, and SC-58635 200 mg QD groups were statistically significantly different from placebo

with regard to time to withdrawal due to lack of arthritis efficacy (Table A.53). The differences between the SC-58635 100 mg BID and SC-58635 200 mg QD groups were not statistically significant ( $p>0.05$ ).

### **Supportive variables:**

The mean changes from Baseline in the Functional Capacity Classification were statistically significantly greater ( $p<0.05$ ) for SC-58635 100 mg BID and SC-58635 200 mg QD at week 2, as compared to placebo (Table A.54). At week 6, the mean changes from Baseline in the Functional Capacity Classification were numerically, but not statistically significantly greater ( $p>0.05$ ) for SC-58635 100 mg BID and SC-58635 200 mg QD, as compared to placebo (Table A.54). Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for SC-58635 100 mg BID and SC-58635 200 mg QD groups compared to placebo at Weeks 2, and 6 (Table A.55). There were no statistically significant differences between the two SC-58635 treatment groups for this variable.

### **Study N49-98-02-087**

### **STUDY OBJECTIVES**

#### **Primary Objective**

The primary objective of this study was to compare the efficacy of SC-58635 200 mg QD and SC-58635 100 mg BID with placebo in treating the signs and symptoms of OA of the knee.

#### **Secondary Objectives**

The secondary objectives of this study were to:

1. Compare the efficacy of SC-58635 200 mg QD with SC-58635 100 mg BID in treating the signs and symptoms of OA of the knee; and
2. Assess the safety of SC-58635 200 mg taken QD for six weeks and SC-58635 100 mg taken BID for six weeks in patients with OA of the knee.

#### **Study Design**

This is a double-blind, randomized, placebo-controlled, multicenter, parallel group study comparing the efficacy of SC-58635 versus placebo in treating the signs and symptoms of OA of the knee.

#### **Intent-to-Treat Patients**

A patient will be included in the Intent-to-Treat Cohort if he or she has OA of the knee and the knee is identified as the index joint, is randomized to treatment and has taken at least one dose of study medication.

#### **Analysis results**

The tables of the analysis results are presented in the appendix.

The patient disposition is listed in Table A.56.

**Primary variables:**

For the primary efficacy variables: the mean and categorical change from baseline of the scores of Patient's Global Assessment of Arthritic Condition, (Tables A.56, A.60) and Physician's Global Assessment of Arthritic Condition (Tables A.57, A.61), the mean change from baseline of Patient's Assessment of Pain (VAS) (Table A.58), WOMAC scores (Tables A.59), SC-58635 100 mg BID and SC-58635 200 mg QD were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. There were no statistically significant differences between SC-58635 100 mg BID and SC-58635 200 mg QD for each primary efficacy assessment.

**Secondary variables:**

The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, and SC-58635 200 mg QD, compared to placebo (Table A.62). The SC-58635 100 mg BID, and SC-58635 200 mg QD groups were statistically significantly different from placebo with regard to time to withdrawal due to lack of arthritis efficacy (Table A.63). The differences between the SC-58635 100 mg BID and SC-58635 200 mg QD groups were not statistically significant ( $p > 0.05$ ).

**Supportive variables:**

The mean changes from Baseline in the Functional Capacity Classification were numerically greater for SC-58635 100 mg BID and SC-58635 200 mg QD at all visits, as compared to placebo (Table A.64), but the differences were mostly not statistically significant. Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for SC-58635 100 mg BID and SC-58635 200 mg QD groups compared to placebo at Weeks 2, and 6 (Table A.65). There were no statistically significant differences between the two SC-58635 treatment groups for this variable.

**Reviewer's Comment:** : In Studies N49-98-06-060 and N49-98-02-087, the SC-58635 100 mg BID, and SC-58635 200 mg QD groups were demonstrated to be statistically superior to the placebo group in the treatment of OA of the knee, in terms of the primary efficacy variables. There were no statistically significant differences between the SC-58635 100 mg BID, and SC-58635 200 mg QD groups. These results were supported by the analyses of the secondary and the supportive variables.

**3. GI analysis****Study N49-96-02-021****Study Design**

This was a double-blind, placebo-controlled, multicenter, parallel group comparison of the efficacy and UGI safety of SC-58635 versus placebo and naproxen in patients with OA of the knee. The study consisted of Arthritis Assessments at pretreatment screening, at Baseline prior to dosing with study drug, and at Week 2, Week 6, and Week 12 following the first dose of study drug. The UGI safety of SC-58635 was assessed with endoscopies performed at Baseline and Week 12 (or Early Termination) and testing was done for *Helicobacter pylori* (*H. pylori*) at Baseline and Week 12 (or Early Termination) Visit. Patients who met the inclusion criteria were randomly assigned to receive SC-58635 50 mg BID, SC-58635 100 mg BID, SC-58635 200 mg BID, naproxen 500 mg BID, or placebo. The duration of treatment was 12 weeks.

A UGI endoscopic examination was performed within seven days prior to the first dose of study medication. The mucosa of the stomach and the duodenum were each assigned a separate score using the scale shown in the following table. Erythema was not included in the mucosal scoring scale.

### Mucosal Scoring Scale

Grade	Description
0	No visible lesions (i.e., normal mucosa)
1	1-10 petechiae
2	>10 petechiae
3	1-5 erosions*
4	6-10 erosions*
5	11-25 erosions*
6	>25 erosions*
7	Ulcer**

\* An erosion was defined as any break in the mucosa without depth

\*\* An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth.

### Patient Populations Analyzed - Endoscopy Analysis

#### Intent-to-Treat (ITT) Cohort- Endoscopy Analysis

The ITT Cohort included all patients who were randomized to treatment and had taken at least one dose of study medication.

#### Evaluation of UGI Endoscopy Results

Crude ulcer rate (score=7) at Week 12 (or Final Visit) were analyzed with CMH tests. For each patient there were three possible outcome categories: known ulcer, known no ulcer and unknown. Last observation carried forward (LOCF) was used for the known ulcer outcome only.

### UGI ENDOSCOPY RESULTS

The number of gastroduodenal ulcers (i.e., a gastric or duodenal score of seven) in each treatment group was determined by endoscopy performed at Baseline and Week 12 (or Early Termination). Observed counts of gastroduodenal ulcer by treatment group and observation timepoint are presented in Table 3.1. Endoscopy results for timepoints prior to Week 12 represent results from Early Termination endoscopies. Crude ulcer rates are presented in Table 3.2. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastroduodenal ulceration showed a statistically significant treatment difference ( $p < 0.001$ ). Ulcers developed in 4 (4%) placebo patients, 8 (5%) SC-58635 50 mg BID patients, 7 (5%) SC-58635 100 mg BID patients, 13 (9%) SC-58635 200 mg BID patients and 34 (23%) naproxen 500 mg BID patients (Table 3.2). Pairwise comparisons showed the incidence of ulceration in the naproxen group to be significantly greater compared with the other

treatment groups ( $p < 0.001$ ). There was no difference over the 12 weeks of the study in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ( $p \geq 0.173$ ). Also, there was no difference in the incidence of ulcers among the SC-58635 groups ( $p \geq 0.204$ ) (Table 3.2). These results were confirmed by analyses of the Final Visit endoscopy that included all patients who had an endoscopy (i.e., excluding only patients without a follow up endoscopy). Based on this analysis 5 (2%) placebo patients, 8 (3%) SC-58635 50 mg BID patients, 7 (3%) SC-58635 100 mg BID patients, 13 (6%) SC-58635 200 mg BID patients and 34 (16%) naproxen 500 mg BID patients developed an ulcer. The incidence of ulceration was significantly greater in the naproxen 500 mg BID group compared with all other treatment groups ( $p < 0.001$ ) and there were no differences between placebo and any of the SC-58635 groups ( $p \geq 0.073$ ). Further, there was no difference in the incidence of ulceration between any of the SC-58635 groups ( $p \geq 0.168$ ) (Table 3.2).

**TABLE 3.1 GASTRODUODENAL ENDOSCOPY RESULTS- N49- 96- 02- 021  
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL  
ITT - KNEE AND HIP PATIENTS**

STUDY DAYS	PLACEBO (N=247)		SC-58635 50MG BID (N=258)		SC-58635 100MG BID (N=239)		SC-58635 200MG BID (N=237)		NAPROXEN 500MG BID (N=233)	
	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
WK 2 (2-28)	63	1	30	2	30	1	25	2	19	2
WK 6 (29-76)	37	1	32	3	34	3	40	2	34	10
WK 12(77-91)	102	2	156	3	148	3	137	9	112	22
>91	10	1	7	0	8	0	6	0	11	0
TOTAL	212	5	225	8	220	7	208	13	176	34

**TABLE 3.2 GASTRODUODENAL ENDOSCOPY RESULTS (a)- N49- 96- 02- 021  
ANALYSIS OF CRUDE ULCER RATE  
ITT - KNEE AND HIP PATIENTS**

	PLACEBO (N=247)	SC-58635 50MG BID (N=258)	SC-58635 100MG BID (N=239)	SC-58635 200MG BID (N=237)	NAPROXEN 500MG BID (N=233)	OVERALL p-VALUE (c)				
WEEK 12										
CRUDE ULCER RATE (a) :						<0.001				
NO ULCER	102 (96%)	156 (95%)	148 (95%)	137 (91%)	112 (77%)					
ULCER	4 (4%)	8 (5%)	7 (5%)	13 (9%)	34 (23%)					
UNKNOWN (WITHOUT ENDO/WITH ENDO)	141 (41/100)	94 (32/62)	84 (20/64)	87 (22/65)	87 (34/53)					
FINAL										
CRUDE ULCER RATE (b) :						<0.001				
NO ULCER	212 (98%)	225 (97%)	220 (97%)	208 (94%)	176 (84%)					
ULCER	5 (2%)	8 (3%)	7 (3%)	13 (6%)	34 (16%)					
UNKNOWN (WITHOUT ENDO/WITH ENDO)	30 (30/0)	25 (25/0)	12 (12/0)	16 (16/0)	23 (23/0)					
p-VALUES FOR TREATMENT COMPARISONS (d) :										
	100MG BID	200MG BID	50MG BID	100MG BID	200MG BID	200MG BID	NAPROXEN	NAPROXEN	NAPROXEN	NAPROXEN
	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.
	PLACEBO	PLACEBO	PLACEBO	50MG BID	50MG BID	100MG BID	PLACEBO	50MG BID	100MG BID	200MG BID
WEEK 12:	0.781	0.173	0.644	0.992	0.204	0.233	<0.001	<0.001	<0.001	<0.001
FINAL:	0.642	0.073	0.472	0.903	0.168	0.221	<0.001	<0.001	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the visit window;

Unknown: other cases; Window is (+/-) 7 days of the scheduled time

(b) Based on the final endoscopy result of each patient

(c) Cochran- Mantel- Haenszel test of overall comparison stratified by baseline status (p- value from Row Mean Scores Differ),

'unknown' patients are excluded from the analysis

(d) Cochran- Mantel- Haenszel test of treatment comparison stratified by baseline status (p- value from Row Mean Scores Differ),

'unknown' patients are excluded from the analysis

Observed counts of gastric ulcer by treatment group and observation timepoint are presented in Table 3.3. Endoscopy results for timepoints prior to Week 12 represent results from Early Termination endoscopies. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.4. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastric ulceration showed a statistically significant treatment difference ( $p < 0.001$ ). Ulcers developed in 4 (4%) placebo patients, 8 (5%) SC-58635 50 mg BID patients, 7 (5%) SC-58636 100 mg BID patients, 10 (7%) SC-58635 200 mg BID patients and 25 (18%) naproxen 500 mg BID patients. Pairwise comparisons showed the incidence of ulceration in the naproxen group to be significantly greater compared with all other treatment groups ( $p \leq 0.004$ ). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ( $p \geq 0.375$ ) or in the incidence of ulcers among the SC-58635 groups ( $p \geq 0.529$ ). The trend in crude erosion/ulcer rate was similar to that of the crude ulcer rate with the pairwise comparisons showing no statistically significant differences between the placebo and SC-58635 groups ( $p \geq 0.459$ ) or between the SC-58635 dose groups ( $p \geq 0.191$ ) and finding statistically significant differences between the naproxen group and all other treatment groups including placebo ( $p < 0.001$ ) (Table 3.4). These results were confirmed by analyses of crude ulcer and erosion/ulcer rates for the Final Visit endoscopy that included all patients who had an endoscopy (i.e., excluding only patients without a follow-up endoscopy). Based on this analysis 5 (2%) placebo patients, 8 (3%) SC-58635 50 mg BID patients, 7 (3%) SC-58635 100 mg BID patients, 10 (5%) SC-58635 200 mg BID patients and 25 (12%) naproxen 500 mg BID patients developed an ulcer. The incidence of ulceration was significantly greater in naproxen 500 mg BID compared with all other treatment ( $p < 0.005$ ) and there were no differences between placebo and any SC-58635 groups ( $p \geq 0.210$ ). Further, there was no difference in the incidence of ulceration between any of the SC-58635 groups ( $p \geq 0.489$ ) (Table 3.4).

TABLE 3.3 GASTRIC ENDOSCOPY RESULTS-- N49- 96- 02- 021  
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL  
ITT - KNEE AND HIP PATIENTS

	PLACEBO		SC-58635 50MG BID		SC-58635 100MG BID		SC-58635 200MG BID		NAPROXEN 500MG BID	
	(N=247)		(N=258)		(N=239)		(N=237)		(N=233)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
WK 2 (2-28)	63	1	30	2	30	1	26	1	19	2
WK 6 (29-76)	37	1	32	3	34	3	41	1	39	5
WK 12 (77-91)	102	2	156	3	148	3	138	8	116	18
>91	10	1	7	0	8	0	6	0	11	0
TOTAL	212	5	225	8	220	7	211	10	185	25

APPEARS THIS WAY  
ON ORIGINAL

**TABLE 3.4 GASTRIC ENDOSCOPY RESULTS (a)- N49- 96- 02- 021  
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE  
ITT - KNEE AND HIP PATIENTS**

	PLACEBO	SC-58635	SC-58635	SC-58635	NAPROXEN					
		50MG BID	100MG BID	200MG BID	500MG BID	OVERALL				
	(N=247)	(N=258)	(N=239)	(N=237)	(N=233)	p-VALUE (d)				
WEEK 12										
CRUDE ULCER RATE (a) :						<0.001				
NO ULCER	102 (96%)	156 (95%)	148 (95%)	138 (93%)	116 (82%)					
ULCER	4 (4%)	8 (5%)	7 (5%)	10 (7%)	25 (18%)					
UNKNOWN (WITHOUT ENDO/WITH ENDO)	141 (41/100)	94 (32/62)	84 (20/64)	89 (22/67)	92 (34/58)					
CRUDE EROSION/ULCER RATE:						<0.001				
NO EROSION/ULCER	76 (72%)	127 (77%)	111 (72%)	106 (72%)	51 (36%)					
EROSION/ULCER (c)	30 (28%)	37 (23%)	44 (28%)	42 (28%)	90 (64%)					
UNKNOWN (WITHOUT ENDO/WITH ENDO)	141 (41/100)	94 (32/62)	84 (20/64)	89 (22/67)	92 (34/58)					
FINAL										
CRUDE ULCER RATE (b) :						<0.001				
NO ULCER	212 (98%)	225 (97%)	220 (97%)	211 (95%)	185 (88%)					
ULCER	5 (2%)	8 (3%)	7 (3%)	10 (5%)	25 (12%)					
UNKNOWN (WITHOUT ENDO/WITH ENDO)	30 (30/0)	25 (25/0)	12 (12/0)	16 (16/0)	23 (23/0)					
CRUDE EROSION/ULCER RATE:						<0.001				
NO EROSION/ULCER	160 (74%)	178 (76%)	165 (73%)	167 (76%)	89 (42%)					
EROSION/ULCER (c)	57 (26%)	55 (24%)	62 (27%)	54 (24%)	121 (58%)					
UNKNOWN (WITHOUT ENDO/WITH ENDO)	30 (30/0)	25 (25/0)	12 (12/0)	16 (16/0)	23 (23/0)					
p-VALUES FOR TREATMENT COMPARISONS (e) :										
	100MG BID	200MG BID	50MG BID	100MG BID	200MG BID	200MG BID	NAPROXEN	NAPROXEN	NAPROXEN	NAPROXEN
	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.
	PLACEBO	PLACEBO	PLACEBO	50MG BID	50MG BID	100MG BID	PLACEBO	50MG BID	100MG BID	200MG BID
WEEK 12										
ULCER RATE:	0.801	0.375	0.658	0.981	0.593	0.529	<0.001	<0.001	<0.001	0.004
EROSION/ULCER RATE:	0.756	0.912	0.459	0.191	0.521	0.598	<0.001	<0.001	<0.001	<0.001
FINAL										
ULCER RATE:	0.657	0.210	0.503	0.893	0.509	0.489	<0.001	<0.001	<0.001	0.005
EROSION/ULCER RATE:	0.573	0.774	0.773	0.336	0.947	0.411	<0.001	<0.001	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the visit window;

