

incidence of endoscopically detected gastroduodenal ulceration and tolerability in patients with Rheumatoid Arthritis.

1. STUDY OBJECTIVES (from study 041 text)

The primary objectives of this study were to:

1. Compare the efficacy of celecoxib 200 mg with that of diclofenac SR 75 mg, when administered twice daily for 24 weeks, in treating the signs and symptoms of rheumatoid arthritis;
2. Compare the incidence of gastroduodenal ulceration in patients receiving celecoxib 200 mg BID with that in patients receiving diclofenac SR 75mgBID for 24 weeks, and
3. Evaluate the long term safety of celecoxib 200 mg taken twice daily for 24 weeks.

Secondary Objective

The secondary objective of this study was to determine the impact of celecoxib on patients' health-related quality of life using the SF-36 Health Survey.

2. Study design:

This study was longer than any other controlled study and involved the broadest geographic range of patients. Inclusion and exclusion criteria were similar to the North American trials. There were however, several important differences compared to the North American trials. The international composition introduces variability based on different educational backgrounds and endoscopic training. Difference in terminology used in endoscopy reports bears this out. The lack of baseline endoscopy in a patient population that did not exclude recent prior use of NSAIDs introduces a significant uncontrolled variable: particularly for a study that defines endoscopic ulceration as an endpoint. The long duration of the study does not mitigate this issue. This design, however does mimic the likely clinical setting in which such medications are used (no baseline endoscopy). The only endoscopy was performed at study conclusion or early termination. No aspirin or anti-ulcer therapy was allowed. "The occasional" use of antacid for symptomatic relief was allowed. The only information regarding H. pylori infection was serologic.

3. Results

i. Demographics: Study groups were comparable for the following relevant parameters: gender, age, race, history of GI intolerance to NSAIDs, GI bleeding, gastroduodenal ulcer, cardiovascular disease. No baseline H.pylori data is available by study design. H. Pylori status based on serology was performed at the end of the study. The ultimate serologic status revealed no meaningful difference between the study groups in terms of H. Pylori status. No data on alcohol and tobacco use is given.

ii. Patient disposition. The calculated study group size was set at approximately 160 each for endoscopic evaluation and 230 each for efficacy based on assumptions described in the protocol. Safety assumptions included an anticipated ulcer rate of 19% in the diclofenac group and a 2-4% ulcer rate in the celecoxib group with a 90% power at 0.05 two- sided test. Since less endoscopic data were assumed necessary only some study centers included endoscopic

evaluation in their protocol. 132 centers in Europe, Israel, New Zealand, Australia, and South Africa participated. Ultimately, however, overenrollment was 42% for efficacy study purposes and 34% for endoscopic purposes. A total of 326 and 329 patients were enrolled into the celecoxib and naproxen groups respectively. At the reviewing team's request, the sponsor analyzed the data on the initial population size of 460 based on the first 460 enrollees to be sure that no overpowering of the study occurred. The results were not meaningfully different.

ii Serious UGI events

Two patients experienced serious UGI events. Both of these events occurred in the diclofenac group.

(from text study041)

“Patient No. SK0001-0512 DER 970620-CL412 (Gastric Ulcer) was a 56 year old female with a history of RA. Concomitant medications included methotrexate, propranolol, and magnesium. The patient was enrolled in the study and randomized to the diclofenac SR 75 mg BID group. Treatment with study drug began on 1 April 1997. On 2 June 1997 the patient began to experience epigastric pain and nausea but without vomiting or melena. On 9 June 1997 the patient complained to her rheumatologist of epigastric pain; she also had increased anemia (no documentation supplied). She denied hematemesis and melena. A rectal exam showed no evidence of melena. Tests for occult stool bleeding were not performed. The study medication was stopped on 9 June 1997 and an endoscopy was performed on 12 June 1997, which revealed “great” gastric ulcer (non-bleeding) of 4x4 cm at the posterior wall in the corporal area with a small blood coagulum on the base. The borders were regular (bleeding did not continue in the time of the investigation). No erosions or petechiae were noted and there were no lesions in the antral portion, the duodenum or the pyloric channel. The patient was hospitalized for treatment on 13 June 1997. The patient was withdrawn from the study due to gastric ulcer. The patient subsequently recovered. Review of the case records by the independent GI committee determined this event was a clinically significant GI event. The Investigator considered that the event was probably related to study drug. The Searle Medical Monitor considered the event to be related to study drug.”

This patient had been on diclofenac just prior to beginning the study. Doxycycline was in use at the time of withdrawal for unknown reasons. Case report data did reveal a clinically significant fall in hemoglobin from 11.6 to 8. This patient had been on diclofenac prior to her study enrollment. This case is indeed considered a clinically significant UGI event.

(from text study 041)

“Patient No. UK0004-0786 DER 970418- CL225 (Gastritis Hemorrhagic) was 75 year old male with a prior history of RA. Concomitant medications included methotrexate, folic acid, and prednisolone. The patient was enrolled in the study and was randomized to the diclofenac SR 75 mg BID. Treatment with study drug began on 27 January 1997. On 20 February 1997 the patient withdrew from the study because of dyspepsia. At the Final Visit the patient refused to permit endoscopy. On 26 February 1997, 30 days after start of treatment, the patient experienced melena. The following day he was very pale and fainted several times. He underwent an emergency endoscopy by a non-study physician which revealed multiple gastric erosions without ulceration. The rheumatologist broke the code on the medication revealing it to be diclofenac SR and admitted the patient to hospital. The patient received four units of blood in the hospital. The patient was released from hospital on 10 March 1997. The Investigator and the Searle Medical

Monitor both considered the event to be probably related to study drug. Review of the case records by the independent GI committee determined this event was a clinically significant GI bleeding event.”

This patient had been on Indomethacin suppositories up until initiation of the study. He withdrew for dyspepsia 6 days before the development of his clinically relevant adverse event occurred. In addition, the lack of baseline endoscopy makes it impossible to know the time course of the development of his ulcer. The Indomethacin used may well have played a role in the development of this ulcer. It is unknown what medications were taken after discontinuation from the study, if any. Based on the predetermined definition of endoscopic evaluability, this case should not be included in the results given the duration of time between withdrawal and clinical event. Despite these protocol violations; for study purposes this reviewer agrees that it should be considered a clinically significant UGI adverse event possibly related to the active comparator.

iv. Endoscopy results

Data validation:

116 endoscopy reports were reviewed. 4 reports did not specify the number of erosions. The coding staff in some cases chose a category of erosion numbers. This may affect the data on overall gastric score but is unlikely to do so in a meaningful way. No original report form was available on 10 patients. In one case a lesion was described as 1-3mm in size but still considered an ulcer. The definition of an ulcer was a lesion with depth and at least 3mm. in diameter. The coding decision was reasonable but highlights the difficulty in measuring the primary endpoint accurately. In future studies, measuring devices should be used and visual documentation should be considered.

Tables 30 and 31 display the ulcer data for study 041.

Table 30 (from study 041)

TABLE 31 GASTROINTESTINAL ENDOSCOPY RESULTS AT THE FINAL VISIT PART 2 OF 5: ANALYSIS OF CRUDE ULCER RATE			
INTENT-TO-TREAT COHORT (ITT)			
	SC-58635 200MG BID (N= 326) (a)	DICLOFENAC 75MG SR BID (N= 329) (a)	p-VALUE (b)
CRUDE ULCER RATE:			<0.001
NO ULCER	204 (96%)	185 (85%)	
ULCER(c)	8 (4%)	33 (15%)	
TOTAL (d)	212(100%)	218(100%)	

(a) All randomized patients

(b) Cochran-Mantel-Haenszel test stratified by center (p-value from Row Mean Scores Differ)

(c) Ulcer is defined as an endoscopy score equal to 7

(d) Includes only patients in endoscopy ITT cohort

Table 31 (from study 041)

TABLE 31 GASTRODUODENAL ENDOSCOPY RESULTS PART 1 OF 5: NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL INTENT-TO-TREAT COHORT (ITT)				
STUDY DAYS	SC-58635 200MG BID (N= 326) (a)		DICLOFENAC 75MG SR BID (N= 329) (a)	
	NO ULCER	ULCER	NO ULCER	ULCER
WK4 (2-42)	9	1	18	6
WK8 (43-70)	3	0	8	4
WK12 (71-98)	4	0	6	1
WK16 (99-126)	3	0	4	3
WK20 (127-154)	9	0	4	3
WK24 (>=155)	176	7	145	16
TOTAL (b)	204	8	185	33

(a) All randomized patients
(b) Includes only patients in endoscopy ITT cohort

The endoscopy data in tables 30 through 31 reveal a statistically significant difference between the two treatment groups. The difference was present for gastric ulcer rate, duodenal ulcer rate and gastric scores.

H. pylori data follows the North American trials in lack of correlation between gastric or duodenal ulcer rate or endoscopic scores and H. pylori status (based on serology at conclusion of the study). Both groups had higher ulcer rates in the H. pylori positive groups but no statistical significance could be shown with the study size available.

Table 32 (from study 041)

TABLE 31 GASTRODUODENAL ENDOSCOPY RESULTS AT THE FINAL VISIT PART 4 OF 5: COMPARISON OF H. PYLORI POSITIVE VS. H. PYLORI NEGATIVE (a) WITHIN EACH TREATMENT GROUP INTENT-TO-TREAT COHORT (ITT)		
	SC-58635 200MG BID (N= 326) (b)	DICLOFENAC 75MG SR BID (N= 329) (b)
ULCER RATE		
PERCENT PATIENTS WITH ULCER		
FOR H. PYLORI (c):		
POSITIVE	7.5 (7/ 93)	21.8 (19/ 87)
NEGATIVE	1.0 (1/ 97)	10.0 (10/100)
POSITIVE - NEGATIVE	6.5	11.8
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (d)	0.139	0.173

(a) Positive (negative) patients should test positive (negative) by serology test
(b) All randomized patients
(c) Includes only patients in endoscopy ITT cohort with known HP status
(d) Cochran-Mantel-Haenszel test stratified by center, performed within each treatment (p-value from Row Mean Scores Differ)

Corticosteroid usage did not correlate with ulcer prevalence in either group. Stratified data were not supplied for other potential risk factors such as history of cardiovascular disease, gastroduodenal ulcer disease, GI bleeding, or GI NSAID intolerance. The baseline data however did show that the 2 groups were well matched in this regard. Unfortunately no stratification is available for alcohol or tobacco use.

v. Summary:

Study 041 revealed a statistically significant lower in ulcer incidence over a 24 week period in patients treated with celecoxib 200mg bid compared to diclofenac SR 75 mg bid. Two clinically significant UGI events occurred in the diclofenac group compared to no such events in the celecoxib group.

V. Clinically significant UGI adverse events:

The sponsor's definition of clinically significant UGI events is presented on page 9 of this review. The lack of clear definition of the terms coffee ground emesis and melena for usage in clinical trials and the imprecise definition of gastric outlet obstruction is of concern. Two cases were classified as significant events related to bleeding where there was no documentation of hemocult positive stool or emesis and without a fall in hemoglobin or hematocrit. A case of gastric outlet obstruction was included where the clinical presentation was indigestion lasting for 20 days without associated vomiting and the endoscopically visualized description was of a "partial gastric outlet obstruction" when presented in the Integrated Summary of Safety information and without significant obstruction when presented within the results of the individual study 022. The reports are reproduced below.

Patient No. US0004-1070 DER No. 970214-CL465 (Gastric Ulcer; GI hemorrhage) was a 62-year old female with a history of OA, glaucoma, orthopnea, dyspnea on exertion, hypertension, cholecystectomy, hysterectomy, non-insulin dependent diabetes, overweight and persistent cold. She had no history of peptic ulcer disease. The patient was enrolled into the study on 15 January 1997 and randomized to receive naproxen 500 mg BID. After 28 days of treatment, the patient was hospitalized for gastrointestinal tract bleeding after experiencing one episode of coffee-ground-like emesis in the morning and two tarry stools in the previous 24 hours. The patient had also been experiencing weakness and nausea. Endoscopy showed one superficial pyloric ulcer and two superficial stomach ulcers on lesser curvature. No active hemorrhage was seen and hemoglobin and hematocrit remained stable throughout hospitalization. A gastric biopsy for *Helicobacter pylori* (*H. pylori*) showed oxyntic gastric mucosa with chronic active gastritis. No *H. pylori* was noted. Treatment included insertion of a nasogastric tube, intravenous fluids, histamine blockers, bismuth subsalicylate, amoxicillin, metronidazole and famotidine. Other concomitant medications included glyburide, benazepril and hydrochlorothiazide. Study medication was discontinued 27 days after the patient started on study drug and the patient was withdrawn from the study. The patient returned unused study medication and refused the Early Termination visit. The patient recovered and was discharged from the hospital after two days. The patient was scheduled for a follow-up esophagogastroduodenoscopy to be performed two weeks after discharge; however she refused any further follow-up for this event. The Investigator was uncertain of the association of these events with study medication. The Searle Medical Monitor considered these events to be related to study medication. This case was determined by the GI Events Committee as a "Clinically Significant GI Bleeding Event" consisting of an

endoscopically identified lesion (2 gastric ulcers and a pyloric channel ulcer) accompanied by melena and hematemesis.

Patient No. US0341-1280 (Hematocrit Decrease, Duodenitis Erosive, Gastritis Erosive) was a 49-year old female with a history of right lung emphysema and osteoarthritis. At Baseline, the patient's hematocrit was 44.0%. *H. pylori* was negative. Endoscopy completed the following day, showed multiple erosions in the antrum with at least 40 punctate bleeding points in the antrum and corpus of the stomach. That same day, the patient was randomized for enrollment and received diclofenac 75 mg BID. The Week 4 endoscopy was performed 22 days later and revealed a 3 cm hiatal hernia, gastritis in the body and antrum of the stomach and 40-50 petechial lesions in the stomach with one erosion measuring 2 mm and containing a small clot. There were two antral erosions measuring 3-5 mm. Three shallow, superficial "ulcers", up to 6 mm in diameter, were noted in the bulb of the duodenum. No bleeding was noted. According to the endoscopist, these lesions had more depth to them than erosions but they were not deep lesions. The Investigator felt these lesions were actually erosions, and not ulcers, because they had no measurable depth. The hematocrit that day was 41.0%. The patient had no abdominal pain, melena, hematemesis or other symptoms of gastrointestinal bleeding. Stools for guaiac were not obtained. The Week 8 endoscopy, completed 28 days later, was negative except for 11-25 gastric petechiae. The patient had one episode of indigestion, which she treated with a single dose of calcium carbonate. The Week 12 endoscopy, completed 29 days after previous endoscopy, revealed 10 petechiae in the antrum of the stomach. An 8 mm AV malformation was also noted in the second portion of the duodenum. CLOtest was negative. Hematocrit that same day was 37.0%. The patient completed the study and no further follow-up was done. Concomitant medications included multivitamins. The patient has recovered. The Investigator was uncertain whether this event was related to study medication. This event was considered a clinically significant GI event by the independent GI events committee.

This case is discussed in the review of study 071.

Patient No. US0002-0335 (Duodenal Ulcer) was an 80-year old female with a history of Meniere's syndrome, tonsilectomy, tooth abscess, rhinorrhea, myopia, scratchy throat, insomnia, stroke, pneumonia, pleurisy, inguinal hernia repair, indigestion, bladder infection, nephritis, foot and hip fractures, synovitis, lumbar and cervical spondylosis, lumbar disc disorder, hip replacement, osteoporosis, osteoarthritis, benign breast nodule (removed), "chemomatrixectomy," onycholysis, seasonal allergies and RA. The patient was randomized to receive naproxen 500 mg BID. After 22 days of treatment, the patient experienced continuous severe indigestion. Maalox was prescribed. Twenty days later, the indigestion continued; therefore, medication was discontinued and the patient was terminated early from the study. Hematocrit at the time of the Early Termination was 37%; hematocrit had been 34% at Screening. Endoscopy performed the following ____ (absent from original report) showed a 4 mm by 11 mm ulcer of the duodenal bulb located on the superior wall and a large postbulbar ulcer of the duodenum located on the anterosuperior wall. This ulcer was deep and the CLOtest was negative for *H. pylori* at the time of endoscopy. Treatment included omeprazole and famotidine. Other concomitant medications included calcium carbonate, alendronate sodium and hydroxyzine embonate. Follow-up upper endoscopy performed 42 days later showed a deformed duodenal bulb with a completely healed medium sized duodenal ulcer located on the anterosuperior wall. No active ulcerations were seen, but scarring of the distal bulb was noted. There was no significant gastric outlet narrowing. CLOtest was again negative. The patient has recovered. The Investigator and the Searle Medical Monitor considered this event to be probably related to

study drug. This event was also determined to be a clinically significant GI adverse event by the GI Events Committee.

In the integrated summary of safety this case is described somewhat differently:

Patient 022-US002-0335 was an 80-year-old female with a history of OA, RA, CVA, indigestion, and osteoporosis. Concomitant medications included calcium carbonate, alendronate, and hydroxyzine. The patient was enrolled in Study 022 and was randomized to naproxen 500 mg BID. After 22 days of treatment, the patient experienced severe indigestion and was treated with Maalox. However, the indigestion continued and 20 days later study medication was discontinued. Endoscopy performed one day after discontinuation revealed a 4 mm by 11 mm ulcer on the superior wall of the duodenal bulb and a large postbulbar ulcer on the anterosuperior wall of the duodenum. This postbulbar ulcer was deep and created a partial gastric outlet obstruction. CLOtest was negative for *H. pylori*. There was no significant decrease in the patient's hemoglobin or hematocrit. The patient was treated with omeprazole and famotidine. This event was classified as **gastric outlet obstruction**.

The reviewer's evaluation of these three cases change the data regarding clinically relevant UGI events. The endoscopic safety conclusions remain unaffected by this issue. None of the studies in the sponsor's submission defined clinically significant UGI events as an endpoint and therefore this issue does not deflect from the robustness of the safety endpoints defined in this submission. This review however does reinforce the consequences of choosing valuable clinically important endpoints and defining them prospectively and clearly.

Table 33 displays the clinically significant UGI events presented by the sponsor and the reviewer's assessment. This table is derived from controlled studies lasting 6-24 weeks. Dose of Celecoxib ranged from 100-400 mg BID.

