

As *Appendix Table A.52* shows, a statistically significant difference ($p < 0.05$) was found between Cx and either placebo or active control for the 19 adverse events listed.

Reviewer's comment: In relating any statistical results (especially in a safety analysis) to clinical relevance it is important to remember that a nontrivial proportion (approximately 5%) of all p-values would be expected to be below 0.05 by chance alone. Also, the level of statistical significance is affected by sample size. For any specific difference between groups, the p-value will decrease as the sample size increases, even when the absolute difference between the groups is relatively small.

Eight of these differences were between Cx and placebo; six of these eight represent a higher incidence for Cx than for placebo: dyspepsia, upper respiratory tract infection, diarrhea, pharyngitis, peripheral edema and flatulence. Of the 13 statistically significant differences between Cx and active control, four represented a higher incidence for Cx: back pain, myalgia, allergy aggravated, and hypertonia.

It should be noted that when the data is reanalyzed looking at only the OA or RA patients in these North American trials, the trends are the same as noted in *Appendix Table A.52*. In addition, the OA data uncovers the observation that SGOT increases are statistically higher for the active control (1.1%) vs. Cx (0.2-0.6%; no increases with Cx at 400 mg).

Appendix Table A.53.1 shows an analysis of AEs for Cx 400 mg BID is compared with placebo and active control. Of the nine events with a statistically significant difference between Cx and placebo, five represent a higher incidence for celecoxib: dyspepsia, diarrhea, pruritus, vomiting, and allergy aggravated. Two events were significantly more common for active control than for Cx: constipation and stomatitis. No other differences in incidence between Cx and active control were statistically significant.

It should be noted that for adverse events considered by the investigators to have uncertain or probable relation to study medication, dyspepsia was noted in 4.7% of placebo patients, 6.0-6.7% of Cx patients (doses from 100 mg-400 mg BID) and 9.9 % of active controls (data not shown). However, in patients with OA, if Cx is given once daily, the incidence of dyspepsia seems to decrease as noted by comparisons in the six-week trials in OA (study 087, $n=472$, dyspepsia = 4.7% with Cx 100 mg BID; study 060, $n=453$, dyspepsia = 4.6% with Cx 200 mg QD, this equals the placebo rate).

Pruritus and vomiting were the two events that were shown to be statistically significantly more common for Cx 400 mg than for placebo, while not having been more common for the lower doses of Cx. However, it should be noted that pruritus also occurred in 2.8% of patients ($n=253$) exposed to Cx 25-40 mg BID and in 2.5% of patients ($n=690$) exposed to Cx 50 mg BID (data not shown). Vomiting occurred in 2.3% of celecoxib 400 mg patients, compared with 0.8% of placebo patients.

The majority of headaches (the most prevalent adverse event) in all treatment groups were described as mild or moderate (data not shown). In the placebo group, a greater proportion of patients reported a severe headache than in all but one (25-40 mg) Cx groups.

Similarly, of all adverse events reported in the GI system (data not shown), most were described as mild or moderate in all treatment groups. In the North American arthritis trials, severe events in this category were reported for 1.9% of patients in the placebo group compared with 1.1 to 3.2% for the Cx and 4.1% in patients receiving active control. The numbers showed similar trends for the individual GI events of highest incidence. For diarrhea, 0.3% of placebo patients reported a severe event which compares to 0.2-0.7% in the Cx-treated patients and 0.1% active control patients. For dyspepsia, 0.4% of placebo patients noted a severe event compared to 0.0-0.7% in Cx-treated patients (highest with Cx 50 mg BID) and 1.5% patients receiving active control.

A comparison between adverse events in patients with OA and RA can be found in *Appendix Table A53.2*. Comparison of the adverse events between OA and RA patients demonstrates no clinically important differences between the populations, despite the differences in mean age (OA patients were, on average, seven years older than RA patients), the systemic nature of RA, and the increased use of concomitant medications to treat RA compared with OA. This analysis of these particular doses of Cx suggests that no special differential safety concerns apply when considering the use of Cx in OA or RA patients.

To this point, adverse events have been characterized in the North American trials. In *Appendix A.53.3* are listed adverse events that occurred with an incidence of $\geq 3\%$ during the international arthritis trials (042 and 041). As can be seen, the types of AEs are the same but incidence rates may differ from the North American trials. For example, headache is not the most prominent event, this is diarrhea. For all adverse the incidence was higher for Cx 200 mg BID than for Cx 100 mg BID. This difference most likely results from, or is at least augmented by, the longer duration of the RA trial (24 weeks compared with six weeks for OA). This data also reinforces the observation that Cx is more like active control than placebo in terms of its adverse event profile.

Summary of the adverse event data reported in NDA 20-998 demonstrate that Cx is a generally safe and well-tolerated drug and can be summarized as follows:

- **Clinically important individual adverse Overall, among all Cx-treated arthritis patients, the most frequent events were headache, dyspepsia, upper respiratory tract infection, diarrhea, and nausea. The overall rate of adverse events for celecoxib patients in controlled arthritis trials was 60.5%, compared to 54.6% for placebo, and 66.7% for active control. The great majority of all adverse events were mild to moderate in severity, and the incidence of withdrawal due to adverse events was similarly low (<10%) in all treatment groups. Adverse events considered to be of uncertain or probable relation to study medication represented approximately 50% of all adverse events and withdrawals in each treatment group.**

- Of note, the "suprathapeutic dose" of Cx (400 mg BID) was tolerated as well as lower doses.
- Examination of OA and RA patients separately did not disclose a significant difference in the pattern or character of adverse events despite the fact that patients with OA were generally older than those with RA.
- Adverse events in postsurgical patients were generally similar to those seen in arthritis patients.
- Subgroup analyses by demographic subgroups based on age, gender, race, and weight also demonstrated no important differences in the pattern of adverse events.
- Long-term treatment with Cx was well tolerated and did not show a significant increase in rate or different pattern of adverse event types than short-term treatment.
- Events that were frequent in occurrence (>1%) and associated with significantly greater incidences or withdrawal rates for Cx than placebo included GI complaints, rashes or itching, peripheral edema, pharyngitis, and upper respiratory tract infection. Among postsurgical patients, the only additional finding of clinical significance was a significantly lower incidence of fever in Cx patients compared to placebo, consistent with an antipyretic activity of celecoxib.

Reviewers comment: The adverse event profile of Cx is consistently more like that of comparator NSAIDs rather than placebo.

Adverse Events Causing Withdrawal

The reasons for withdrawal from all the controlled OA and RA studies (North American and International, does not include open-label) are presented in *Appendix Table A.48*. Very few patients in these studies were withdrawn for being lost to follow-up, for violation of entry criteria, or for protocol noncompliance. In these arthritis studies, the incidence of withdrawal due to adverse events varied from 3.2% (25-40 mg BID, data not shown in table) to 8.1% (200 mg BID) among the Cx groups (this compares to 6.1% and 10.7% in the placebo and active control groups, respectively). No increase in the incidence of withdrawal for adverse event with increasing doses is apparent when all doses are considered; none of the Cx groups are comparable to the pooled rate for the active controls. The lowest and highest incidences are likely related to length of study since the 200 mg QD dosage was only studied in six-week studies, while the 200 mg BID dosage group is the only group that includes a six-month study (i.e. Study 041). Similarly, the OA/RA patients who were studied at the 25-40 mg BID doses were in trials of 2-4 weeks duration.

The appendix table (Table A.48) also does not include the patients in the phase 1 and pain trials. There were, as might be expected from the nature of these trials, few patients who withdrew from all of these trials for adverse events (27/778 \approx 3.5%). Interestingly, the

bulk of the patients in the Pain trials (dental or surgical), withdrew from these trials with the main reason being because of treatment failure, not adverse event (see *Appendix A.49*).

The results of the reasons for withdrawal for the OA and RA patients that were enrolled into the long-term study (i.e. 024) are depicted in *Appendix Table A.50*. Again, higher doses of Cx do not seem to be associated with decreased tolerability as witnessed by withdrawals for adverse event. The OA patients in this study started at 100 mg BID with the option of titrating up to 200 mg BID, while RA patients took higher doses, starting at 200 mg BID with the option of titrating up to 300 mg BID and then 400 mg BID. Nonetheless, no increase in withdrawal due to adverse events is noted for RA patients.

Reviewer's comment: Considering the longer term arthritis trials (i.e. by removal of the 200 mg QD and 25-50 mg BID results), the rate of withdrawal for adverse events for all doses of Cx appears better than comparators but NOT equivalent to placebo.

Another way to help understand the clinical significance of an adverse event, is whether it leads a patient to withdraw from the study. Presented in *Appendix Table A.54* are adverse events causing withdrawal with an incidence of $\geq 1\%$ between Cx (100 mg BID, 200 mg QD, and 200 mg BID), placebo and active controls in all the North American arthritis trials.