Unknown: other cases; Window is (+/-) 7 days of the scheduled time

(b) Based on the final endoscopy result of each patient

(c) Erosion/ Ulcer is defined as an endoscopy score equal to 3,4,5,6,7

(d) Cochran- Mantel- Haenszel test of overall comparison stratified by baseline status (p- value from Row Mean Scores Differ),

'unknown' patients are excluded from the analysis

(e) Cochran- Mantel- Haenszel test of treatment comparison stratified by baseline status (p- value from Row Mean Scores Differ),

'unknown' patients are excluded from the analysis

Observed counts of duodenal ulcer by treatment group and observation timepoint are presented in Table 3.5. Endoscopy results for timepoints prior to Week 12 represent results from Early Termination endoscopies. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.6. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing duodenal ulceration showed a statistically significant treatment difference (p<0.001). Ulcers developed in 3 (2%) SC-58635 200 mg BID patients and 11 (8%) naproxen 500 mg BID patients. No ulcers were reported in patients in the placebo, SC-58635 50 mg BID, and SC-58635 100 mg BID treatment groups. Pairwise comparisons showed the incidence of ulceration in the naproxen group to be significantly greater compared with all other treatment groups (p ≤0.012). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups (p>0.218) or in the incidence of ulcers among the SC-58635 groups (p ≥ 0.079). The trend in crude erosion/ulcer rate was similar to that of the crude ulcer rate with the pairwise comparisons showing no statistically significant differences between the placebo and SC-58635 groups (p ≥ 0.487) or between the SC-58635 dose groups (p ≥0.320) and finding statistically significant differences between the naproxen group and all other treatment groups including

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placebo ( $p < 0.001$ ) (Table 3.6). These results were confirmed by analyses of crude ulcer and erosion/ulcer rates for the Final Visit endoscopy that included all patients who had an endoscopy (i.e., excluding only patients without a follow-up endoscopy). Based on this analysis 3 (1%) SC-58635 200 mg BID patients and 11 (5%) naproxen 500 mg BID patients developed an ulcer. There were no ulcers in the placebo, or SC-58635 50 mg BID or 100 mg BID groups. The incidence of ulceration was significantly greater in naproxen 500 mg BID compared with all other treatment ( $p < 0.016$ ) and there were no differences between placebo and any SC-58635 treatment groups ( $p \geq 0.106$ ). Further, there was no difference in the incidence of ulceration between any of the SC-58635 treatment groups ( $p \geq 0.098$ ) (Table 3.6).

**TABLE 3.5 DUODENAL ENDOSCOPY RESULTS -- N49- 96- 02- 021  
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL  
ITT - KNEE AND HIP PATIENTS**

STUDY DAYS	PLACEBO		SC-58635		SC-58635		SC-58635		NAPROXEN	
	(N=247)		(N=258)		(N=239)		(N=237)		(N=233)	
	NO ULCER	ULCER								
WK 2 (2-28)	64	0	32	0	31	0	26	1	20	1
WK 6 (29-76)	38	0	35	0	37	0	41	1	39	5
WK 12 (77-91)	104	0	158	0	151	0	145	1	129	5
>91	11	0	7	0	8	0	6	0	11	0
TOTAL	217	0	232	0	227	0	218	3	199	11

**TABLE 3.6 DUODENAL ENDOSCOPY RESULTS (a)- N49- 96- 02- 021  
DUODENAL ENDOSCOPY RESULTS (a)  
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE  
ITT - KNEE AND HIP PATIENTS**

WEEK 12	PLACEBO		SC-58635		SC-58635		SC-58635		NAPROXEN		OVERALL p-VALUE (d)
	(N=247)		(N=258)		(N=239)		(N=237)		(N=233)		
	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	
CRUDE ULCER RATE (a):											<0.001
NO ULCER	104 (100%)	158 (100%)	151 (100%)	145 (98%)	129 (92%)						
ULCER	0 (0%)	0 (0%)	0 (0%)	3 (2%)	11 (8%)						
UNKNOWN (WITHOUT ENDO/WITH ENDO)	143 (41/102)	100 (32/68)	88 (20/68)	89 (22/67)	93 (34/59)						
CRUDE EROSION/ULCER RATE:											<0.001
NO EROSION/ULCER	99 (95%)	147 (93%)	145 (96%)	140 (95%)	111 (79%)						
EROSION/ULCER (c)	5 (5%)	11 (7%)	6 (4%)	8 (5%)	29 (21%)						
UNKNOWN (WITHOUT ENDO/WITH ENDO)	143 (41/102)	100 (32/68)	88 (20/68)	89 (22/67)	93 (34/59)						
FINAL											
CRUDE ULCER RATE (b):											<0.001
NO ULCER	217 (100%)	232 (100%)	227 (100%)	218 (99%)	199 (95%)						
ULCER	0 (0%)	0 (0%)	0 (0%)	3 (1%)	11 (5%)						
UNKNOWN (WITHOUT ENDO/WITH ENDO)	30 (29/1)	26 (26/0)	12 (12/0)	16 (16/0)	23 (23/0)						
CRUDE EROSION/ULCER RATE:											<0.001
NO EROSION/ULCER	206 (95%)	213 (92%)	215 (95%)	212 (96%)	174 (83%)						
EROSION/ULCER (c)	11 (5%)	19 (8%)	12 (5%)	9 (4%)	36 (17%)						
UNKNOWN (WITHOUT ENDO/WITH ENDO)	30 (29/1)	26 (26/0)	12 (12/0)	16 (16/0)	23 (23/0)						
p-VALUES FOR TREATMENT COMPARISONS (e):											
	100MG BID	200MG BID	50MG BID	100MG BID	200MG BID	200MG BID	NAPROXEN	NAPROXEN	NAPROXEN	NAPROXEN	
	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.	
PLACEBO	PLACEBO	PLACEBO	50MG BID	50MG BID	100MG BID	PLACEBO	50MG BID	100MG BID	200MG BID		
WEEK 12											
ULCER RATE:	#	0.218	#	#	0.079	0.142	0.004	<0.001	<0.001	<0.001	0.012
EROSION/ULCER RATE:	0.885	0.487	0.629	0.320	0.992	0.533	<0.001	<0.001	<0.001	<0.001	<0.001
FINAL											
ULCER RATE:	#	0.153	#	#	0.098	0.136	<0.001	<0.001	<0.001	<0.001	0.016
EROSION/ULCER RATE:	0.632	0.756	0.106	0.246	0.160	0.599	<0.001	0.002	<0.001	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the visit window;

Unknown: other cases; Window is (+/-) 7 days of the scheduled time

(b) Based on the final endoscopy result of each patient

(c) Erosion/ Ulcer is defined as an endoscopy score equal to 3,4,5,6,7

(d) Cochran- Mantel- Haenszel test of overall comparison stratified by baseline status (p- value from Row Mean Scores Differ),

'unknown' patients are excluded from the analysis

(e) Cochran- Mantel- Haenszel test of treatment comparison stratified by baseline status (p- value from Row Mean Scores Differ),

'unknown' patients are excluded from the analysis

# P- value is not calculable

**Reviewer's Comment:** In study N49- 96- 02- 021, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group were significantly greater compared with all other treatment groups ( $p \leq 0.05$ ). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ( $p > 0.05$ ) or in the incidence of ulcers among the SC-58635 groups ( $p \geq 0.05$ ).

### Study N49-98-06-062

#### Study Design

This was a randomized, double-blind, multicenter, parallel group comparison of the cumulative incidence of gastroduodenal ulcers in OA or RA patients receiving SC-58635 with those receiving naproxen. The study consisted of 12 weeks of treatment with visits occurring at Screening/Baseline, and 4, 8 and 12 weeks after the first dose of study medication. Endoscopies were performed pretreatment and 4, 8, and 12 weeks after the first dose of study medication. Patients who met the inclusion criteria were randomly assigned to receive either SC-58635 200 mg BID or naproxen 500 mg BID for 12 weeks.

#### STUDY OBJECTIVES

##### Primary Objective

The primary objective of this study was to compare the cumulative (up to 12 weeks) incidence of gastroduodenal ulcer associated with SC-58635 200 mg BID with that of naproxen 500 mg BID in patients with OA or RA.

#### UGI ENDOSCOPY AND ARTHRITIS EFFICACY RESULTS

##### Data Sets Analyzed

All randomized patients who received at least one dose of study medication (n=536) were included in the Endoscopy and Arthritis Efficacy ITT Cohorts.

Counts of gastroduodenal ulcers by treatment group and observation time are presented in Table 3.7. Crude ulcer rates are presented in Table 3.8. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportion of patients developing gastroduodenal ulceration showed a statistically significant treatment difference ( $p < 0.001$ ). Ulcers developed in 18 (9%) SC-58635 200 mg BID patients and 87 (41%) naproxen 500 mg BID patients. These results were confirmed by analysis of Final Visit endoscopies that included all patients who had endoscopy (i.e., excluding only patients without a Week 12 or Early Termination endoscopy). Based on this analysis 20 (8%) SC-58635 200 mg BID patients and 89 (35%) naproxen 500 mg BID patients developed a gastroduodenal ulcer over the course of the study and this difference was statistically significant ( $p < 0.001$ ) (Table 3.8).

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**TABLE 3.7 GASTRODUODENAL ENDOSCOPY RESULTS-- N49- 97- 02- 062  
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT**

STUDY	DAYS	SC- 58635 200MG BID (N= 269)		NAPROXEN 500MG BID (N= 267)	
		NO ULCER	ULCER	NO ULCER	ULCER
	2-20	12	3	6	3
WEEK 4	(21-35)	242	7	200	44
	36-48	6	0	7	0
WEEK 8	(49-63)	222	5	156	26
	64-76	2	0	1	0
WEEK 12	(77-91)	193	3	127	14
	>91	7	2	3	2

**TABLE 3.8 GASTRODUODENAL ENDOSCOPY RESULTS-- N49- 97- 02- 062  
ANALYSIS OF CRUDE ULCER RATE-ITT**

	SC-58635	NAPROXEN	
	200MG BID	500MG BID	
	(N=269)	(N=267)	p-VALUE (c)
WEEK 0-4			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	242 (96%)	200 (81%)	
ULCER	10 (4%)	47 (19%)	
UNKNOWN (WITHOUT & WITH ENDO)	17 (5/12)	20 (14/6)	
WEEK 0-8			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	222 (94%)	156 (68%)	
ULCER	15 (6%)	73 (32%)	
UNKNOWN (WITHOUT & WITH ENDO)	32 (3/29)	38 (10/28)	
WEEK 0-12			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	193 (91%)	127 (59%)	
ULCER	18 (9%)	87 (41%)	
UNKNOWN (WITHOUT & WITH ENDO)	58 (3/55)	53 (10/43)	
WEEK 0-FINAL (b)			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	246 (92%)	168 (65%)	
ULCER	20 (8%)	89 (35%)	
UNKNOWN (WITHOUT & WITH ENDO)	3 (3/0)	10 (10/0)	

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.

(b) Based on the final endoscopy result of each patient.

(c) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. Non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of gastric ulcers by treatment group and observation time are presented in Table 3.9. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.10. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastric ulceration showed a statistically significant treatment difference ( $p < 0.001$ ). Ulcers developed in 12 (6%) SC-58635 200 mg BID patients and 74 (37%) naproxen 500 mg BID patients. These results were confirmed by analyses of Final Visit endoscopies that included all patients who had an endoscopy (i.e., excluding only patients without a Week 12 or Early Termination endoscopy). Based on this analysis 13 (5%) SC-58635 200 mg BID patients compared to 76 (30%) naproxen 500 mg BID patients developed an ulcer and this difference was statistically significant ( $p < 0.001$ ). The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the difference between the SC-58635 and naproxen groups being statistically significant ( $p < 0.001$ ).

TABLE 3.9 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 062  
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635		NAPROXEN	
	200MG BID (N=269)		500MG BID (N=267)	
STUDY DAYS	NOULCER	ULCER	NOULCER	ULCER
2-20	14	1	8	1
WEEK 4 (21-35)	243	6	206	38
36-48	6	0	7	0
WEEK 8 (49-63)	225	2	160	22
64-76	2	0	1	0
WEEK 12 (77-91)	193	3	128	13
>91	8	1	3	2

TABLE 3.10 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 062  
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT

	SC-58635		NAPROXEN		p-VALUE (d)
	200MG BID (N=269)		500MG BID (N=267)		
WEEK 0-12					
CRUDE ULCER RATE (a)					<0.001
NO ULCER	193 (94%)		128 (63%)		
ULCER	12 (6%)		74 (37%)		
UNKNOWN (WITHOUT & WITH ENDO)	64 (3/61)		65 (10/55)		
CRUDE EROSION/ULCER RATE (b)					<0.001
NO EROSION/ULCER	162 (79%)		65 (32%)		
EROSION/ULCER	43 (21%)		137 (68%)		
UNKNOWN (WITHOUT & WITH ENDO)	64 (3/61)		65 (10/55)		
WEEK 0-FINAL (c)					
CRUDE ULCER RATE (a)					<0.001
NO ULCER	253 (95%)		181 (70%)		
ULCER	13 (5%)		76 (30%)		
UNKNOWN (WITHOUT & WITH ENDO)	3 (3/0)		10 (10/0)		
CRUDE EROSION/ULCER RATE (b)					<0.001
NO EROSION/ULCER	180 (68%)		59 (23%)		
EROSION/ULCER	86 (32%)		198 (77%)		
UNKNOWN (WITHOUT & WITH ENDO)	3 (3/0)		10 (10/0)		

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.

(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.

(c) Based on the final endoscopy result of each patient.

(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. Non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of duodenal ulcers by treatment group and observation time are presented in Table 3.11. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.12. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing duodenal ulceration showed a statistically significant treatment difference ( $p=0.002$ ). Ulcers developed in 8 (4%) SC-58635 200 mg BID patients and 19 (12%) naproxen 500 mg BID patients. These results were confirmed by analyses of Final Visit endoscopies that included all patients who had an endoscopy (i.e., excluding only patients without a Week 12 or Early Termination endoscopy). Based on this analysis, 9 (3%) SC-58635 200 mg BID patients compared to 19 (7%) naproxen 500 mg BID patients developed an ulcer and this difference was statistically significant ( $p=0.030$ ). The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the difference between the SC-58635 and naproxen groups being statistically significant ( $p=0.017$ ).

TABLE 3.11 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 062  
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635		NAPROXEN	
	200MG BID		500MG BID	
	(N=269)		(N=267)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER
2-20	13	2	6	3
WEEK 4 (21-35)	247	2	234	10
36-48	6	0	7	0
WEEK 8 (49-63)	224	3	177	5
64-76	2	0	2	0
WEEK 12 (77-91)	195	1	140	1
>91	8	1	5	0

TABLE 3.12 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 062  
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT

	SC-58635		NAPROXEN		p-VALUE (d)
	200MG BID		500MG BID		
	(N=269)		(N=267)		
WEEK 0-12					
CRUDE ULCER RATE (a)					0.002
NO ULCER	195 (96%)		139 (88%)		
ULCER	8 (4%)		19 (12%)		
UNKNOWN (WITHOUT & WITH ENDO)	66 (3/63)		109 (10/99)		
CRUDE EROSION/ULCER RATE (b)					0.017
NO EROSION/ULCER	176 (87%)		125 (79%)		
EROSION/ULCER	27 (13%)		33 (21%)		
UNKNOWN (WITHOUT & WITH ENDO)	66 (3/63)		109 (10/99)		
WEEK 0-FINAL (c)					
CRUDE ULCER RATE (a)					0.030
NO ULCER	257 (97%)		238 (93%)		
ULCER	9 (3%)		19 (7%)		
UNKNOWN (WITHOUT & WITH ENDO)	3 (3/0)		10 (10/0)		
CRUDE EROSION/ULCER RATE (b)					<0.001
NO EROSION/ULCER	222 (83%)		173 (67%)		
EROSION/ULCER	44 (17%)		84 (33%)		
UNKNOWN (WITHOUT & WITH ENDO)	3 (3/0)		10 (10/0)		

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.