Table 33

	Celecoxib proposed dosages (n=3753)	Ibuprofen 800 mg tid (n=346)	Diclofenac 75 mg bid (n=716)	Naproxen 500 mg bid (n=1366)
Sponsor's tabulation	2	1	3	5
Reviewer's tabulation	2	1	2	3

This table is derived from multiple studies, including 4 studies without baseline endoscopies in patients recently on NSAIDs. These events were not defined as study endpoints. The table includes several different active comparators. The small number of events from merged data in each cell along with the flaws in endpoint definition would suggest caution in interpreting this data. A large study designed to define the relative risks of clinically significant UGI events associated with the use of celecoxib compared to NSAIDs is recommended.

VI. Reviewer's overall conclusions:

1. The varied and multiple studies summarized above convincingly showed that celecoxib, used at the proposed dosages of 100 to 200 mg twice a day, was associated with a statistically significantly lower incidence of gastroduodenal ulcers and gastric erosions compared to naproxen 500mg BID in all three pivotal studies reviewed. The one study comparing celecoxib 200mg BID to ibuprofen 800 mg TID revealed robust support for the safety claims related to gastroduodenal lesions.
2. The data comparing celecoxib to diclofenac were inconclusive. There was one study (041) indicating endoscopic safety superiority of celecoxib over diclofenac while a second study (071) showed no significant differences. The study where no differences were shown, however, had a larger evaluable endoscopy cohort and included a baseline, ulcer free endoscopy before randomization. This gave a truer de novo and drug related ulcer incidence than the other study. Furthermore, the multiple interval endoscopies over time, all revealing a lack of statistical difference between the groups, add statistical support to this conclusion. On the other hand, study 041 was a study of longer duration. The ulcer statistics were as expected in the context of the other trials. 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 celecoxib in the other studies over 12-24 weeks. The diclofenac associated ulcer rate of 10% in study 071 was similar to the 11% gastroduodenal ulcer rate previously reported among 175 patients receiving diclofenac 50mg bid to tid in a double blind multicenter study of diclofenac and diclofenac/misoprostol. Baseline and 12 week endoscopy were performed in this study as well. The clinically significant UGI event rates did not differentiate the UGI toxicity of these two drugs either. It is concluded that there are no compelling data to suggest that diclofenac and celecoxib use are associated with statistically significant differences in UGI gastroduodenal ulcer rates at the doses and durations studied.
3. None of the studies in this submission statistically addressed the issue of comparability to placebo. Numerical data in this review did suggest a difference between placebo and celecoxib. Naproxen and ibuprofen in studies 021, 022, 062 and 041 were associated with a 300-900% higher incidence of ulcers compared to the placebo groups in studies 021 and 022. Celecoxib was associated with a 50-300% higher incidence compared to the placebo groups in studies 021 and 022.
4. Interesting information regarding *H. pylori* infection can be gleaned from these studies. The lack of consistent association between *H. pylori* and ulcer incidence across all treatment groups is in keeping with the medical literature on this subject. Regardless of the methodology (serology with flexure test, CLO test, histology or concordance of methodologies) no consistent correlation was ~~used~~ ^{seen}. The lack of correlation in the placebo group is surprising given the wealth of literature showing an association between *H. pylori* infection and gastroduodenal ulcer in the absence of other apparent risk factors. The small number of patients in the placebo ulcer group may explain this finding. In addition, the patients studied do not represent a naïve population. They all had previously been on NSAIDs for their arthritic condition. This may well have affected gastric mucosal susceptibility to injury. Adaptation of the gastric mucosa, cytoprotective mechanisms and upregulation of protective mediators may be operational. These poorly defined factors and the relatively small ulcer populations in these studies may also play a role in the results. Finally, a review by Laine in the March 1993 Gastroenterology Clinics of North America on *H. pylori* and NSAIDs gives a good pathophysiologic and empiric review of this subject and suggest no connection between *H. pylori* and NSAID related ulcers.⁶ Although an

interventional study by Chan published in 1997 strongly supported a connection between *H.pylori* infection and NSAID related ulcers, the current data along with data presented by Laine appear more compelling.⁷

5. When data from the five pivotal endoscopic studies reviewed were combined, there was a statistically significant ulcerogenic effect of low dose aspirin in the celecoxib group. This rate, however was still lower than the ulcer rate among the NSAID groups. This aspirin effect was not seen with statistical significance in the placebo group. This subgroup however was much smaller than the celecoxib groups combined. It is postulated that there may have been a statistically significant effect of aspirin on ulcer rate in the placebo group had the group size been larger. There was no effect of aspirin in the active NSAID comparators when taken as a whole. It appears counterintuitive that two mucosa-damaging chemicals do not have an additive effect. These results may reflect a biological interaction between aspirin and NSAIDs on the gastroduodenal mucosa. Another plausible explanation is that the NSAIDs alone have a much more powerful effect on the gastric mucosa than the aspirin, obscuring any small additive effect. The data presented from study 022 however seemed striking. In this study 0/16 naproxen treated on aspirin patients developed ulcers compared to 37/194 patients on no aspirin. The marked difference of patients per cell (16 vs 194) makes interpretation of these findings difficult. Although these data appear to suggest a protective effect of aspirin on naproxen related ulcers, an effect supported by statistics, the other studies did not even support this finding as a trend. These trials, however, were not designed to analyze the role of aspirin co-administration and overinterpretation of one data subset would be unwise. It seems valid to conclude that in these studies, aspirin did increase the ulcer risk in celecoxib treated patients and that this increase could be measured. This risk, however, remains lower than the risk of gastroduodenal ulcers associated with the use of naproxen or ibuprofen.
6. The review notes several design flaws including, imprecise data collection methodology and vague endpoint definitions that should be improved in future studies in this area. As outlined in the individual study reviews, simplification of the case report forms and closer adherence by endoscopists to the requirements of the protocol would likely improve the quality of the data collected.

Methodological problems are of concern as well. When size of a lesion is relevant, such as the 3mm lower limit for definition of an ulcer, a standardized form of measurement is recommended. The intra and interobserver variability in distinguishing a 2mm from a 3mm lesion with endoscopic estimation has not been defined and is likely to be large. This methodological problem alone makes it difficult to compare data from this submission to data from the medical literature. Within the submission however, the controlled, randomized and blinded nature of the execution of the study protocols should maintain the integrity of comparative data.

The endpoints of greatest clinical concern when studying the commonly used NSAIDs are the complications of perforation, clinically relevant bleeding, obstruction and death. These events occur with low frequency but because of the high prevalence of the use of NSAIDs the absolute public health risk is high. For this reason, endoscopically proven ulcers have been defined as the surrogate of choice in this submission. Future studies should address the true clinically meaningful endpoints to corroborate the assumption that the development or presence of ulcers correlate with adverse clinical outcomes (and to quantify this relationship if present). Such studies must use clear and relevant endpoints to address this issue. Three out of 11 cases presented by the

sponsor as clinically significant UGI events within their controlled studies and described in the text of this review were not felt to meet reasonable criteria. This lack of standardization of definitions and procedures is of concern for future studies.

The endoscopic data presented in this submission are sufficiently robust and statistically significant, that the methodological problems described do not impact on the conclusions described above.

VII. Recommendations for regulatory action

1. It is recommended that the sponsor be permitted to claim less gastroduodenal lesions associated with celecoxib 100-200 mg bid compared to ibuprofen 800 mg tid or naproxen 500 mg bid. This recommendation is based on the results of studies 021, 022, 071 and 062.
2. It is recommended that the sponsor not be permitted to claim less gastrointestinal injury associated with celecoxib 100-200 mg bid compared to diclofenac 75 mg bid. This recommendation is based on the data from studies 071 and 041.
3. It is recommended that the sponsor not be permitted to make claims regarding comparability to placebo. This recommendation is based on the results of studies 021 and 022 as well as using placebo group data from these studies in analyzing studies 071, 062 and 041.
4. It is recommended that the sponsor not be permitted to make claims regarding superiority in the rates of clinically significant UGI events compared to NSAIDs based on the lack of adequate data.
5. It is recommended that future studies with well defined and clinically important UGI endpoints be planned to address safety claims related to clinically significant UGI endpoints. These studies and post marketing experience will be needed to accurately define the relationship between this new molecular entity and the class of drugs currently in use and described as NSAIDs.
6. It is recommended that future studies include as an objective the evaluation any associated risk with the use of celecoxib in combination with low dose aspirin in the populations likely to be prescribed celecoxib if approved.


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DRAFT MEMORANDUM

FROM: Douglas C. Throckmorton, M.D., Medical Officer
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THROUGH: Shaw Chen, M.D., Medical Team Leader
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TO: Victoria Lutwak, Project Manager
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Robert DeLap, M.D., Ph.D., Acting Division Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products (DAAODP), HFD-550

SUBJECT: NDA 20-998
NAME OF DRUG: Celecoxib (SC-58635)
TRADE NAME: Celebrex
FORMULATION: Capsules for oral administration.

RELATED APPLICATIONS: None

PROPOSED INDICATIONS: 1) Acute and chronic use in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis; and
2) Management of pain.

SPONSOR: Searle

DATE CONSULT RECEIVED: 7.15.98

DATE DRAFT CONSULT COMPLETED: 11.6.98

ISSUES TO BE ADDRESSED: 1) Review of NDA 20-998 Cardiac and Renal Safety Database.
2) Review of three 'Renal' studies in NDA 20-998.

Douglas C. Throckmorton, M.D.

0.0 Overall Renal and Cardiac Safety Consultant Summary

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. Work in animals has also suggested the up-regulation of COX-2 following volume contraction. 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 potentially 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 the drug for <180 days. With regard to 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 database (e.g., serum bicarbonate, arterial pH) were performed as part of any trial in the NDA. With this exception, the database was sufficient to assess 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. The trials enrolled small numbers of patients for short trial durations. Under the conditions of those trials, both celecoxib and the comparator NSAIDs inhibited prostaglandin PGE₂ and 6-keto-PGF₁-alpha by the kidney to more or less the same extent. Both had significant inhibitory effects on the excretion of these urinary prostaglandins when compared with placebo.

There was sufficient evidence to conclude that celecoxib has significant **renal effects**, as reflected in the pattern of lab abnormalities associated with celecoxib 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 both celecoxib and the other NSAIDs have similar renal effects.

Within the limitations of the database there is no evidence to suggest that celecoxib has unique renal 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. While there were no clear cases of celecoxib-induced renal failure in the controlled database, there were several individuals taking celecoxib who were withdrawn from the long-term open-label trial because of renal adverse events, including acute renal failure (as well as, edema and worsening hypertension). It remains to be determined is whether renal injury will occur following celecoxib at the same rate that is seen with other NSAIDs.

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 are clearly distinguished from placebo.

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1.0 Materials Utilized in Review

1.1 Materials from NDA

1. NDA 20-998, volumes: 1.1-1.3; 1.129; 1.134-1.43; 1.425-1.442.
- 2: NDA 20-998, submitted in CANDAs format.

1.2 Other Resources

No separate consultations, including outside experts or advisory committee proceedings, were obtained during this NDA review. Where appropriate, the results of the literature review are included in the Mechanisms of Action section below, and in the integrated Safety Summary (section 4.1-4.2).

2.0 to 2.7 Background Information

The background information below is drawn from the sponsor's summary and from the published literature. Please see pertinent primary reviews for further details.

2.1 Chemistry

Celecoxib is a diarylsubstituted pyrazole and has the following structural formula: 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

2.2 Mechanism of Action

Celecoxib is a member of a novel class of anti-inflammatory and analgesic agents known as specific cyclooxygenase type 2 (COX-2) inhibitors. Celecoxib causes persistent inhibition of COX-2 through an interaction with a distinct region of the active site. Therapeutic concentrations of celecoxib maximally inhibit the formation of prostaglandins by COX-2. In animal models, inhibition of COX-2 has been observed to have anti-inflammatory, analgesic, antipyretic and anti-proliferative effects. In animals, these effects of celecoxib occur at concentrations that inhibit COX-2 *in vitro*. At therapeutic concentrations, the sponsor reports that celecoxib does not inhibit the constitutive isoenzyme (COX-1) which functions to produce prostaglandins involved in maintenance of the GI mucosal barrier, platelet aggregation and renal function.

There is limited information about the role that COX-2 plays in the kidney. In rats and dogs, COX-2 is constitutively expressed in the macula densa and adjacent epithelial cells of the cortical collecting duct (references 1,2). The authors of these papers speculate that COX-2 was critical for the response to volume-contraction, perhaps by regulating renin release from the macula densa. It has also been reported that COX-2 is not normally present in adult human kidneys, but is up-regulated in lupus nephritis reference 3).

2.3 Pharmacokinetics/ pharmacology/ pharmacodynamics

Pharmacokinetics: The pharmacokinetics of celecoxib have been evaluated in approximately 1500 individuals. In addition to healthy, young and elderly volunteers (male and female), pharmacokinetic measurements have been done in patients and also in special populations including individuals with hepatic or renal impairment. The table below summarizes the pharmacokinetics of celecoxib (per the sponsor).

Table 2.3.1 Summary of single dose disposition kinetics of celecoxib in healthy subjects^a.

Parameter	Mean (90 % CI)
C _{max} , (ng/ mL)	598 (54)
T _{max} , (hr)	3.42 (45)
AUC (48), (ng/ mL)* hr	6270 (30)
AUC (inf), (ng/ mL)* hr	6694 (30)
T _{1/2} , (hr)	11.7 (39)
V _z /F, (L/ 70 kg)	533 (51)
CL/ F, (L/ hr/ 70 kg)	31.7 (34)
Relative bioavailability, (%)	99 (95- 104)

a. Data from proposed labeling, NDA 20-998 vol. 1.1

Pre-clinical renal pharmacology and pharmacodynamics

Celecoxib was tested for its effect on urinary volume and electrolyte excretion in rats at oral doses from 5 to 500 mg/kg. Celecoxib decreased urinary volume 28 to 43% between 15 and 500 mg/kg with a plateau in effect from 50 to 500 mg/kg. Sodium excretion was decreased with celecoxib doses from 50 to 500 mg/kg by 17 to 36% with a plateau in effect from 150 to 500 mg/kg. Chloride excretion was decreased by celecoxib doses from 50 to 500 mg/kg by 16 to 35% with a plateau in effect from 150 to 500 mg/kg. Urinary osmolarity was increased by celecoxib doses of 15 to 500 mg/kg by 16 to 38% with a plateau in effect from 150 to 500 mg/kg.

In a high-dose study, celecoxib was administered 600 mg/kg/day to male rats for 7 days. In this study, celecoxib had no effect on urinary volume or urinary excretion of PGE₂. Plasma levels of celecoxib reached 6.99 g/mL on day 7 at 5 h after dosing. As a control, indomethacin (4 mg/kg/day) lowered PGE₂ urinary levels and volume only on day 3.

2.4 Metabolism

Metabolism: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. The methyl group of celecoxib is hydroxylated to a primary alcohol that is further metabolized to a carboxylic acid. A minor amount of the carboxylic acid metabolite is conjugated to glucuronic acid to form the 1- O- glucuronide. The metabolites are inactive as COX- 1 or COX- 2 inhibitors. *In vitro* studies indicate that celecoxib is not an inhibitor of cytochromes P450 2C9, 2C19 or 3A4, and though not a substrate, is a relatively weak inhibitor of cytochrome P450 2D6. However, celecoxib at plasma concentrations achieved in humans, at the recommended doses, is not expected to substantially inhibit the metabolism of other drugs that are metabolized via the 2D6 isozyme. Clinical data to confirm this expectation are not available.

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with no detectable unchanged drug recovered in the urine. Celecoxib is excreted as the acid metabolite predominantly in the feces (approximately 54% of the administered dose) and to a lesser extent in the urine (approximately 18% of the administered dose).

2.5.1 Renal Toxicology

1) 2-week administration to mice

Lesions consistent with test-article associated renal injury were found to three males (95S0745, 95S0746, and 95S0747) and four females (95S0754, 95S0755, 95S0756, and 95S0762) from the 1000 mg/kg/day dosage group. All seven animals demonstrated a nephropathy characterized by focal degeneration of renal tubules with regeneration, epithelial basophilia, intraluminal casts (cellular or hyaline) and a minimal mononuclear cell interstitial infiltrate. In all animals the lesion was slight to mild except for one 1000 female (95S0754) where it involved the cranial 1/3 of the left kidney (corresponding to a macroscopic lesion). The sponsor noted that while these lesions are sometimes seen in aged mice, but would not be expected in mice this age.

One incidence of renal papillary necrosis (moderate, Grade 3 of 5) was also seen in a male receiving 1000 mg/kg/day.

2) 4-week administration to dogs

No histologic damage was reported in the 25 mg/kg dose group. Slight to moderate acute renal papillary necrosis was diagnosed in four animals including one male given 50 mg/kg, two females given 100 mg/kg, and one male given 250 mg/kg. Notable was the slight acute unilateral papillary necrosis that was seen in one female in the 100 mg/kg reversal group.

Per the sponsor, later studies using lower-doses of celecoxib did not demonstrate any histologic evidence of renal toxicity. The sponsor then concluded that the 'absence of renal papillary necrosis in chronic rodent studies' suggested that celecoxib 'is different from NSAIDs.'

2.5.2 Cardiac Toxicology

1) Acute infusion to guinea pigs

The cardiopulmonary effects of celecoxib were examined in an acute guinea pig model. The only effect notes, per the sponsor, was a small but significant increase in systolic blood pressure.

2) Acute administration to anesthetized dogs

The only significant effect noted in this model was an increase in left-ventricular end-diastolic pressures seen at the higher doses in 2/4 dogs. No effect on blood pressure or other vital signs was detected.

2.6 Proposed Renal and Cardiac Labeling

Below are sections of the proposed label that pertain to celecoxib renal efficacy and/or safety. The statements for each section are per the sponsor, and come from the proposed labeling section of the NDA. A discussion of the appropriateness of each of the statements will be included in the Integrated Safety Summary (section 5.3 and 5.4).

Dosing: The maximum proposed dose of celecoxib 400 mg per day in divided doses.

Pharmacodynamics: Celecoxib causes persistent inhibition of COX- 2 through a novel interaction with a distinct region of the active site. Therapeutic concentrations of celecoxib maximally inhibit the formation of prostaglandins by COX- 2. At therapeutic concentrations celecoxib does not inhibit the constitutive isoenzyme (COX- 1) which functions to produce prostaglandins involved in maintenance of the GI mucosal barrier, platelet aggregation and renal function.