Overall, the incidences of any adverse event causing withdrawal in the OA population ranged from 3.3% (200 mg QD) to 10.1% (400 mg BID) in patients receiving celecoxib. A dose response relationship appears evident if the 200 mg QD (six week trial) data are excluded. The highest incidence occurred in patients receiving active control. Thirteen events led to withdrawal in at least 1% of patients in any treatment group. It should be noted that this number is increased by inclusion of the celecoxib 400 mg BID group, which includes only 99 patients. Any adverse event leading to withdrawal of one patient from that treatment group would meet the criterion of $>1\%$ incidence. However, the trend for increasing adverse events with increasing doses is still apparent when the RA patients who also received 400 mg BID is considered (*Appendix Table A.54*). Only one event (urticaria) led to withdrawal in a significantly higher percentage of Cx vs. placebo patients (*Appendix Table A.54*). As can be seen, withdrawals were statistically significantly different between Cx and active control for rash and pruritus (greater for Cx).

It should be noted that an analysis of incidences of adverse events causing withdrawal in the controlled arthritis trials compared between celecoxib 400 mg BID and both placebo and active control revealed no statistically significant differences.

Regarding the long-term, open-label trial experience, the most common events causing withdrawal were the same types of events characterized in the randomized portion of the trials. No obvious patterns of increases are evident across the intervals.

Table 48. Most Common AEs Causing Withdrawal : Long-Term Open Label¹

Adverse event	Interval					
	1-90	91-180	181-270	271-360	361-450	451-540
No. entered interval	4499	3540	2373	1576	970	294
Rash	0.4	<0.1	0.0	<0.1	0.0	0.0
Dyspepsia	0.3	<0.1	0.2	0.0	0.0	0.0
Abdominal pain	0.2	0.2	0.1	0.3	0.2	0.0
Diarrhea	0.2	0.2	0.0	0.0	0.2	0.0
Pruritis	0.2	<0.1	0.0	0.0	0.0	0.0
Dizziness	0.1	0.2	0.0	<0.1	0.0	0.0
Fatulence	0.1	<0.1	0.0	0.0	0.0	0.0
Headache	0.1	<0.1	0.0	0.1	0.0	0.0
Nausea	0.1	0.1	0.0	<0.1	0.1	0.0

1. At least 5 patients. Summarized by Interval of Withdrawal.

In summary, the rate of withdrawal for adverse events for all doses of Cx appears better than comparators but NOT equivalent to placebo. Withdrawals were statistically significantly different between Cx and active control for rash and pruritus (greater for Cx). An analysis of incidences of adverse events causing withdrawal in the controlled arthritis trials compared between celecoxib 400 mg BID and both placebo and active control revealed no statistically significant differences.

Serious Adverse Events

Reviewer's comment: Interested readers should read the safety review by Dr. Villalba and the cardiorenal and gastrointestinal consults.

Serious adverse events, whether or not unexpected or considered to be associated with the use of the drug, were defined:

- as fatal,
- as life-threatening,
- as permanently disabling,
- as requiring, or prolonging, inpatient hospitalization,
- as a congenital anomaly,
- as a cancer, or
- as an overdose

With the exception of those in the long-term open label study, all of the serious adverse events reported in this submission occurred before the new regulations for reporting serious adverse events took effect on April 6, 1998. All serious adverse events in this summary, including those from the long-term open label study, were therefore reported in accordance with the regulations in effect prior to this date.

Overall, the incidences of SAEs were low with Cx as noted in the following table:

Table 49. Serious Adverse Event (SAE) Rates in NDA 20-998¹

Type of Trial	Placebo	Cx	Active Control
NA arthritis	30/1864 (1.6%)	75/5704 (1.3%)	39/2098 (1.9%)
Long-term, Open-label	-	244/4499 (5.4%)	-
International arthritis	-	15/672 (2.2%)	20/670 (3.0%)
Dental pain	0/205 (0%)	1/531 (0.2%)	0/189 (0%)
Surgical pain	4/100 (4.0%)	3/217 (1.4%)	2/106 (1.9%)

1. From Tables 22.1-22.6 (ISS). Includes trials 005, 012, 013, 020, 021, 022, 023, 024, 025, 027, 028, 029, 041, 042, 047, 054, 060, 062, 070, 071, 080 and 087.

As can be seen, the highest percentage of patients with a SAE was seen in the long-term open label trial. This is to be expected considering the longer exposure of patients in this trial.

Table 50 below shows the numbers of patients and episodes of serious adverse events occurring in the North American and International arthritis trials combined, summarized by treatment group. The two highest incidences are for Cx 200 mg BID and for active control. This is most likely because these are the two doses that were used in the International RA study, Study 041, which was of 24 weeks' duration. All other trials represented in the table were of 12 weeks' duration or shorter.

Table 50. Overall Incidences of SAEs by Dose: Controlled Arthritis Trials¹

	Placebo	Celecoxib (mg)						Active Control
		25-40 BID	50 BID	100 BID	200 OD	200 BID	400 BID	
No. patients	1864	253	690	2125	453	2240	615	2768
Any SAE	30 (1.6)	1 (0.4)	5 (0.7)	26 (1.2)	2 (0.4)	49 (2.2)	7 (1.1)	2768 (2.1)

1. From Table 22.2 (ISS). Includes trials 012, 013, 020, 021, 022, 023, 041, 042, 047, 054, 060, 062, 070, 071, and 087.

The most common events in this population (at least three patients in any treatment group) are neuralgia, abdominal pain, angina pectoris, coronary artery disorder, myocardial infarction, pulmonary embolism, pneumonia, and basal cell carcinoma. Serious adverse events occurring in the long-term open-label trial (024) are summarized in the Table 51 by dose regimen and length of exposure.

Table 51. Overall Incidences of SAEs: Long-Term Trial¹

	100 mg BID	200 mg BID	300 mg BID	400 mg BID	Any Dose
No. with serious event	56	114	35	42	244
No. pt-yrs	519	1271	340	465	2672
Rate of events/100 pt-yrs	11	9	10	9	9

1. From Tables 22.2 and 4.3 (ISS).

The most common SAEs in this study (eight or more patients) were basal cell carcinoma (17 patients), myocardial infarction (15 patients), coronary artery disorder (12 patients), angina (11 patients), cerebrovascular disorder (10 patients), back pain (eight patients), and injury accidental (eight patients).

One SAE occurred in the dental pain studies: a rectal carcinoma was discovered in a patient who received a single dose of Cx 100 mg. Nine SAEs occurred in the surgical pain trials: four in placebo patients (back pain, dysphagia, abscess, and healing impaired); one in a patient receiving Cx 100 mg (pneumothorax); two in patients receiving Cx 200 mg (ileus and infection); and two in patients receiving active control (cellulitis and infection).

In summary, none of the serious adverse events (SAEs) that have occurred in NDA 20-998 were considered by the Searle Safety Monitor or by a panel of external safety consultants to be related to study medication.

Reviewer's comment: There is an apparent excess of myocardial infarction in elderly patients receiving celecoxib. This topic is addressed under the "Cardiovascular" section of this review and, in detail, in the cardiorenal consult.

Deaths:

Reviewer's comment: Interested readers should read the extensive discussion of this topic in the cardiorenal consult.

In the Cx program to date, which includes the 120 day safety update (letter date: October 28, 1998, cutoff date of update: July 24, 1998), there have been a total of 44 deaths which are summarized in table 52.

Table 52. Disposition of Deaths in the ISS and Safety Update

	Reported in ISS		New Reports in Safety Update		Cumulative Total	
	Cx	Active Control	Cx	Active Control	Cx	Active Control
Controlled arthritis trials	4	4	0	0	4	4
Pain Studies	0	0	0	1*	0	1
Long-term open label study	18	-	6	-	24	-
Ongoing/other studies	1	1*	0	0	1	0
Surgical pain 075	0	0	1b	1b	1b	1b
Surgical pain 082	0	1*	-	-	-	-
Open label 058	1	-	-	-	1	-
Alzheimer's 1Q5-001	6b	6b	2b	2b	8b	8b
Chemoprevention 1Q4-001	1b	1b	-	-	1b	1b
Subtotal	23	5	6	0	29	5
Blinded (b)	7		3		10	
Grand Total	35		9		44	

* This death in study 082 was reported as a death in an ongoing study in the ISS; it is now counted as a death in a completed surgical pain study, but not added to the total of new reports in the Safety Update.

As can be seen, although 35 deaths were reported in the ISS, 26 of them are described further both below and/or in the renal safety consultation. Of the 9 new deaths reported in the Safety Update, six will be described briefly. Since the cutoff date for the Safety Update was July 24, 1998, there were three additional deaths noted in Text Table 18 of the Safety Update that occurred during the treatment between July 25, 1998 and September 11, 1998. These patients are summarized as follows:

- Pt number (024-US0007-007051); DER Number (970912-CL896). 63 y/o female taking Cx 300 mg BID on 67. Cause of death listed as carcinoma.
- Pt number (024-US0090-090028); DER Number (980917-CL561). 61 y/o male taking Cx 100 mg BID on day 327. Cause of death listed as MI.
- Pt number (024-US121-121022); DER number (980910-CL790). 63 y/o male taking Cx 400 mg BID on day 496. Cause of death listed as unknown.
- Pt number (024-US0015-0150041); DER number (980527-CL495). 58 y/o female taking Cx 400 mg BID on day 614. Cause of death listed as ventricular fibrillation/aortic stenosis.
- Pt number (024-US0211-2110005); DER number (980702-CL081). 65 y/o male taking Cx 200 mg BID on day 244. Cause of death listed as CHF.
- Pt number (0870092). 75 y/o male taking 300 mg BID on day 414. Cause of death listed as cancer.