(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.

(c) Based on the final endoscopy result of each patient.

(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. Non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

**Reviewer's Comment:** In study N49- 97- 02- 062, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group were significantly greater compared with the SC-58635 group ( $p \leq 0.05$ ).

### Study N49- 97- 02- 071

#### Study Design

This was a randomized, double-blind, multicenter, parallel group comparison of the cumulative incidence of gastroduodenal ulcers in OA or RA patients receiving SC-58635 with those receiving diclofenac or ibuprofen. The study consisted of 12 weeks of treatment with visits occurring at Screening/Baseline, and 4, 8, and 12 weeks after the first dose of study medication. Endoscopies were performed Pretreatment and 4, 8, and 12 weeks after the first dose of study medication. Patients who met the inclusion criteria were

randomly assigned to receive SC-58635 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID for 12 weeks.

**STUDY OBJECTIVES**

**Primary Objective**

The primary objective of this study was to compare the cumulative (up to 12 weeks) incidence of gastroduodenal ulcers associated with SC-58635 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA.

Counts of patients with gastroduodenal ulcers by treatment group and observation time are presented in Table 3.13. Crude ulcer rates are presented in Table 3.14. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportion of patients developing gastroduodenal ulceration showed a statistically significant treatment difference ( $p < 0.001$ ). Ulcers developed in 25 (9%) SC-58635 200 mg BID patients, 36 (12%) diclofenac 75 mg BID patients, and 78 (28%) ibuprofen 800 mg TID patients. Pairwise comparisons indicated these differences were statistically significant for the SC-58635 200 mg BID group compared to the ibuprofen 800 mg TID group and for the diclofenac group compared to the ibuprofen group ( $p < 0.001$ ). These results were confirmed by analysis of Final Visit endoscopies that included all patients who had a posttreatment endoscopy. Based on this analysis, 25 (7%) SC-58635 200 mg BID patients, 36 (10%) diclofenac 75 mg BID patients, and 78 (23%) ibuprofen 800 mg TID patients developed a gastroduodenal ulcer over the course of the study. Pairwise comparisons indicated a statistically significant difference for the SC-58635 treatment group compared to the ibuprofen group and the diclofenac group compared to the ibuprofen group ( $p < 0.001$ ) (Table 3.14).

**TABLE 3.13 GASTRODUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071  
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT**

STUDY DAYS	SC-58635		DICLOFENAC		IBUPROFEN	
	200MG BID		75MG BID		800MG TID	
	(N=365)		(N=387)		(N=345)	
	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
2-20	9	0	12	0	8	2
WEEK 4 (21-35)	324	13	332	18	281	40
36-48	14	1	10	1	7	1
WEEK 8 (49-63)	289	6	296	9	226	14
64-76	13	1	10	1	13	1
WEEK 12 (77-91)	269	4	270	7	198	20
>91	6	0	4	0	2	0

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TABLE 3.14 GASTRODUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071  
ANALYSIS OF CRUDE ULCER RATE-ITT

	SC-58635	DICLOFENAC	IBUPROFEN		SC-58635 VS	SC-58635 VS	DICLOFENAC VS
	200MG BID	75MG BID	800MG TID	OVERALL	DICLOFENAC	IBUPROFEN	IBUPROFEN
	(N=365)	(N=387)	(N=345)	p-VALUE (c)	p-VALUE (c)	p-VALUE (c)	p-VALUE (c)
WEEK 0-4							
CRUDE ULCER RATE (a)				<0.001	0.370	<0.001	<0.001
NO ULCER	324 (96%)	332 (95%)	281 (87%)				
ULCER	13 (4%)	18 (5%)	42 (13%)				
UNKNOWN (WITHOUT & WITH ENDO)	28 (19/9)	37 (25/12)	22 (15/7)				
WEEK 0-8							
CRUDE ULCER RATE (a)				<0.001	0.220	<0.001	<0.001
NO ULCER	289 (94%)	296 (91%)	226 (80%)				
ULCER	20 (6%)	28 (9%)	57 (20%)				
UNKNOWN (WITHOUT & WITH ENDO)	56 (9/47)	63 (15/48)	62 (12/50)				
WEEK 0-12							
CRUDE ULCER RATE (a)				<0.001	0.138	<0.001	<0.001
NO ULCER	269 (91%)	270 (88%)	198 (72%)				
ULCER	25 (9%)	36 (12%)	78 (28%)				
UNKNOWN (WITHOUT & WITH ENDO)	71 (9/62)	81 (15/66)	69 (11/58)				
WEEK 0-FINAL (b)							
CRUDE ULCER RATE (a)				<0.001	0.123	<0.001	<0.001
NO ULCER	331 (93%)	336 (90%)	256 (77%)				
ULCER	25 (7%)	36 (10%)	78 (23%)				
UNKNOWN (WITHOUT & WITH ENDO)	9 (9/0)	15 (15/0)	11 (11/0)				

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.

(b) Based on the final endoscopy result of each patient.

(c) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of patients with gastric ulcers by treatment group and observation time are presented in Table 3.15. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.16. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastric ulceration showed a statistically significant treatment difference ( $p < 0.001$ ). Ulcers developed in 23 (8%) SC-58635 200 mg BID patients, 27 (9%) diclofenac 75 mg BID patients and 60 (23%) ibuprofen 800 mg TID patients and this difference was statistically significant for the SC-58635 group compared to the ibuprofen group and for the diclofenac group compared to the ibuprofen group ( $p < 0.001$ ). These results were confirmed by analyses of Final Visit endoscopies that included all patients who had a posttreatment endoscopy. Based on this analysis, 23 (6%) SC-58635 200 mg BID patients compared to 27 (7%) diclofenac 75 mg BID patients and 60 (18%) ibuprofen 800 mg TID patients developed an ulcer and this difference was statistically significant for the SC-58635 group compared to the ibuprofen group as well as the diclofenac group compared to the ibuprofen group ( $p < 0.001$ ).

The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the difference between the SC-58635 and ibuprofen group and the difference between the diclofenac and ibuprofen group being statistically significant ( $p < 0.001$ ).

**TABLE 3.15 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 071  
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT**

STUDY DAYS	SC-58635		DICLOFENAC		IBUPROFEN	
	200MG BID		75MG BID		800MG TID	
	(N=365)		(N=387)		(N=345)	
	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
2-20	9	0	12	0	8	2
WEEK 4 (21-35)	325	12	336	14	294	27
36-48	14	1	10	1	7	1
WEEK 8 (49-63)	290	5	299	7	230	10
64-76	13	1	10	1	13	1
WEEK 12 (77-91)	270	4	274	4	199	19
>91	6	0	4	0	2	0

**TABLE 3.16 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 071  
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT**

	SC-58635	DICLOFENAC	IBUPROFEN	OVERALL p-VALUE (d)	SC-58635 VS DICLOFENAC	SC-58635 VS IBUPROFEN	DICLOFENAC VS IBUPROFEN
	200MG BID (N=365)	75MG BID (N=387)	800MG TID (N=345)		p-VALUE (d)	p-VALUE (d)	p-VALUE (d)
WEEK 0-12							
CRUDE ULCER RATE (a)				<0.001	0.515	<0.001	<0.001
NO ULCER	270 (92%)	274 (91%)	199 (77%)				
ULCER	23 (8%)	27 (9%)	60 (23%)				
UNKNOWN (WITHOUT & WITH ENDO)	72 (9/63)	86 (15/71)	86 (11/75)				
CRUDE EROSION/ULCER RATE (b)				<0.001	0.224	<0.001	<0.001
NO EROSION/ULCER	226 (77%)	223 (74%)	117 (45%)				
EROSION/ULCER	67 (23%)	78 (26%)	142 (55%)				
UNKNOWN (WITHOUT & WITH ENDO)	72 (9/63)	86 (15/71)	86 (11/75)				
WEEK 0-FINAL (c)							
CRUDE ULCER RATE				<0.001	0.534	<0.001	<0.001
NO ULCER	333 (94%)	345 (93%)	274 (82%)				
ULCER	23 (6%)	27 (7%)	60 (18%)				
UNKNOWN (WITHOUT & WITH ENDO)	9 (9/0)	15 (15/0)	11 (11/0)				
CRUDE EROSION/ULCER RATE				<0.001	0.426	<0.001	<0.001
NO EROSION/ULCER	221 (62%)	228 (61%)	105 (31%)				
EROSION/ULCER	135 (38%)	144 (39%)	229 (69%)				
UNKNOWN (WITHOUT & WITH ENDO)	9 (9/0)	15 (15/0)	11 (11/0)				

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.

(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.

(c) Based on the final endoscopy result of each patient for crude ulcer rate and based on the highest score for each patient during treatment for crude erosion/ ulcer rate.

(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of patients with duodenal ulcers by treatment group and observation time are presented in Table 3.17. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.18. Over the 12 weeks of the study, for patients with know ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week12 window), the overall comparison of the proportions of patients developing duodenal ulceration showed a statistically significant treatment difference (p<0.001). Ulcers developed in 3 (1%) SC-58635 200 mg BID patients, 14 (5%) diclofenac 75 mg BID patients, and 22 (9%) ibuprofen 800 mg TID patients and these differences were statistically significant for the SC-58635 group compared to the ibuprofen group (p<0.001), and for the SC-58635 group compared to the diclofenac group (p=0.007). These results were confirmed by analyses of Final Visit endoscopies that included all patients who had a posttreatment endoscopy. Based on this analysis 3 (<1%) SC-58635 200 mg BID patients compared to 14

(4%) diclofenac 75 mg BID patients and 22 (7%) ibuprofen 800 mg TID patients developed an ulcer and these differences were statistically significant for the SC-58635 group compared to the ibuprofen group ( $p < 0.001$ ) and for the SC-58635 group compared to the diclofenac group ( $p = 0.008$ ).

The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the differences between the SC-58635 and ibuprofen groups and the SC-58635 and diclofenac groups and the diclofenac and ibuprofen groups being statistically significant at 0-Week 12 ( $p \leq 0.015$ ).

**TABLE 3.17 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071  
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT**

STUDYDAYS	SC-58635		DICLOFENAC		IBUPROFEN	
	NOULCER	ULCER	NOULCER	ULCER	NOULCER	ULCER
2-20	9	0	12	0	10	0
WEEK4 (21-35)	336	1	342	8	305	16
36-48	15	0	11	0	8	0
WEEK8 (49-63)	294	1	303	2	236	4
64-76	14	0	11	0	14	0
WEEK12 (77-91)	272	1	273	4	216	2
>91	6	0	4	0	2	0

**- TABLE 3.18 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071  
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT**

	SC-58635	DICLOFENAC	IBUPROFEN	OVERALL p-VALUE (d)	SC-58635 VS DICLOFENAC	SC-58635 VS IBUPROFEN	DICLOFENAC VS IBUPROFEN
	200MG BID (N=365)	75MG BID (N=387)	800MG TID (N=345)		p-VALUE (d)	p-VALUE (d)	p-VALUE (d)
WEEK 0-12							
CRUDE ULCER RATE (a)				<0.001	0.007	<0.001	0.055
NO ULCER	272 (99%)	273 (95%)	216 (91%)				
ULCER	3 (1%)	14 (5%)	22 (9%)				
UNKNOWN (WITHOUT & WITH ENDO)	90 (9/81)	100 (15/85)	107 (11/96)				
CRUDE EROSION/ULCER RATE (b)				<0.001	0.003	<0.001	0.015
NO EROSION/ULCER	258 (94%)	252 (88%)	191 (80%)				
EROSION/ULCER	17 (6%)	35 (12%)	47 (20%)				
UNKNOWN (WITHOUT & WITH ENDO)	90 (9/81)	100 (15/85)	107 (11/96)				
WEEK 0-FINAL (c)							
CRUDE ULCER RATE				<0.001	0.008	<0.001	0.093
NO ULCER	353 (99%)	358 (96%)	312 (93%)				
ULCER	3 (<1%)	14 (4%)	22 (7%)				
UNKNOWN (WITHOUT & WITH ENDO)	9 (9/0)	15 (15/0)	11 (11/0)				
CRUDE EROSION/ULCER RATE				<0.001	0.006	<0.001	0.008
NO EROSION/ULCER	314 (88%)	307 (83%)	248 (74%)				
EROSION/ULCER	42 (12%)	65 (17%)	86 (26%)				
UNKNOWN (WITHOUT & WITH ENDO)	9 (9/0)	15 (15/0)	11 (11/0)				

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.

(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.

(c) Based on the final endoscopy result of each patient for crude ulcer rate and based on the highest score for each patient during treatment for crude erosion/ ulcer rate.

(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

**Reviewer's Comment:** In study N49- 97- 02- 071, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group to be significantly greater compared with the SC-58635 group and the diclofenac group ( $p \leq 0.05$ ). There was no difference in the incidence of gastroduodenal and gastric ulcers

in the SC-58635 group and the diclofenac group ( $p > 0.05$ ). The incidence of duodenal ulcers in the diclofenac group was significantly greater compared with the SC-58635 group ( $p \leq 0.05$ ).

There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ( $p > 0.05$ ) or in the incidence of ulcers among the SC-58635 groups ( $p \geq 0.05$ ).

#### **4. Integrated safety:**

##### **12 week studies**

The 12-week studies and the 6-week studies were pooled separately for the safety analysis. The results are listed in Tables 4.1-4.8. The frequencies of reported adverse events are listed by body system and treatment groups. Individual adverse events within a certain body system are listed (in italic) if the p-value for the differences among treatment groups were  $\leq 0.05$  and the percentage for at least one of the treatment groups exceeds 1%. The p-values were from the Mantel-Haenszel chi-square test. Since the Mantel-Haenszel chi-square test is only asymptotically reliable, and the frequencies of reported adverse events are usually low, caution should be exercised while interpreting these p-values.

Table 4.1 lists the frequencies of all reported adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test) in the following body systems: Gastro-intestinal system, skin and appendages. Within "body as a whole", the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): Dema Peripheral, allergic reaction, and chest pain. Within "General and peripheral nervous system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): headache. Within "Gastro-intestinal system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): Abdominal pain, constipation, dyspepsia, flatulence, vomiting. Within "Musculo-skeletol system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): arthralgia. Within "skin and appendages", the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): rash. Within "urinary system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): micturition frequency.