Pharmacokinetics: The pharmacokinetics of Celebra have been evaluated in approximately 1500 individuals. In addition to healthy, young and elderly volunteers (male and female), pharmacokinetic measurements have been done in patients and also in special populations including individuals with hepatic or renal impairment.

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with no detectable unchanged drug recovered in the urine.

Special studies (Safety)

Renal: Celebra has no deleterious effects on renal function. Administration of Celebra at doses of 200 and 400 mg BID for periods of 7- 10 days was studied in elderly subjects and patients with moderate renal impairment.

Dosage Adjustment in Special Populations

Renal insufficiency: Because celecoxib is predominantly metabolized by the liver and none of the metabolites are pharmacologically active, no dosage adjustment is necessary in patients with mild to moderate renal insufficiency. In elderly volunteers with age related reductions in GFR ($> 65 \text{ mL/ min/ } 1.73 \text{ m}^2$) and in patients with moderate renal insufficiency (GFR 35- 60 mL/ min/ 1.73 m^2), celecoxib pharmacokinetics were comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine and estimated creatinine clearance and celecoxib clearance. Patients with severe renal insufficiency have not been studied and therefore should use the lowest effective dose.

Precautions

General

Because Celebra has no effect on platelet function, it should not be used for cardiovascular prophylaxis.

Renal effects: The effect of Celebra in advanced renal disease (GFR $<40 \text{ mL/ min/ } 1.73 \text{ m}^2$) has not been studied. No prospective studies have been conducted in patients with considerable dehydration, advanced renal disease, congestive heart failure or liver dysfunction.

Use in Elderly: In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers.

ACE-Inhibitors and Diuretics

Although prospective studies of Celebra with ACE inhibitors and diuretics have not been conducted, no increased incidence of adverse reactions indicative of elevations in blood pressure were seen in clinical trials in which arthritis patients were taking Celebra concurrently with ACE inhibitors, or diuretics. No increased incidence of adverse reactions indicative of sodium retention or renal impairment were seen in clinical trials in patients taking Celebra concurrently with diuretics.

Aspirin:

Celebra has been administered to patients taking aspirin up to 325 mg per day. Low doses of aspirin have been associated with ulcers. Thus concomitant use of Celebra with aspirin may result in an increased rate of GI ulceration compared to when Celebra is used alone.

3.0 Description of Clinical Data Sources

3.1 Primary Source Data

A total of 29 clinical pharmacology and 22 phase II/III clinical efficacy trials were performed as part of the celecoxib development. Of these, 13 clinical trials were performed to compare celecoxib with other NSAIDs. Three of these latter studies focused on the renal effects of celecoxib: study 010 (Renal effects in the elderly); study 033 (Na⁺/volume depletion and renal effects); and study 036 (Renal effects in chronic renal insufficiency). These three trials will be examined individually.

In total, the safety database used for this consult includes 13,072 individuals enrolled in clinical trials. More than 75% of these individuals had either osteo- or rheumatoid- arthritis, and enrolled in trials of ≥ 2 weeks duration.

3.1.1 Study Type and Design/Patient Enumeration

3.1.2 Demographics

The first table summarizes the subject exposure to celecoxib in the entire database.

Table 3.1.2.1 Summary of Celecoxib-treated subjects in the NDA 20-998 database^a.

Study Design	# Of Treated Subjects	# of Unique Subjects ^b
Phase I: Single Dose	294	251
Phase I: Multiple Dose	398	270
Phase I: Drug Interactions	260	131
Phase I: Hepatic	48	48
Phase I: Renal	23	23
Arthritis: OA	4280	4151
Arthritis: RA	2096	2086
Arthritis: Long-term Open-label	4499	1757
Analgesia: Dental pain	531	529
Analgesia: Surgical pain	217	217
Combined Studies	12646	9463

a. Data from NDA Integrated Summary of Safety Information, table 2.11.

b. Does not count individuals more than once who received celecoxib as part of more than one trial.

3.1.3 Extent of Exposure (dose/duration)

Dose Exposure to Celecoxib

The next table summarizes the celecoxib exposure according to the dose of celecoxib for all studies in the NDA.

Table 3.1.3.1 Summary of celecoxib exposure by dose from NDA 20-998^a.

Treatment and Dose	Treated Subjects	Unique Treated Subjects
Celecoxib Single Dose (5-1200 mg)	825	780
Celecoxib Multi-Dose		
5-50 mg	959	948
100 mg	4872	3261
200 mg per day	564	500
200 mg	4562	3272
400 mg	721	665
600 – 1200 mg	20	20
Celecoxib +Other Drug	123	17
Total	12646	9463
Comparator Agents		
Placebo	2450	1354
Active Controls	3343	2255
Total	5793	3609
Overall Total	18439	13072

a. Data from NDA 20-998, Integrated Summary of Safety, Text Table 5.

3.1.3 Extent of Exposure (dose/duration) (cont)

Duration Exposure to Celecoxib

The chronic exposure data comes from the trials in osteoarthritis (OA) or rheumatoid arthritis (RA). This will be the database used primarily for the assessment of renal and cardiac safety. The table below summarizes the duration of patient exposure in the OA/ RA database, broken into three categories: 0-6 weeks; 6 weeks to 6 months; and greater than 6 months. Note that there are very few subjects who received celecoxib with long-term (>180 days) exposure to celecoxib in a controlled trial (n=39). A larger number received celecoxib in open-label trials for >180 days (n=1809).

Table 3.1.3.2 Duration of arthritis patient exposed to celecoxib in the NDA 20-998 database^a.

	25-50 mg	100 mg	200 mg	300 mg	400 mg	Total ^b
OR-RA Controlled Trials						
1-42 days	462	888	818	0	308	2476
43-180 days	481	1237	1836	0	307	3861
>180 days	0	0	39	0	0	39
OA-RA Uncontrolled (Open-Label) Trials						
1-42 days	110	1689	1527	768	200	4294
43-180 days	310	970	1509	451	489	3729
>180 days	0	236	941	222	410	1809
Total	1363	5020	6670	1441	1714	16208

a. Data from NDA 20-998, vol. 1.426, Table 3.4

b. There were 18 additional patients who received other doses (i.e., 200 mg in am, 300 mg in pm). These are included in the safety review but not this table.

The sponsor also summarized exposure to celecoxib in patient-years of exposure for all subjects in the arthritis trials. The results are shown below.

Table 3.1.3.3 Duration of exposure to celecoxib, by patient-years, in the NDA 20-998 database^a.

	50 mg	100 mg	200 mg qD	200 mg BID	300 mg	400 mg	Any Dose ^b
OR-RA Controlled Trials	116	289	47	466	0	87	1020
OA-RA Uncontrolled (Open-Label) Trials	75	518	0	1271	340	465	2672
OA-RA Controlled & Uncontrolled Trials	117	680	47	1567	340	499	3267

a. Data from NDA 20-998, Integrated Summary of Safety, Table 4.3. Patients are counted only once per treatment group.

b. There were 18 additional patients who received other doses (i.e., 200 mg in am, 300 mg in pm). These are included in the safety review but not this table.

The demographics of the subjects enrolled in the North American arthritis trials are summarized below.

Table 3.1.3.4 Demographics of the North American arthritis trials in NDA 20-998^a.

Demographic	Placebo N=1864	Celecoxib N=5704	Active Controls N=2098
Age			
Mean	60.0	59.5	58.8
>64	731 (39.2%)	2117 (37.1%)	737 (35.1%)
Ethnicity			
White	1629 (87.4%)	4844 (84.9%)	1792 (85.4%)
Black	156 (8.4%)	580 (10.2%)	216 (10.3%)
Hispanic	67 (3.6%)	219 (3.8%)	78 (3.7%)
Asian	4 (0.2%)	34 (0.6%)	6 (0.3%)
Other	8 (0.4%)	27 (0.5%)	6 (0.3%)
Gender			
Female	1324 (71.0%)	3986 (69.9%)	1427 (68.0%)
Male	540 (29.0%)	1718 (30.1%)	671 (32.0%)

a. Data from NDA Integrated Safety Summary, table 6.1.

3.1.3 Extent of Exposure (dose/duration) (cont)

The sponsor collected information on the past medical histories of the subjects enrolled in the trials as well. Below are the incidences of relevant cardiac and renal medical history (arranged according to ICD-9 codes) in the North American controlled trials. Unlisted ICD-9 codes occurred at <1.0% or were considered non-significant for purposes of this review. Overall, a significant fraction of the subjects had hypertension. A much smaller % had a history of significant cardiac disease or renal disease. No information about smoking history is available.

Table 3.1.3.5 Significant cardiac and renal past medical history in the celecoxib North American controlled trials^a.

	Placebo N=1864 ^b	Celecoxib 25- 400 mg N=5704 ^c	Active Controls N=2098 ^d
Cardiovascular Disease			
Angina Pectoris	57 (3.1%)	194 (3.4%)	75 (3.6%)
Coronary Atherosclerosis	70 (3.8%)	201 (3.5%)	82 (3.9%)
Congestive Heart Failure	24 (1.3%)	63 (1.1%)	25 (1.2%)
Hypertension (not otherwise specified)	732 (39.3%)	2172 (38.1%)	749 (35.7%)
CABG	31 (1.7%)	118 (2.1%)	39 (1.8%)
Myocardial Infarction (not otherwise specified)	54 (2.9%)	167 (2.9%)	74 (3.5%)
Endocrine Disease			
Diabetes Type I (uncomplicated)	26 (1.4%)	89 (1.5%)	34 (1.6%)
Diabetes Type II (uncomplicated)	114 (6.1%)	408 (7.2%)	156 (7.4%)
Hypothyroid	234 (12.6%)	659 (11.6%)	241 (11.5%)
Hyperlipidemia	108 (5.8%)	376 (6.6%)	137 (6.5%)
Obesity	131 (7.0%)	389 (6.8%)	148 (7.1%)
Renal/ GU Disease			
Renal calculus	64 (3.4%)	206 (3.6%)	93 (4.4%)
Hematuria	29 (1.6%)	65 (1.1%)	17 (0.8%)
UTI	95 (5.1%)	231 (4.0%)	76 (3.6%)

a. Data from NDA Integrated Safety Summary, Appendix 8.2. The database used includes studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Collected ICD-9 codes were used to calculate incidence rates for each group.

Regarding the demographics of the subjects in the long-term, open-label study, these will be similar to those in the table above. This is because all of the subjects in the open-label trial first enrolled (and completed) one of the shorter trials prior to entry into the open-label, long-term trial.

The renal effects of celecoxib specifically in three small trials and as part of the overall safety database. The three 'Renal Effects' trials are reviewed in section 4.0. Note that the longest period of exposure to study drug was 7 days in these three trials.

Table 3.1.3.6 Summary of 'Renal Effects' Trials in the NDA 20-998 database.

Study #	Short Title	Duration of Exposure to Study Drug	# of Control Subjects ^a	# of Celecoxib Subjects
010	Renal Effects in the Elderly	10 Days	27	26
033	Na ⁺ /Volume Depletion and Renal Effect	7 Days	21 ^a	21
036	Renal Effects in Chronic Renal Insufficiency	7 Days	52 ^a	23

a. Includes subjects who received active controls.

3.1.4 Renal Data Collected in the NDA Database

Renal adverse events were collected both during the 3 trials summarized above, and as part of the overall adverse event reporting for the rest of the clinical program. In the three 'Renal Effects' trials specific measures of renal function were measured (i.e., urine prostaglandin excretion). These will be discussed in the trial summaries below. For the clinical trials as a whole, adverse events were identified either through periodic meetings between the subjects and investigators, or through the use of subject diaries. Serious adverse events were likewise identified, and transmitted to the sponsor immediately.

For evaluation of clinical laboratory results, the sponsor set upper and lower limits representing values of potential clinical relevance, along with cutoff values considered to represent lower and upper extremes. The table below shows the relevant boundaries for the renal laboratory adverse events. Note that no extreme value for bicarbonate was established. At this reviewer's request, the sponsor stated that... 'we have checked the clinical studies in our NDA 20-998 and can confirm that there are no studies which tested for bicarbonate either by gas determination or in serum.' (Letter, 8.7.98).

Table 3.1.4.1 Mid-range and extreme value limits for evaluation of clinical lab results in NDA 20-998^a.

Lab Test	Lower Extreme	Lower Mid-Range Limit	Higher Mid-Range Limit	Upper Extreme
Serum Measurements				
Creatinine	N/A	N/A	176.8 µmol/L (=2 mg/dl)	265.2 µmol/L (=3 mg/dl)
BUN	N/A	N/A	9.3 mmol/L (=27 mg/dl)	14.3 mmol/L (=42 mg/dl)
Sodium	120 mmol/L	135 mmol/L	140 mmol/L	160 mmol/L
Potassium	2.0 mmol/L	3.5 mmol/L	5.0 mmol/L	6.0 mmol/L
Chloride	75 mmol/L	90 mmol/L	110 mmol/L	130 mmol/L
Calcium	>15% below Baseline, or <1.7 mmol/L	2.0 mmol/L	2.74 mmol/L	3.74 mmol/L
Inorganic phosphorus	0.32 mmol/L	0.97 mmol/L	1.61 mmol/L	2.42 mmol/L
Urinalysis				
Protein	N/A	N/A	Trace	1+ (300 mg/24h)
Blood	N/A	N/A	Trace	1+
Glucose	N/A	N/A	Trace	1+ (1 g/24h)
pH	N/A	4	8	8.5
Specific gravity	N/A	1.003	1.030	1.040
RBC	N/A	N/A	5/hpf	10/hpf
WBC	N/A	N/A	10/hpf	20/hpf
Ketones	N/A	N/A	Trace	1+
Urine bilirubin	N/A	N/A	Trace	1+

a. Data from NDA 20-998, Integrated Summary of Safety, Text Table 3.

3.1.5 Cardiac Data Collected in the NDA Database

While no trials specifically addressed the question of cardiovascular effects of celecoxib, certain elements of cardiovascular safety were collected as part of the assessment of each subject: blood pressure; heart rate; weight. The occurrence of lab abnormalities for creatine phosphokinase was also collected. As part of the safety database, other cardiovascular adverse events (AEs) were collected, including the occurrence of: cardiac ischemia, arrhythmias, strokes, and hypertension.

3.2 Data from Secondary Sources/ Published Literature

Aside from the published literature, no secondary sources of data were used in this consult. Two approaches were used to identify relevant published literature relevant to the current submission.

First, this reviewer conducted an independent literature review, through a keyword search of Medline. Second, the sponsor has provided a literature review, which was cross-referenced with the above reviews to assure completeness. The cut-off for consideration of articles in this NDA was approximately January of 1998. This literature review has been incorporated into the background section of this introduction, and into the integrated safety summary where appropriate. References appear at the end of the Integrated Renal/ Cardiac Safety Summary, section 5.3.

3.3.1 Comment on Adequacy of Clinical Experience

The database includes a total of 9463 subjects in the clinical database who were exposed to celecoxib. With regard to the number of subjects exposed, a total of 7718/ 9463 subjects (82%) received celecoxib at a dose of ≥ 100 mg per day (dosed as 50 mg BID). Without regard to the duration of exposure, this yields a 95% likelihood of detecting at least one occurrence of adverse events occurring at a rate of between 1/1000 and 1/10,000. Less information, obviously, will be available regarding the incidence rates for adverse events.

With regard to the duration of exposure, very few subjects (39) in the arthritis trials were exposed to celecoxib for >6 months as part of a controlled trial (active or placebo). A larger number (1809) were exposed for >6 months as part of open-label arthritis studies. As a consequence of this, the detection of common AEs that result from chronic exposure (i.e., myocardial infarction, elevated blood pressure), will simply be impossible, since no comparison group is available. More uncommon severe AEs (i.e., vasculitis, pancytopenia) may be detected as occurring in the open-label data, although their incidence will be impossible to determine.

3.3.2 Comment on Data Quality and Completeness

Specifics regarding the completeness of the database for NDA 20-998 will be made during the reviews of the three 'renal' trials, and in the combined Renal/ Cardiac Safety Review (section 4.0 to 4.2 below).

Regarding overall patient exposure, the ability to detect an effect of long-term exposure to celecoxib on AEs is limited by the lack of control data beyond 12 weeks. Inferences regarding long-term toxicity must therefore be drawn from the longer-term open-label data.

Regarding lab data collection, follow-up for abnormal laboratories was dependent on the individual investigators.

Regarding the renal safety review, no information about the acid-base status of any individuals was collected as part of the NDA (i.e., no serum bicarbonates, no arterial pH measurements). This concern was conveyed to the sponsor, and will be discussed further as part of the Safety review.

Regarding cardiac safety review, no information on ECG abnormalities was routinely collected or analyzed.

The Case Report Forms were submitted for all subjects who withdrew from the studies, including both medical and non-medical drop-outs. These were submitted as PDF files on optical discs, and are sufficient for review.

The datasets were submitted both in SAS and hardcopy.

In summary, the data quality and completeness is acceptable for a medical review with emphasis on the renal and cardiac safety. Specific problems regarding the adequacy of the data are noted at appropriate points in the review document.

4.1 Review of Protocol N49-96-02-010 (abbreviated 010 hereafter)

4.1.1 Title of Study

Clinical protocol to evaluate the effects of celecoxib at doses of 200 mg BID and 400 mg BID on renal function and urinary prostaglandins in healthy elderly subjects.

4.1.2 Sites of Investigation and Investigators

Study was conducted by Gerald Schulman at Vanderbilt University Medical Center.

4.1.3 Background

Initial protocol: August 21, 1996

Two protocol amendments:

1. October 15, 1996

The first protocol amendment had the following aims:

- 1) To change the days of the Urinary Prostaglandins (PGE and 6-keto-PGF) collection.
- 2) To change the Schedule of Observations and Procedures which is a result of this amendment.
- 3) To change the Case Report Forms (CRFs) which are a result of this amendment.
- 4) To correct the Baseline Physical CRF.

2. January 2, 1997

This amendment changed the status of this study from a "double-blind" study to a "single-blind" study.