Reviewer's comment: Therefore, it appears that the total number of deaths in patients taking Cx as of the writing of this review is 29. Eighteen (18) were in study 024, four (4) in the controlled trials and one (1) in the other studies listed—all of these 23 patients were reported in the ISS. The six (6) additional deaths

were in the Safety Update and they are listed above in the bulleted items.

As noted in table 52, six of these new deaths occurred in the long-term, open label study and three occurred in two ongoing (blinded) trials.

It should be noted that NONE of these deaths were considered by the Monitor or the panel of safety consultants to have been related to study medication.

There were 26 deaths in patients who participated in studies included in the NDA. A narrative listing of all of the deaths is to be found in Appendix two of this consult. A total of eight subjects who enrolled in controlled arthritis trials died. Six deaths occurred during controlled arthritis studies, and two following discontinuation of study drug. Four of the individuals in the controlled arthritis group who died received celecoxib, while four received active control drug. The individuals in bold letters died of cardiovascular disease.

Table 53. Deaths: Controlled Trials in the NDA 20-998^a

Subject #	Age/ Sex	Treatment	Duration of Tx	Cause of Death
Deaths During Study Drug Administration				
	70/M	Celecoxib 200 mg BID	81	Gallbladder carcinoma with liver metastasis
	68/M	Naproxen 500 mg BID	63	Brain-stem infarct
	78/M	Ibuprofen 800 mg TID	29	Obstructive pulmonary disease
	53/F	Diclofenac 75 mg BID	1	Hypertensive cardiovascular disease
	67/M	Naproxen 500 mg BID	47	Pulmonary embolus
	56/M	Celecoxib 200 mg QD	30	Arteriosclerotic Cardiovascular disease
Deaths After Drug D/C				
	62/F	Celecoxib 100 mg BID	26/ 54	Pulmonary carcinoma
	80/F	Celecoxib 200 mg BID	6/45	MI

a. Data from Integrated Safety Summary, Text Table 67. Table shows all deaths from controlled trials, including those that occurred after the study drug was discontinued. For those two subjects, the # of days after drug discontinuation for the death is shown after the day of death.

Ten deaths occurred during the long-term open-label study prior to the database cutoff date (November 21, 1997), and are summarized in table 54 below. The duration of treatment ranged from 15 to 273 days, with a final regimen of 200 mg BID for four patients, 300 mg BID for two patients and 400 mg BID for four patients. The subjects in bold letters (9/10, 90%) died of cardiovascular disease.

Table 54. Deaths in the Long-Term Trial Prior to NDA Cutoff Date^a

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
	65/F	Celecoxib 400 mg BID	196	Myocardial rupture post-MI
	76/M	Celecoxib 200 mg BID	45	MI, cardiac failure
	58/M	Celecoxib 400 mg BID	273	MI
	83/F	Celecoxib 300 mg BID	193	Coronary thrombosis
	80/M	Celecoxib 200 mg BID	159	Massive coronary
	59/M	Celecoxib 200 mg BID	246	Ischemic heart disease
	60/M	Celecoxib 400 mg BID	155	Adenocarcinoma
	84/F	Celecoxib 400 mg BID	243	Respiratory failure, CHF
	52/M	Celecoxib 300 mg BID	114	MI
	57/F	Celecoxib 200 mg BID	15	Subarachnoid hemorrhage

a. Data from Integrated Safety Summary, Text Table 66.

There were also five deaths in the long-term, open-label study between the database cutoff (November 21, 1997) date and May 1, 1998. These deaths are listed in table 55 below; all were due to cardiovascular disease (and are shown in bold letters).

Table 55. Deaths: Long-Term Open-Label Trial After NDA Cutoff^a

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
	74/M	Celecoxib 400 mg BID	336	Heart block
	71/M	Celecoxib 400 mg BID	32	Coronary artery disorder
	71/F	Celecoxib 400 mg BID	37	MI
	61/F	Celecoxib 400 mg BID	471	MI
	78/F	Celecoxib 200 mg BID	88	Aortic Aneurysm

a. Data from Integrated Safety Summary, Text Table 67.

Finally, there were five deaths that occurred more than 28 days after the last dose in any study reported in this NDA (note that the two patients in the 020 trial are included in the table above) and are summarized in table 56. Two of these patients died after participation in trial 020 and three died following participation in Study 024. Of the five celecoxib subjects in this group, two died of cardiovascular disease (40%).

Table 56. Deaths That Occurred More than 28 Days After Last Dose^a.

Subject #	Age/Sex	Treatment	Day of Death	Days after Last Dose	Cause of Death
	62/F	Celecoxib 100 mg BID	26	54	Pulmonary carcinoma
	80/F	Celecoxib 200 mg BID	6	45	MI
	66/M	Celecoxib 400 mg BID	334		Anterior MI
	66/M	Celecoxib 200 mg BID	173	29	Sepsis, pneumonitis
	77/F	Celecoxib 200 mg BID	111	36	Pulmonary carcinoma

a. Data from Integrated Safety Summary, Text Tables 66 and 68.

Total Mortality

Depending on the population used for the denominator, mortality can be calculated in two ways using the information from the Cx database, summarized in table 57 and 58 below. The first way uses the number of subjects exposed to the drug in each treatment group, independent of the duration of that exposure (Table 57).

Table 57. Deaths per Patients Exposed in NDA 20-998^a.

Population	Number of Deaths	Number of Exposed Subjects	Crude Mortality Incidence
<i>Controlled North American OARA Trials</i>			
Deaths during Trial			
<i>Placebo</i>	0	1864	0%
<i>Celecoxib</i>	2	6376 ^c	0.03%
<i>Active Control</i>	4	2768	0.14%
All known deaths^b			
- <i>Placebo</i>	0	1864	0%
- <i>Celecoxib</i>	4	6376 ^c	0.06%
- <i>Active Control</i>	4	2768	0.14%
<i>Long-term, Open-label Trial</i>			
Deaths before cut-off date	10	5155	0.19%
Known deaths during celecoxib use	15 ^d	5155	0.29%
All known deaths^e	18	5155	0.35%

a. Data from Integrated Safety Summary, including Text Tables 65-68 and Summary table 2.9. Confirmed with the sponsor.

b. Includes one death in the active control group and two deaths in the celecoxib group after trial completion. These deaths occurred >28 days after last dose of study medication.

c. For all patients who received celecoxib. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97). Also includes three deaths that occurred >28 days after last reported use of celecoxib (see tables above).

- d. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial.
 e. Number equals the total number of individual patients in the OA and RA trials (4151 and 2086, see earlier tables).

It is also fruitful to calculate mortality using the data on patient-years of exposure as the denominator as in the table 58 below.

Table 58. Mortality Rate: Deaths per Patient-Years of Exposure

Population	Number of Deaths	Patient-yrs of Exposure ^a	Mortality Rate
Controlled N.A. OA/RA Trials			
Deaths during Trial			
Placebo	0	208	0.00%
Celecoxib	2	1020	0.19%
Active Control	4	535	0.75%
All known deaths^b			
Placebo	0	208	0.00%
Celecoxib	4	1020	0.39%
Active Control	4	535	0.74%
Long-term, Open-label Trial			
Deaths before cut-off date	10	2672	0.37%
Known deaths during celecoxib use	15 ^d	4274	0.35%
All known Deaths^e	18	4274	0.42%

a. Data from Integrated Safety Summary, including Text Tables 65-68.

b. Includes one death in the active control group and two deaths in the celecoxib group after trial completion. These deaths occurred >28 days after last dose of study medication.

Mortality Rate due to Cardiovascular (CV) Disease and for Total Mortality

As noted table 59 below, the crude rates of death due to CV disease in both the Cx and active control groups were higher than placebo:

Table 59. Cardiovascular Mortality Rates: North American Arthritis Trials¹

	No. deaths	No. Exposed	Pt-years of Exposure	Mortality Incidence	Mortality Rate
Cardiac deaths in trial					
Placebo	0	1864	208	0.00%	0.00%
Celecoxib	1	6376	1020	0.02%	0.10%
Active control	2	2768	535	0.07%	0.37%
All known cardiac deaths²					
Placebo	0	1864	208	0.00%	0.00%
Celecoxib	2	6376	1020	0.03%	0.20%
Active control	2	2768	535	0.07%	0.37%

1. Data from Text Tables 65-65, ISS.

2. Includes one death in active control group and two deaths in the Cx group after trial completion. These deaths occurred >28 days after last dose of study medication.

It should be noted that these relationships between treatment groups and CV deaths when analyzed by Kaplan-Meier plots (see cardiorenal consult for more details).