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Table 4.1 Number of Subjects Reporting All-Causalities Adverse Events (12 week studies)

	Placebo N=685	50mg BID N=692	100mg BID N=664	200mg BID N=672	Naproxan N=656	
Body System	N(%)	N(%)	N(%)	N(%)	N(%)	P-Value*
APPLICATION SITE DISORDERS	5 (0.7)	5 (0.7)	12 (1.8)	6 (0.9)	2 (0.3)	0.576
AUTONOMIC NERVOUS SYSTEM DISORDERS	11 (1.6)	5 (0.7)	13 (2.0)	19 (2.8)	14 (2.1)	0.052
BODY AS A WHOLE-GENERAL DISORDERS	109 (15.9)	106 (15.3)	115 (17.3)	120 (17.9)	105 (16.0)	0.536
DEMA PERIPHERAL	8 (1.2)	14 (2.0)	12 (1.8)	25 (3.7)	15 (2.3)	0.026
ALLERGIC REACTION	0 (0.0)	0 (0.0)	3 (0.5)	7 (1.0)	1 (0.2)	0.048
CHEST PAIN	3 (0.4)	2 (0.3)	4 (0.6)	6 (0.9)	9 (1.4)	0.016
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	163 (23.8)	148 (21.4)	160 (24.1)	150 (22.3)	121 (18.4)	0.057
HEADACHE	140 (20.4)	115 (16.6)	129 (19.4)	110 (16.4)	90 (13.7)	0.003
ENDOCRINEDISORDERS	1 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	4 (0.6)	0.099
GASTRO-INTESTINAL SYSTEM DISORDERS	158 (23.1)	161 (23.3)	171 (25.8)	183 (27.2)	222 (33.8)	<.001
ABDOMINAL PAIN	21 (3.1)	28 (4.0)	29 (4.4)	34 (5.1)	37 (5.6)	0.014
CONSTIPATION	11 (1.6)	10 (1.4)	14 (2.1)	17 (2.5)	35 (5.3)	<.001
DYSPEPSIA	53 (7.7)	55 (7.9)	54 (8.1)	69 (10.3)	79 (12.0)	0.002
FLATULENCE	8 (1.2)	16 (2.3)	11 (1.7)	10 (1.5)	24 (3.7)	0.018
VOMITING	3 (0.4)	6 (0.9)	9 (1.4)	10 (1.5)	9 (1.4)	0.049
HEARING AND VESTIBULAR DISORDERS	5 (0.7)	6 (0.9)	6 (0.9)	5 (0.7)	2 (0.3)	0.350
HEARTRATE AND RHYTHM DISORDERS	4 (0.6)	5 (0.7)	3 (0.5)	6 (0.9)	6 (0.9)	0.421
LIVER AND BILIARY SYSTEM DISORDERS	6 (0.9)	5 (0.7)	5 (0.8)	5 (0.7)	7 (1.1)	0.722
METABOLIC AND NUTRITIONAL DISORDERS	14 (2.0)	30 (4.3)	26 (3.9)	37 (5.5)	23 (3.5)	0.076
MUSCULO-SKELETAL SYSTEM DISORDERS	38 (5.5)	31 (4.5)	33 (5.0)	34 (5.1)	20 (3.0)	0.088
ARTHRALGIA	15 (2.2)	12 (1.7)	7 (1.1)	6 (0.9)	7 (1.1)	0.030
MYO ENDO PERICARDIAL & VALVE DISORDERS	5 (0.7)	1 (0.1)	5 (0.8)	7 (1.0)	2 (0.3)	0.941
NEOPLASM	3 (0.4)	3 (0.4)	5 (0.8)	2 (0.3)	2 (0.3)	0.627
PLATELET, BLEEDING & CLOTTING DISORDERS	8 (1.2)	7 (1.0)	8 (1.2)	6 (0.9)	12 (1.8)	0.377
PSYCHIATRICDISORDERS	43 (6.3)	35 (5.1)	42 (6.3)	41 (6.1)	38 (5.8)	0.975
RED BLOOD CELL DISORDERS	1 (0.1)	3 (0.4)	3 (0.5)	4 (0.6)	4 (0.6)	0.178
REPRODUCTIVE DISORDERS, FEMALE	5 (0.7)	8 (1.2)	8 (1.2)	5 (0.7)	9 (1.4)	0.485
REPRODUCTIVE DISORDERS, MALE	2 (0.3)	1 (0.1)	1 (0.2)	2 (0.3)	0 (0.0)	0.408
RESISTANCE MECHANISM DISORDERS	9 (1.3)	18 (2.6)	19 (2.9)	15 (2.2)	14 (2.1)	0.470
RESPIRATORY SYSTEM DISORDERS	120 (17.5)	136 (19.7)	145 (21.8)	137 (20.4)	133 (20.3)	0.194
SKIN AND APPENDAGES DISORDERS	49 (7.2)	46 (6.6)	31 (4.7)	35 (5.2)	33 (5.0)	0.044
RASH	21 (3.1)	15 (2.2)	13 (2.0)	8 (1.2)	10 (1.5)	0.017
SPECIAL SENSES OTHER, DISORDERS	0 (0.0)	2 (0.3)	2 (0.3)	1 (0.1)	0 (0.0)	0.779
URINARY SYSTEM DISORDERS	19 (2.8)	20 (2.9)	26 (3.9)	24 (3.6)	20 (3.0)	0.557
MICTURITION FREQUENCY	0 (0.0)	3 (0.4)	7 (1.1)	5 (0.7)	5 (0.8)	0.048
VASCULAR (EXTRACARDIAC) DISORDERS	3 (0.4)	3 (0.4)	6 (0.9)	3 (0.4)	3 (0.5)	0.944
VISIONDISORDERS	9 (1.3)	13 (1.9)	11 (1.7)	8 (1.2)	9 (1.4)	0.698
WHITECELLANDRESIDISORDERS	5 (0.7)	2 (0.3)	2 (0.3)	0 (0.0)	3 (0.5)	0.242

\* p values were from the Mantel-Haenszel chi-square test

Table 4.2 lists the frequencies of all reported treatment related (relationship with treatment coded as “uncertain” or “probable” by the investigators) adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test) in the following body systems: Autonomic nervous system, Gastro-intestinal system. Within “central and peripheral nervous system”, the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): cramped legs. Within “Gastro-intestinal system”, the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): Abdominal pain, constipation, dyspepsia, flatulence, nausea, vomiting. Within “respiratory system”, the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): coughing. Within “skin and appendages”, the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): rash.

Table 4.2 Number of Subjects Reporting Treatment-Related Adverse Events (12 week studies)

	Placebo	50mg BID	100mg BID	200mg BID	Naproxan	
	N=685	N=692	N=664	N=672	N=656	
Body System	N(%)	N(%)	N(%)	N(%)	N(%)	P-Value*
APPLICATION SITE DISORDERS	0(0.0)	2(0.3)	4(0.6)	3(0.4)	1(0.2)	0.469
AUTONOMIC NERVOUS SYSTEM DISORDERS	5(0.7)	3(0.4)	7(1.1)	12(1.8)	10(1.5)	0.020
BODY AS A WHOLE-GENERAL DISORDERS	35(5.1)	52(7.5)	56(8.4)	59(8.8)	45(6.9)	0.126
CARDIOVASCULAR DISORDERS, GENERAL	1(0.1)	0(0.0)	0(0.0)	1(0.1)	1(0.2)	0.661
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	93(13.6)	75(10.8)	99(14.9)	85(12.6)	68(10.4)	0.264
<i>CRAMPS LEGS</i>	1(0.1)	2(0.3)	1(0.2)	7(1.0)	6(0.9)	0.008
ENDOCRINE DISORDERS	0(0.0)	0(0.0)	1(0.2)	0(0.0)	1(0.2)	0.306
GASTRO-INTESTINAL SYSTEM DISORDERS	109(15.9)	121(17.5)	135(20.3)	144(21.4)	171(26.1)	<.001
<i>ABDOMINAL PAIN</i>	16(2.3)	24(3.5)	26(3.9)	28(4.2)	33(5.0)	0.009
<i>CONSTIPATION</i>	8(1.2)	7(1.0)	10(1.5)	10(1.5)	24(3.7)	0.001
<i>DYSPEPSIA</i>	41(6.0)	44(6.4)	44(6.6)	54(8.0)	65(9.9)	0.003
<i>FLATULENCE</i>	7(1.0)	14(2.0)	10(1.5)	9(1.3)	20(3.0)	0.039
<i>NAUSEA</i>	21(3.1)	19(2.7)	20(3.0)	26(3.9)	31(4.7)	0.048
<i>VOMITING</i>	1(0.1)	4(0.6)	7(1.1)	9(1.3)	6(0.9)	0.033
HEARING AND VESTIBULAR DISORDERS	3(0.4)	3(0.4)	4(0.6)	3(0.4)	2(0.3)	0.762
HEARTRATE AND RHYTHM DISORDERS	1(0.1)	3(0.4)	2(0.3)	6(0.9)	5(0.8)	0.050
LIVER AND BILIARY SYSTEM DISORDERS	5(0.7)	5(0.7)	4(0.6)	5(0.7)	5(0.8)	0.936
METABOLIC AND NUTRITIONAL DISORDERS	12(1.8)	18(2.6)	16(2.4)	27(4.0)	15(2.3)	0.193
MUSCULO-SKELETAL SYSTEM DISORDERS	15(2.2)	12(1.7)	16(2.4)	14(2.1)	6(0.9)	0.191
MYO ENDO PERICARDIAL & VALVE DISORDERS	3(0.4)	1(0.1)	3(0.5)	3(0.4)	1(0.2)	0.709
NEOPLASM	3(0.4)	2(0.3)	1(0.2)	1(0.1)	0(0.0)	0.067
PLATELET, BLEEDING & CLOTTING DISORDERS	6(0.9)	4(0.6)	5(0.8)	4(0.6)	7(1.1)	0.717
PSYCHIATRIC DISORDERS	27(3.9)	23(3.3)	31(4.7)	29(4.3)	24(3.7)	0.847
RED BLOOD CELL DISORDERS	1(0.1)	2(0.3)	2(0.3)	3(0.4)	4(0.6)	0.136
REPRODUCTIVE DISORDERS, FEMALE	3(0.4)	3(0.4)	6(0.9)	4(0.6)	3(0.5)	0.815
REPRODUCTIVE DISORDERS, MALE	0(0.0)	1(0.1)	0(0.0)	1(0.1)	0(0.0)	0.982
RESISTANCE MECHANISM DISORDERS	4(0.6)	8(1.2)	4(0.6)	5(0.7)	7(1.1)	0.624
RESPIRATORY SYSTEM DISORDERS	29(4.2)	41(5.9)	43(6.5)	43(6.4)	29(4.4)	0.737
<i>COUGHING</i>	1(0.1)	4(0.6)	3(0.5)	3(0.4)	8(1.2)	0.029
SKIN AND APPENDAGES DISORDERS	35(5.1)	32(4.6)	20(3.0)	27(4.0)	23(3.5)	0.111
<i>RASH</i>	17(2.5)	12(1.7)	9(1.4)	8(1.2)	7(1.1)	0.026
SPECIAL SENSES OTHER, DISORDERS	0(0.0)	2(0.3)	2(0.3)	0(0.0)	0(0.0)	0.500
URINARY SYSTEM DISORDERS	10(1.5)	8(1.2)	15(2.3)	10(1.5)	8(1.2)	0.935
VASCULAR (EXTRACARDIAC) DISORDERS	1(0.1)	1(0.1)	2(0.3)	1(0.1)	2(0.3)	0.563
VISION DISORDERS	4(0.6)	9(1.3)	7(1.1)	4(0.6)	4(0.6)	0.559
WHITE CELL AND RES DISORDERS	3(0.4)	0(0.0)	2(0.3)	0(0.0)	1(0.2)	0.264

\* p values were from the Mantel-Haenszel chi-square test

Table 4.3 lists the frequencies of all reported severe adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test) in the following body systems: platelet, bleeding and clotting system, reproductive system (female). Within "Gastro-intestinal system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ( $p \leq 0.05$  by the Mantel-Haenszel chi-square test): dyspepsia.

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Table 4.3 Number of Subjects Reporting All-Causalities Severe Adverse Events (12 week studies)

	Placebo	50mgBID	100mgBID	200mgBID	Naproxan	
	N=685	N=692	N=664	N=672	N=656	
Body System	N(%)	N(%)	N(%)	N(%)	N(%)	P-Value*
APPLICATIONSITEDISORDERS	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.487
AUTONOMIC NERVOUS SYSTEM DISORDERS	0(0.0)	0(0.0)	0(0.0)	2(0.3)	1(0.2)	0.095
BODY AS A WHOLE-GENERAL DISORDERS	8(1.2)	10(1.4)	9(1.4)	16(2.4)	5(0.8)	0.909
CARDIOVASCULAR DISORDERS, GENERAL	1(0.1)	1(0.1)	0(0.0)	1(0.1)	1(0.2)	0.974
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	17(2.5)	17(2.5)	16(2.4)	14(2.1)	15(2.3)	0.677
GASTRO-INTESTINAL SYSTEM DISORDERS	16(2.3)	15(2.2)	16(2.4)	12(1.8)	23(3.5)	0.308
DYSPEPSIA	1(0.1)	5(0.7)	4(0.6)	5(0.7)	8(1.2)	0.031
HEART RATE AND RHYTHM DISORDERS	1(0.1)	1(0.1)	1(0.2)	0(0.0)	1(0.2)	0.748
LIVER AND BILIARY SYSTEM DISORDERS	2(0.3)	0(0.0)	1(0.2)	0(0.0)	2(0.3)	0.971
METABOLIC AND NUTRITIONAL DISORDERS	0(0.0)	1(0.1)	1(0.2)	0(0.0)	0(0.0)	0.633
MUSCULO-SKELETAL SYSTEM DISORDERS	6(0.9)	4(0.6)	3(0.5)	7(1.0)	1(0.2)	0.313
MYO ENDO PERICARDIAL& VALVE DISORDERS	3(0.4)	0(0.0)	0(0.0)	4(0.6)	0(0.0)	0.621
NEOPLASM	1(0.1)	1(0.1)	1(0.2)	0(0.0)	2(0.3)	0.724
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	0(0.0)	0(0.0)	1(0.1)	3(0.5)	0.012
PSYCHIATRIC DISORDERS	3(0.4)	1(0.1)	3(0.5)	1(0.1)	1(0.2)	0.370
REPRODUCTIVE DISORDERS, FEMALE	0(0.0)	0(0.0)	1(0.2)	0(0.0)	3(0.5)	0.031
RESISTANCE MECHANISM DISORDERS	2(0.3)	0(0.0)	2(0.3)	1(0.1)	1(0.2)	0.803
RESPIRATORY SYSTEM DISORDERS	6(0.9)	7(1.0)	2(0.3)	5(0.7)	5(0.8)	0.627
SKIN AND APPENDAGES DISORDERS	3(0.4)	5(0.7)	3(0.5)	1(0.1)	2(0.3)	0.282
URINARY SYSTEM DISORDERS	0(0.0)	1(0.1)	2(0.3)	0(0.0)	0(0.0)	0.704
VASCULAR (EXTRACARDIAC) DISORDERS	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.160
VISION DISORDERS	0(0.0)	0(0.0)	2(0.3)	0(0.0)	0(0.0)	0.982
WHITE CELL AND RES DISORDERS	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.487

\* p values were from the Mantel-Haenszel chi-square test

Table 4.4 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) severe adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ( $p < 0.05$  by the Mantel-Haenszel chi-square test) in the following body systems: platelet, bleeding and clotting system.

Table 4.4 Number of Subjects Reporting Treatment-Related severe Adverse Events (12 week studies)

	Placebo	50mgBID	100mgBID	200mgBID	Naproxan	
	N=685	N=692	N=664	N=672	N=656	
Body System	N(%)	N(%)	N(%)	N(%)	N(%)	P-Value*
AUTONOMIC NERVOUS SYSTEM DISORDERS	0(0.0)	0(0.0)	0(0.0)	2(0.3)	1(0.2)	0.095
BODY AS A WHOLE-GENERAL DISORDERS	2(0.3)	5(0.7)	3(0.5)	7(1.0)	0(0.0)	0.782
CARDIOVASCULAR DISORDERS, GENERAL	1(0.1)	0(0.0)	0(0.0)	0(0.0)	1(0.2)	0.982
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	8(1.2)	7(1.0)	10(1.5)	5(0.7)	6(0.9)	0.540
GASTRO-INTESTINAL SYSTEM DISORDERS	7(1.0)	13(1.9)	13(2.0)	8(1.2)	18(2.7)	0.088
METABOLIC AND NUTRITIONAL DISORDERS	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.487
MUSCULO-SKELETAL SYSTEM DISORDERS	4(0.6)	1(0.1)	1(0.2)	3(0.4)	0(0.0)	0.171
MYO ENDO PERICARDIAL & VALVE DISORDERS	1(0.1)	0(0.0)	0(0.0)	1(0.1)	0(0.0)	0.632
NEOPLASM	1(0.1)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.138
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.3)	0.042
PSYCHIATRIC DISORDERS	2(0.3)	0(0.0)	1(0.2)	0(0.0)	1(0.2)	0.500
REPRODUCTIVE DISORDERS, FEMALE	0(0.0)	0(0.0)	1(0.2)	0(0.0)	1(0.2)	0.306
RESISTANCE MECHANISM DISORDERS	1(0.1)	0(0.0)	1(0.2)	1(0.1)	1(0.2)	0.699
RESPIRATORY SYSTEM DISORDERS	2(0.3)	1(0.1)	0(0.0)	1(0.1)	1(0.2)	0.549
SKIN AND APPENDAGES DISORDERS	2(0.3)	5(0.7)	2(0.3)	1(0.1)	2(0.3)	0.446
URINARY SYSTEM DISORDERS	0(0.0)	0(0.0)	1(0.2)	0(0.0)	0(0.0)	0.987
VASCULAR (EXTRACARDIAC) DISORDERS	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.160

\* p values were from the Mantel-Haenszel chi-square test

**Reviewer's comments :**

In the three 12-week studies, the frequencies of reported adverse events by body system in the treatment groups were statistically significant (Table 4.1) in the Gastro-intestinal system ( $p < 0.001$ , with naproxan group having the highest frequency), skin and appendages ( $p = 0.044$ , Placebo group had the highest frequency) and the respiratory system ( $p = 0.024$ , the two SC-58635 groups had the highest frequency). The frequencies of the following reported adverse events (by individual events) in the treatment groups were statistically significant (Table 4.1): Dema Peripheral ( $p = 0.026$ , SC-58635 200 mg bid group had the highest frequency), allergic reaction ( $p = 0.048$ , SC-58635 200 mg bid group had the highest frequency), and chest pain ( $p = 0.016$ , the naproxan group had the highest frequency), headache ( $p = 0.003$ , placebo group had the highest frequency), Abdominal pain ( $p = 0.014$ , the SC-58635 200 mg bid group and the naproxan group had the highest frequencies), constipation ( $p < 0.001$ , the naproxan group had the highest frequency), dyspepsia ( $p = 0.002$  the SC-58635 200 mg bid group and the naproxan group had the highest frequencies), flatulence ( $p = 0.018$ , the naproxan group had the highest frequency), vomiting ( $p = 0.049$ , the SC-58635 100 and 200 mg bid groups and the naproxan group had higher frequencies), arthralgia ( $p = 0.030$ , the placebo group had highest frequency), rash ( $p = 0.017$ , the placebo group had the highest frequency), micturition frequency ( $p = 0.048$ , the placebo group had lowest frequency).