4.1.4 Study Design

This was a single-center, single-blind, randomized, active-controlled, multiple-dose, crossover study to determine the effect of celecoxib on renal function and urinary prostaglandin excretion in healthy elderly subjects. A group of 29 healthy elderly subjects (19 female and 10 male) who were 65 to 85 years old received either celecoxib 200 mg BID for five days followed by celecoxib 400 mg BID for the next five days, or they received naproxen 500 mg BID for 10 days. After taking one of these treatment regimens and undergoing a seven-day washout period, subjects were crossed over to receive the other treatment regimen. Twenty-four subjects completed both treatment regimens.

Two groups were formed: Sequence A; and Sequence B.

Sequence A received drugs in the following order: celecoxib 200 mg BID for 5 days, then 400 mg BID for 5 days, followed by Naproxen 500 mg BID for 10 days.

Sequence B received Naproxen 500 mg BID for 10 days, followed by celecoxib 200 mg BID for 5 days, then 400 mg BID for 5 days

Prior to and during each Treatment Period, blood and urine samples were collected for calculation of glomerular filtration rate (GFR). Blood samples were also drawn to measure serum electrolytes, serum creatinine, blood urea nitrogen (BUN), and plasma concentrations of celecoxib and naproxen. Twenty-four hour urine samples were collected daily to determine the urinary excretion of PGE₂, 6-keto-PGF₁-alpha, electrolytes (sodium, potassium, and calcium), and creatinine. The primary aim of the study was to collect data on the renal effects of celecoxib, especially GFR, urinary PGE₂ excretion, and urinary 6-keto-PGF₁-alpha excretion. In addition, the effects of celecoxib were compared with naproxen, another NSAID with a pharmacokinetic profile similar to celecoxib.

4.1.5 Primary and Secondary Endpoints

There were no specified primary or secondary endpoints in this phase I-II study.

Primary study objectives:

1. Evaluate the effect of celecoxib on renal function in healthy elderly subjects; and
2. Assess the effect of celecoxib on urinary excretion of PGE₂ and 6-keto-PGF₁

Secondary study objectives:

1. Compare the effects of celecoxib 200/400 mg and naproxen 500 mg on renal function and urinary excretion of PGE₂ and 6-keto-PGF₁-alpha in healthy, elderly subjects; and
2. Evaluate the safety and pharmacokinetics of celecoxib 200/400 mg compared to naproxen 500 mg administered in elderly subjects for 10 days.

4.1.6 Number of subjects/ randomization

A total of 24 evaluable subjects (16 female and 8 male) completed both Treatment Periods of the cross-over study.

4.1.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

1. Be aged 65 to 85 years of age, inclusive;
2. Have a physical examination that reveals no clinically significant abnormalities, in the Investigator's opinion, during the Pretreatment Visit;
3. Have normal clinical laboratory test results during the Pretreatment Visit or, if abnormal, are not clinically significant in the Investigator's opinion;
4. Have a creatinine clearance estimated to be $> 65 \text{ ml/min/1.73 m}^2$ during the 2 Pretreatment Visit;
5. Have a GFR $> 60 \text{ ml/min/1.73 m}^2$ as measured by Glofil at Pretreatment 2 Admission Visit;
6. Have blood pressure $\leq 150/90$ during the Pretreatment Visit;
7. Have a negative drug toxicology screen during the Pretreatment Visit;
8. Have a negative hepatitis B surface antigen test obtained during the Pretreatment Visit;
9. Weigh $\leq 45 \text{ kg}$ and must be within $\pm 30\%$ of ideal body weight; and
10. Have provided written informed consent prior to admission to this study.

Exclusion Criteria

1. a history of any clinically significant illness, in the Investigator's opinion, within the three months prior to the Pretreatment Visit;
2. a history of hypersensitivity (e.g., anaphylactoid or cutaneous reaction) to cyclooxygenase inhibitors, sulfonamides or iodine;
3. taken any NSAID within 10 days before receiving the first dose of study medication;
4. used any medication within 14 days prior to or before Treatment Period I with the following exceptions: estrogen therapy, bulk laxatives, $<325 \text{ mg}$ aspirin daily and Maalox for GI symptoms; phenergan or compazine may be taken during the Glofil procedure only;
5. a history of significant substance abuse, drug addiction or alcoholism in the last 3 years;
6. used a tobacco product 48 hours prior to the first dose of study medication;
7. urinary incontinence;
8. presence of anemia (hematocrit $< 36.0\%$; hemoglobin $< 12.1 \text{ g/dL}$) during Pretreatment Visit);
9. inability to abstain from sexual activity from 48 hours (Day -4) prior to the time of admission to the study unit until the end of each Treatment Period (males only);
10. received any investigational medication within 30 days prior to Treatment Period I or is scheduled to receive an investigational drug other than study medications described in this protocol, during the course of this study; or,
11. been previously admitted to this study.

4.1.8 Dosage/ Administration

Two groups were formed: Sequence A; and Sequence B.

Sequence A received drugs in the following order: celecoxib 200 mg BID for 5 days, then 400 mg BID for 5 days, followed by Naproxen 500 mg BID for 10 days.

Sequence B received Naproxen 500 mg BID for 10 days, followed by celecoxib 200 mg BID for 5 days, then 400 mg BID for 5 days

4.1.9 Duration/ Adjustment of Therapy

Reasons for subject discontinuation from the study:

1. The subject develops symptoms that require medical intervention.
2. The subject develops an intercurrent illness that would require non-study medication.
3. If the subject's serum creatinine increases by 50% or if the subject's GFR decreases by 30%, the subject should be discontinued from the study. If the changes in the serum creatinine and GFR are discrepant, the subject will be reevaluated.
4. The subject withdraws his/her consent.
5. The Investigator determines it to be in the subject's best interest.
6. Searle discontinues the study.

4.1.10 Safety and Efficacy Endpoints Measured

Table 4.1.10.1 Timetable for clinical observations and lab measurements in the protocol #010^a.

Procedure/ Test	Pre-Tx -16 t -3	Pre-Tx -2	Baseline -1	Treatment Period 1 Days 1-10	Washout Days 11-17	Period 2 (As 1)	Early Term.
History	X						
Physical	X		X	X	X		X
Hepatitis B Screen	X						
Clinical Labs ⁱ	X			X ^b		X	X
Serum BUN/ Crt				X ^c		X	X
Creatinine clearance	X						
Vital Signs/ weights	X			X ^d		X	X
ECG	X						
Drug/ Alcohol Screen		X			X		
Urine Na, K, and Vol.		X	X	X ^e	X	X	X
Urine Prostaglandins		X	X	X ^f	X	X	X
GFR				X ^g		X ^g	
Celecoxib Levels				X ^h		X ^h	
Adverse Events			X	X		X	X

a. Data from NDA volume 1.134, table 3.

b. On days 1 and 10.

c. On days 1, 6, and 10.

d. On days 1, 3, 5, 7, 6, and 10.

e. Daily for days 1-10.

f. Days 1, 3, 4, 6, 8, and 9.

g. Days 1 and 6.

h. Days 1, 5, 6, and 10.

i. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, total protein, albumin, calcium, phosphorus, creatine kinase); and (3) Urinalysis (specific gravity, pH, protein, microscopic analysis).

4.1.11 Statistical Considerations

Sample Size

This is a double-blind, randomized, comparator controlled, crossover, 10 day multiple dose study. A total of 24 evaluable subjects (16 female and 8 male) will complete the study. The sample size of 24 evaluable subjects was calculated based on a published standard deviation in change of GFR from control to naproxen of 8.5 mL/minute. Assuming that the within-subject variability of celecoxib and naproxen in this study is the same as in that published study, a sample size of 24 subjects for the study will be sufficient to detect a difference of a GFR reduction of 10% in celecoxib versus a GFR reduction of 25% in naproxen at an alpha level of 0.05 and power of 80%.

Multiplicity

No adjustment for multiplicity was proposed.

Interim Analyses

There were no interim analyses.

Statistical Analysis

1) Statistical Methods for study 010

Treatment difference between celecoxib and naproxen were tested and 95% confidence intervals of the mean difference calculated, based on the log-transformed data and ANOVA for the standard two-way crossover design. First-order of carryover (from the first treatment to the second baseline and second-order carryover (from the first treatment to the second treatment) was investigated, and if normality could not be assumed on either the original or the log-transformed scale, a nonparametric procedure appropriate for this crossover design was used in the analysis.

4.1.11 Statistical Considerations (cont)

Exploratory Analysis

For the celecoxib treatment, an exploratory linear regression analysis will be performed with the observed AUC as an independent variable and change from baseline in urinary prostaglandins on Days 5 and 10 as the dependent variable. A plot was provided between the dependent variable and the independent variable to graphically depict the results and check any non-linearity. In addition, an analysis with AUC replaced by C_{max} was performed. An exploratory linear regression analysis was performed with the 4-hr plasma samples on Days 1 and 6 as the independent variable and change in GFR as the dependent variable.

Safety Analysis

Safety was analyzed by looking at the incidence of treatment-emergent adverse events, changes in laboratory values from baseline, vital signs and temperatures, and physical examinations. AEs were collected during the period of the trial, with no follow-up for AEs after subject discharge.

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4.1.12 Efficacy Outcomes for protocol

4.1.12.1 Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the 29 healthy elderly subjects enrolled in study 010 are summarized below. The subjects were broken into two groups, depending on the order in which they received celecoxib and naproxen.

Table 4.1.12.1.1 Demographics of protocol #010^a.

Demographic	Sequence A	Sequence B
Total Randomized	14	15
Gender		
Male	6 (43%)	4 (27%)
Female	8 (57%)	11 (73%)
Race (n (%))		
Caucasian	14 (100%)	15 (100%)
Black	0 (0%)	0 (0%)
Hispanic	0 (0%)	0 (0%)
Age (yrs) (Mean±sd)	69.6±3.6	70.7±4.5
Mean Weight, kg (±SD)	70±16	72±11
Baseline GFR (ml/min/1.73 m²)		
Day 2	83±17	82±9
Day 6 of washout	86±18	77±6

a. Data from NDA volume 1.134, Table 5.

4.1.12.2 Disposition of Subjects

Fewer subjects in the high-dose group completed the trial, with 5/7 drop-outs in this group being due to clinical AEs.

Table 4.1.12.2.1 Summary of subjects entered into study 010^a.

	Celecoxib	Naproxen
Entered	14	15
Completed	12	12
Discontinued: Total	2	3
Protocol Non-compliance	2	3
AEs	0	0
Other	0	0

a. Data from NDA volume 1.134, table 3.

4.1.12.2a Subject Selection

No information is available about subject selection in study 010.

4.1.12.2b Protocol Violations & Deviations

Six subjects had minor protocol violations at time of entry, related to inclusion criteria. These were judged by the sponsor to be not of clinical significance and all subjects were continued in the study.

Five subjects did not complete the study due to receipt of excluded or inappropriate drug (3) or due to difficulty completing GFR measurement (2).

4.1.12.2c Concomitant Therapies used after Trial Initiation

No information about concomitant medications is available.

4.1.12.2d Analyses of Study 010 Results

Changes in GFR

When data from both period one and two were used, mean GFR at Baseline was 80.0 mL/min/1.73 m² prior to celecoxib administration and 84.3 mL/min/1.73 m² prior to naproxen treatment. Mean GFR was unchanged with celecoxib averaging 0.86 ml/min/1.73 m² below Baseline on Day 1 (200 mg BID) and 1.1 ml/min/1.73 m² below Baseline on Day 6 (400 mg BID). In contrast, with naproxen mean GFR was 5.3 mL/min/1.73 m² lower than Baseline on Day 1 and 7.5 mL/min/1.73 m² below Baseline on Day 6, representing a 6% and a 9% decline in GFR, respectively. A statistically significant reduction (p=0.004) in GFR with naproxen was detected on Day 6 when compared to the effect of celecoxib. These results are shown graphically and in tabular form below.

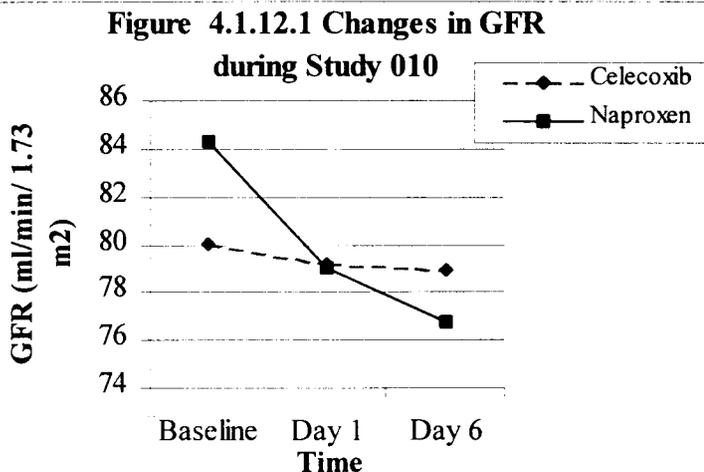


Table 4.1.12.2d.1 Changes in GFR during study 010^a.

Period and Group measured Mean±SD (Change from Baseline)	Celecoxib group	Naproxen group
All Evaluable Subjects (n=24)		
GFR at baseline	80±12.8	84±14
GFR on Day One	79.2±13 (-0.864)	79.0±19 (-5.31)
GFR on Day Six	78.9±14 (-1.110)	76.8±19 (-7.53) ^b
Subjects during Period One (n=12)		
GFR at baseline	83.3±16	82.4±12
GFR on Day One	81.5±10 (-1.7)	82.2±12 (-0.148)
GFR on Day Six	81.2±12 (-2.0)	74.7±6 (-7.6)

a. Data from NDA volume 1.134 Table 9.

b. Indicates nominal significance for comparison from baseline p<0.05.

For the patients who initially received naproxen (sequence B), there was not complete return to baseline GFR at the end of the 6 day washout period. Due to this potentially confounding factor, an analysis of the first period alone was also performed. For this group, GFR was largely unchanged in the naproxen group at day one (-0.148 from baseline). A larger decline in GFR was seen at 6 days of naproxen therapy (-7.6). For the subjects who received celecoxib, the mean changes in GFR for days one and six were -1.8 and -2.1 ml/min/1.73 m² respectively. There was no significant differences between the effects of naproxen and celecoxib on GFR at either 1 or 6 days when period one was analyzed separately (see table below).

4.1.12.2d Analyses of Study 010 Results (cont)

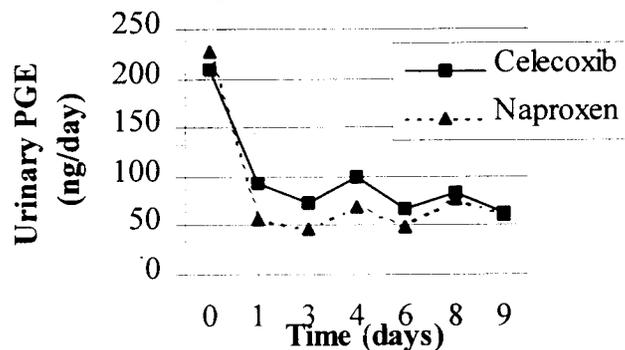
From both periods, there were also 5 individuals in the Naproxen group who had a greater than 20% decrease in GFR measured at either day one or six. No individual in the celecoxib group had a similar decline.

Changes in urinary PGE₂ excretion

Urinary PGE₂ excretion was measured at pretreatment (Days -2 and Washout Day 6), Baseline (Days -1 and Washout Day 7), and Days 1, 3, 4, 6, 8, and 9 of each Treatment Period. For all evaluable data, there was a statistically significant reduction ($p < 0.042$) in the urinary excretion of PGE₂ from baseline with celecoxib and naproxen administration. The magnitude of this reduction was consistent across the treatment interval for both celecoxib (-51 to -72%) and naproxen (-71 to -80%) and was not affected by the increase of the celecoxib dose from 200 mg BID to 400 mg BID on Day 6 (although the sample size was small to detect such a difference).

One individual (#9208) excreted 3X more PGE₂ than the standard deviation for the mean of the entire group. While his results are included in the results discussed above, the graph below shows the time-course of prostaglandin inhibition for the two groups minus the data from subject #9208. There was no significant difference between the two groups with regard to the degree of inhibition of PGE₂ release.

Figure 4.1.12.2d.2 Time-course for Urinary Prostaglandin Production in Study 010

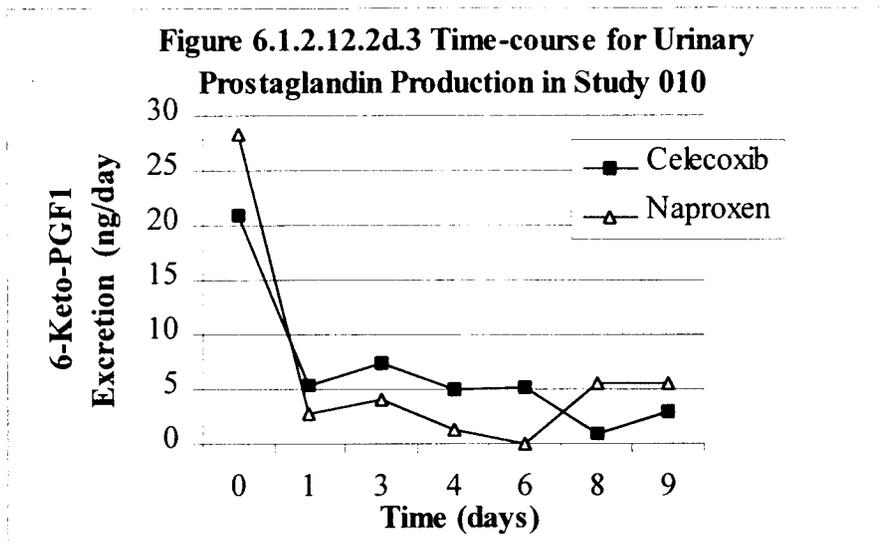


Changes in urinary 6-Keto-PGF₁-alpha excretion

Urinary PGF₁ excretion was measured at pretreatment (Days -2 and Washout Day 6), Baseline (Days -1 and Washout Day 7), and Days 1, 3, 4, 6, 8, and 9 of each Treatment Period. At Baseline, urinary excretion of 6-keto-PGF₁ averaged 28.22 ng/day and 31.46 ng/day in the celecoxib and naproxen treatments, respectively. Urinary 6-keto-PGF₁ excretion was significantly reduced ($p < 0.013$) by both treatments on Day 1, Day 3, Day 4, Day 6, Day 8 and Day 9. The mean amount of PGF₁ excreted decreased ranged from 18.41 to 25.46 ng/day for celecoxib and from 24.13 to 31.46 ng/day with naproxen treatment. In a majority of subjects, 6-keto-PGF₁ concentrations in urine fell to undetectable levels (<10 pg/ml) at most time points following celecoxib or naproxen administration. This analytical limitation creates uncertainty as to the true magnitude of the reduction in urinary 6-keto-PGF₁ excretion with either treatment. Mean decreases in urinary 6-keto-PGF₁ excretion were comparable for celecoxib 200 mg BID and 400 mg BID doses. No significant differences were detected between celecoxib and naproxen throughout the treatment interval ($p > 0.067$).