Of interest, table 60 compares the rates of CV mortality in patients arranged according to highest dose of Cx received in the long-term trial.

Table 60. Cardiovascular Mortality Rates by Increasing Dose: Long-Term Trial^{1,2}

Cx dose (BID)	No. deaths	Patient-years of exposure ⁴	Crude Mortality Rate ³
100 mg	0	519	0%
200 mg	4	1271	0.31%
300 mg	2	340	0.59%
400 mg	3	465	0.64%

1. Data from Text Tables 65-68, ISS.
2. Deaths occurred prior to cutoff of Nov. 21, 1997.
3. Mortality in deaths/pt-years (x100)
4. Data from Appendix Table 4.3, ISS.

Conclusions regarding deaths due to cardiovascular causes:

It appears that most of the deaths in both the controlled trials and the open-label extension are from CV causes. Combined with the apparent relationship with Cx dose (Table 60), this suggests that there is some association between Cx use and cardiovascular mortality. As has been noted elsewhere in this review, the lack of effect of Cx on platelets may help to explain these results compared to active control (probably not to placebo). However, the rates with Cx appear to be lower those seen with active controls (Table 59) suggesting this is not a good explanation.

It would appear that any adequate interpretation of these results is confounded by a number of factors. The population studied is generally older (with a substantial percentage of geriatric patients) with their associated increased CV risks factors (i.e. increased use of meds, more diabetes, hypertension, etc.). The number of events is small making adequate statistical conclusions difficult since a few deaths in the placebo group (for example) can dramatically change results. Also, in the long-term study of Cx, there are no control groups which forces reliance on the use of other large databases which may not properly mimic the subjects in these trials.

Therefore, it is not possible to conclude that use of Cx is associated with excess CV mortality. However, it is also not possible to rule it out. The "large and simple" trials currently underway looking at GI endpoints, along with post-marketing use should clarify this issue.

Surgical Safety:

No outstanding safety issues have been demonstrated during the clinical trials conducted to investigate the treatment of pain. However, short-term studies are not

expected to be a significant source for detecting adverse events of investigational new drugs.

Conclusions Regarding Cx Safety:

The safety of Cx was addressed throughout NDA 20-998. This NDA represents not only a new molecular entity in Cx, it also would appear to represent the first compound with properties sufficient to distinguish itself as "selective" or "specific" for COX-2. Therefore, it is appreciated that a discussion of the safety of Cx may, or may not, represent a discussion regarding the theoretical advantages of COX-2 selective or specific. Only time, and more compounds of similar characteristics, will answer these questions.

Overall, and as a conclusion, Cx has demonstrated that it is a safe compound when given in the range of doses studied in the analgesic and arthritis trials of this NDA. Particular safety issues are summarized as follows:

- 1 Considering both the controlled North American and International arthritis trials, along with the placebo- and active control patients added to the long-term, safety trial, there were 8044 (4223 OA, 2098 RA, 1723 open-label) unique patients exposed to Cx at the time of the NDA database cutoff. By adding in the Phase 1 and Pain subjects, this number increases to 9574 patients/subjects to Cx at any dose. This number further increases to 10,704 patients/subjects by adding the new patients in the 120-Day Safety Update.
- 2 Compared to placebo, Cx does not affect platelet function as demonstrated by *ex vivo* platelet aggregation to collagen or arachidonate and TxB₂ levels, even when given at supratherapeutic doses. Celecoxib also did not significantly increase bleeding times when compared to placebo; technical variability limits interpretation. Serum TxB₂ levels were not reduced by Cx to sufficiently enough affect platelet function. Adverse event and clinical laboratory data indicated that Cx use was not associated with hemorrhagic events related to platelet function. Thrombotic events, including MIs, occurred. Consequently, patients that require thromboprophylaxis may still require low dose aspirin or other antiplatelet agents.
- 3 The multiple studies convincingly show that Cx, used at the proposed dosages of 100 to 200 mg BID, was associated with a statistically significantly lower incidence of gastroduodenal ulcers and gastric erosions compared to naproxen 500 mg BID in all three pivotal studies. The one study comparing Cx 200 mg BID to ibuprofen 800 mg TID revealed robust support for the safety claims related to gastroduodenal lesions.
- 4 The data comparing Cx to diclofenac were inconclusive. Study 041 suggested endoscopic superiority over diclofenac but study 071 showed no significant differences. However, study 071 had a larger evaluable endoscopy cohort and ulcer-free baseline endoscopy giving a better picture of the *de novo* and drug related ulcer incidence. On the other hand, study 041 was a study of longer duration. The 4% ulcer incidence at 4 weeks and 7% final cumulative ulcer rate at 12 weeks in study 071 was within the range of ulcer rates on Cx in the other studies over 12-24 weeks.

- 5 None of the GI studies were designed to address the issue of comparability to placebo.
- 6 The lack of consistent association between *H. pylori* and ulcer incidence across all treatment was seen regardless of the methodology used to detect this infection.
- 7 When data from the five pivotal endoscopic studies are combined, there is a statistically significant ulcerogenic effect of low-dose aspirin in the Cx group. This aspirin enhanced rate, however, was still lower than the ulcer rate among the NSAID groups. There was no effect of aspirin in the active NSAID comparators when taken as a whole. Nonetheless, these trials were not designed to analyze the role of aspirin co-administration. The risk of ulceration of Cx and aspirin use, however, remains lower than the risk of gastroduodenal ulcers associated with the use of naproxen or ibuprofen.
- 8 Endoscopically-defined ulcers have been defined as the surrogate of choice in this NDA. Future studies need to address the true clinically meaningful endpoints to corroborate the assumption that the development or presence of endoscopic ulcers correlates with adverse clinical outcomes and to quantify this relationship, if possible. The lack of standardization of definitions and procedures is of concern for such future studies.
- 9 No measurements of acid-base balance (e.g. serum bicarbonate, arterial pH) performed as part of any trial in the NDA. Therefore, an adverse effect of Cx on acid-base balance cannot be excluded, particularly in the context of the observed increase in hyperchloremia.
- 10 Both Cx and comparator NSAIDs (in short-term trials) inhibited prostaglandin PGE₂ and 6-keto-PGF₁ α excretion by the kidney to more or less the same extent. Both had significant inhibitory effects on the excretion of urinary prostaglandins when compared to placebo. Cx caused slightly less of a decrease in GFR in one study (010). Both Cx and naproxen inhibited serum renin and urinary (11-dehydro-TxB₂) thromboxane levels.
- 11 There was an association between Cx administration and the development of clinically significant edema (especially peripheral edema), similar to comparator NSAIDs, and clearly distinguished from placebo. Both naproxen and Cx cause sodium retention. There was no statistically significant association between ≥ 1 kg weight gain and the occurrence of 'peripheral edema' in a subset of patients with edema as an AE, although a higher % of both the Cx and active control group patients had both.
- 12 There was an association between Cx administration and the development of worsened hypertension in susceptible individuals, again similar to NSAIDs, and clearly distinguished from placebo.
- 13 There is a definite association between Cx use and an increased incidence of hypophosphatemia, and hyperchloremia compared to placebo and similar to active controls. There was no increase in bony fractures in those individuals with these abnormalities, 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. The clinical consequences of these changes remain to be determined.
- 14 There was a trend towards an increase incidence of elevated serum creatinine values and elevated BUN with proteinuria in both the Cx and active control groups relative to placebo.

- 15 The laboratory surrogates for renal toxicity suggest, but do not confirm, a link between Cx use and clinically relevant nephrotoxicity similar to NSAIDs.
- 16 There is no evidence to suggest that Cx has unique renal toxicities not shared by NSAIDs, or evidence of a renal toxicity caused by NSAIDs that occurs at a significantly higher incidence rate with Cx.
- 17 The pattern of AEs reported in both the controlled and the long-term trials is similar to that expected for NSAIDs.
- 18 There were several individuals taking Cx who were withdrawn from the long-term trials because of renal AEs including acute renal failure, edema and worsened hypertension.
- 19 While there were no clear cut cases of Cx-induced renal failure requiring dialysis, it remains to be determined whether severe renal injury will occur at the same rate that is seen with NSAIDs.
- 20 The renal effects of Cx are clearly distinguished from placebo.
- 21 The NDA does not reveal a strong signal pointing towards substantial clinically serious renal disease (i.e. large numbers of patients with acute renal failure requiring dialysis, nephrotic syndrome, papillary necrosis, interstitial nephritis). This will require a larger database.
- 22 The endocrine/metabolic safety profile of Cx is certainly no worse than the active controls.
- 23 Analysis of the data from the elderly population demonstrates that Cx is safe and well tolerated in the elderly, and poses no apparent additional safety considerations which do not apply to the younger age group.
- 24 Myocardial infarction was noted to occur at a higher rate in Cx than placebo patients. In the long-term trial, the predominate (90%+) cause of death for patients taking Cx at any dose was cardiovascular. The majority of these deaths represented progression of previously known CV disease. There is no apparent relationship between any given duration of exposure to Cx and increased mortality. The administration of Cx cannot be linked to any rare or unusual cardiac toxicities based on the available data. The available data do suggest the effects of Cx are similar to NSAIDs with regard to the "cardiac" effects of hypertension and edema.
- 25 Rashes and related cutaneous reactions were among the more frequently noted AEs associated with Cx treatment. The rashes were generally mild in severity, and often associated with urticaria or pruritus. Rash was the single most common reason for withdrawal from study treatment. There was an increase in incidence of rash at higher Cx doses (maximal with the 400 mg BID dose) suggesting a dose-response relationship. Importantly, there were no serious cutaneous reactions associated with Cx treatment.
- 26 In view of the possible etiologic link to sulfonamide sensitivity, physicians should exercise caution in prescribing CX to patients with a known history of systemic sulfa reaction.
- 27 Respiratory events were common in all treatment groups and occurred at similar incidence, suggesting that the high frequency simply reflected the common nature of

these disorders in the general population. Bronchitis and associated bronchospasm are not apparent to be exacerbated by celecoxib.