The frequencies of reported treatment-related adverse events by body system in the treatment groups were statistically significant (Table 4.2) in the autonomic nervous system ( $p = 0.020$ , with the SC-58635 200 mg bid group and the naproxan group having the highest frequencies), the Gastro-intestinal system ( $p < 0.001$ , with naproxan group having the highest frequency), heart and rhythm system ( $p = 0.05$ , with the SC-58635 200 mg bid group and the naproxan group having the highest frequencies). The frequencies of the following reported adverse events (by individual events) in the treatment groups were statistically significant (Table 4.2): Leg cramps ( $p = 0.008$ , the SC-58635 200 mg bid group and the naproxan group had the highest frequencies), abdominal pain ( $p = 0.009$ , the SC-58635 200 mg bid group and the naproxan group had the highest frequencies), constipation ( $p = 0.001$ , the naproxan group had the highest frequency), dyspepsia ( $p = 0.003$ , the SC-58635 200 mg bid group and the naproxan group had the highest frequencies), flatulence ( $p = 0.039$ , the naproxan group had the highest frequency), nausea ( $p = 0.048$ , the naproxan group had the highest frequency), vomiting ( $p = 0.033$ , the SC-58635 100 and 200 mg bid groups and the naproxan group had higher frequencies), coughing ( $p = 0.029$ , the naproxan group had highest frequency), rash ( $p = 0.026$ , the placebo group had the highest frequency).

The frequencies of reported severe adverse events by body system in the treatment groups were statistically significant (Table 4.3) in the platelet, bleeding and clotting system ( $p = 0.020$ , the SC-58635 200 mg bid group and the naproxan group had higher frequencies), female reproductive system ( $p = 0.031$ , the naproxan group had the highest frequency). The frequencies of the following reported adverse events (by individual events) in the treatment groups were statistically significant (Table 4.3): dyspepsia ( $p = 0.031$ , the naproxan group had the highest frequency).

The frequencies of reported severe treatment-related adverse events by body system in the treatment groups were statistically significant (Table 4.4) in the platelet, bleeding and clotting system ( $p = 0.042$ , the naproxan group being the only group with this event).

**6 week studies:**

Table 4.5 lists the frequencies of all reported adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ( $p < 0.05$  by the Mantel-Haenszel chi-square test) in the following body systems: Musculo-skeletal system, respiratory system.

Table 4.5 Number of Subjects Reporting All-Causalities Adverse Events (6 week studies)

Body System	Placebo N=476	100mg BID N=474	200mg QD N=454	
	N (%)	N (%)	N (%)	P-Value*
APPLICATION SITE DISORDERS	0(0.0)	3(0.6)	1(0.2)	0.513
AUTONOMIC NERVOUS SYSTEM DISORDERS	7(1.5)	8(1.7)	8(1.8)	0.725
BODY AS A WHOLE-GENERAL DISORDERS	60(12.6)	61(12.9)	48(10.6)	0.346
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	2(0.4)	0(0.0)	0.998
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	103(21.6)	88(18.6)	96(21.1)	0.839
ENDOCRINE DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
GASTRO-INTESTINAL SYSTEM DISORDERS	66(13.9)	89(18.8)	71(15.6)	0.446
HEARING AND VESTIBULAR DISORDERS	4(0.8)	5(1.1)	3(0.7)	0.772
HEART RATE AND RHYTHM DISORDERS	1(0.2)	2(0.4)	1(0.2)	0.969
LIVER AND BILIARY SYSTEM DISORDERS	0(0.0)	3(0.6)	0(0.0)	0.998
METABOLIC AND NUTRITIONAL DISORDERS	8(1.7)	7(1.5)	9(2.0)	0.728
MUSCULO-SKELETAL SYSTEM DISORDERS	23(4.8)	15(3.2)	11(2.4)	0.045
MYO ENDO PERICARDIAL & VALVE DISORDERS	1(0.2)	0(0.0)	1(0.2)	0.978
NEOPLASM	1(0.2)	1(0.2)	0(0.0)	0.388
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	2(0.4)	1(0.2)	0.457
PSYCHIATRIC DISORDERS	20(4.2)	16(3.4)	14(3.1)	0.356
RED BLOOD CELL DISORDERS	0(0.0)	1(0.2)	2(0.4)	0.146
REPRODUCTIVE DISORDERS, FEMALE	4(0.8)	2(0.4)	6(1.3)	0.436
REPRODUCTIVE DISORDERS, MALE	1(0.2)	0(0.0)	1(0.2)	0.978
RESISTANCE MECHANISM DISORDERS	5(1.1)	10(2.1)	6(1.3)	0.720
RESPIRATORY SYSTEM DISORDERS	39(8.2)	55(11.6)	58(12.8)	0.024
SKIN AND APPENDAGES DISORDERS	26(5.5)	17(3.6)	15(3.3)	0.096
SPECIAL SENSES OTHER, DISORDERS	0(0.0)	0(0.0)	2(0.4)	0.077
URINARY SYSTEM DISORDERS	9(1.9)	6(1.3)	4(0.9)	0.182
VASCULAR (EXTRACARDIAC) DISORDERS	0(0.0)	2(0.4)	1(0.2)	0.457
VISION DISORDERS	6(1.3)	4(0.8)	8(1.8)	0.506
WHITE CELL AND RES DISORDERS	1(0.2)	0(0.0)	1(0.2)	0.978

\*p values were from the Mantel-Haenszel chi-square test

Table 4.6 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ( $p < 0.05$  by the Mantel-Haenszel chi-square test) in the following body systems: Musculo-skeletal system.

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Table 4.6 Number of Subjects Reporting Treatment-Related Adverse Events (6 week studies)

Body System	Placebo N=476 N (%)	100mg BID N=474 N (%)	200mg QD N=454 N (%)	P-Value*
APPLICATION SITE DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
AUTONOMIC NERVOUS SYSTEM DISORDERS	5(1.1)	3(0.6)	5(1.1)	0.944
BODY AS A WHOLE-GENERAL DISORDERS	15(3.2)	16(3.4)	10(2.2)	0.396
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	1(0.2)	0(0.0)	0.999
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	37(7.8)	32(6.8)	40(8.8)	0.564
GASTRO-INTESTINAL SYSTEM DISORDERS	46(9.7)	56(11.8)	47(10.4)	0.723
HEARING AND VESTIBULAR DISORDERS	1(0.2)	1(0.2)	2(0.4)	0.513
HEART RATE AND RHYTHM DISORDERS	1(0.2)	2(0.4)	1(0.2)	0.969
LIVER AND BILIARY SYSTEM DISORDERS	0(0.0)	3(0.6)	0(0.0)	0.998
METABOLIC AND NUTRITIONAL DISORDERS	5(1.1)	5(1.1)	7(1.5)	0.497
MUSCULO-SKELETAL SYSTEM DISORDERS	6(1.3)	4(0.8)	0(0.0)	0.020
MYO ENDO PERICARDIAL & VALVE DISORDERS	0(0.0)	0(0.0)	1(0.2)	0.212
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
PSYCHIATRIC DISORDERS	10(2.1)	7(1.5)	7(1.5)	0.507
RED BLOOD CELL DISORDERS	0(0.0)	0(0.0)	2(0.4)	0.077
REPRODUCTIVE DISORDERS, MALE	0(0.0)	0(0.0)	1(0.2)	0.212
RESISTANCE MECHANISM DISORDERS	0(0.0)	1(0.2)	1(0.2)	0.370
RESPIRATORY SYSTEM DISORDERS	4(0.8)	7(1.5)	7(1.5)	0.339
SKIN AND APPENDAGES DISORDERS	18(3.8)	6(1.3)	10(2.2)	0.111
SPECIAL SENSES OTHER, DISORDERS	0(0.0)	0(0.0)	2(0.4)	0.077
URINARY SYSTEM DISORDERS	2(0.4)	1(0.2)	0(0.0)	0.158
VASCULAR (EXTRACARDIAC) DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
VISION DISORDERS	4(0.8)	0(0.0)	5(1.1)	0.639

\* p values were from the Mantel-Haenszel chi-square test

Table 4.7 lists the frequencies of all reported severe adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were not statistically significantly different ( $p > 0.05$  by the Mantel-Haenszel chi-square test) in all the body systems.

Table 4.7 Number of Subjects Reporting All-Causalities Severe Adverse Events (6 week studies)

Body System	Placebo N=476 N (%)	100mg BID N=474 N (%)	200mg QD N=454 N (%)	P-Value*
AUTONOMIC NERVOUS SYSTEM DISORDERS	2(0.4)	0(0.0)	0(0.0)	0.084
BODY AS A WHOLE-GENERAL DISORDERS	9(1.9)	3(0.6)	5(1.1)	0.263
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	1(0.2)	0(0.0)	0.999
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	5(1.1)	8(1.7)	8(1.8)	0.369
GASTRO-INTESTINAL SYSTEM DISORDERS	7(1.5)	9(1.9)	5(1.1)	0.652
METABOLIC AND NUTRITIONAL DISORDERS	2(0.4)	0(0.0)	0(0.0)	0.084
MUSCULO-SKELETAL SYSTEM DISORDERS	3(0.6)	1(0.2)	0(0.0)	0.067
MYO ENDO PERICARDIAL & VALVE DISORDERS	1(0.2)	0(0.0)	1(0.2)	0.978
NEOPLASM	1(0.2)	0(0.0)	0(0.0)	0.221
PSYCHIATRIC DISORDERS	1(0.2)	1(0.2)	0(0.0)	0.388
REPRODUCTIVE DISORDERS, FEMALE	0(0.0)	0(0.0)	2(0.4)	0.077
RESISTANCE MECHANISM DISORDERS	0(0.0)	3(0.6)	0(0.0)	0.998
RESPIRATORY SYSTEM DISORDERS	0(0.0)	2(0.4)	1(0.2)	0.457
SKIN AND APPENDAGES DISORDERS	5(1.1)	1(0.2)	1(0.2)	0.070
URINARY SYSTEM DISORDERS	1(0.2)	0(0.0)	0(0.0)	0.221

\* p values were from the Mantel-Haenszel chi-square test

Table 4.8 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) severe adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were not statistically significantly different ( $p > 0.05$  by the Mantel-Haenszel chi-square test) in all the body systems.

Table 4.8 Number of Subjects Reporting Treatment-Related severe Adverse Events (6 week studies)

Body System	Placebo N=476	100mg BID N=474	200mg QD N=454	
	N (%)	N (%)	N (%)	P-Value*
AUTONOMIC NERVOUS SYSTEM DISORDERS	2 (0.4)	0 (0.0)	0 (0.0)	0.084
BODY AS A WHOLE-GENERAL DISORDERS	3 (0.6)	1 (0.2)	0 (0.0)	0.067
CARDIOVASCULAR DISORDERS, GENERAL	0 (0.0)	1 (0.2)	0 (0.0)	0.999
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	4 (0.8)	3 (0.6)	3 (0.7)	0.742
GASTRO-INTESTINAL SYSTEM DISORDERS	6 (1.3)	5 (1.1)	2 (0.4)	0.194
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.2)	0 (0.0)	0 (0.0)	0.221
MUSCULO-SKELETAL SYSTEM DISORDERS	1 (0.2)	0 (0.0)	0 (0.0)	0.221
MYO ENDO PERICARDIAL & VALVE DISORDERS	0 (0.0)	0 (0.0)	1 (0.2)	0.212
PSYCHIATRIC DISORDERS	1 (0.2)	0 (0.0)	0 (0.0)	0.221
RESPIRATORY SYSTEM DISORDERS	0 (0.0)	1 (0.2)	0 (0.0)	0.999
SKIN AND APPENDAGES DISORDERS	3 (0.6)	0 (0.0)	1 (0.2)	0.233

\*p values were from the Mantel-Haenszel chi-square test

**Reviewer's comments :** In the two 6-week studies, the frequencies of reported adverse events by body system in the treatment groups were statistically significant (Table 4.5) in the musculo-skeletal system ( $p=0.045$ , Placebo group had the highest frequency) and the respiratory system ( $p=0.024$ , the two SC-58635 groups had higher frequencies). The frequencies of reported treatment related adverse events by body system in the treatment groups were statistically significant (Table 4.6) in the musculo-skeletal system ( $p=0.020$ , Placebo group had the highest frequency). The frequencies of all other reported adverse events, reported treatment-related adverse events, reported severe adverse events, reported treatment-related severe adverse events for the treatment groups were not statistically significant.

**Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):**

**Efficacy Results:**

In Studies N49-96-02-020, N49-96-02-021 and N49-98-06-054, the SC-58635 100 mg BID, and SC-58635 200 mg BID groups were demonstrated to be statistically superior to the placebo group in the treatment of OA of the knee, in terms of the primary efficacy variables. There were no statistically significant differences between the SC-58635 100 mg BID, SC-58635 200 mg BID groups, and the naproxen group. These results were supported by the analyses of the secondary and the supportive variables.

In Studies N49-98-06-060 and N49-98-02-087, the SC-58635 100 mg BID, and SC-58635 200 mg QD groups were demonstrated to be statistically superior to the placebo group in the treatment of OA of the knee, in terms of the primary efficacy variables. There were no statistically significant differences between the SC-58635 100 mg BID, and SC-58635 200 mg QD groups. These results were supported by the analyses of the secondary and the supportive variables.

**Gastro-intestinal results:**

In study N49- 96- 02- 021, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group were significantly greater compared with all other treatment groups ( $p \leq 0.05$ ). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ( $p > 0.05$ ) or in the incidence of ulcers among the SC-58635 groups ( $p \geq 0.05$ ).

In study N49- 97- 02- 062, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group were significantly greater compared with the SC-58635 group ( $p \leq 0.05$ ).

In study N49- 97- 02- 071, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group to be significantly greater compared with the SC-58635 group and the diclofenac group ( $p \leq 0.05$ ). There was no difference in the incidence of gastroduodenal and gastric ulcers in the SC-58635 group and the diclofenac group ( $p > 0.05$ ). The incidence of duodenal ulcers in the diclofenac group was significantly greater compared with the SC-58635 group ( $p \leq 0.05$ ).

**Conclusion:**

The sponsor demonstrated that the SC-58635 100 mg BID, 200 bid, 200 mg QD groups were statistically superior to the placebo group in the treatment of OA of the knee, or the hip. The SC-58635 groups had lower incidence of ulceration (gastroduodenal, gastric, duodenal) than the naproxan group. In general, the frequency of reported adverse events for the SC-58635 groups were lower than the naproxan group.

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HFD 550  
NDA 20-998  
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HFD-550/Ms. Lutwak  
HFD-725/Dr. Huque  
HFD-725/Dr. Lin  
HFD-725/Dr. Gao  
HFD-344/Dr. Carreras  
HFD-725 Chron.