If a similar analysis was performed after excluding subject #9208, baseline urinary excretion of 6-keto-PGF₁ averaged 21.49 ng/day and 28.42 ng/day for celecoxib and naproxen, respectively. The reduction from baseline in urinary 6-keto-PGF₁ excretion with celecoxib 200 mg BID and 400 mg BID ranged from 14.011 ng/day to 20.636 ng/day ($p < 0.017$ all time points). In comparison, the mean reduction from Baseline with naproxen ranged from 22.292 ng/day to 28.418 ng/day ($p < 0.001$ all time points). The reductions in urinary 6-keto-PGF₁ excretion appeared to be greater with naproxen when compared to celecoxib, and reached statistical significance on Day 3 and Day 6 ($p < 0.041$). This data is presented in the figure below.

4.1.12.2d Analyses of Study 010 Results (cont)



Gender differences in prostaglandin excretion

In a sub-set analysis, the sponsor examined the role of gender in the rates of prostaglandin excretion and the effects of study drugs. Both males and females exhibited sustained decreases in mean urinary 6-keto-PGF1 excretion from baseline with naproxen and celecoxib. Males were observed to have mean baseline urinary 6-keto-PGF1 excretion rates about twice that of females. In both males and females, urinary 6-keto-PGF1 excretion fell dramatically and often to undetectable levels with either treatment.

Excretion of sodium, calcium, potassium, and creatinine

Excretion of these cations and creatinine were measured throughout the trial. The results are presented in tabular form below.

For sodium, celecoxib and naproxen were associated with comparable effects on urinary sodium excretion for both the magnitude of the observed changes and the temporal pattern. Pairwise comparisons using repeated measures ANOVA revealed no clinically significant differences between treatments. There was also no significant difference in urinary sodium excretion between the 200 and 400 mg doses of celecoxib (see table below).

Overall, both drugs were associated with sodium retention. On a cumulative basis, subjects retained an average of at least 160.4 mmol of sodium on Days 1 through 9 of celecoxib treatment compared to 29.9 mmol of sodium retained during 9 days of naproxen treatment (a nominally significant difference). This occurred at a time when dietary intake of sodium was relatively constant throughout the study and similar to the baseline period.

For potassium excretion, there were no statistically significant differences observed between treatment groups with regard to change from baseline at any time point (see table below) for urinary potassium excretion.

For calcium excretion, urinary calcium excretion was not affected by celecoxib or naproxen administration, when compared to urinary calcium excretion at baseline. There were no statistically significant differences between treatment groups with regard to change from baseline at any time point.

With regard to urinary creatinine excretion, it was not affected by celecoxib or naproxen treatment, when compared to baseline urinary creatinine excretion. There were no statistically significant differences between treatment groups with regard to change from baseline at any time point.

4.1.12.2d Analyses of Study 010 Results cont)

Table 4.1.12.2d.2 Changes in urinary excretion of sodium, potassium, calcium and creatinine during study 010^a.

Period and Group measured Mean±SD (Change from Baseline)	Celecoxib group	Naproxen group
Urinary Sodium (mmol/day)		
Baseline	137.4±50	126.9±33
Day 1	96.7±24	78.4±26
Day 5	131.6±40	147±55
Day 9	124.8±49	141±58
Urinary Potassium (mmol/day)		
Baseline	53.6±18	54.2±18
Day 1	48.6±17	49.1±20
Day 5	57.0±19	78.9±85
Day 9	59.0±26	63.0±22
Urinary Calcium (mmol/day)		
Baseline	6.9±3.4	7.2±3.4
Day 1	6.4±3.5	6.3±2.9
Day 5	7.2±3.9	8.0±3.5
Day 9	6.9±3.6	8.1±4.6
Urinary Creatinine (mmol/day)		
Baseline	8.5±2.6	9.0±2.6
Day 1	8.2±2.2	8.4±2.4
Day 5	8.5±2.2	8.7±2.4
Day 9	8.2±2.4	8.7±2.8

a. Data from NDA volume 1.134 Tables 12-15. Shown are representative days. See NDA for full data.

4.1.13 Safety Outcomes

The adverse events, serious adverse events, and subject discontinuations are included in sections 8.1 and 8.2.

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below. The number of subjects with any SAE and subject discontinuations due to AEs were

Table 4.1.13.1 Clinical adverse experience (AE) summary from protocol #010^a.

Clinical event shown as # of subjects (% of 26 exposed subjects)	Celecoxib 200 mg BID	Celecoxib 400 mg BID	Naproxen 500 mg BID
With Any AE	7 (27%)	12 (46%)	15 (56%)
With Serious AE	0 (0%)	1 (4%)	0 (0%)
Discontinued due to an AE	0 (0%)	0 (0%)	0 (0%)
Discontinued due to Lab AE	0 (0%)	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 1.134.

4.1.13.1 Comparisons of Defined Safety Endpoints

Due to the small sample size, no formal comparisons are performed. The adverse events are included in the overall safety analysis in section 8.1.

4.1.13.2 Comments on Specific Safety Parameters

Deaths

No deaths occurred during the trial.

Serious Adverse Events

One serious adverse event occurred in the celecoxib 400 mg dose group.

Subject No. US0001-0204, (Injury-Accidental), was a 68-year-old male with a history of cerebellar ataxia, appendectomy, pilonidal cyst and urolithiasis. The subject was enrolled into the study on 17 January 1997 and randomized into Treatment Sequence 1. Three days after completion of the first study period (i.e., treatment with celecoxib 200/400 mg BID), the subject was struck while driving his car. He was hospitalized for an overnight observation and administered i.v. Toradol for pain along with deep heat treatments. The subject was released the following day in stable condition. No lacerations or fractures were noted. The subject was removed from the study due to the criteria set forth in the protocol (Protocol Non-compliance).

4.1.14 Study 010 Efficacy Summary

This study investigated the short-term effects of celecoxib and naproxen on several parameters of renal function and on the excretion of prostaglandins. The population studied were healthy elderly individuals.

1. After six days, there was a small, significant, decrease in GFR in the patients who received naproxen (averaging 7 cc/min of creatinine clearance, see table 4.1.12.2.d.1). Patient who took celecoxib for the same period of time had a smaller decline in GFR (1-2 cc/min of creatinine clearance). This result was driven by 5 individuals with a >20% decline in their GFR (see below).

2. After 6 days, more individuals in the naproxen group had declines in GFR of >20% (5) compared with the celecoxib group (0).

3. Both celecoxib and naproxen inhibit PGE₂ and 6-keto-PGF₁ excretion (see figures 4.1.2.12.2d.2 and 3). While both drugs inhibited PGE₂ excretion equally, there was a trend towards greater inhibition of 6-keto-PGF₁ excretion by naproxen.

4. Administration of both celecoxib and naproxen were associated with sodium retention (see table 4.1.12.2.d.2). There were no significant effect of either celecoxib or naproxen on calcium, potassium, or creatinine excretion.

4.1.15 Study 010 Safety Summary

1. There were no deaths and one Serious Adverse Event, unrelated to celecoxib administration.
2. There were no incidences of acute renal failure.

4.1.16 Study 010 Reviewer's Conclusions

With regard to efficacy, this trial in healthy elderly demonstrates that both naproxen and celecoxib inhibit the excretion of both PGE₂ and 6-keto-PGF₁. The use of celecoxib for 6 days in this study was associated with a slightly smaller decline in GFR. This was driven by wide subject variability in the naproxen group (5 subjects had a >20% decline in GFR). Both naproxen and celecoxib cause sodium retention.

As regards safety, the trial is underpowered to comment on the occurrence of common renal adverse events. No unexpected toxicities were detected.

4.2 Review of Protocol E49-96-02-033 (hereafter abbreviated 'study 033').

4.2.1 Title of Study

Clinical protocol to evaluate the effects of SC-58635 (celecoxib) and Naproxen on renal function and urinary prostaglandins in sodium and volume depleted subjects.

4.2.2 Sites of Investigation and Investigators

Study was conducted by Hans Brunner, M.D., at the University Hospital, Lausanne Switzerland.

4.2.3 Background

Initial protocol: August 21, 1996

Protocol amendments:

There were three protocol amendments, dated October 23 and 28, 1996, and 12 November 1996. All three amendments dealt with minor administrative changes.

4.2.4 Study Design

This was a single-center, double-blind, randomized, placebo-controlled, multiple-dose, parallel-group, outpatient study. Forty-two (42) subjects were randomized to receive either celecoxib 200 mg BID, celecoxib 400 mg BID, naproxen 500 mg BID or placebo BID for six consecutive days followed by a single morning dose on the seventh day. A listing of the safety and efficacy measurements is found in the table below.

PreTreatment Phase (Day -14 to -5)

Following screening, the subject had samples collected for several baseline values: prostaglandin excretion; hormone levels; and renal function. The subjects' renal function was evaluated at the second Pretreatment Visit. GFR was calculated from a sinistrine clearance procedure and RBF was calculated using PAH clearance. The fractional excretion of sodium, lithium, and potassium were also calculated from the appropriate urine and serum samples.

Low Sodium and Low Volume Period (Day -4 through Day -1)

The low sodium and low volume period consisted of the four days immediately prior to the start of study drug administration. Subjects were outpatients during this period, but took all low sodium meals (3 g/day or approximately 50 mmol/day) at the investigative site. On Day -4, each subject received a single dose of furosemide 40 mg.

Treatment Period (Day 1 through Day 7)

The treatment period was the seven days during which subjects received study medication in randomized, blinded fashion. Subjects were outpatients, but continued to report to the investigative unit for all meals. Study medication was administered every 12 hours during the first 6 days, and on the morning of day 7. Subjects whose urinary sodium excretion was ≥ 75 mmol/day for two consecutive days during this period were to be withdrawn from the study, as it was assumed that they had been noncompliant with the study diet. They were to be replaced. Renal Blood Flow (RBF) and GFR were measured at the end of hospital day 6, as it was in the pre-treatment period.

Posttreatment Period (Day 8)

Subjects returned to the investigative unit on Day 8 for a final physical examination, measurement of vital signs and weight, and clinical laboratory tests including hematology, clinical chemistry, and urinalysis (including a final 24 hour urine collection for prostaglandin excretion).

4.2.5 Primary and Secondary Endpoints

Primary study objectives:

The primary objectives of this study were to:

1. Compare the changes in GFR from pre- to post-dose measurements of Day 1 and Day 7 between celecoxib and naproxen treatment groups; and
2. Compare the changes in urinary PGs (PGE₂ and 6-keto-PGF1-alpha, a metabolite of prostacyclin, PGI₂) from predose (Day -2 and Day -1) through Day 7 postdose, between the celecoxib and naproxen treatment groups.

4.2.5 Primary and Secondary Endpoints (cont)

Secondary study objectives:

The secondary objectives of this study were to evaluate the changes between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7 for:

1. Renal blood flow (mL/min);
2. Plasma renin activity (ng angiotensin I released /mL/hr);
3. Plasma aldosterone (pg/mL) and plasma atrial natriuretic peptide (fmol/mL);
4. Fractional urinary sodium, potassium, and lithium clearances; and
5. Serum thromboxane (ng/mL).
6. The safety and pharmacokinetics of celecoxib in sodium- and volume-depleted healthy subjects. A safety measure of particular interest (per the sponsor) was the 24-hour uric acid concentration on Days 1, 3, and 7. Pharmacokinetic variables of interest were the plasma concentrations of celecoxib and naproxen on Days 1 and 7, and the urinary concentrations of celecoxib metabolite celecoxib on Days 1 and 7.

4.2.6 Number of subjects/ randomization

A total of 24 evaluable subjects (16 female and 8 male) completed both Treatment Periods of the cross-over study.

4.2.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

1. Been a male between 18 and 45 years of age inclusive;
2. Had a physical examination during the Pretreatment Period that revealed no clinically significant abnormalities;
3. Had normal clinical laboratory test results during the Pretreatment Period or, if abnormal, were not clinically significant;
4. Had a GFR > 100 mL/min/1.73 m² during the Pretreatment Period;
5. Had normal blood pressure (BP < 140/90 mmHg) during the Pretreatment Period;
6. Had a negative drug screen during the Pretreatment Period;
7. Had a negative HIV screen during the Pretreatment Period;
8. Had a negative hepatitis B surface antigen screen during the Pretreatment Period;
9. Weighed >50 kg and been within 20% of ideal body; and
10. Provided documented written informed consent prior to admission to this study.

Exclusion Criteria

1. A history of any clinically significant illness within the three months prior to the start of the Pretreatment Period;
2. A history of hypersensitivity (e.g., anaphylactoid or cutaneous reaction) to COX inhibitors or sulfonamides, or a history of lactose intolerance;
3. Used any NSAIDs within 10 days of the start of the Pretreatment Period or other medications within 14 days of the start of the Treatment Period;
4. A history of substance abuse, drug addiction, or alcoholism within the last three years;
5. Used a tobacco product or consumed alcohol within 48 hours prior to the Pretreatment Period or were unable to abstain from tobacco and alcohol products throughout the entire length of the study;
6. Urinary incontinence;
7. Anemia (hemoglobin <13 g/dL and hematocrit <39%);
8. Received any investigational medication within 30 days prior to this study, or were expected to receive any investigational medication during the study;
9. An inability to abstain from any sexual activity from Day -4 throughout the entire length of the study; or,
10. Been previously admitted to this study.

4.2.8 Dosage/ Administration

Forty-two (42) subjects were randomized to receive either celecoxib 200 mg BID, celecoxib 400 mg BID, naproxen 500 mg BID or placebo BID for six consecutive days followed by a single morning dose on the seventh day.

4.2.9 Duration/ Adjustment of Therapy

Reasons for subject discontinuation from the study:

1. Urinary sodium values were ≥ 75 mmol/L for two consecutive days during the Treatment Period or on both Day -2 and Day -1 of the Low Sodium and Low Volume Period;
2. Serum creatinine increased by 50% over Pretreatment assessments;
3. The subject was sexually active during the study;
4. Developed symptoms that required medical intervention;
5. Developed an intercurrent illness that required any concomitant medication;
6. Withdrawal of consent;
7. The Investigator determined it was in the subject's best interest to withdraw; or
8. Searle discontinued the study.

4.2.10 Safety and Efficacy Endpoints Measured

Table 4.2.10.1 Timetable for clinical observations and lab measurements in study 033^a.

Procedure/ Test	Pre-Tx	Low-Na ⁺ , Low-Volume Period				Treatment Period							Post-Tx Period
	-14 to -5	-4	-3	-2	-1	1	2	3	4	5	6	7	8
History	X												
Physical	X					X							
Drugs, Hepatitis B/ HIV Screen	X												
Clinical Labs ^b	X					X		X					X
Urine Vol, Na, K, Crt	X		X	X	X	X ^c	X	X ^c	X	X	X	X	X ^c
Na, Li, K clearance	X		X	X	X	X	X	X	X	X	X	X	
Vital Signs/ weights	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X												
Serum Thromboxane						X							X
Urine Prostaglandins	X		X	X	X	X	X	X	X	X	X	X	
GFR, RBF	X					X							X
Low-Na ⁺ Diet		X	X	X	X	X	X	X	X	X	X		
Lasix, 40 mg		X											
Celecoxib Levels						X							X
Adverse Events						X							

a. Data from NDA volume 1.137, table 1.

b. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, total protein, albumin, calcium, phosphorus, creatine kinase); and (3) Urinalysis (specific gravity, pH, RBC/hpf, protein, glucose, ketones, bilirubin).

c. Urinary uric acid was also measured.

4.2.11 Statistical Considerations

Demographics and Baseline Characteristics

All randomized subjects were included in these analyses. Baseline demographic characteristics (age and race) were summarized within treatment groups and descriptive statistics (i.e., mean, standard deviation, median, and range) were calculated. The groups were compared with respect to demographics, including baseline renal function values, using the Kruskal-Wallis test, and with respect to race using the Fisher's Exact test.

Subject Population Analyzed

All analyses relating to renal function were performed on the Intent-to-Treat (ITT) Cohort (all randomized subjects who took at least one dose of study medication).

4.2.11 Statistical Considerations (cont)

Glomerular Filtration Rates

Changes from predosing to postdosing GFRs were summarized and descriptive statistics were provided. Overall differences among treatments using a Kruskal-Wallis test and paired t-tests. Pairwise comparisons were also carried out for the differences between celecoxib 200 mg and naproxen groups, celecoxib 200 mg and placebo groups, celecoxib 400 mg and naproxen groups, celecoxib 400 mg and placebo groups, and celecoxib 200 mg and celecoxib 400 mg groups using a repeated-measures ANOVA model.

Renal Blood Flow (RBF) and Fractional Excretion of Sodium, Potassium, and Lithium

Except for plotting mean RBF values, or mean fractional excretion of sodium, potassium, and lithium against study drug plasma concentrations, the statistical analyses for these secondary variables of interest were identical to that for GFR, described above.

Renal Prostaglandins

Pairwise comparisons between the effects of treatments on urinary prostaglandins were carried out for the differences between the celecoxib 200 mg and naproxen groups, celecoxib 200 mg and placebo groups, celecoxib 400 mg and naproxen groups, celecoxib 400 mg and placebo groups, and celecoxib 200 mg and celecoxib 400 mg groups. The differences also were analyzed using a repeated-measures ANOVA model.

Serum Thromboxane, Plasma Renin Activity, Plasma Aldosterone, and Atrial Natriuretic Peptide

Serum TxB₂, plasma PRA, aldosterone and ANP values on Days 1 and 7 were summarized and descriptive statistics were provided. Mean changes for each variable from their respective daily predosing values were summarized and overall differences were analyzed using an ANCOVA with Baseline as the covariate. PRA, and plasma aldosterone and ANP values were not analyzed statistically, but are presented by subject in the data listings.