- 28 Review of the data regarding central and peripheral nervous system and psychiatric AEs does not reveal a pattern suggestive of deleterious effects from Cx use.
- 29 The available data does not suggest that Cx is associated with an increased risk of infection.
- 30 The most frequent adverse events were headache, dyspepsia, upper respiratory tract infection, diarrhea, and nausea.
- 31 Events that were frequent in occurrence (>1%) and associated with significantly greater incidences or withdrawal rates for Cx than placebo included GI complaints, rashes or itching, peripheral edema, pharyngitis, and upper respiratory tract infection.
- 32 The rate of withdrawal for adverse events for all doses of Cx appears better than comparators but NOT equivalent to placebo.
- 33 None of the serious adverse events that have occurred in NDA 20-998 appear to be obviously related to use of Cx.
- 34 No outstanding safety issues have been demonstrated during the clinical trials conducted to investigate the treatment of pain.
- 35 The data indicate that there was not an increased risk of neoplasms or malignancies for patients taking Cx.
- 36 None of the data suggest that Cx is associated with deleterious effects on the musculoskeletal system, including increases in the incidence of fractures.

Overall Discussion/Conclusions Regarding Celecoxib:

It has been argued that Cx represents a compound that is "selective" or "specific" for COX-2. The exact definition of a COX-2 selective agent, and as to whether it is moderately or highly selective or specific has yet to be adequately addressed. Of note, the number of peer-reviewed articles on this topic is increasing and the WHO has recently declared Cx to be in a unique therapeutic class based upon its mechanism of action (MOA). Therefore, in this review, it could be asked how much are we testing the drug, the theory of the drug, or both?

Although the exposure to Cx in this NDA has been large, this is still a "NDA" look at the drug, not a post-marketing look. Many of the questions (regarding both safety and efficacy) that need to be answered, can not be adequately addressed until Cx has been in the market and accumulated the exposures with such marketing. For example, one of these issues includes what will happen with widespread exposure in patients who are not aware or adequately questioned about having allergies to sulfonamide-containing products. This is a universal problem of extrapolating results from clinical trials where patients are "included" or "excluded" from the experience in "all comers" once a compound is approved.

Regarding safety, many would argue that since non-selective NSAIDs also inhibit COX-2, any safety concerns from this perspective should already be obvious from the numerous compounds approved and widely used to date. Others would argue that we do not know the consequences of "long-term, high-grade" inhibition of COX-2 and what types of compensatory mechanisms may come into play in this situation. It must be noted that the distribution and molecular biology of COX-2 is rapidly evolving.

Therefore, when considering the safety of COX-2 agents from a MOA standpoint, it may really depend on the particular tissue/target and whether or not COX-2 is present, and under what conditions. For example, the safety of COX-2 agents would theoretically be different in a target such as platelets which are widely assumed not to have COX-2 (because they have no nuclear machinery to make an inducible enzyme); from the safety profile in an organ where COX-2 is present, such as the kidney. Intermediate between these "clear-cut" extremes would be an organ such as the stomach which may only have significant levels of COX-2 during a "diseased" state such as infection with *Helicobacter pylori* or during the healing phase of an ulcer's natural history.

It must also be noted here that, from a safety perspective, COX-2 agents may not behave like non-selective agents because of nature of the target, COX-2. In the early understanding of COX-2, drugs such as Cx were thought to target only an inducible enzyme. Even though it is now appreciated that COX-2 is expressed constitutively in some areas (like kidney, brain, pancreas), COX-2 (unlike COX-1) is inducible. This would suggest that the body has a mechanism to overcome inhibition of COX-2, this does not appear to be the case with COX-1. That there may be such "upregulation" of COX-2 is suggested by the "dose-creep" phenomenon noted in the open-label, long-term trials with OA and RA (see below).

The following patient summary, taken from the 120-Day Safety Update represents many of the issues surrounding Cx and COX-2 agents:

Clearly, this patient developed a "clinically relevant" UGI event and she was in a risk group to have such an event. It could be argued that she was at a greater risk because she increased her dose of Cx, but she increased this dose for a reason, apparently she and her physician felt she needed it.

While most ($\approx 70\%$) patients with OA or RA in the open-label, long-term studies increased their dose of Cx, most did not an event similar to this patient. This "dose creep" is recognized to occur with other drugs, including NSAIDs. It could be argued that this creep seems to occur for both the "analgesic" and "anti-inflammatory" doses of Cx since it did occur in patients with both OA and RA. However, the end doses appear higher in patients with RA vs. patients with OA; the latter is considered to have less of an inflammatory component than RA.

In conclusion, Celebrex had demonstrated that is generally safe and effective for treating the signs and symptoms of OA and RA. Trials for analgesia were not adequate enough to conclude that Celebrex is an analgesic but this is expected with ongoing trials. Similarly, the clinical significance of the lower rates of endoscopic ulcers associated with Celebrex has yet to be established. In organs where COX-2 is present, such as the kidney, Celebrex looks more like a traditional NSAID. On the other hand, in targets where COX-2 is absent (such as platelets), Celebrex looks more like placebo. Overall, Celebrex is comparable to (or better than) active control NSAIDs while tending to be worse than (or, at times, comparable to) placebo.

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Appendices

Deaths in NDA 20-998

Reviewer's comment: The following section is from the Appendix of the Cardioresnal Review

Deaths in the Celecoxib NDA Database

9.1.1 Deaths in patients who enrolled in a controlled arthritis trial

A total of eight subjects who enrolled in controlled arthritis trials died. Five deaths occurred during controlled arthritis studies, and three following discontinuation of study drug. The narratives for those subjects who died while receiving study drug are in the first section below. The narratives for the subjects who died after discontinuation of study drug are found in section 9.1.2 below.

Five of the individuals in the controlled arthritis group who died received celecoxib, while three received active control drug.

Table 9.1.1.1 Deaths during controlled trials in the NDA 20-998 database^a.

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
Deaths During Study Drug Administration	70/M	Celecoxib 200mg BID	81	Gallbladder carcinoma with liver metastasis
	68/M	Naproxen 500mg BID	63	Brain-stem infarct
	78/M	Ibuprofen 800mg TID	29	Obstructive pulmonary disease
	53/F	Diclofenac 75 mg BID	1	Hypertension CV disease
	56/M	Celecoxib 200mg QD	30	Arteriosclerotic cardiovascular disease
Deaths After Drug D/C	62/F	Celecoxib 100mg BID	26/ 54	Pulmonary carcinoma
	80/F	Celecoxib 200mg BID	6/ 45	MI
	67/M	Naproxen 500mg BID	47/ NA	Pulmonary embolus

a. Data from Integrated Safety Summary, Text Table 67. Table shows all deaths from controlled trials, including those that occurred after the study drug was discontinued. For those three subjects, the # of days after drug discontinuation for the death is shown after the day of death.

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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.

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

Ten deaths occurred during the long-term open-label study prior to the database cutoff date (November 21, 1997), and are summarized below. The duration of treatment ranged from 15 to 273 days, with a final regimen of 200 mg BID for four patients, 300 mg BID for two patients and 400 mg BID for four patients.

Table 9.1.2.1 Deaths During the Long-Term Open Label Trial Prior to Database Cutoff Date of November 21, 1997^a.

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
	65/F	Celecoxib 400 mg BID	196	Natural causes
	76/M	Celecoxib 200 mg BID	45	MI, cardiac failure
	58/M	Celecoxib 400 mg BID	273	MI
	83/F	Celecoxib 300 mg BID	193	Coronary thrombosis
	80/M	Celecoxib 200 mg BID	159	Massive coronary
	59/M	Celecoxib 200 mg BID	246	Ischemic heart disease
	60/M	Celecoxib 400 mg BID	155	Adenocarcinoma
	84/F	Celecoxib 400 mg BID	243	Respiratory failure, CHF
	52/M	Celecoxib 300 mg BID	114	MI
	57/F	Celecoxib 200 mg BID	15	Subarachnoid hemorrhage

a. Data from Integrated Safety Summary, Text Table 66.