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**Appendix: Tables**

**A.1 Statistical analyses for study N49-96-02-020**

Table A.1 Patient disposition- N49-96-02-020

	Placebo	SC-58635 50mg BID	SC-58635 100mg BID	SC-58635 200mg BID	NAPROXEN 500mg BID	Total
Randomized	204	203	197	202	198	1004
Week 2	171	178	179	187	184	899
Week 6	115	146	132	150	142	685
Week 12	91	118	116	129	116	570
ITT	203	203	197	202	198	1003

**A.1.1 Primary variables- primary analyses**

Table A.2 Primary variable: Patients global assessment of Arthritis mean change from baseline--study N49-96-02-020

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	203	-0.61895207	-0.67900843	-0.63917919
50. mg	203	-0.90561260	-0.87891660	-0.91815870
100 mg	197	-1.17165707	-1.19406587	-1.15334698
200 mg	202	-1.13214075	-1.12947462	-1.08819098
Naproxen (NP)	198	-1.07153909	-1.08962113	-0.95467074
Contrast				
100mg vs. PL		p= 0.0001	p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0001	p= 0.0001
100mg vs. 200mg		p=0.6469	p=0.4880	p=0.4972
100mg vs. NP		p=0.2482	p=0.2645	p=0.0395
200mg vs. NP		p=0.4819	p=0.6684	p=0.1638

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Table A.3 Primary variable: Physician's global assessment of Arthritis  
mean change from baseline--study N49-96-02-020

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	203	-0.58588367	-0.68200648	-0.66317528
50 mg	203	-0.88053921	-0.92895679	-0.92367101
100 mg	197	-1.15172312	-1.15154308	-1.13488857
200 mg	202	-1.06804926	-1.10181045	-1.01661487
Naproxen (NP)	198	-1.05470934	-1.09601711	-1.01241875
<b>Contrast</b>				
100mg vs. PL		p= 0.0001	p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0001	p= 0.0001
100mg vs. 200mg		p= 0.2969	p= 0.5730	p= 0.2003
100mg vs. NP		p= 0.2289	p= 0.5313	p= 0.1870
200mg vs. NP		p= 0.8678	p= 0.9476	p= 0.9637

Table A.4 Primary variable: Patients' assessment of Pain (VAS)  
mean change from baseline--study N49-96-02-020

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	201	-12.1062014	-16.6474573	-15.0586010
50 mg	203	-18.3721644	-17.9189424	-15.9747610
100 mg	196	-26.1486246	-25.9293698	-23.1436807
200 mg	201	-24.5744804	-24.4642813	-22.0998937
Naproxen (NP)	197	-27.2728161	-26.9555508	-22.7110434
<b>Contrast</b>				
100mg vs. PL		p= 0.0001	p= 0.0005	p= 0.0031
200mg vs. PL		p= 0.0001	p= 0.0030	p= 0.0094
100mg vs. 200mg		p=0.5139	p=0.5793	p=0.7015
100mg vs. NP		p=0.6432	p=0.6997	p=0.8746
200mg vs. NP		p=0.2632	p=0.3459	p=0.8224

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Table A.5 Primary variable: Womac composite score  
mean change from baseline--study N49-96-02-020

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	182	-3.5685252	-5.5530410
50 mg	174	-9.6524175	-9.6284772
100 mg	175	-13.4348877	-13.6402678
200 mg	181	-12.5459744	-12.0828427
Naproxen (NP)	177	-11.8750061	-11.3339654
Contrast			
100mg vs. PL		p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0001
100mg vs. 200mg		p=0.5486	p=0.3544
100mg vs. NP		p=0.2960	p=0.1734
200mg vs. NP		p=0.6500	p=0.6554

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Table A.6 Primary variable: Womac pain score  
mean change from baseline--study N49-96-02-020

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	201	-0.70188403	-1.22582027
50 mg	197	-1.97598478	-2.01497020
100 mg	196	-3.00114460	-3.11755073
200 mg	201	-2.79725690	-2.71633237
Naproxen (NP)	198	-2.69704223	-2.37705744
Contrast			
100mg vs. PL		p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0001
100mg vs. 200mg		p=0.5205	p=0.2592
100mg vs. NP		p=0.3398	p=0.0382
200mg vs. NP		p=0.7514	p=0.3387

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Table A.7 Primary variable: Womac joint stiffness  
mean change from baseline--study N49-96-02-020

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	202	-0.32961202	-0.52364706
50 mg	197	-0.89110028	-0.89737084
100 mg	196	-1.23084194	-1.23065992
200 mg	201	-1.20807264	-1.11553949
Naproxen (NP)	195	-1.13532232	-1.11453603
Contrast			
100mg vs. PL		p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0001
100mg vs. 200mg		p=0.8741	p=0.4467
100mg vs. NP		p=0.5097	p=0.4465
200mg vs. NP		p=0.6127	p=0.9947

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Table A.8 Primary variable: Womac physical functions  
mean change from baseline--study N49-96-02-020

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	184	-2.58857972	-3.93638477
50 mg	174	-6.79507377	-6.83882973
100 mg	176	-9.31779900	-9.47018393
200 mg	181	-8.51862356	-8.10791944
Naproxen (NP)	180	-8.02677075	-7.79015304
Contrast			
100mg vs. PL		p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0006
100mg vs. 200mg		p=0.4595	p=0.2645
100mg vs. NP		p=0.2331	p=0.1697
200mg vs. NP		p=0.6472	p=0.7935

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Table A.9 Primary variable: Patients global assessment of Arthritis  
categorical change from baseline--study N49-96-02-020

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg.	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	203	36 (17.7%)	153 (75.4%)	14 (6.9%)	45 (22.2%)	141 (69.5%)	17 (8.4%)	49 (24.1%)	135 (66.5%)	19 (9.4%)
50 mg	203	49 (24.1%)	152 (74.9%)	2 (1%)	55 (27.1%)	144 (70.9%)	4 (2.0%)	54 (26.6%)	147 (72.4%)	2 (1%)
100 mg	197	72 (36.6%)	124 (62.9%)	1 (0.5%)	80 (40.6%)	115 (58.4%)	2 (1.0%)	69 (35%)	126 (64%)	2 (1%)
200 mg	202	70 (34.7%)	132 (65.4%)	0 (0%)	75 (37.1%)	126 (62.4%)	1 (0.5%)	72 (35.6%)	128 (63.4%)	2 (1%)
Naproxen (NP)	198	65 (32.8%)	131 (66.2%)	2 (1%)	66 (33.3%)	129 (65.2%)	3 (1.5%)	58 (29.3%)	137 (69.2%)	3 (1.5%)
pairwise comparison										
100mg vs. PL		p= 0.001			p= 0.001			p= 0.001		
200mg vs. PL		p= 0.001			p= 0.001			p= 0.001		
100mg vs. 200mg		p=0.745			p=0.523			p=0.897		
100mg vs. NP		p=0.405			p=0.127			p=0.208		
200mg vs. NP		p=0.601			p=0.360			p=0.163		

\*Imp=Improved, Nchg=No change, Wors=worsened

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Table A.10 Primary variable: Physician's global assessment of Arthritis categorical change from baseline--study N49-96-02-020

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	203	29 (14.3%)	168 (82.8%)	6 (3%)	44 (21.7%)	152 (74.9%)	7 (3.5%)	42 (20.7%)	152 (74.9%)	9 (4.4%)
50 mg	203	51 (25.1%)	148 (72.9%)	4 (2%)	64 (31.5%)	135 (66.5%)	4 (2%)	60 (29.6%)	139 (68.5%)	4 (2%)
100 mg	197	68 (34.5%)	128 (65%)	1 (0.5%)	72 (36.6%)	122 (61.9%)	3 (1.5%)	71 (36%)	123 (62.4%)	3 (1.5%)
200 mg	202	54 (26.7%)	147 (72.8%)	1 (0.5%)	65 (32.2%)	136 (67.3%)	1 (0.5%)	64 (31.7%)	137 (67.8%)	1 (0.5%)
Naproxen (NP)	198	65 (32.8%)	131 (66.2%)	2 (1%)	70 (35.4%)	126 (63.6%)	2 (1%)	65 (32.8%)	131 (66.2%)	2 (1%)
pairwise comparison										
100mg vs. PL		p= 0.001			p= 0.001			p= 0.001		
200mg vs. PL		p= 0.001			p= 0.006			p= 0.003		
100mg vs. 200mg		p=0.096			p=0.447			p=0.448		
100mg vs. NP		p=0.675			p=0.862			p=0.558		
200mg vs. NP		p=0.218			p=0.556			p=0.867		

\*Imp=Improved, Nchg=No change, Wors=worsened

**A.1.2 Secondary Variables**

Table A.11 Secondary variable: Patients' withdrawal due to lack of efficacy study N49-96-02-020

Treatment	withdrawal due to lack of efficacy		pairwise comparison
	Yes N (%)	No N (%)	
Placebo (PL)	79 (38.9%)	124 (61.1%)	100mg vs. PL: p= 0.001 200mg vs. PL : p= 0.002 100mg vs. 200mg: p=0.344 100mg vs. NP: p=0.162 200mg vs. NP: p=0.645
50 mg	61 (30.05%)	142 (69.95%)	
100 mg	40 (20.3%)	157 (79.7%)	
200 mg	49 (24.3%)	153 (75.7%)	
Naproxen (NP)	52 (26.3%)	146 (73.7%)	

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Table A.12 Secondary variable: Time to withdrawal due to lack of efficacy study N49-96-02-020

Treatment	Number of withdrawal N (%)	Time to withdrawal Mean (s.e.)	pairwise comparison (Log-rank test)
Placebo (PL)	79 (38.9%)	51.48 ( 1.99)	100mg vs. PL: p= 0.0001 200mg vs. PL : p= 0.0002 100mg vs. 200mg: p=0.0647 100mg vs. NP: p=0.2948 200mg vs. NP: p=0.5297
50 mg	61 (30.05%)	57.12 ( 1.64)	
100 mg	40 (20.3%)	57.88 ( 1.40)	
200 mg	49 (24.3%)	68.84 ( 1.80)	
Naproxen (NP)	52 (26.3%)	57.03 ( 1.54)	

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Table A.13 Secondary variable: APS Pain scale—Total score study N49-96-02-020

Treatment	N	day 1	day 2	day3	day4	day5	day 6	day 7
Placebo (PL)	144	-1.84	-3.25	-4.40	-4.98	-5.66	-5.60	-6.26
50 mg	142	-2.73	-5.66	-6.62	-6.89	-7.38	-7.51	-7.99
100 mg	143	-3.43	-7.53	-8.11	-9.45	-10.69	-11.62	-11.61
200 mg	142	-3.08	-6.14	-8.08	-9.30	-10.16	-11.45	-11.71
Naproxen (NP)	144	-4.63	-8.88	-10.17	-10.91	-11.70	-12.25	-11.75
Contrast								
100mg vs. PL: p=		0.1892	0.0015	0.0115	0.0028	0.0011	0.0002	0.0011
200mg vs. PL : p=		0.3063	0.0319	0.0122	0.0040	0.0034	0.0002	0.0009
100mg vs. 200mg: p=		0.7722	0.2995	0.9846	0.9172	0.7328	0.9123	0.9526
100mg vs. NP: p=		0.3176	0.3154	0.1583	0.3280	0.5052	0.6921	0.9305
200mg vs. NP: p=		0.1987	0.0417	0.1542	0.2808	0.3147	0.6138	0.9782

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A.1.3 Supportive variables:

Table A.14 Supportive variable: Functional capacity classification mean change from baseline--study N49-96-02-020

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	203	-0.096	-0.135	-0.125
50 mg	203	-0.153	-0.156	-0.134
100 mg	197	-0.232	-0.203	-0.220
200 mg	202	-0.192	-0.227	-0.214
Naproxen (NP)	198	-0.210	-0.196	-0.167
Contrast				
100mg vs. PL: p=		0.0004	0.1017	0.0335
200mg vs. PL : p=		0.0115	0.0264	0.0461
100mg vs. 200mg: p=		0.2927	0.5676	0.8853
100mg vs. NP: p=		0.5750	0.8664	0.2349
200mg vs. NP: p=		0.6241	0.4583	0.2936

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Table A.15 Supportive variable: Osteoarthritis severity index  
mean change from baseline--study N49-96-02-020

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	203	-1.529	-1.841	-1.928
50 mg	203	-3.063	-3.201	-3.212
100 mg	197	-3.460	-3.845	-3.754
200 mg	202	-3.482	-3.656	-3.346
Naproxen (NP)	198	-3.427	-3.539	-2.958
<b>Contrast</b>				
100mg vs. PL: p=		0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0003
100mg vs. 200mg: p=		0.9502	0.6343	0.3044
100mg vs. NP: p=		0.9250	0.4428	0.0461
200mg vs. NP: p=		0.8750	0.7674	0.3272

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## A.2 Statistical analyses for study N49-96-02-021

Table A.16 Patient disposition- N49-96-02-021

	Placebo	SC-58635 50mg BID	SC-58635 100mg BID	SC-58635 200mg BID	NAPROXEN 500mg BID	Total
Randomized	242	252	239	233	226	1192
Week 12	119	168	165	154	147	
ITT	242	252	239	233	226	1192

### A.2.1 Primary variables- primary analyses

Table A.17 Primary variable: Patients global assessment of Arthritis  
mean change from baseline--study N49-96-02-021

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	242	-0.6651	-0.7583	-0.6814
50 mg	252	-0.9795	-1.0542	-0.9979
100 mg	239	-1.0425	-1.0417	-0.9507
200 mg	233	-1.1367	-1.1245	-1.0804
Naproxen (NP)	226	-1.1840	-1.2078	-1.1111
<b>Contrast</b>				
100mg vs. PL: p=		0.0001	0.0015	0.0032
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.2317	0.3569	0.1575
100mg vs. NP: p=		0.0751	0.0671	0.0832
200mg vs. NP: p=		0.5543	0.3613	0.7419

APPEARS THIS WAY  
ON ORIGINAL

Table A.18 Primary variable: Physician's global assessment of Arthritis  
mean change from baseline--study N49-96-02-021

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	242	-0.6326	-0.7094	-0.6644
50 mg	252	-0.9157	-1.0005	-1.0089
100 mg	239	-0.9614	-1.0098	-0.9858
200 mg	233	-1.0695	-1.0356	-1.0216
Naproxen (NP)	226	-1.1188	-1.1964	-1.1078
Contrast				
100mg vs. PL: p=		0.0001	0.0003	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.1521	0.7553	0.6657
100mg vs. NP: p=		0.0388	0.0256	0.1449
200mg vs. NP: p=		0.5204	0.0561	0.3067

APPEARS THIS WAY  
ON ORIGINAL

Table A.19 Primary variable: Patients' assessment of Pain (VAS)  
mean change from baseline--study N49-96-02-021

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	242	-12.9351	-14.5968	-11.9606
50 mg	252	-21.4726	-21.7162	-20.2688
100 mg	239	-20.3037	-21.7429	-19.6386
200 mg	233	-26.4443	-24.1312	-21.0025
Naproxen (NP)	226	-26.5621	-24.9980	-25.3095
Contrast				
100mg vs. PL: p=		0.0006	0.0023	0.0012
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.0045	0.3121	0.5674
100mg vs. NP: p=		0.0041	0.1726	0.0187
200mg vs. NP: p=		0.9571	0.7177	0.0753

APPEARS THIS WAY  
ON ORIGINAL

Table A.20 Primary variable: Womac composite score  
mean change from baseline--study N49-96-02-021

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	240	-4.9853	-5.4287
50 mg	247	-10.3067	-12.8876
100 mg	237	-11.7026	-11.9927
200 mg	230	-12.1559	-11.5236
Naproxen (NP)	225	-12.6084	-13.9321
Contrast			
100mg vs. PL: p=		0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.7203	0.7514
100mg vs. NP: p=		0.4771	0.1933
200mg vs. NP: p=		0.7246	0.1091

APPEARS THIS WAY  
ON ORIGINAL

Table A.21 Primary variable: Womac pain score mean change from baseline--study N49-96-02-021

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	242	-1.2028	-1.3588
50 mg	248	-2.1322	-2.7939
100 mg	237	-2.3993	-2.5667
200 mg	232	-2.6182	-2.5282
Naproxen (NP)	226	-2.8409	-3.0053
Contrast			
100mg vs. PL: p=		0.0001	0.0003
200mg vs. PL : p=		0.0001	0.0005
100mg vs. 200mg: p=		0.4513	0.9090
100mg vs. NP: p=		0.1317	0.1971
200mg vs. NP: p=		0.4501	0.1634

APPEARS THIS WAY ON ORIGINAL

Table A.22 Primary variable: Womac joint stiffness mean change from baseline--study N49-96-02-021

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	242	-0.5815	-0.5059
50 mg	248	-0.9079	-1.1926
100 mg	237	-1.0004	-1.1022
200 mg	232	-1.1395	-1.0918
Naproxen (NP)	226	-1.2022	-1.2612
Contrast			
100mg vs. PL: p=		0.0013	0.0001
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.2901	0.9418
100mg vs. NP: p=		0.1280	0.2724
200mg vs. NP: p=		0.6375	0.2443

APPEARS THIS WAY ON ORIGINAL

Table A.23 Primary variable: Womac physical functions mean change from baseline--study N49-96-02-021

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	240	-3.2340	-3.5925
50 mg	250	-7.2830	-8.8585
100 mg	237	-8.3051	-8.3216
200 mg	231	-8.3940	-7.8901
Naproxen (NP)	225	-8.5207	-9.6258
Contrast			
100mg vs. PL: p=		0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.9236	0.6881
100mg vs. NP: p=		0.8174	0.2285
200mg vs. NP: p=		0.8928	0.1116