Pharmacokinetic Data

Plasma concentrations of study medication are listed by subject in the data listings. Summary statistics for the plasma concentrations of celecoxib and naproxen are provided by dose group and by study day. Summary statistics for the urinary concentrations of the celecoxib metabolite SC-62807 are presented by dose group and study day.

Statistical Determination of Sample Size

The sample size of 10 subjects per treatment group was based on clinical judgment. Assuming a standard error of 3 mL/min/1.73 m² at both Day 1 and Day 4 and coefficient of correlation between the Day 1 and Day 4 measurements of 0.5, the intra-subject standard deviation can be estimated as 7.35 mL/min/1.73 m². A mean difference in change from Baseline in creatinine clearance between two treatment groups of 9.74 mL/min/1.73 m² or larger can be detected with a sample size of 10 subjects per treatment group, assuming an intra-subject standard deviation of 7.35 mL/min/1.73 m², at a significance level of 0.05 (two-sided) and 80% power. Using a standard deviation for the change in urinary urinary-6-keto-PGF₁ of 2.1 ng/hour, a difference in mean change from Baseline in urinary-6-keto-PGF₁ D between two treatment groups of 2.78 ng/hour or larger can be detected with a sample size of 10 subjects per treatment group, assuming a standard deviation of 2.1 ng/hour, at significance = 0.05 and 80% power.

Statistical/Analytical Issues

The sponsor used Day -1 data to compute Baseline urinary PGs instead of an average of the Day -2 and Day -1 values since the Day -1 data were collected closer to the initiation of dosing on Day 1. All calculations involving 24-hour urine collections were done using the actual duration of urine collection. An ad hoc analysis was performed to calculate the intra-subject variance of the two predose GFR, RBF and partial sodium, potassium and lithium clearance values that were obtained on Days 1 and 7. This analysis was performed because there appeared to be considerable variation in these values.

Handling of Missing Data

There were no imputation methods used for missing data in the analysis.

Multiplicity

No adjustment for multiplicity was proposed.

4.2.11 Statistical Considerations (cont)

Interim Analyses

There were no interim analyses.

Safety Analysis

Every randomized subject who received study medication was included in the safety analysis. All adverse events were coded and summarized by treatment group. The incidence of treatment-emergent adverse events was tabulated and tested for significance using a paired t-test. Clinical laboratory data also were summarized and treatment groups compared using the Kruskal-Wallis Test applied to change from Baseline. Using a Chi-square test, shifts in laboratory values were compared across treatment groups in terms of the number of subjects showing an increase, decrease, and no change, with respect to the normal range. Values outside the normal range at Baseline and Posttreatment were identified and presented in a 3x3 shift table by treatment group. Depending on the number of non-zero cells, the Stuart-Maxwell Test or the McNemar's Test was used to determine significant distributional changes from Baseline to Posttreatment within treatment group. Scatter plots were used to graphically depict the results. The incidence of clinically relevant changes in laboratory tests from Baseline to Posttreatment was tabulated by treatment group.

Laboratory values considered to be clinically relevant are listed in the table that follows:

- SGOT (AST): ≥ 3 x upper limits of normal (ULN)
- SGPT (ALT): ≥ 3 x ULN
- Alkaline Phosphatase: ≥ 1.25 x ULN
- Total Bilirubin: ≥ 1.5 x ULN
- Creatinine: ≥ 1.3 x ULN
- BUN: ≥ 2.0 x ULN
- Hematocrit: a decrease ≥ 5 percentage points (from Baseline value)
- Hemoglobin: a decrease ≥ 2 g/dL (from Baseline value)
- WBC: $< 3000/PL$
- Platelets: $< 100,000/PL$

Summary statistics for vital signs and body weight and mean changes from Baseline to Posttreatment were calculated and compared across treatment groups using the Kruskal-Wallis Test.

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4.2.12 Efficacy Outcomes for protocol

4.2.12.1 Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the 42 subjects enrolled in protocol #033 are summarized below. Note that there was a significant difference in between the two 'baseline' GFRs measured prior to study drug administration in the celecoxib 200 BID group.

Table 6.2.3.12.1.1 Demographics of protocol #033^a.

Demographic	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10
Gender				
Male	11 (100%)	11 (100%)	10 (100%)	10 (100%)
Female	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Race (n (%))				
Caucasian	10 (91%)	10 (91%)	9 (90%)	9 (90%)
Black	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hispanic	1 (9%)	1 (9%)	1 (10%)	1 (10%)
Other				
Age (yrs) (Mean±sd)	23.3±3	26.4±5	23.0±3	24.5±5
Mean Weight, kg (±SD)	74±5	74±6	74±11	78±8
Baseline GFR (ml/min/1.73 m²)				
Pretreatment	119±13	134±13	121±23	127±10
Day 1, Pre-dose	117±12	101±19 ^b	104±18	115±21

a. Data from NDA volume 1.137, Table 4.

b. P value <0.001 comparing two GFRs for celecoxib 200 mg BID group.

4.2.12.2 Disposition of Subjects

The table below shows the disposition of subjects in study 033.

Table 4.2.12.2.1 Summary of subjects entered into protocol #033^a.

	Placebo	Celecoxib 200 BID	Celecoxib 400 BID	Naproxen 500 BID
Entered	11	11	10	10
Completed	10 (91%)	11 (100%)	10 (100%)	10 (100%)
Discontinued: Total	1 (9%)	0 (0%)	0 (0%)	0 (0%)
Protocol Non-compliance	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AEs	1 (9%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 1.137, table 3.

b. Subject 0030 withdrew due to an AE prior to the first dose of study medication.

4.2.12.2a Subject Selection

No information is available about subject selection in protocol #033.

4.2.12.2b Protocol Violations & Deviations

1. Pertaining to dosing with study medication, one subject missed one dose of study medication. Subject 0001 did not receive the second dose of naproxen on Day 3.

2. Related to concomitant medications (which were prohibited in the study), seven subjects took nine concomitant meds. One of these was withdrawn. Concomitant meds used included: hexetidine/ chlorhexidine; azithromycin; acyclovir; topical hydrocortisone; and anti-acne preparation; and acetaminophen for a headache.

4.2.12.2c Concomitant Therapies used after Trial Initiation

No concomitant medications were to be used during the trial, and such use constituted a protocol violation.

4.2.12.2d Analyses of Study 033 Trial Results

Primary study objectives

1. Compare the changes in GFR from pre- to post-dose measurements of Day 1 and Day 7 between celecoxib and naproxen treatment groups.

The effect of short-term administration of celecoxib on GFR was first analyzed by comparing the average GFRs taken before the first dose Days 1 and 7. There were no significant differences between the study groups detected, and no significant decline in mean GFT detected in any dose group. When examined hour by hour (data not shown), no consistent effect of any drug or dose –group on GFR was detected. There was also no evidence of a temporal association between plasma levels of celecoxib and naproxen and changes in GFR. As the sponsor notes... 'Changes in GFR were erratic across treatments and the standard errors of treatment means were large, therefore limiting interpretation of the data.' (NDA vol. 1.137, p. 49).

Table 4.2.12.2d.1 Effect of celecoxib and naproxen on GFR in study #033^a.

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10
Day One Pre-dose				
Mean±SD	116.8±12	100.7±15	104±115	109±15
Within-subject SD	12.2	15.4	7.0	20.4
Day Seven Pre-Dose				
Mean±SD	116.8±13	105.5±19	101.3±16	125.1±22
Within-subject SD	13.2	18.6	16.5	22.3

a. Data from NDA volume 1.137, table 3.

b. Subject 0030 withdrew due to an AE prior to the first dose of study medication.

2. Compare the changes in urinary PGs (PGE₂ and 6-keto-PGF1-alpha , a metabolite of prostacyclin, PGI₂) from predose (Day -2 and Day -1) through Day 7 postdose, between the celecoxib and naproxen treatment groups.

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4.2.12.2d Analyses of Study 033 Trial Results

Primary study objectives (cont)

Urinary PGE₂

For urinary PGE₂, there were no statistically significant differences between study drug groups between the Pre-dose values for Days 1 and 7. There was a large variability in urinary PGE₂ excretion for all treatment groups; the range between observed individuals for many time points was 100-fold or greater. Similarly, pairwise comparison using a repeated-measures ANOVA found no statistically significant differences between treatment groups.

Urinary 6-keto-PGF₁-alpha

Analysis of the 6-keto-PGF₁-alpha excretion was again hindered by extremely wide subject to subject variability. This can be seen below in the wide standard deviations and ranges for the baseline 6-keto-PGF₁-alpha excretion. Note also the higher basal rate of 6-keto-PGF₁-alpha in the naproxen group. The table below shows the changes from baseline for the study groups. Given the broad standard deviations and ranges of individual excretion rates, there was a trend towards decreased 6-keto-PGF₁-alpha excretion in the naproxen group, compared with placebo and the two celecoxib groups. This was particularly true during days 2-6. The celecoxib 400 mg dose group also tended to have lower 6-keto-PGF₁-alpha excretion rates than placebo throughout the study.

Table 4.2.12.2.d.2 Effect of celecoxib and naproxen on renal 6-keto-PGF₁-alpha excretion in 033^a.

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value ^b
Baseline (Day -1)					
Mean±SD	90.4±43	77.7±37	95.0±50	134.0±107	--
Range	31.8 - 176.7	0.00 - 142.0	48.3 - 207.9	0.00 - 320.0	--
<i>Difference from Baseline</i>					
Day 1 Pre-dose					
Mean±SD	-16.4±58	-14.2±16	-51.7±36	-72.5±83	0.112
Range	-176 - +30	-41 - +20	-106 - -1	-237 - +32	
Day 2 Pre-dose					
Mean±SD	-3.6±44	-30.0±39	-37.9±35	-89.8±63	0.003
Range	-64 - +63	-111 - +27	-107 - +17	-196 - 0	
Day 3 Pre-dose					
Mean±SD	-15.5±62	-20.0±45	-55.1±17	-88.8±76	0.037
Range	-177 - +42	-111 - +64	-88 - -25	-222 - 0	
Day 4 Pre-dose					
Mean±SD	-3.5±34	-41±35	-61±35	-81±69	<0.001
Range	-43 - +63	-71 - -30	-96 - -28	-320 - 0.00	
Day 5 Pre-dose					
Mean±SD	-33.8±64	-29.0±27	-61.4±23	-109.4±92	0.036
Range	-177 - +41	-71 - +30	-96 - -28	-321 - 0.00	
Day 6 Pre-dose					
Mean±SD	-20.6±53	-30.9±33	-65.8±37	-90.9±62	0.014
Range	-129 - +47	-111 - +24	-135 - -16	-186 - 0.00	
Day 7 Pre-Dose					
Mean±SD	17.3±44	-10.9±33	-40.9±39	-78.1±71	0.002
Within-subject SD	-54 - +90	-55 - +39	-107 - +11	-257 - 0.00	

a. Data from NDA volume 1.137, table 12.

b. P value using ANCOVA.

Per the sponsor, repeated measures analysis showed significant differences between placebo and both celecoxib 400 mg and naproxen with regard to 6-keto-PGF₁-alpha excretion.

4.2.12.2d Analyses of Study 033 Trial Results

Secondary study objectives:

1. Changes in Renal Blood Flow (RBF) between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

The primary times of comparison were between the RBF obtained just prior to the first dose on Day one, and the only dose on Day seven. For this analysis, as shown below, there were no statistically significant differences between treatment groups for any RBF value. The within-subject variability was, as with GFR, approximately 10% (range 5.7 to 19.4%).

Table 4.2.12.2d.3 Effect of celecoxib and naproxen on RBF in study 033^a.

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10
Day One Pre-dose				
Mean±SD	532.1±96	492.2±79	538.3±118	512.3±88
Median	522.5	476	552	514.3
Day Seven Pre-Dose				
Mean±SD	545.9±73	524.7±96	541.4±130	565.1±53
Median	536.5	505.5	516.5	560.8
P-Value^c	0.659	0.212	0.886	0.142

a. Data from NDA volume 1.137, table 3.

b. Subject 0030 withdrew due to an AE prior to the first dose of study medication.

c. Using paired t-test comparing day one and day seven, per the sponsor.

2. Changes in serum thromboxane levels between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

The mean serum Thromboxane (TxB2) levels for each treatment group are shown below. At day 7, there was a statistically significant effect of naproxen to decrease TxB2 levels, compared with placebo, evident within 2 hours of the first dose. No significant effect of celecoxib on TxB2 levels was detected.

Table 4.2.12.2d.4 Effect of celecoxib and naproxen on serum thromboxane levels in study 033^a.

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	
DAY ONE					
Baseline (30 mins Predose)					
Mean±SD	216.5±83	228.2±97	188.7±63	223.8±78	
Range	118 - 382	91 - 460	65 - 280	133 - 339	
Difference from Pre- to Post-Dose					
Mean±SD	-3.1±64	-21.9±134	-9.3±64	-219.2±77	<0.0001
Range	-98 - +97	-301 - +212	-118 - +88	-330 - -129	
DAY SEVEN					
Baseline (30 mins Predose)					
Mean±SD	185.1±93	219.9±55	222.3±83	16.5±8	
Range	59 - 316	139 - 335	63 - 333	6 - 31	
Difference from Pre- to Post-Dose					
Mean±SD	24±93	-19.5±50	-30.0±44.8	-13.9±8	0.001
Range	-176 - +153	-95 - +84	-86 - +51	-26 - -4	

a. Data from NDA volume 1.137, table 14.

c. Using ANCOVA, per the sponsor.

4.2.12.2d Analyses of Study 033 Trial Results

Secondary study objectives (cont):

3. Changes in plasma renin activity between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

At day one, plasma renin activity fell in all groups after administration of study drug (including placebo). There was no significant differences detected between placebo and any of the active drug groups.

At day seven, plasma renin activity levels fell significantly after administration of study drug in both of the celecoxib groups and in the naproxen group, relative to the placebo group (which rose slightly). There was no significant difference between the changes seen in either of the celecoxib groups and the naproxen group.

Table 4.2.12.2d.5 Effect of celecoxib and naproxen on plasma renin activity in study #033^a.

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value
DAY ONE					
Baseline (30 mins Predose)					
Mean±SD	1.8±0.4	2.3±1.5	1.6±0.8	1.8±0.3	--
Range	1.1 – 2.6	0.9 – 5.3	0.51 – 2.9	1.1 – 2.3	--
Difference from Pre- to Post-Dose					
Mean±SD	-0.38±0.34	-0.41±0.53	-0.48±0.42	-0.41±0.31	0.582 ^b
Range	-0.8 - -0.2	-1.5 - -0.49	-1.4 - -0.19	-1.15 - -0.1	
DAY SEVEN					
Baseline (30 mins Predose)					
Mean±SD	1.1±0.5	1.0±0.7	0.87±0.5	0.76±0.3	--
Range	0.39 – 2.1	0.30 – 2.4	0.29 – 1.8	0.37 – 1.3	--
Difference from Pre- to Post-Dose					
Mean±SD	+0.26±0.47	-0.114±0.27	-0.166±0.3	-0.116±0.3	0.013
Range	-0.43 - +1.0	-0.73 - +0.3	-0.6 - +0.3	-0.89 - +0.3	

a. Data from NDA volume 1.137, table 14.

b. Using ANCOVA, per the sponsor.

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4.2.12.2d Analyses of Study 033 Trial Results

Secondary study objectives (cont):

4. Changes in plasma aldosterone and atrial natriuretic peptide levels between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

At day one, serum aldosterone levels fell in all treatment groups, with no significant differences seen between active drug and placebo.

At day seven, the pre-dose serum aldosterone levels were lower in all groups when compared with the day one pre-dose value. Serum aldosterone levels also fell after study drug administration, again with no significant differences between the active drug groups (celecoxib or naproxen) and placebo. As with other hormonal measurements in the trial, extremely broad standard deviations reflected large between-subject variability.

Table 4.2.12.2d.6 Effect of celecoxib and naproxen on plasma renin activity in study 033^a.

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value ^b
DAY ONE					
Baseline (30 mins Predose)					
Mean±SD	124.5±70	82.5±32	82.4±43	103.6±81	
Range	53 – 250	36 – 126	31 – 179	33 – 240	
Difference from Pre- to Post-Dose					
Mean±SD	-29.5±93	-4.2±33	-3.9±44	-23.3±47	0.986
Range	-198 - +106	-53 - +55	-47 - +56	-122 - +56	
DAY SEVEN					
Baseline (30 mins Predose)					
Mean±SD	78.8±34	60.4±23	59.5±21	57.0±16	
Range	37 – 150	32 – 100	34 – 98	32 – 80	
Difference from Pre- to Post-Dose					
Mean±SD	-14.9±30	-14.5±16	-8.1±18	-12.5±17	0.915
Range					

a. Data from NDA volume 1.137, table 18.

b. Using ANCOVA, per the sponsor.

Serum atrial natriuretic peptide levels did not change from normal values at any time during the study, and no significant differences were detected between placebo and active drug groups. See NDA vol. 1.137, table 19 for details.

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4.2.12.2d Analyses of Study 033 Trial Results

Secondary study objectives (cont):

5. Changes in fractional urinary sodium, potassium, and lithium clearances between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

Fractional excretion of sodium (FeNa)

The first table summarizes the changes in the FeNa from pre-dose day one to pre-dose day 7. For all groups, FeNa rose between the pre-dose on day one and the pre-dose on day 7. There was no significant difference between groups with regard to their effect on FeNa, measured from pre-dose day 1 to pre-dose day 7. There was also no significant difference between the effects of celecoxib (either dose) and naproxen on FeNa.

Table 4.2.12.2d.7 Effect of celecoxib and naproxen on fractional urinary sodium excretion (FeNa) in study #033^a.

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value
PRE-DOSE DAY ONE Baseline (30 mins Predose) Mean±SD	0.0030±0. 0017	0.0039±0. 0026	0.0044±0. 0036	0.0040±0. 0024	0.673
PRE-DOSE DAY SEVEN Baseline (30 mins Predose) Mean±SD	0.0043±0. 0023	0.0065±0. 0050	0.0064±0. 0044	0.0056±0. 0037	0.647
DIFFERENCE FROM PRE-DOSE DAY 7 TO PRE-DOSE DAY 1 Mean±SD	0.0013±0. 0024	0.0026±0. 0037	0.0020±0. 0020	0.0016±0. 0023	0.933
P-value^c	0.118	0.039	0.011	0.056	

a. Data from NDA volume 1.137, table 21.2.

b. Using ANCOVA, per the sponsor.

c. Using paired T-test, per the sponsor.