There were also five deaths in the long-term open label study between the database cutoff date and May 1, 1998. Their narratives are included below.

Table 9.1.2.2 Deaths During the Long-Term Open Label Trial After Database Cutoff Date of November 21, 1997^a.

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
	74/M	Celecoxib 400 mg BID	336	Heart block
	71/M	Celecoxib 400 mg BID	32	Coronary artery disorder
	71/F	Celecoxib 400 mg BID	37	MI
	61/F	Celecoxib 400 mg BID	471	MI
	78/F	Celecoxib 200 mg BID	88	Aneurysm

a. Data from Integrated Safety Summary, Text Table 67.

Finally, there were six deaths that occurred more than 28 days after last dose in any study reported in this New Drug Application. Two of these patients died after participation in trial 020, one died after participation in Study 021, and three died following participation in Study 024. The narratives for these subjects are also included below.

Table 9.1.3 Deaths That Occurred More than 28 Days After Last Dose^a.

Subject #	Age/ Sex	Treatment	Day of Death	Days after Last Dose	Cause of Death
	62/F	Celecoxib 100 mg BID	26	54	Pulmonary carcinoma
	80/F	Celecoxib 200 mg BID	6	45	MI
	67/M	Naproxen 500 mg BID	47		Pulmonary embolus
	65/M	Celecoxib 400 mg BID	334		Anterior MI
	66/M	Celecoxib 200 mg BID	173	29	Sepsis, pneumonitis
	77/F	Celecoxib	111	36	Pulmonary

a. Data from Integrated Safety Summary, Text Tables 66 and 68.

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Table A.1 Schedule of Observations and Procedures (Protocol 020)

	Screening Visit Day -14 to -2	Baseline Visit Day 0	Week 2 Day 14 ±1 day	Week 6 Day 42 ±2 days	Week 12 Day 84 ±2 days	Early Termination
Informed Consent	X					
Medical History	X					
Physical Examination	X					
Clinical Lab Tests (a)	X		X	X(b)	X	X
QOL Assessment (c)		X	X		X	X
OA Assessments	X(d)	X	X	X	X	X
Discontinue NSAID or analgesic (e)	X					
Meet Flare Criteria		X				
Signs and Symptoms		X	X	X	X	X
APS Pain Measure (f)		X				
Patient Assessment of Function (f)		X				
Blood Samples for Plasma PK Levels (g)			X			
Dispense Study Medication		X	X	X		
Return & Count Study Med			X	X	X	
Dispense Concurrent Medications Diary Card		X	X	X		
Retrieve Concurrent Medications Diary Card			X	X	X	X
<p>a) Clinical laboratory tests included: Hematology (white blood cell [WBC] count with differential, red blood cell [RBC] count, hemoglobin, hematocrit, platelet count [estimate not acceptable], prothrombin time [PT], partial thromboplastin time [PTT]; Biochemistry (sodium, potassium, chloride, calcium, inorganic phosphorus, BUN, creatinine, total protein, albumin, total bilirubin, uric acid, glucose, alkaline phosphatase, AST [SGOT], ALT [SGPT], creatine kinase [CK]); and Urinalysis (pH, specific gravity, WBC, RBC, protein, glucose, ketones, bilirubin). Serum pregnancy test for women of childbearing potential at Screening visit only.</p> <p>b) PT and PTT tests were not performed at the Week 6 Visit.</p> <p>c) SF-36 Health Survey.</p> <p>d) Screening Arthritis Assessment data were collected by Searle but not entered in the database.</p> <p>e) Patients discontinued oxaprozin and/or piroxicam at least four days before the Baseline Arthritis Assessments.</p> <p>f) American Pain Society (APS) Pain Measure and Patient Assessment of Function were completed by the patient during the Baseline Visit and daily for the first seven days of dosing with study medication. Patients enrolled in study prior to 8 August 1996 who already began taking study medication were not required to complete questionnaires.</p> <p>g) Three blood draws were to be taken from 200 patients (approximately 40 per treatment group) at selected sites between Day 7 and 28 after first dose for determination of SC-58635 plasma levels.</p>						

Table A.2 Baseline demographics (study 020, 021, 054-pooled)

Baseline Characteristic	Placebo (n=664 ^a)	Celecoxib			Naproxen 500 mg BID (n=631)
		50 mg BID (n=671)	100 mg BID (n=644 ^a)	200 mg BID (n=648)	
12-Week Pivotal Studies 020, 021, and 054)					
Baseline Demographic Characteristics					
Age (years)					
Mean (Std. Dev.)	62.3 (10.22)	61.6 (11.09)	61.9 (11.31)	61.9 (11.43)	62.7 (11.09)
Range	30-87	21-93	24-88	25-88	19-89
<65 years - N (%)	361 (54%)	378 (56%)	358 (56%)	353 (54%)	334 (53%)
≥65 years - N (%)	303 (46%)	293 (44%)	286 (44%)	295 (46%)	297 (47%)
Race/Ethnic Origin					
Asian - N (%)	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
Black - N (%)	59 (9%)	80 (12%)	63 (10%)	71 (11%)	65 (10%)
Caucasian - N (%)	577 (87%)	574 (86%)	569 (88%)	555 (86%)	553 (88%)
Hispanic - N (%)	22 (3%)	13 (2%)	7 (1%)	18 (3%)	11 (2%)
Other - N (%)	4 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)
Gender					
Female - N (%)	466 (70%)	444 (66%)	441 (68%)	451 (70%)	430 (68%)
Male - N (%)	198 (30%)	227 (34%)	203 (32%)	197 (30%)	201 (32%)
Baseline Index Joint and Disease Duration					
Baseline Index Joint					
Knee - N (%)	446 (67%)	455 (68%)	437 (68%)	435 (67%)	424 (67%)
Hip - N (%)	218 (33%)	216 (32%)	207 (32%)	213 (33%)	207 (33%)
Disease Duration - Years					
Mean (Std. Dev.)	9.0 (8.93)	8.4 (8.18)	8.6 (8.00)	8.5 (8.44)	8.8 (8.84)
Range					
<5 years - N (%)	257 (39%)	281 (42%)	255 (40%)	273 (42%)	264 (42%)
≥5 years - N (%)	407 (61%)	390 (58%)	389 (60%)	375 (58%)	367 (58%)

Table A.3 Baseline demographics (protocol 060, 087-pooled)

Week Pivotal Studies 060 and 087)			
Baseline Characteristic	Placebo (n=476) ^a	Celecoxib	
		100 mg BID (n=474)	200 mg QD (n=454)
Baseline Demographic Characteristics			
Age (years)			
Mean (Std. Dev.)	61.9 (11.49)	62.5 (11.16)	62.0 (11.59)
Range	18-89	27-89	29-88
<65 years - N (%)	260 (55%)	254 (54%)	257 (57%)
≥65 years - N (%)	215 (45%)	220 (46%)	197 (43%)
Race/Ethnic Origin			
Caucasian - N (%)	418 (88%)	408 (86%)	392 (86%)
Black - N (%)	42 (9%)	50 (11%)	41 (9%)
Hispanic - N (%)	7 (1%)	9 (2%)	6 (1%)
Asian - N (%)	1 (<1%)	0 (0%)	1 (<1%)
Other - N (%)	7 (1%)	6 (1%)	14 (3%)
Gender			
Female - N (%)	333 (70%)	321 (68%)	306 (67%)
Male - N (%)	143 (30%)	153 (32%)	148 (33%)
Disease Duration - Years			
Mean (Std. Dev.)	9.1 (8.47)	9.4 (8.79)	9.1 (7.92)
Range			
<5 years - N (%)	172 (36%)	158 (33%)	149 (33%)
≥5 years - N (%)	304 (64%)	316 (67%)	305 (67%)

Table A.4 WOMAC Index

How much pain do you have?

- walking on a flat surface
- going up or down stairs
- at night while in bed
- sitting or lying
- standing upright

Amount of joint stiffness

- 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?

Ability to move around and to look after yourself - degree of difficulty

- | | |
|------------------------------|------------------------------|
| - descending stairs | - rising from bed |
| - ascending stairs | - taking off socks/stockings |
| - rising from sitting | - lying in bed |
| - standing | - getting in/out of bath |
| - bending to floor | - sitting |
| - walking on flat surface | - getting on/off toilet |
| - getting in/out of car | - heavy domestic duties |
| - going shopping | - light domestic duties |
| - putting on socks/stockings | |

Score: none, mild, moderate, severe, extreme

Table A.5: Osteoarthritis Severity Index (knee)

Inquiries Related to Pain	Points*
Nocturnal pain	
- none	0
- only on movement or in certain positions	1
- without movement	2
Duration of morning stiffness or pain after getting up	
- none	0
- less than 15 minutes	1
- 15 minutes or more	2
Remaining standing for 30 minutes increases pain	
- no	0
- yes	1
Pain on walking	
- none	0
- only after walking some distance	1
- very early after starting to walk and increasing	2
Pain or discomfort when getting up from the sitting position	
- no	0
- yes	1
Inquiries related to maximum walking distance	
- Unlimited	0
- More than 1 km (0.62 miles), but limited	1
- About 1 km (0.62 miles, about 15 minutes)	2
- From 500 to 900 m (547-985 yards, about 8-15 minutes)	3
- From 300 to 500 m (328-547 yards)	4
- From 100 to 300 m (109-328 yards)	5
- Less than 100 m (109 yards)	6
- With one walking stick or crutch	+1
- With two walking sticks or crutches	+2
Inquiries related to activities of daily living*	
- Can you go up a standard flight of stairs?	0 to 2
- Can you go down a standard flight of stairs?	0 to 2
- Can you squat completely?	0 to 2
- Can you walk on uneven ground?	0 to 2

*Point Score: No difficulty = 0; With difficulty = 1; Impossible = 2.