APPEARS THIS WAY ON ORIGINAL

Table A.24 Primary variable: Patients global assessment of Arthritis categorical change from baseline--study N49-96-02-021

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	242	39 (16.1%)	193 (79.8%)	10 (4.1%)	61 (25.2%)	163 (67.4%)	18 (7.4%)	54 (22.3%)	169 (69.8%)	19 (7.9%)
50 mg	252	68 (27%)	176 (69.8%)	8 (3.2%)	91 (36.1%)	151 (59.9%)	10 (4%)	85 (33.7%)	155 (61.5%)	12 (4.8%)
100 mg	239	73 (30.5%)	161 (67.4%)	5 (2.1%)	84 (35.2%)	150 (62.8%)	5 (2.1%)	75 (31.4%)	157 (65.7%)	7 (2.9%)
200 mg	233	79 (33.9%)	150 (64.4%)	4 (1.7%)	87 (37.3%)	140 (60.1%)	6 (2.6%)	84 (36.1%)	140 (60.1%)	9 (3.9%)
Naproxen (NP)	226	81 (35.8%)	144 (63.7%)	1 (0.4%)	87 (38.5%)	135 (59.7%)	4 (1.8%)	83 (36.7%)	138 (61.1%)	5 (2.2%)
pairwise comparison										
100mg vs. PL		p= 0.001			p= 0.003			p= 0.005		
200mg vs. PL		p= 0.001			p= 0.001			p= 0.001		
100mg vs. 200mg		p=0.418			p=0.685			p=0.386		
100mg vs. NP		p=0.153			p=0.443			p=0.207		
200mg vs. NP		p=0.542			p=0.724			p=0.712		

\*Imp=Improved, Nchg=No change, Wors=worsened

Table A.25 Primary variable: Physician's global assessment of Arthritis categorical change from baseline--study N49-96-02-021

APPEARS THIS WAY  
ON ORIGINAL

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	242	42 (17.4%)	188 (77.7%)	12 (5%)	52 (21.5%)	175 (72.3%)	15 (6.2%)	50 (20.7%)	177 (73.1%)	15 (6.2%)
50 mg	252	59 (23.4%)	187 (74.2%)	6 (2.4%)	78 (31%)	167 (66.3%)	7 (2.8%)	80 (31.8%)	165 (65.5%)	7 (2.8%)
100 mg	239	65 (27.2%)	172 (72%)	2 (0.8%)	75 (31.4%)	161 (61.4%)	3 (1.3%)	73 (30.5%)	162 (67.8%)	4 (1.7%)
200 mg	232	70 (30.2%)	159 (68.5%)	3 (1.3%)	75 (32.3%)	153 (66%)	4 (1.7%)	72 (31%)	155 (66.8%)	5 (2.2%)
Naproxen (NP)	226	74 (32.7%)	152 (67.3%)	0 (0%)	86 (38.1%)	139 (61.5%)	1 (0.4%)	77 (34.1%)	148 (65.5%)	1 (0.4%)
pairwise comparison										
100mg vs. PL		p= 0.001			p= 0.002			p= 0.002		
200mg vs. PL		p= 0.001			p= 0.001			p= 0.002		
100mg vs. 200mg		p=0.535			p=0.888			p=0.973		
100mg vs. NP		p=0.153			p=0.109			p=0.325		
200mg vs. NP		p=0.432			p=0.150			p=0.350		

\*Imp=Improved, Nchg=No change, Wors=worsened

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ON ORIGINAL

**A.2.2 Secondary Variables**

Table A.26 Secondary variable: Patients' withdrawal due to lack of efficacy study N49-96-02-021

Treatment	withdrawal due to lack of efficacy		pairwise comparison
	Yes N (%)	No N (%)	
Placebo (PL)	89 (36.8%)	153 (63.2%)	100mg vs. PL: p= 0.001 200mg vs. PL : p= 0.002 100mg vs. 200mg: p=0.935 100mg vs. NP: p=0.323 200mg vs. NP: p=0.367
50 mg	56 (22.2%)	196 (77.8%)	
100 mg	51 (21.3%)	188 (78.7%)	
200 mg	49 (21%)	184 (79%)	
Naproxen (NP)	40 (17.7%)	186 (82.3%)	

APPEARS THIS WAY  
ON ORIGINAL

Table A.27 Secondary variable: Time to withdrawal due to lack of efficacy study N49-96-02-021

Treatment	Number of withdrawal N (%)	Time to withdrawal Mean (s.e.)	pairwise comparison (Log-rank test)
Placebo (PL)	89 (36.8%)	53.45 ( 1.70)	100mg vs. PL: p= 0.0001 200mg vs. PL : p= 0.0002 100mg vs. 200mg: p=0.8698 100mg vs. NP: p=0.3672 200mg vs. NP: p=0.4656
50 mg	56 (22.2%)	58.04 ( 1.18)	
100 mg	51 (21.3%)	60.64 ( 1.26)	
200 mg	49 (21%)	66.82 ( 1.29)	
Naproxen (NP)	40 (17.7%)	65.52 ( 1.19)	

APPEARS THIS WAY  
ON ORIGINAL

Table A.28 Secondary variable: APS Pain scale—Total score change from baseline--study N49-96-02-021

Treatment	N	day 1	day 2	day3	day4	day5	day 6	day 7
Placebo (PL)	169	-3.24	-2.84	-3.36	-3.14	-4.02	-4.71	-4.65
50 mg	171	-4.15	-5.55	-6.58	-7.27	-8.17	-8.12	-8.90
100 mg	165	-3.93	-5.58	-7.12	-8.45	-9.26	-9.59	-9.80
200 mg	159	-4.85	-6.98	-9.00	-10.0	-10.61	-11.42	-11.41
Naproxen (NP)	170	-4.15	-6.97	-8.43	-9.14	-10.07	-10.67	-11.12
<b>Contrast</b>								
100mg vs. PL: p=		0.5540	0.0379	0.0068	0.0002	0.0003	0.0009	0.0007
200mg vs. PL : p=		0.1718	0.0018	0.0001	0.0001	0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.4424	0.2977	0.1832	0.2829	0.3542	0.2210	0.2936
100mg vs. NP: p=		0.8498	0.2910	0.3405	0.6251	0.5693	0.4627	0.3786
200mg vs. NP: p=		0.5574	0.9937	0.6884	0.5488	0.7099	0.6108	0.8494

APPEARS THIS WAY  
ON ORIGINAL

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ON ORIGINAL

**A.2.3 Supportive variables:**

**Table A.29 Supportive variable: Functional capacity classification mean change from baseline--study N49-96-02-021**

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	242	-0.0702	-0.0676	-0.0596
50 mg	252	-0.1470	-0.1709	-0.1587
100 mg	239	-0.1409	-0.1743	-0.1452
200 mg	233	-0.1638	-0.1700	-0.1511
Naproxen (NP)	226	-0.1523	-0.1801	-0.1983
<b>Contrast</b>				
100mg vs. PL: p=		0.0265	0.0021	0.0149
200mg vs. PL : p=		0.0035	0.0033	0.0096
100mg vs. 200mg: p=		0.4769	0.9010	0.8682
100mg vs. NP: p=		0.7254	0.8700	0.1369
200mg vs. NP: p=		0.7253	0.7754	0.1881

**APPEARS THIS WAY ON ORIGINAL**

**Table A.30 Supportive variable: Osteoarthritis severity index mean change from baseline--study N49-96-02-021**

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	242	-1.6331	-2.0256	-1.8696
50 mg	252	-2.5995	-3.3148	-3.3546
100 mg	238	-2.7644	-3.2627	-2.9097
200 mg	233	-3.2425	-3.5425	-3.3177
Naproxen (NP)	226	-3.2944	-4.1611	-3.6957
<b>Contrast</b>				
100mg vs. PL: p=		0.0002	0.0002	0.0029
200mg vs. PL : p=		0.0001	0.0005	0.0001
100mg vs. 200mg: p=		0.1201	0.4316	0.2454
100mg vs. NP: p=		0.0878	0.0125	0.0267
200mg vs. NP: p=		0.8681	0.0869	0.2889

**APPEARS THIS WAY ON ORIGINAL**

**A.3 Statistical analyses for study N49-96-02-054**

**Table A.31 Patient disposition- N49-96-02-054**

	Placebo	SC-58635 50mg BID	SC-58635 100mg BID	SC-58635 200mg BID	NAPROXEN 500mg BID	Total
Randomized	217	216	207	213	207	1060
Week 12	79	111	111	119	118	
ITT	217	216	207	213	207	1060

**A.3.1 Primary variables- primary analyses**

**Table A.32 Primary variable: Patients global assessment of Arthritis mean change from baseline--study N49-96-02-054**

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	217	-0.6065	-0.5781	-0.5213
50 mg	216	-0.9316	-1.0197	-0.9269
100 mg	207	-1.1649	-1.1207	-1.0673
200 mg	213	-1.1082	-1.1012	-0.9292
Naproxen (NP)	207	-1.1949	-1.1043	-1.1256
<b>Contrast</b>				
100mg vs. PL: p=		0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.4840	0.8320	0.1456
100mg vs. NP: p=		0.7120	0.8593	0.5415
200mg vs. NP: p=		0.2846	0.9731	0.0389

APPEARS THIS WAY ON ORIGINAL

**Table A.33 Primary variable: Physician's global assessment of Arthritis mean change from baseline--study N49-96-02-054**

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	217	-0.6381	-0.6304	-0.5901
50 mg	216	-0.9189	-1.0612	-0.9818
100 mg	207	-1.0867	-1.0715	-1.0420
200 mg	213	-1.0684	-1.1214	-0.9705
Naproxen (NP)	207	-1.1016	-1.0694	-1.0750
<b>Contrast</b>				
100mg vs. PL: p=		0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.8148	0.5706	0.4266
100mg vs. NP: p=		0.8498	0.9814	0.7148
200mg vs. NP: p=		0.6712	0.5549	0.2453

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Table A.34 Primary variable: Patients' assessment of Pain (VAS)  
mean change from baseline--study N49-96-02-054

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	217	-11.8009	-13.2092	-11.1376
50 mg	216	-19.6990	-21.4598	-18.9751
100 mg	207	-24.3893	-25.0731	-23.2957
200 mg	213	-24.4477	-23.8946	-19.3496
Naproxen (NP)	207	-26.5364	-24.7886	-22.2511
Contrast				
100mg vs. PL: p=		0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0012
100mg vs. 200mg: p=		0.9796	0.6358	0.1235
100mg vs. NP: p=		0.3498	0.9095	0.6850
200mg vs. NP: p=		0.3605	0.7195	0.2574

APPEARS THIS WAY  
ON ORIGINAL

Table A.35 Primary variable: Womac composite score  
mean change from baseline--study N49-96-02-054

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	217	-3.3653	-4.6050
50 mg	214	-7.6257	-8.0025
100 mg	207	-11.6808	-10.2635
200 mg	211	-11.6437	-10.8441
Naproxen (NP)	205	-12.7083	-12.3809
Contrast			
100mg vs. PL: p=		0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.9764	0.6814
100mg vs. NP: p=		0.4166	0.1372
200mg vs. NP: p=		0.3987	0.2792

APPEARS THIS WAY  
ON ORIGINAL

Table A.36 Primary variable: Womac pain score  
mean change from baseline--study N49-96-02-054

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	217	-0.7217	-0.9835
50 mg	215	-1.7759	-1.6781
100 mg	207	-2.6096	-2.2333
200 mg	211	-2.5371	-2.4038
Naproxen (NP)	207	-2.8593	-2.6814
Contrast			
100mg vs. PL: p=		0.0001	0.0002
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.8041	0.6072
100mg vs. NP: p=		0.3944	0.1787
200mg vs. NP: p=		0.2706	0.4032

APPEARS THIS WAY  
ON ORIGINAL

Table A.36 Primary variable: Womac joint stiffness  
mean change from baseline--study N49-96-02-054

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	217	-0.2940	-0.4128
50 mg	216	-0.7510	-0.8079
100 mg	207	-1.0140	-1.0074
200 mg	211	-1.0312	-1.0145
Naproxen (NP)	205	-1.1033	-1.1367
Contrast			
100mg vs. PL: p=		0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.8955	0.9593
100mg vs. NP: p=		0.4984	0.3540
200mg vs. NP: p=		0.5836	0.3795

Table A.37 Primary variable: Womac physical functions  
mean change from baseline--study N49-96-02-054

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	217	-2.3261	-3.1682
50 mg	215	-5.4474	-5.4793
100 mg	207	-8.0330	-6.9910
200 mg	211	-8.0963	-7.5191
Naproxen (NP)	207	-8.7029	-8.4480
Contrast			
100mg vs. PL: p=		0.0001	0.0002
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.9453	0.6088
100mg vs. NP: p=		0.4698	0.1600
200mg vs. NP: p=		0.5114	0.3687

APPEARS THIS WAY  
ON ORIGINAL

Table A.38 Primary variable: Patients global assessment of Arthritis  
 categorical change from baseline--study N49-96-02-054

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	217	35 (16.1%)	171 (78.8%)	11 (5.1%)	38 (17.5%)	162 (74.7%)	17 (7.8%)	36 (16.6%)	164 (75.6%)	17 (7.8%)
50 mg	216	51 (23.6%)	160 (74.1%)	5 (2.3%)	67 (31%)	143 (66.2%)	6 (2.8%)	56 (25.9%)	153 (70.8%)	7 (3.2%)
100 mg	207	67 (32.4%)	137 (66.2%)	3 (1.5%)	71 (34.3%)	131 (63.3%)	5 (2.4%)	65 (31.4%)	137 (66.2%)	5 (2.4%)
200 mg	213	75 (35.2%)	132 (62%)	6 (2.8%)	78 (36.6%)	126 (59.2%)	9 (4.2%)	61 (28.6%)	142 (66.7%)	10 (4.7%)
Naproxen (NP)	207	66 (31.9%)	138 (66.7%)	3 (1.5%)	63 (30.4%)	139 (67.2%)	5 (2.4%)	70 (33.8%)	131 (63.3%)	6 (2.9%)
pairwise comparison										
100mg vs. PL		p= 0.001			p= 0.001			p= 0.001		
200mg vs. PL		p= 0.001			p= 0.001			p= 0.002		
100mg vs. 200mg		p=0.690			p=0.823			p=0.360		
100mg vs. NP		p=0.919			p=0.424			p=0.669		
200mg vs. NP		p=0.618			p=0.315			p=0.186		

\*Imp=Improved, Nchg=No change, Wors=worsened

Table A.39 Primary variable: Physician's global assessment of Arthritis  
 categorical change from baseline--study N49-96-02-054

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	217	37 (17.1%)	172 (79.3%)	8 (3.7%)	42 (19.4%)	166 (76.5%)	9 (4.2%)	39 (18%)	169 (77.9%)	9 (4.2%)
50 mg	216	55 (25.5%)	158 (73.2%)	3 (1.4%)	68 (31.5%)	144 (66.7%)	4 (1.9%)	59 (27.3%)	152 (70.4%)	5 (2.3%)
100 mg	207	60 (29%)	145 (70.1%)	2 (1%)	70 (33.8%)	135 (65.2%)	2 (1%)	66 (31.9%)	139 (67.2%)	2 (1%)
200 mg	213	69 (32.4%)	140 (65.7%)	4 (1.9%)	80 (37.6%)	128 (60.1%)	5 (2.4%)	63 (29.6%)	145 (68.1%)	5 (2.4%)
Naproxen (NP)	207	63 (30.4%)	141 (68.1%)	3 (1.5%)	63 (30.4%)	139 (67.2%)	5 (2.4%)	66 (31.9%)	136 (65.7%)	5 (2.4%)
pairwise comparison										
100mg vs. PL		p= 0.001			p= 0.001			p= 0.001		
200mg vs. PL		p= 0.001			p= 0.001			p= 0.003		
100mg vs. 200mg		p=0.551			p=0.557			p=0.482		
100mg vs. NP		p=0.811			p=0.357			p=0.832		
200mg vs. NP		p=0.724			p=0.139			p=0.633		

\*Imp=Improved, Nchg=No change, Wors=worsened

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### A3.2 Secondary Variables

Table A.40 Secondary variable: Patients' withdrawal due to lack of efficacy study N49-96-02-054