Fractional excretion of potassium (FeK)

The FeK tended to rise slightly in all active treatment groups from pre-dose day 1 to pre-dose day 7, and all in the placebo group. The administration of naproxen was associated with a non-significantly higher FeK than either of the celecoxib groups over the same period.

Table 4.2.12.2d.8 Effect of celecoxib and naproxen on fractional urinary potassium excretion (FeK) in study #033^a.

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value
PRE-DOSE DAY ONE Baseline (30 mins Predose) Mean±SD	0.188±0.055	0.249±0.095	0.225±0.083	0.155±0.039	0.035
PRE-DOSE DAY SEVEN Baseline (30 mins Predose) Mean±SD	0.170±0.06	0.271±0.11	0.236±0.09	0.198±0.099	0.075
DIFFERENCE FROM PRE-DOSE DAY 7 TO PRE-DOSE DAY 1 Mean±SD	-0.018±0.042	+0.022±0.096	+0.011±0.117	+0.043±0.091	0.447
P-value^c	0.223	0.456	0.771	0.128	

a. Data from NDA volume 1.137, table 22.2.

b. Using ANCOVA, per the sponsor.

c. Using paired T-test, per the sponsor.

4.2.12.2d Analyses of Study 033 Trial Results

Secondary study objectives (cont)

Fractional excretion of lithium (FeLi)

There was no significant differences in the changes in FeLi from predose day one and predose day seven. The naproxen group did show a significant trend towards a decrease in FeLi over the same time period.

Table 4.2.12.2d.9 Effect of celecoxib and naproxen on fractional urinary lithium excretion (FeLi) in study 033^a.

	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10	P-value
PRE-DOSE DAY ONE Baseline (30 mins Predose) Mean±SD	0.17±0.077	0.19±0.054	0.20±0.038	0.19±0.062	0.60
PRE-DOSE DAY SEVEN Baseline (30 mins Predose) Mean±SD	0.21±0.079	0.20±0.084	0.19±0.050	0.14±0.036	0.097
DIFFERENCE FROM PRE-DOSE DAY 7 TO PRE-DOSE DAY 1 Mean±SD P-value ^c	0.04±0.08 0.172	0.01±0.09 0.760	0.0±0.06 0.922	-0.05±0.04 0.007	0.057

a. Data from NDA volume 1.137, table 23.2.

b. Using ANCOVA, per the sponsor.

c. Using paired T-test, per the sponsor.

6. Safety and pharmacokinetics of celecoxib in sodium- and volume-depleted healthy subjects.

The reader is referred to the pharmacologist's review for the examination of the pharmacokinetics of celecoxib.

4.2.13 Safety Outcomes

The adverse events, serious adverse events, and subject discontinuations are included in sections 8.1 and 8.2.

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below. The number of subjects with any SAE and subject discontinuations due to AEs were

Table 4.2.13.1 Clinical adverse experience (AE) summary from study 033^a.

Clinical event shown as # of subjects (% of exposed subjects)	Placebo N=11	Celecoxib 200 BID N=11	Celecoxib 400 BID N=10	Naproxen 500 BID N=10
With Any AE	9(90%)	6(55%)	6(60%)	9(90%)
With Serious AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued due to an AE	1 (9%)	0 (0%)	0 (0%)	0 (0%)
Discontinued due to Lab AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 1.137.

4.2.13.1 Comparisons of Defined Safety Endpoints

Due to the small sample size, no formal comparisons are performed. The adverse events are included in the overall safety analysis in section 8.1.

4.2.13.2 Comments on Specific Safety Parameters

Deaths

There were no deaths in the trial.

Serious Adverse Events

There were no serious adverse events in the trial.

Discontinuations due to Adverse Events

One subject in the placebo group was discontinued before receiving study drug due to coughing, wheezing, and stridor during an infusion of sinistrine and PAH.

4.2.14 Study 033 Efficacy Summary

This study investigated the short-term effects of celecoxib and naproxen on several parameters of renal function and on the excretion of prostaglandins. The population studied were healthy young subjects who underwent a mild volume and sodium-restriction. Overall, the subjects were not truly volume-depleted, as demonstrated by their high baseline FeNa and relatively low serum renins. There was also tremendous variability from patient to patient, making any interpretation the data from this study difficult.

1. Large inter- and intra-patient variability limited the interpretation of study 033 data.
2. No effects of celecoxib and naproxen on GFR or renal blood flow were detected (table 4.2.12.2d.1 and 4.2.12.2d.3).
3. No significant effects of celecoxib and naproxen on PGE₂ excretion were detected.
4. Both naproxen and celecoxib inhibited 6-keto-PGF₁-alpha excretion. There was a trend towards a greater inhibition in the higher dose and celecoxib (400 BID) when compared with celecoxib 200 mg BID. Naproxen also had a greater effect to inhibit 6-keto-PGF₁-alpha excretion than did either dose of celecoxib (table 4.2.12.2d.2).
5. Both naproxen and celecoxib appeared to decrease serum thromboxane levels at the end of day 7. This effect was nominally significant only for naproxen (see table 4.2.12.2d.4).
6. Both naproxen and celecoxib decreased serum renin levels to similar levels at the end of day 7 (table 4.2.12.2d.6).
7. There were no significant effects of either celecoxib or naproxen on the fractional excretion of either sodium or potassium (tables 4.2.12.2d.7 and 4.2.12.2d.8).

4.2.15 Study 033 Safety Summary

1. There were no deaths and one Serious Adverse Event, unrelated to celecoxib administration.
2. There were no incidences of acute renal failure.

4.2.16 Study 033 Reviewer's Conclusions

With regard to efficacy, this trial in healthy subjects demonstrates that both naproxen and celecoxib inhibit the excretion of 6-keto-PGF₁. While the intent of the trial was to examine the effects of celecoxib in volume-contracted patients, this was not achieved. Both celecoxib and naproxen inhibited serum renin activity and thromboxane levels. No significant effects of either naproxen or celecoxib on GFR, renal blood flow, sodium/potassium excretion, or urinary PGE₂ levels were detected, in part due to wide subject variability.

As regards safety, the trial is underpowered to comment on the occurrence of common renal adverse events. No unexpected toxicities were detected.

4.3 Review of Protocol N49-97-06-036 (abbreviated 'study 036' in this review).

4.3.1 Title of Study

Integrated clinical and statistical report to evaluate the effect of SC-58635 200 mg BID and naproxen 500 mg BID on renal function and urinary prostaglandins in patients with stable chronic renal insufficiency.

4.3.2 Sites of Investigation and Investigators

Study was conducted by 11 investigators at 11 study sites in the U.S., of whom 10 enrolled at least one subject.

4.3.3 Background

Initial protocol: Feb. 4, 1997

Protocol amendments:

There were five protocol amendments, March 7, April 25, May 8, July 9, and August 6, 1997.

1. *March 7, 1997:* amendment had the following purposes:

- a. Change the Medical Monitor and Statistician for this study;
- b. Change the GFR entry criteria and medical history;
- c. Modify sample size calculations;
- d. Have all patients as inpatients; and
- e. Amend CRFs to reflect the above changes.

2. *April 25, 1997:* amendment was for minor administrative changes.

3. *May 8, 1997:* amendment expanded the weight range requirements for inclusion into the study, and modified the serum thromboxane assay instructions.

4. *July 9, 1997:* amendment allowed up to two additional days in the Unit to achieve a steady state urinary sodium level (<120 mEq) prior to receiving study medication, and allowed the use of a measured creatinine clearance may be used in lieu of the Cockcroft-Gault Estimation of GFR (inclusion criteria #4).

5. *August 6, 1997:* amendment changed the inclusion criteria, to exclude subjects with serum Cr >3 mg/dl.

4.3.4 Study Design

This was a multiple-center, double-blind, randomized, placebo-controlled, multiple-dose, parallel-group study to compare the changes in the glomerular filtration rate (GFR) and urinary prostaglandins (PGE₂ and 6-keto-PGF) after administration of celecoxib or naproxen to patients with stable chronic renal insufficiency. Seventy-five (75) patients with stable chronic renal insufficiency received either celecoxib 200 mg BID, naproxen 500 mg BID or placebo for six consecutive days followed by a single morning dose on Day 7. Patients were evaluated in a 14-day Pretreatment Period, a seven-day Treatment Period and a three-day Posttreatment Period.

Changes in plasma renin activity (PRA), sodium, potassium and creatinine clearances, serum thromboxane B₂ (Tx_B) and urinary 11-dehydro Tx_B were compared between treatment groups. Plasma concentrations of celecoxib and naproxen and urine concentrations of the celecoxib metabolites were measured and descriptively analyzed with the GFRs.

In the first part of the Pretreatment Period (four to 13 days before the first dose of drug administration), patient eligibility was determined by a medical history, physical examination, 12-lead electrocardiogram, clinical laboratory tests (hematology, biochemistry and urinalysis), and an estimated GFR. If female of childbearing potential, a serum pregnancy test was performed.

Eligible patients received a sodium-restricted diet of 80 mEq for the three baseline visits (Day -3 to Day -1). Twenty-four-hour urine collections were obtained starting on Day -2 and Day -1 for measurement of total volume, sodium, potassium, creatinine, PGs and 11-dehydro Tx_B. In addition, on Day -1 each patient underwent a physical examination (including pregnancy test if applicable). Signs and symptoms present at that time were recorded. Patients then continued a 80 mEq sodium diet throughout the treatment period. Prior to drug administration on Day 1 of the Treatment Period (Day 1 to Day 7), clinical laboratory tests were drawn, including PRA and serum Tx_B. Several of these 2 laboratory tests were then reassessed throughout the treatment period (see table below). GFR, sodium, potassium and creatinine clearances were also measured and plasma and urine samples for pharmacokinetic analysis of celecoxib and plasma samples for naproxen were collected on Day 1 and Day 7.

4.3.4 Study Design (cont)

A 24-hour urine collection for urinary PGs and 11-dehydro-TxB2 were collected starting on Day 2 and again starting on Day 6. Weight, blood pressure and pulse will be measured each morning, and adverse symptoms and concomitant medications were recorded throughout the Treatment Period.

In the posttreatment period (Days 8-10), patients had a physical examination, and clinical laboratory assessments.

Safety was assessed by physical examinations, clinical laboratory assessments, weight, blood pressure and pulse, and adverse signs and symptoms.

4.3.5 Primary and Secondary Endpoints

There were no specified primary or secondary endpoints in this phase I-II study.

Primary study objectives:

The primary objective of this study was to determine the effect of celecoxib on renal function in patients with stable chronic renal insufficiency by:

1. Comparing the effects of celecoxib on GFR to naproxen treatment; and
2. Comparing the effects of celecoxib on urinary PGE2 and 6-keto-PGF1-alpha. excretion to naproxen treatment.

Secondary study objectives:

The secondary objectives of this study were to evaluate the effects of celecoxib compared to naproxen treatment on:

1. PRA;
2. Fractional excretion of sodium and potassium;
3. Creatinine clearance;
4. Serum TxB2 (ng/mL); and
5. Urinary 11-dehydro TxB2 excretion.
6. The final secondary objectives of this study were to evaluate the safety and pharmacokinetics (PK) of celecoxib in subjects with stable chronic renal insufficiency.

4.3.6 Number of subjects/ randomization

A total of 75 subjects were enrolled at 10 sites in the study: 25 in the placebo group; 23 in the celecoxib 200 mg BID group; and 27 in the naproxen 500 mg BID group.

4.3.7 Inclusion/ Exclusion Criteria

Inclusion Criteria

1. Been of legal age of consent;
2. If female of childbearing potential, agreed to participate in this study by providing written informed consent, been using adequate contraception since her last menses and used adequate contraception during the study, not been lactating, and had a negative serum pregnancy test within 24 hours prior to receiving the first dose of study medication;
3. Had renal disease [defined as elevated serum creatinine and decreased GFR (see below)];
4. Had a GFR between 40 and 60 mL/min/1.73m² based on the Cockcroft-Gault Estimation or a measured creatinine clearance;
5. Had a stable serum creatinine \leq 3.0 mg/dL during the Treatment Period (stable was defined as no change in serum creatinine of \geq 1 mg/dL in the past six months);
6. Had discontinued all NSAIDs at least 10 days before the Pretreatment Period with the exception of \leq 325 mg aspirin/day;
7. Weighed \geq 50 kg and was within -20% to +40% of ideal body weight (as provided by the Metropolitan Life Insurance Table which is in Appendix 6 of the original protocol); and
8. Had provided documented written informed consent prior to admission to this study.

Exclusion Criteria

1. Any clinically active systemic diseases which would, in the judgment of the Investigator and in consultation with the Searle Medical Monitor, compromise patient safety or the scientific integrity of the study [other than diabetes and its complications, RA or OA, hypertensive complications and complications secondary to renal disease itself];
2. AST (SGOT) or ALT (SGPT) ≥ 1.5 x the upper limit of normal at baseline, or any other laboratory abnormalities, other than those related to chronic renal insufficiency, or diabetes, thought to be clinically significant in the opinion of the Investigator;
3. Been diagnosed as having or having been treated for esophageal, gastric, pyloric channel or duodenal ulceration within 30 days prior to receiving the first dose of study medication;
4. Presence of more than moderate anemia (hemoglobin < 10 g/dL, hematocrit $< 30\%$);
5. Urinary incontinence;
6. A history of renal transplant;
7. If male, an inability to abstain from any sexual activity from 96 hours prior to admission to the unit and continuing throughout the entire length of the study;
8. A known hypersensitivity to NSAIDs, COX inhibitors, sulfonamides, intolerance to lactose or hereditary fructose intolerance;
9. A history of substance abuse, drug addiction or alcoholism within the last three years;
10. Used a tobacco product or consumed alcohol within 48 hours prior to the Pretreatment Period or was unable to abstain from tobacco and alcohol products throughout the entire length of the study;
11. Received any investigational medication within 30 days prior to the Treatment Period or was expected to receive any investigational medication during the study other than celecoxib; and
12. Been previously admitted to this study.

4.3.8 Dosage/ Administration

Patients were randomized to receive either celecoxib 200 mg BID, naproxen 500 mg BID or placebo for six consecutive days followed by a single morning dose on Day 7.

4.3.9 Duration/ Adjustment of Therapy

Patients withdrawn prior to beginning study medication (i.e., Day 1) were to have been replaced. Data collected for any such withdrawn patient was not included in the analyses. If patients withdrew for any reason after beginning study drug, he or she was also replaced, and their safety data were included in the analyses. Patients could have been withdrawn from this study for any of the following reasons:

1. The patient's serum creatinine increased by 50% over Pretreatment assessments;
2. The patient missed more than one dose of study drug;
3. The patient developed symptoms that required medical intervention;
4. The patient had two 24 hour urine samples during the Treatment Period that contained > 120 mEq sodium each;
5. The patient developed an intercurrent illness that required non-study drug;
6. The patient withdrew his/her consent;
7. The Investigator determined it to be in the patient's best interest; or
8. Searle discontinued the study.

Concomitant Medications

Use of any medication other than the drug provided for this study was to have been avoided, whenever possible, during the Treatment Period. Use of antineoplastic drugs and chronic analgesics were prohibited. Acetaminophen use was specifically discouraged. In the event that medications other than study drug was used, the drug name, dosage, regimen, reason for therapy and therapy dates were.

4.3.10 Safety and Efficacy Endpoints Measured

Table 4.3.10.1 Timetable for clinical observations and lab measurements in the study 036^a.

	PreTreatment Period					Treatment Period							Post-Treatment Period		
	-13 to -4	-3	-2	-1		1	2	3	4	5	6	7	8	9	10
Informed Consent	X														
History	X														
ECG	X														
Physical Exam	X			X											
Clinical/ Urine labs ^b	X					X		X ^c		c			X		
Serum TxB2, renin activity						X						X			
24 hr Urine Prostaglandins & 11-dehydro TxB2			X	X		X					X				
24 hr Urine Na, K, Crt						X						X			
GFR	X ^d					X						X			
Na, K Clearance						X						X			
Study Drug						X	X	X	X	X	X	X			
Plasma/ Urine PK						X						X	X	X	X
Collection of Signs/Sxs				X											

a. Data from NDA volume 1.139, table 1.

b. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, total protein, albumin, calcium, phosphorus, creatine kinase); and (3) Urinalysis (specific gravity, pH, RBC/hpf, protein, glucose, ketones, bilirubin).

c. BUN, Na, K, Crt only.

d. Cockcroft-Gault derived or using measured urine creatinine clearance.

4.3.11 Statistical Considerations

Demographics and Baseline Characteristics

All randomized patients were included in these analyses. Homogeneity across the three treatment groups in terms of gender and race were analyzed using Fisher's Exact Test. The Kruskal-Wallis Test was used to determine homogeneity across the treatment groups with respect to age, height, weight, and vital signs (blood pressure and pulse).

Patient Population Analyzed

Primary and secondary measures were analyzed using an Intent-to-Treat (ITT) Cohort, defined as all randomized patients who received at least one dose of study drug and were not withdrawn from the study. Additionally, the normalized GFR and secondary urinary fractional excretion variables (sodium and potassium) and creatinine clearances were also analyzed at 60 minute intervals using a Modified ITT Cohort, which excluded patients whose GFR could not be calculated due to missing urine or plasma inulin samples or exceeded 175 mL/min/1.73m².

Evaluation of Renal Function and Pharmacokinetic Measures

Descriptive statistics were computed for all primary and secondary variables. These statistics were presented by treatment group and time. Baseline biological variables were compared across treatment groups using the Kruskal-Wallis Test. All inferential analyses were two sided tests with alpha = 0.05. Statistical inferential comparisons were made between celecoxib 200 mg, naproxen 500 mg and placebo on the three primary variables: GFR, urinary PGE2 excretion, and urinary 6-keto-PGF1 alpha excretion. GFR was analyzed as the change from Day 1 predose to Day 7 postdose using 30- and 60 minute intervals. For the 30 minute intervals, 3 predose measurements and 6 postdose measurements were evaluated for both days. The mean of the three predose measurements served as the Baseline, and changes from Baseline were calculated for the six postdose time points. For the 60 minute intervals, one predose measurement and three postdose measurements were evaluated for both days. The predose measurement was the Baseline (0-60 minutes predose), and changes from Baseline were calculated for the three postdose timepoints. The major GFR analysis was a repeated ANOVA for Days 1 and 7.