Table A.6: Osteoarthritis Severity Index (hip)

Inquiries Related to Pain	Points*
Nocturnal pain	
- none	0
- only on movement or in certain positions	1
- without movement	2
Duration of morning stiffness or pain after getting up	
- none	0
- less than 15 minutes	1
- 15 minutes or more	2
Remaining standing for 30 minutes increases pain	
- no	0
- yes	1
Pain on walking	
- none	0
- only after walking some distance	1
- very early after starting to walk and increasing	2
Pain or discomfort when getting up from the sitting position	
- no	0
- yes	1
Inquiries related to maximum walking distance	
- Unlimited	0
- More than 1 km (0.62 miles), but limited	1
- About 1 km (0.62 miles, about 15 minutes)	2
- From 500 to 900 m (547-985 yards, about 8-15 minutes)	3
- From 300 to 500 m (328-547 yards)	4
- From 100 to 300 m (109-328 yards)	5
- Less than 100 m (109 yards)	6
- With one walking stick or crutch	+1
- With two walking sticks or crutches	+2
Inquiries related to activities of daily living*	
- Can you put on socks by bending forward?	0 to 2
- Can you pick up an object from the floor?	0 to 2
- Can you go up a standard flight of stairs?	0 to 2
- Can you get into and out of a car?	0 to 2

*Point Score. No difficulty = 0; With difficulty = 1; Impossible = 2.

Table A.7.1 Physician's Global Assessment (Protocol 054)

**PHYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 1 OF 4: OBSERVED MEANS (a) (b)**

	INTENT-TO-TREAT COHORT (ITT)			
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)
BASELINE				
N	217	216	207	213
MEAN	3.8	3.8	3.8	3.9
STD DEV	0.60	0.60	0.56	0.60
WEEK 2				
N	217	216	207	213
MEAN	3.2	2.9	2.7	2.8
STD DEV	0.86	0.83	0.81	0.83
WEEK 6				
N	217	216	207	213
MEAN	3.2	2.8	2.7	2.7
STD DEV	0.91	0.94	0.93	0.98
WEEK 12				
N	217	216	207	213
MEAN	3.2	2.9	2.8	2.9
STD DEV	0.90	0.98	0.95	1.02

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor)

**PHYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 2 OF 4: CATEGORICAL CHANGE ANALYSIS, NUMBER OF PATIENTS (a) (b)**

	INTENT-TO-TREAT COHORT (ITT)						LINEAR TREND P-VALUE (d)
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)		
WEEK 2							<0.001
IMPROVED (b)	37 (17%)	55 (25%)	60 (29%)	69 (32%)	69 (33%)		
NO CHANGE	172 (79%)	158 (73%)	145 (70%)	140 (65%)	141 (67%)		
WORSENE (c)	8 (4%)	3 (1%)	2 (1%)	4 (2%)	3 (1%)		
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)		
WEEK 6							<0.001
IMPROVED (b)	42 (19%)	66 (31%)	70 (34%)	80 (38%)	63 (30%)		
NO CHANGE	166 (76%)	144 (67%)	135 (65%)	128 (60%)	139 (67%)		
WORSENE (c)	9 (4%)	4 (2%)	2 (1%)	5 (2%)	5 (2%)		
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)		
WEEK 12							0.001
IMPROVED (b)	39 (18%)	59 (27%)	66 (32%)	62 (30%)	66 (32%)		
NO CHANGE	169 (78%)	152 (70%)	139 (67%)	145 (68%)	136 (66%)		
WORSENE (c)	9 (4%)	5 (2%)	2 (1%)	5 (2%)	5 (2%)		
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)		

P-VALUES FOR TREATMENT COMPARISONS (a) :

	-----PRIMARY-----				-----SECONDARY-----					
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
	PLACEBO	PLACEBO	PLACEBO	50MG BID	50MG BID	100MG BID	PLACEBO	50MG BID	100MG BID	200MG BID
WEEK 2:	0.001*	<0.001*	0.005	0.346	0.219	0.263	<0.001	0.242	0.620	0.789
WEEK 6:	<0.001*	<0.001*	<0.001	0.510	0.327	0.324	0.002	0.535	0.467	0.182
WEEK 12:	<0.001*	0.009*	0.004	0.237	0.811	0.693	<0.001	0.005	0.925	0.516

(a) This table is based on the last observation carried forward approach
(b) Improved is defined as reduction of at least two grades from baseline for grades 3-5 or a change in grade from 1 to 2
(c) Worsened is defined as an increase of at least two grades from baseline for grades 1-3 or a change in grade from 4 to 5
(d) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Nonzero Correlation); Naproxen group was excluded
(e) Cochran-Mantel-Haenszel test of treatment comparison stratified by center (Row Mean Scores Differ)
* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.7.2 Physician's Global Assessment-continued (Protocol 054)

	INTENT-TO-TREAT COHORT (ITT)					OVERALL P-VALUE (c)	LINEAR TREND P-VALUE (d)
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	MAPROXEN 500MG BID (N=207)		
WEEK 2							
OBSERVED MEAN CHANGE	-0.6	-0.9	-1.1	-1.1	-1.1	<0.001	<0.001
STD DEV	0.94	0.93	0.83	0.93	0.87		
LS MEAN CHANGE (e)	-0.6	-0.9	-1.1	-1.1	-1.1		
WEEK 6							
OBSERVED MEAN CHANGE	-0.6	-1.0	-1.0	-1.2	-1.0	<0.001	<0.001
STD DEV	1.00	1.01	1.01	1.00	0.96		
LS MEAN CHANGE (e)	-0.6	-1.1	-1.1	-1.1	-1.1		
WEEK 12							
OBSERVED MEAN CHANGE	-0.6	-0.9	-1.0	-1.0	-1.0	<0.001	<0.001
STD DEV	0.98	1.06	1.02	1.00	1.05		
LS MEAN CHANGE (e)	-0.6	-1.0	-1.0	-1.0	-1.1		

	C-RATIO WITH 95% CONFIDENCE INTERVALS (e):		
	50MG BID VS. MAPROXEN	100MG BID VS. MAPROXEN	200MG BID VS. MAPROXEN
WEEK 2:	0.83 (0.71 to 0.97)	0.99 (0.85 to 1.14)	0.97 (0.84 to 1.10)
WEEK 6:	0.99 (0.84 to 1.17)	1.00 (0.85 to 1.19)	1.05 (0.89 to 1.24)
WEEK 12:	0.91 (0.76 to 1.09)	0.97 (0.81 to 1.15)	0.90 (0.75 to 1.06)

P-VALUES FOR TREATMENT COMPARISONS (f):

	PRIMARY		SECONDARY							
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	MAPROXEN VS. PLACEBO	MAPROXEN VS. 50MG BID	MAPROXEN VS. 100MG BID	MAPROXEN VS. 200MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.031	0.054	0.815	<0.001	0.019	0.850	0.671
WEEK 6:	<0.001*	<0.001*	<0.001	0.937	0.490	0.571	<0.001	0.925	0.981	0.555
WEEK 12:	<0.001*	<0.001*	<0.001	0.502	0.899	0.427	<0.001	0.298	0.715	0.245

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement

(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 0.796 for week 2, 0.897 for week 6, and 0.916 for week 12

(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded

(e) C-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group

(f) From a contrast statement from Analysis of Covariance model in (c)

* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.8.1 Patient's global assessment (Protocol 054)

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 1 OF 4: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT)*

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	216	207	213	207
MEAN	3.4	3.4	3.9	4.0	3.9
STD DEV	0.62	0.64	0.61	0.59	0.64
WEEK 2					
N	217	216	207	213	207
MEAN	3.3	2.9	2.7	2.6	2.7
STD DEV	0.90	0.88	0.95	0.90	0.88
WEEK 6					
N	217	216	207	213	207
MEAN	3.3	2.9	2.8	2.8	2.8
STD DEV	0.97	0.97	0.99	1.08	1.01
WEEK 12					
N	217	216	207	213	207
MEAN	3.4	2.9	2.8	3.0	2.8
STD DEV	0.95	1.01	1.02	1.09	1.06

(a) This table is based on the last observation carried forward approach.
 (b) Scale ranged from 1 (very good) to 5 (very poor).
 * By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication.