Treatment	withdrawal due to lack of efficacy		pairwise comparison
	Yes N (%)	No N (%)	
Placebo (PL)	112 (51.6%)	105 (48.4%)	100mg vs. PL: p= 0.001
50 mg	76 (35.2%)	140 (64.8%)	200mg vs. PL : p= 0.001
100 mg	61 (29.5%)	146 (70.5%)	100mg vs. 200mg: p=0.404
200 mg	55 (25.8%)	158 (74.2%)	100mg vs. NP: p=0.269
Naproxen (NP)	51 (24.6%)	156 (75.4%)	200mg vs. NP: p=0.780

Table A.41 Secondary variable: Time to withdrawal due to lack of efficacy study N49-96-02-054

Treatment	Number of withdrawal N (%)	Time to withdrawal Mean (s.e.)	pairwise comparison (Log-rank test)
Placebo (PL)	112 (51.6%)	42.9 (1.89)	100mg vs. PL: p= 0.0001
50 mg	76 (35.2%)	58.5 (1.95)	200mg vs. PL : p= 0.0001
100 mg	61 (29.5%)	57.9 (1.54)	100mg vs. 200mg: p=0.5444
200 mg	55 (25.8%)	56.5 (1.46)	100mg vs. NP: p=0.3690
Naproxen (NP)	51 (24.6%)	60.9 (1.61)	200mg vs. NP: p=0.7719

Table A.42 Secondary variable: APS Pain scale—Total score mean change from baseline--study N49-96-02-054

Treatment	N	day 1	day 2	day3	day4	day5	day 6	day 7
Placebo (PL)	212	-1.33	-2.37	-2.99	-3.48	-2.55	-3.07	-3.76
50 mg	211	-3.49	-5.64	-7.62	-8.49	-8.79	-8.75	-9.28
100 mg	205	-4.41	-7.68	-8.76	-9.05	-9.67	-9.59	-10.11
200 mg	206	-4.43	-8.30	-10.09	-11.79	-12.04	-12.19	-12.71
Naproxen (NP)	202	-5.10	-8.53	-10.23	-11.69	12.53	-13.20	-13.24
Contrast								
100mg vs. PL: p=		0.0013	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0012	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.9808	0.5679	0.2573	0.0226	0.0566	0.0430	0.0502
100mg vs. NP: p=		0.4719	0.4355	0.2117	0.0291	0.0222	0.0053	0.0190
200mg vs. NP: p=		0.4863	0.8321	0.9026	0.9311	0.6954	0.4360	0.6890

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**A.3.3 Supportive variables:**

**Table A.43 Supportive variable: Functional capacity classification  
mean change from baseline--study N49-96-02-054**

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	217	-0.0848	-0.0811	-0.0541
50 mg	216	-0.1462	-0.1999	-0.1680
100 mg	207	-0.1444	-0.1818	-0.1787
200 mg	213	-0.1576	-0.1769	-0.1388
Naproxen (NP)	207	-0.1667	-0.1708	-0.1782
<b>Contrast</b>				
100mg vs. PL: p=		0.0797	0.0075	0.0013
200mg vs. PL : p=		0.0309	0.0103	0.0269
100mg vs. 200mg: p=		0.6991	0.8979	0.3030
100mg vs. NP: p=		0.5158	0.7722	0.9892
200mg vs. NP: p=		0.7888	0.8704	0.3096

**Table A.44 Supportive variable: Osteoarthritis severity index  
mean change from baseline--study N49-96-02-054**

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	215	-1.4542	-1.7450	-1.4957
50 mg	216	-2.5635	-3.3241	-2.7100
100 mg	207	-3.6189	-3.8207	-3.7520
200 mg	212	-3.0516	-3.7315	-3.0864
Naproxen (NP)	206	-3.3079	-3.5016	-3.0947
<b>Contrast</b>				
100mg vs. PL: p=		0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.0709	0.8060	0.0688
100mg vs. NP: p=		0.3258	0.3834	0.0746
200mg vs. NP: p=		0.4160	0.5283	0.9819

**A.4 Statistical analyses for study N49-96-02-060**

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**Table A.45 Patient disposition- N49-96-02-060**

	Placebo	SC-58635 100mg BID	SC-58635 200mg QD	Total
Randomized	232	231	223	686
Week 2	186	213	210	609
Week 6	146	194	182	522
ITT	231	231	222	684

**A.4.1 Primary variables- primary analyses**

**Table A.46 Primary variable: Patients global assessment of Arthritis mean change from baseline--study N49-96-02-060**

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	231	-0.7782	-0.8337
100 mg BID	231	-1.2456	-1.3102
200 mg QD	222	-1.2661	-1.3156
Contrast			
100mg BID vs. PL: p=		0.0001	0.0001
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD: p=		0.8087	0.9537

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**Table A.47 Primary variable: Physician's global assessment of Arthritis mean change from baseline--study N49-96-02-060**

Treatment	N	week 2	week 6
Placebo (PL)	231	-0.7766	-0.8233
100 mg BID	231	-1.2733	-1.3102
200 mg QD	222	-1.2832	1.3249
Contrast			
100mg BID vs. PL: p=		0.0001	0.0001
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD: p=		0.9006	0.8659

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**Table A.48 Primary variable: Patients' assessment of Pain (VAS) mean change from baseline--study N49-96-02-060**

Treatment	N	week 2	week 6
Placebo (PL)	231	-12.8962	-14.7662
100 mg BID	231	-25.5027	-28.4604
200 mg QD	222	-26.1202	-27.6791
Contrast			
100mg BID vs. PL: p=		0.0001	0.0001
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD: p=		0.7796	0.7473

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Table A.49 Primary variable: Womac scores  
mean change from baseline at week 6--study N49-96-02-060

Treatment	Variables			
	composite (N)	pain (N)	joint stiffness (N)	physical functions (N)
Placebo (PL)	-6.638 (229)	-1.490 (231)	-0.572 (230)	-4.496 (230)
100 mg BID	-14.055 (229)	-3.099(230)	-1.220 (230)	-9.683 (229)
200 mg QD	-12.830 (219)	-2.872 (220)	-1.165 (220)	-8.771 (219)
Contrast				
100mg BID vs. PL: p=	0.0001	0.0001	0.0001	0.0001
200mg QD vs. PL : p=	0.0001	0.0001	0.0001	0.0001
100mg BID vs. 200mg QD : p=	0.3853	0.4730	0.6953	0.3805

Table A.50 Primary variable: Patients global assessment of Arthritis  
categorical change from baseline--study N49-96-02-060

Treatment	N	week 2			week 6		
		Imp*	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	231	52 (22.5%)	168 (72.7%)	11 (4.8%)	59 (25.5%)	161 (69.7%)	11 (4.8%)
100 mg	231	88 (38.1%)	141 (61%)	2 (0.9%)	98 (42.4%)	131 (56.7%)	2 (0.9%)
200 mg	222	85 (38.3%)	135 (60.8%)	2 (0.9%)	94 (42.3%)	120 (54.1%)	8 (3.6%)
pairwise comparison							
100mg BID vs. PL: p=		p= 0.001			p= 0.001		
200mg QD vs. PL : p=		p= 0.001			p= 0.001		
100mg BID vs. 200mg QD : p=		p=0.971			p=0.725		

\*Imp=Improved, Nchg=No change, Wors=worsened

Table A.51 Primary variable: Physician's global assessment of Arthritis  
categorical change from baseline--study N49-96-02-060

Treatment	N	week 2			week 6		
		Imp*	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	231	48 (20.8%)	174 (75.3%)	9 (3.9%)	57 (24.7%)	165 (71.4%)	9 (3.9%)
100 mg	231	89 (38.5%)	141 (61%)	1 (0.4%)	100 (43.3%)	130 (56.3%)	1 (0.4%)
200 mg	222	91 (41%)	130 (58.6%)	1 (0.5%)	95 (42.8%)	123 (55.4%)	4 (1.8%)
pairwise comparison							
100mg BID vs. PL: p=		p= 0.001			p= 0.001		
200mg QD vs. PL : p=		p= 0.001			p= 0.001		
100mg BID vs. 200mg QD : p=		p=0.597			p=0.786		

\*Imp=Improved, Nchg=No change, Wors=worsened

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**A.4.2 Secondary Variables**

**Table A.52 Secondary variable: Patients' withdrawal due to lack of efficacy study N49-96-02-060**

Treatment	withdrawal due to lack of efficacy		pairwise comparison
	Yes N (%)	No N (%)	
Placebo (PL)	56 (24.2%)	175 (75.8%)	100mg BID vs. PL: p= 0.001 200mg QD vs. PL: p= 0.001 100mg BID vs. 200mg QD : p=0.528
100 mg BID	18 (7.8%)	213 (92.2%)	
200 mg QD	21 (9.5%)	201 (90.5%)	

**Table A.53 Secondary variable: Time to withdrawal due to lack of efficacy study N49-96-02-060**

Treatment	Number of withdrawal N (%)	Time to withdrawal Mean (s.e.)	pairwise comparison (Log-rank test)
Placebo (PL)	56 (24.2%)	24.9 (0.52)	100mg BID vs. PL: p= 0.0001 200mg QD vs. PL: p= 0.0001 100mg BID vs. 200mg QD : p=0.4780
100 mg	18 (7.8%)	26.9 (0.29)	
200 mg	21 (9.5%)	32.2 (0.42)	

**A.4.3 Supportive variables:**

**Table A.54 Supportive variable: Functional capacity classification mean change from baseline--study N49-96-02-060**

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	231	-0.0809	-0.1061
100 mg BID	231	-0.1945	-0.1543
200 mg QD	222	-0.1651	-0.1442
<b>Contrast</b>			
100mg BID vs. PL: p=		0.0013	0.1695
200mg QD vs. PL : p=		0.0180	0.2808
100mg BID vs. 200mg QD : p=		0.4100	0.7767

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**Table A.55 Supportive variable: Osteoarthritis severity index mean change from baseline--study N49-96-02-060**

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	231	-2.1802	-2.4225
100 mg BID	231	-4.0974	-3.9485
200 mg QD	222	-3.8164	-4.1540
<b>Contrast</b>			
100mg BID vs. PL: p=		0.0001	0.0001
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD : p=		0.4151	0.5683

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**A.5 Statistical analyses for study N49-96-02-087**

Table A.56 Patient disposition- N49-96-02-087

	Placebo	SC-58635 100mg BID	SC-58635 200mg QD	Total
Randomized	244	243	231	718
Week 2	207	227	218	652
Week 6	164	194	191	549
ITT	243	241	231	715

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**A.5.1 Primary variables- primary analyses**

Table A.56 Primary variable: Patients global assessment of Arthritis mean change from baseline--study N49-96-02-087

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	243	-0.7774	-0.8215
100 mg BID	241	-1.1282	-1.0598
200 mg QD	231	-1.1245	-1.1946
Contrast			
100mg BID vs. PL: p=		0.0001	0.0077
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD: p=		0.9625	0.1355

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Table A.57 Primary variable: Physician's global assessment of Arthritis mean change from baseline--study N49-96-02-087

Treatment	N	week 2	week 6
Placebo (PL)	243	-0.7324	-0.7844
100 mg BID	241	-1.1235	-1.0318
200 mg QD	231	-1.0800	-1.1658
Contrast			
100mg BID vs. PL: p=		0.0001	0.0025
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD: p=		0.5525	0.1060

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Table A.58 Primary variable: Patients' assessment of Pain (VAS) mean change from baseline--study N49-96-02-087

Treatment	N	week 2	week 6
Placebo (PL)	243	-12.4032	-14.9532
100 mg BID	241	-22.4852	-21.1526
200 mg QD	231	-21.0834	-23.4803
Contrast			
100mg BID vs. PL: p=		0.0001	0.0107
200mg QD vs. PL : p=		0.0001	0.0006
100mg BID vs. 200mg QD: p=		0.5197	0.3441

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Table A.59 Primary variable: Womac scores  
mean change from baseline at week 6--study N49-96-02-087

Treatment	Variables			
	composite (N)	pain (N)	joint stiffness (N)	physical functions (N)
Placebo (PL)	-8.098 (239)	-1.588 (239)	-0.780 (239)	-5.677 (240)
100 mg BID	-13.308 (238)	-2.596 (239)	-1.294 (240)	-9.361 (239)
200 mg QD	-13.934 (226)	-2.994 (226)	-1.197 (226)	-9.724 (226)
Contrast				
100mg BID vs. PL: p=	0.0011	0.0053	0.0004	0.0013
200mg QD vs. PL : p=	0.0003	0.0001	0.0050	0.0005
100mg BID vs. 200mg QD : p=	0.6983	0.2763	0.5093	0.7538

Table A.60 Primary variable: Patients global assessment of Arthritis  
categorical change from baseline--study N49-96-02-087

Treatment	N	week 2			week 6		
		Imp*	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	243	56 (23.1%)	176 (72.4%)	11 (4.5%)	65 (26.8%)	160 (65.8%)	18 (7.4%)
100 mg	241	99 (41.1%)	137 (56.9%)	5 (2.1%)	90 (37.3%)	143 (59.3%)	8 (3.3%)
200 mg	231	71 (30.7%)	160 (69.3%)	0 (0%)	87 (37.7%)	143 (61.9%)	1 (0.4%)
pairwise comparison							
100mg BID vs. PL: p=	p= 0.001			p= 0.004			
200mg QD vs. PL : p=	p= 0.010			p= 0.001			
100mg BID vs. 200mg QD : p=	p=0.046			p=0.640			

\*Imp=Improved, Nchg=No change, Wors=worsened

Table A.61 Primary variable: Physician's global assessment of Arthritis  
categorical change from baseline--study N49-96-02-087

Treatment	N	week 2			week 6		
		Imp*	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	243	47 (19.3%)	188 (77.4%)	8 (3.3%)	59 (24.3%)	172 (70.8%)	12 (4.9%)
100 mg	240	93 (38.8%)	144 (60%)	3 (1.3%)	84 (35%)	151 (62.9%)	5 (2.1%)
200 mg	231	66 (28.6%)	164 (71%)	1 (0.4%)	80 (34.6%)	151 (65.4%)	0 (0%)
pairwise comparison							
100mg BID vs. PL: p=	p= 0.001			p= 0.004			
200mg QD vs. PL : p=	p= 0.005			p= 0.002			
100mg BID vs. 200mg QD : p=	p=0.030			p=0.823			

\*Imp=Improved, Nchg=No change, Wors=worsened

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**A.5.2 Secondary Variables**

Table A.62 Secondary variable: Patients' withdrawal due to lack of efficacy study N49-96-02-087

Treatment	withdrawal due to lack of efficacy		pairwise comparison
	Yes N (%)	No N (%)	
Placebo (PL)	55 (22.6%)	188 (77.4%)	100mg BID vs. PL: p= 0.001 200mg QD vs. PL: p= 0.001 100mg BID vs. 200mg QD : p=0.776
100 mg BID	27 (11.2%)	214 (88.8%)	
200 mg QD	24 (10.4%)	207 (89.6%)	

Table A.63 Secondary variable: Time to withdrawal due to lack of efficacy study N49-96-02-087

Treatment	Number of withdrawal N (%)	Time to withdrawal Mean (s.e.)	pairwise comparison (Log-rank test)
Placebo (PL)	55 (22.6%)	34 (0.76)	100mg BID vs. PL: p= 0.0006
100 mg	27 (11.2%)	30.2 (0.37)	200mg QD vs. PL: p= 0.0002
200 mg	24 (10.4%)	32.2 (0.39)	100mg BID vs. 200mg QD : p=0.7635

**A.5.3 Supportive variables:**

Table A.64 Supportive variable: Functional capacity classification mean change from baseline--study N49-96-02-087

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	243	-0.1125	-0.1248
100 mg BID	241	-0.1592	-0.1802
200 mg QD	231	-0.1573	-0.2003
Contrast			
100mg BID vs. PL: p=		0.1357	0.1286
200mg QD vs. PL : p=		0.1571	0.0408
100mg BID vs. 200mg QD : p=		0.9528	0.5857

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Table A.65. Supportive variable: Osteoarthritis severity index  
mean change from baseline--study N49-96-02-087

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	243	-2.1231	-2.3701
100 mg BID	241	-3.7945	-3.6065
200 mg QD	230	-3.5535	-3.5918
Contrast			
100mg BID vs. PL: p=		0.0001	0.0005
200mg QD vs. PL : p=		0.0001	0.0007
100mg BID vs. 200mg QD : p=		0.4670	0.9675

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**Arthritis Advisory Committee**

**December 1, 1998**

**NDA 20-998 Celebrex™ (celecoxib) Searle**

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# **Rheumatoid Arthritis**

## **Statistical Review**