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 2 OF 4: CATEGORICAL CHANGE ANALYSIS, NUMBER OF PATIENTS (b) (c)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	LINEAR TREND P-VALUE (d)
WEEK 2						
IMPROVED (b)	35 (16%)	51 (24%)	67 (32%)	75 (35%)	66 (32%)	<0.001
NO CHANGE	172 (79%)	162 (75%)	137 (66%)	132 (62%)	138 (67%)	
WORSENER (c)	10 (5%)	5 (2%)	3 (1%)	5 (2%)	3 (1%)	
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)	
WEEK 6						
IMPROVED (b)	38 (18%)	67 (31%)	71 (34%)	78 (37%)	63 (30%)	<0.001
NO CHANGE	162 (75%)	143 (66%)	131 (63%)	126 (59%)	139 (67%)	
WORSENER (c)	17 (8%)	6 (3%)	5 (2%)	9 (4%)	5 (2%)	
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)	
WEEK 12						
IMPROVED (b)	36 (17%)	56 (26%)	65 (31%)	61 (29%)	70 (34%)	0.001
NO CHANGE	164 (76%)	153 (71%)	137 (66%)	142 (67%)	131 (63%)	
WORSENER (c)	17 (8%)	7 (3%)	5 (2%)	10 (5%)	6 (3%)	
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)	

p-VALUES FOR TREATMENT COMPARISONS (e) :

	PRIMARY		SECONDARY							
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 2:	<0.001*	<0.001*	0.016	0.044	0.017	0.427	<0.001	0.072	0.954	0.784
WEEK 6:	<0.001*	<0.001*	<0.001	0.543	0.423	0.402	<0.001	0.037	0.464	0.246
WEEK 12:	<0.001*	0.007*	0.004	0.258	0.794	0.606	<0.001	0.151	0.577	0.174

(a) This table is based on the last observation carried forward approach.
 (b) Improved is defined as reduction of at least two grades from baseline for grade 3-5 or a change in grade from 3 to 1.
 (c) Worsener is defined as an increase of at least two grades from baseline for grade 1-3 or a change in grade from 4 to 5.
 (d) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Mantel-Haenszel Correlation). Naproxen group was excluded.
 (e) Cochran-Mantel-Haenszel test of treatment comparison stratified by center (Fleiss Mean Scores Differ).
 * Statistically significant according to the Hochberg procedure (primary pairwise comparisons only).

Table A.8.2 Patient's global assessment (Protocol 054)

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 3 OF 4: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT (ITT)

	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	MAPROXEN 500MG BID (N=207)	OVERALL P-VALUE (c)	LINEAR TREND P-VALUE (d)			
WEEK 2										
OBSERVED MEAN CHANGE	-0.6	-0.9	-1.2	-1.1	-1.2	<0.001	<0.001			
STD DEV	0.96	0.92	0.90	0.96	0.90					
LS MEAN CHANGE (c)	-0.6	-0.9	-1.2	-1.1	-1.2					
WEEK 6										
OBSERVED MEAN CHANGE	-0.5	-0.9	-1.1	-1.1	-1.1	<0.001	<0.001			
STD DEV	1.00	1.02	1.05	1.08	0.99					
LS MEAN CHANGE (c)	-0.6	-1.0	-1.1	-1.1	-1.1					
WEEK 12										
OBSERVED MEAN CHANGE	-0.5	-0.8	-1.1	-1.0	-1.1	<0.001	<0.001			
STD DEV	1.00	1.06	1.06	1.07	1.07					
LS MEAN CHANGE (c)	-0.5	-0.9	-1.1	-0.9	-1.1					
Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):										
	50MG BID VS. MAPROXEN			100MG BID VS. MAPROXEN		200MG BID VS. MAPROXEN				
WEEK 2:	0.78 (0.65 to 0.91)			0.97 (0.85 to 1.12)		0.93 (0.85 to 1.07)				
WEEK 6:	0.92 (0.77 to 1.10)			1.01 (0.86 to 1.20)		1.00 (0.84 to 1.16)				
WEEK 12:	0.82 (0.68 to 0.99)			0.95 (0.79 to 1.13)		0.83 (0.68 to 1.00)				
P-VALUES FOR TREATMENT COMPARISONS (f):										
	-----PRIMARY-----			-----SECONDARY-----						
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	MAPROXEN VS. PLACEBO	MAPROXEN VS. 50MG BID	MAPROXEN VS. 100MG BID	MAPROXEN VS. 200MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.604	0.028	0.464	<0.001	0.001	0.712	0.285
WEEK 6:	<0.001*	<0.001*	<0.001	0.273	0.375	0.832	<0.001	0.358	0.855	0.973
WEEK 12:	<0.001*	<0.001*	<0.001	0.139	0.961	0.146	<0.001	0.036	0.541	0.539

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement
 (c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate.
 the corresponding ROOT MSE are: 0.825 for week 2, 0.941 for week 6, and 0.967 for week 12
 (d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
 (e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group
 (f) From a contrast statement from Analysis of Covariance model in (c)
 * Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.9.1 Patient's Assessment of Arthritis Pain (protocol 020)

	INTENT-TO-TREAT COHORT (ITT) *				
	PLACEBO (N=202)	SC-50635 50MG BID (N=203)	SC-50635 100MG BID (N=197)	SC-50635 200MG BID (N=202)	NSAID 500MG BID (N=198)
BASELINE					
N	201	203	196	201	197
MEAN	59.4	66.9	68.0	68.9	71.4
STD DEV	17.13	18.13	16.17	15.43	24.97
WEEK 2					
N	201	203	196	201	197
MEAN	36.1	49.2	41.9	44.0	42.2
STD DEV	26.24	25.83	25.77	24.96	26.53
WEEK 6					
N	201	203	196	201	197
MEAN	31.1	49.3	41.6	43.8	41.9
STD DEV	29.04	26.83	27.84	27.05	29.07
WEEK 12					
N	201	203	196	201	197
MEAN	32.7	50.9	43.8	45.5	45.8
STD DEV	29.41	28.29	28.85	29.23	29.29

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 100 (mm) with lower score as better
 * By definition, in this and subsequent efficacy tables, the ITT cohort includes only those patients who had at least one dose of study medication

**TABLE 18
 PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
 PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)**

	INTENT-TO-TREAT COHORT (ITT)					OVERALL P-VALUE (c)	LINEAR TREND P-VALUE (d)
	PLACEBO (N=202)	SC-50635 50MG BID (N=203)	SC-50635 100MG BID (N=197)	SC-50635 200MG BID (N=202)	NSAID 500MG BID (N=198)		
WEEK 2							
OBSERVED MEAN CHANGE	-13.3	-17.7	-26.1	-24.9	-29.2	<0.001	<0.001
STD DEV	23.28	25.99	26.19	24.81	26.88		
LS MEAN CHANGE (c)	-12.1	-18.6	-26.1	-24.6	-27.3		
WEEK 6							
OBSERVED MEAN CHANGE	-18.3	-17.7	-26.4	-25.1	-29.8	<0.001	<0.001
STD DEV	27.38	29.22	27.76	26.40	30.28		
LS MEAN CHANGE (c)	-16.6	-17.9	-25.9	-24.5	-27.0		
WEEK 12							
OBSERVED MEAN CHANGE	-16.7	-16.0	-24.1	-23.3	-25.6	0.002	<0.001
STD DEV	29.05	29.81	27.31	29.18	29.14		
LS MEAN CHANGE (c)	-15.1	-16.0	-23.1	-22.1	-22.7		

Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):

	50MG BID VS. NSAID	100MG BID VS. NSAID	200MG BID VS. NSAID
WEEK 2:	0.67 (0.53 to 0.84)	0.96 (0.80 to 1.15)	0.90 (0.74 to 1.09)
WEEK 6:	0.66 (0.51 to 0.85)	0.96 (0.78 to 1.18)	0.91 (0.74 to 1.12)
WEEK 12:	0.70 (0.51 to 0.84)	1.02 (0.80 to 1.30)	0.97 (0.76 to 1.25)

P-VALUES FOR TREATMENT COMPARISONS (f):

	PRIMARY			SECONDARY				
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. 100MG BID	100MG BID VS. 200MG BID	NSAID VS. PLACEBO	NSAID VS. 50MG BID	NSAID VS. 100MG BID	NSAID VS. 200MG BID
WEEK 2:	<0.001*	<0.001*	0.009	0.001	0.018	0.514	<0.001	<0.001
WEEK 6:	<0.001*	0.003*	0.628	0.002	0.013	0.579	<0.001	<0.001
WEEK 12:	0.003*	0.009*	0.735	0.008	0.023	0.781	0.005	0.014

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 100 (mm) with negative change indicating improvement
 (c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding R² are: 33.93 for week 2, 26.22 for week 6, and 27.82 for week 12
 (d) From a contrast statement from Analysis of Covariance model in (c), NSAID group was excluded
 (e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-50635 group versus NSAID group
 (f) From a contrast statement from Analysis of Covariance model in (c)
 * Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table/Figure A.9.2 Patient's Assessment of Arthritis Pain (020)