4.3.11 Statistical Considerations (cont)

Three analyses were performed: the change for Day 1 postdose minus predose; the change for Day 7 postdose minus predose; and the change for Day 7 postdose minus Day 1 predose. The analysis model included treatment as the independent variable and the Baseline GFR as covariate. The protocol specified model with treatment, investigative site, and treatment by site interaction as factors was not used due to the small number of patients enrolled at the majority of investigative sites. Supportive analyses were performed using analysis of covariance (ANCOVA) at each of the postdose time points on Days 1 and 7. Paired treatment comparisons were performed using linear contrasts, and p-values were reported.

Urinary PGE2 and 6-keto-PGF1 alpha excretion were analyzed as the change from Baseline (Day -1) to Days 2 and 6. A repeated measures ANOVA (across Days 2 and 6) was performed using the change from Baseline. ANCOVA was computed separately for the change from Baseline to Days 2 and 6. The independent variables in the analysis models were the same as those described for GFR. Paired treatment comparisons were performed using linear contrasts.

Serum TxB2 and PRA were measured on Days 1 and 7 at 30 minutes predose and 4 hours postdose. ANCOVA was used for the change from Baseline (30 minutes predose); that is, postdose minus predose with the predose values as covariates. ANCOVA was employed separately for the two days. The independent variables in the analysis were the same as those for the GFR. The overall treatment comparison p-value was reported.

Fractional excretion of sodium and potassium, and creatinine clearances were analyzed separately as the change from Day 1 predose to Day 7 postdose. There were three predose measurements and six postdose measurements for both days for the 30 minute interval analysis, and there was one predose measurement and three postdose measurements for both days for the 60 minute interval analysis. The statistical methods were identical to those for GFR.

Urinary excretion of 11-dehydro TxB2 was measured on Days 2 and 6, and the statistical methods were identical to those for PGE2 and 6-keto-PGF1-alpha.

A discussion of the tools used for the pharmacokinetic analysis is deferred to the pharmacology reviewers.

Multiplicity

No adjustment for multiplicity was proposed.

Interim Analyses

There were no interim analyses.

Safety Analysis

Every randomized patient who received at least one dose of study drug was included in the safety analysis. All adverse events were coded and summarized by treatment group. The incidence of treatment-emergent adverse events was tabulated by treatment group and body system, and by frequency of treatment group. Using a paired t-test, clinical laboratory data were tested for significant changes within treatment groups from Baseline to Posttreatment (Day 8). Significant changes were tabulated by treatment group. Clinical laboratory data were summarized and treatments compared using the Kruskal-Wallis. Values outside the normal range were identified, and scatter plots were used to graphically depict results. Shift tables (below, within, and above the normal range) and the Stuart-Maxwell Test or McNemar's Test (depending on the number of non-zero cells) were used to determine significant distributional changes over the course of the study. Shifts in laboratory values were compared across treatments in terms of the number of patients showing an increase, decrease, and no change, with respect to the normal range, using a chi-square test. The following laboratory test values were considered clinically relevant and were summarized for each treatment:

AST (SGOT) and ALT (SGPT): $\geq 3 \times$ upper limits of normal value (ULN)

Alkaline Phosphatase: $\geq 1.25 \times$ ULN

Total Bilirubin: $\geq 1.5 \times$ ULN

Creatinine: $\geq 1.3 \times$ ULN

BUN: $\geq 2.0 \times$ ULN

Hematocrit: a decrease ≥ 5 percent points (relative to a patient's Baseline value)

Hemoglobin: a decrease ≥ 2 g/dL (relative to a patient's Baseline value)

WBC: $< 3000/\mu\text{L}$

Platelets: $< 100,000/\mu\text{L}$

4.3.12 Efficacy Outcomes for protocol 036

Primary Measures of Evaluation

The primary evaluation measures were:

1. GFR;
2. Urinary PGE2 excretion; and
3. Urinary 6-keto-PGF1-alpha excretion.

Secondary Measures of Evaluation

The secondary evaluation measures were:

1. PRA;
2. Serum TxB2 concentration;
3. Fractional sodium excretion;
4. Fractional potassium excretion;
5. Creatinine clearance;
6. Urinary 11-dehydro TxB2 excretion;
7. PK analysis; and
8. Safety measures.

4.3.12.1 Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the 75 subjects enrolled in study 036 are summarized below.

Table 4.3.12.1.1 Demographics of study 036^a.

Demographic	Placebo N=25	Celecoxib 200 BIDs N=23	Naproxen 500 BID N=27
Gender			
Male	9	12	15
Female	16	11	12
Race (n (%))			
Caucasian	12 (48%)	9 (39%)	18 (76%)
Black	12 (48%)	14 (61%)	8 (30%)
Hispanic	0 (0%)	0 (0%)	0 (0%)
Other	1 (4%)	0 (0%)	1 (4%)
Age (yrs) (Mean±sd)	66.8±11	63.2±11	65.1±11

a. Data from NDA volume 1.139, Table 4.

b. P value <0.001 comparing two GFRs for celecoxib 200 mg BID group.

In other data, the celecoxib group had significantly higher mean systolic BP (147.1±17 mm Hg) when compared with the placebo group (140.6±17 mm Hg). There was no significant differences in the mean weight, height, pulse rate, or diastolic BP. There was also no significant differences between the three groups with regard to other medical history, including renal disease, hypertension, and diabetes. Finally, baseline renal function, as assessed by 24 hour urine collections for Na, Cr, K, and volume, were not significantly different in the three study groups. As discussed in the previous trials, the subject-to-subject variability was quite large.

4.3.12.2 Disposition of Subjects

The table below shows the disposition of subjects in study 036.

Table 4.3.12.2.1 Summary of subjects entered into study 036^a.

	Placebo	Celecoxib 200 BID	Naproxen 500 BID
Entered	25	23	27
Completed	23 (92%)	22 (96%)	26 (96%)
Discontinued: Total	2 (8%)	1 (4%)	1 (4%)
Protocol Non-compliance	0 (0%)	1 (4%)	0 (0%)
AEs	2 (8%)	0 (0%)	1 (4%)
Other	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA volume 1.139, table 3.

4.3.12.2a Subject Selection

No information is available about subject selection in study 036.

4.3.12.2b Protocol Violations & Deviations

Per the sponsor, several of the subjects enrolled in the trial were later found not to have 'sufficient' renal insufficiency, as specified in the original protocol. A decision was made to allow such subjects in the trial, including subjects whose serum crt was ≤ 3.0 mg/dl. Overall 26 subjects violated one or more entry criteria (of the 75 total subjects!). The 26 subjects were in the following groups: 9 placebo patients; 7 SC-58635 200 mg BID patients; and 10 naproxen 500 mg subjects.

These violations fell into the following categories, and were felt not to be of sufficient severity to warrant removal from the study.

1) Two patients (one placebo patient and one SC-58635 200 mg BID patient) did not have renal disease, as originally defined as an elevated serum creatinine and specified GFR (Inclusion Criterion

2). Nineteen patients (six placebo patients, five SC-58635 200 mg BID patients, and eight naproxen 500 mg BID patients) did not have a GFR between 40- 60 mL/min/1.73m² based on the Cockcroft-Gault estimation, or a measured creatinine clearance (Inclusion Criterion 4).

3) Six patients (two placebo patients, two celecoxib 200 mg BID patients, and two naproxen 500 mg BID patients) did not have a serum creatinine (i.e., 1.3-2.5 mg/dL or 1.3-3.0 mg/dL males or females during the Pretreatment Period; Inclusion Criterion

4) Six patients (two placebo patients, two celecoxib 200 mg BID patients, and two naproxen 500 mg BID patients) did not have a body weight ≥ 50 kg and -20 to +40% of ideal body weight (Inclusion Criterion 7).

5) Two placebo patients and one celecoxib patient had moderate anemia as defined by a hemoglobin < 10 g/dL and hematocrit $< 30\%$ during screening or prior to entering the study.

6) One celecoxib patient had an SGPT > 1.5 ULN upon entry into the study. One celecoxib 200 mg BID patient (0007-0112) had two 24 hour urinary sodium excretion values that each were > 120 mEq.

4.3.12.2c Concomitant Therapies used after Trial Initiation

No concomitant medications were to be used during the trial, and such use constituted a protocol violation.

4.3.12.2d Analyses of Study 036 Trial Results

Primary study objectives

1. Compare the changes in GFR from pre- to post-dose measurements of Day 1 and Day 7 between celecoxib and naproxen treatment groups.

The effect of short-term administration of celecoxib on GFR was first analyzed by comparing the average GFRs taken before the first dose Days 1 and 7. The sponsor noted wide variability at the 30 minute time point, which was averaged with the pre-dose value to obtain the baseline GFR. To correct this, the results of 60 minute GFRs were analyzed with the pre-dose values in order to obtain a more satisfactory 'mean baseline GFR.' There were no significant differences between the study groups detected, and no significant decline in mean GFR detected in any dose group. When examined hour by hour (data not shown), no consistent effect of any drug or dose -group on GFR was detected. There was also no evidence of a temporal association between plasma levels of celecoxib and naproxen and changes in GFR.

Table 4.3.12.2d.1 Effect of celecoxib and naproxen on GFR in study 036^a.

	Placebo N=25	Celecoxib 200 BID N=23	Naproxen 500 BID N=27
Day One Pre-dose			
Mean \pm SD	31.8 \pm 8.6	31.5 \pm 16	36.9 \pm 12
Range	18 to 51	5 to 78	16 to 61
Day Seven Pre-Dose			
Mean \pm SD	34.4 \pm 16	35.4 \pm 14	37.0 \pm 16
Range	15 to 68	11 to 61	7 to 77

a. Data from NDA volume 1.139, table 10.

4.3.12.2d Analyses of Study 036 Trial Results

Primary study objectives (cont)

2. Compare the changes in urinary PGs (PGE₂ and 6-keto-PGF1-alpha, a metabolite of prostacyclin, PGI₂) from predose through pre-dose on Day 7, between the celecoxib and naproxen treatment groups.

Urinary PGE2

For urinary PGE2, there was a statistically significant difference between study drug groups between the Pre-dose values for Days 1 and 7. As shown in the table below, there was a significantly greater decrease in PGE2 excretion in the naproxen group from day one to day 6 than in the placebo group (shown as shaded). There was also a trend towards a decrease in the celecoxib group (within large standard deviations). No significant difference between the naproxen and celecoxib groups was detected.

Table 4.3.12.2.d.2 Effect of celecoxib and naproxen on PGE2 excretion in study 036^a.

	Placebo N=25	Celecoxib 200 BID N=23	Naproxen 500 BID N=27
Day One Pre-dose			
Mean	398.8±674	445.6±874	623.3±623
Range	55 to 3432	37 to 4766	18 to 12979
Day Six Pre-Dose			
Mean±SD	381.5±445	227.2±352	132.5±131
Range	81 - 2195	18 - 1639	11 - 454
Change from Baseline			
Mean±SD	-36.1±843	-231.8±568	-509.6±1398 ^b
Range	-3351 to +1889	-2666 to +191	-7169 to +40

a. Data from NDA volume 1.139, table 11.

b. P-value <0.05 using Repeated Measures ANOVA vs. placebo.

Urinary 6-keto-PGF1-alpha

Analysis of the 6-keto-PGF1-alpha excretion was again hindered by extremely wide subject to subject variability. This can be seen below in the wide standard deviations and ranges for the 6-keto-PGF1-alpha excretion (at Day -1 and 6). The table below shows the changes from baseline for the study groups at day 6. Despite the broad standard deviations and ranges of individual excretion rates, there was a significantly lower 6-keto-PGF1-alpha in both the celecoxib and naproxen groups, compared with placebo. There was no significant difference between the effects of celecoxib and naproxen.

Table 4.3.12.2.d.3 Effect of celecoxib/ naproxen on 6-keto-PGF1-alpha excretion in study 036^a.

	Placebo N=25	Celecoxib 200 BID N=23	Naproxen 500 BID N=27
Day One Pre-dose			
Mean	34.1±28	36.9±40	32.2±21
Range	0 - 137	6 - 147	7 - 105
Day Six Pre-Dose			
Mean±SD	37.9±23	14.8±12	11.2±13
Range	12 - 112	0 - 41	0 - 50
Change from Baseline			
Mean±SD	1.7±23	-23.2±37 ^b	-20.9±20 ^b
Range	-43 - +50	-124 - +19	-57 - +13

a. Data from NDA volume 1.139, table 10.

b. P-value <0.05 using Repeated Measures ANOVA vs. placebo.

4.3.12.2d Analyses of Study 036 Trial Results

Secondary study objectives:

1. Compare the changes in urinary 11-dehydro thromboxane A2 (TxA2) from baseline through day 6, between the celecoxib and naproxen treatment groups.

At day 6, the decrease in TxA2 excretion in the naproxen group was significantly greater than in either the placebo or the celecoxib group. The TxA2 excretion in the celecoxib group did not differ significantly from placebo, although there was a numerical decline in TxA2 excretion in the celecoxib group.

Table 4.3.12.2d.4 Effect of celecoxib and naproxen on TxA2 excretion in study 036^a.

	Placebo N=25	Celecoxib 200 BID N=23	Naproxen 500 BID N=27
Day Minus One Pre-dose			
Mean	1402±856	1558±1045	1299±736
Range	148 - 3471	318 - 4301	447 - 3941
Day Six Pre-Dose			
Mean±SD	1756±950	1572±1002	592±522
Range	677 - 3830	280 - 4792	168 - 2924
Change from Baseline			
Mean±SD	+305±1200	-38.7±651	-731.6±737
Range	-2204 - +3004	-1551 - +1203	-3100 - +719

a. Data from NDA volume 1.139, table 10.

b. P-value <0.05 using Repeated Measures ANOVA vs. placebo and vs. celecoxib.

2 Compare the changes in serum thromboxane levels through day 7, between the celecoxib and naproxen treatment groups.

Naproxen caused an immediate (4 hrs) and sustained (7 days) suppression of serum thromboxane levels that differed significantly from both celecoxib and placebo. Celecoxib had no significant effect on serum TxA2 levels. As before, there was a broad subject to subject variability.

Table 4.3.12.2d.5 Effect of celecoxib and naproxen on TxA2 serum levels in study 036^a.

	Placebo N=25	Celecoxib 200 BID N=23	Naproxen 500 BID N=27
Day Minus One Pre-dose			
Mean	55.1±74	33.7±68	64.6±86
Range	0 - 204	0 - 240	0 - 237
Day Six Pre-Dose			
Mean±SD	70.7±94	37.3±64	3.5±57
Range	0 - 325	0 - 188	0 - 19

a. Data from NDA volume 1.139, table 10.

b. P-value <0.05 using Repeated Measures ANOVA vs. placebo and vs. celecoxib.

4.3.12.2d Analyses of Study 036 Trial Results

Secondary study objectives:

3. Changes in plasma renin activity between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

At day one, plasma renin activity fell non-significantly by 4 hours after administration of either celecoxib or naproxen. At day seven, plasma renin activity fell non-significantly in the naproxen group (from 2.7 to 1.8), but rose slightly in the celecoxib group. There was no significant difference between the changes seen in either of the celecoxib groups and the naproxen group and placebo.

Table 4.3.12.2d.6 Effect of celecoxib and naproxen on plasma renin activity in study 036^a.

	Placebo N=23	Celecoxib 200 BID N=22	Naproxen 500 BID N=26
DAY ONE			
Baseline (30 mins Predose)			
Mean±SD	2.9±3.9	3.1±2.9	2.7±5.4
Range	0 - 12	0 - 12	0 - 27
DAY SEVEN			
Baseline (30 mins Predose)			
Mean±SD	4.6±8.4	2.2±1.7	1.8±3.9
Range	0 - 13	0 - 12	0 - 20

a. Data from NDA volume 1.139, table 15.

5. Changes in fractional urinary sodium and potassium clearances between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

Fractional excretion of sodium (FeNa)

The first table summarizes the changes in the FeNa from pre-dose day one to pre-dose day 7. For celecoxib and naproxen, FeNa rose significantly between the pre-dose on day one and the pre-dose on day 7. There was no significant difference between celecoxib and naproxen with regard to their effect on FeNa, measured from pre-dose day 1 to pre-dose day 7. The data are again made more difficult to interpret by subject-subject variability.

Table 4.3.12.2d.7 Effect of celecoxib and naproxen on fractional urinary sodium excretion (FeNa) in study 036^a.

	Placebo N=23	Celecoxib 200 BID N=22	Naproxen 500 BID N=26
PRE-DOSE DAY ONE			
Baseline (30 mins Predose)			
Mean±SD	0.0269±0.029	0.0276±0.000.027	0.0288±0.042
Range	0.006 - 0.134	0.003 - 0.115	0.005 - 0.207
PRE-DOSE DAY SEVEN			
Baseline (30 mins Predose)			
Mean±SD	0.023±0.024	0.0273±0.0.025	0.0406±0.0.055
Range	0.003 - 0.111	0.002 - 0.122	0.003 - 0.251
DIFFERENCE FROM DAY 7 TO PRE-DOSE DAY 1^b			
Mean±SD	-0.0077±0.029	+0.0077±0.022	+0.0052±0.02
P-value ^c	0.864	0.033	0.042

a. Data from NDA volume 1.139, tables 16 and 17.

b. Data from Pre-dose Day 1 and Day 7 (0 - 1 hour postdose).

c. Using paired T-test, per the sponsor.

4.3.12.2d Analyses of Study 036 Trial Results

Secondary study objectives (cont):

Fractional excretion of potassium (FeK)

The FeK tended to rise slightly in all active treatment groups from pre-dose day 1 to pre-dose day 7, and all in the placebo group. The administration of naproxen was associated with a non-significantly higher FeK than either of the celecoxib groups over the same period.

Table 4.3.12.2d.8 Effect of study drugs on fractional urinary K⁺ excretion (FeK) in study 036^a.

	Placebo N=23	Celecoxib 200 BID N=22	Naproxen 500 BID N=26
PRE-DOSE DAY ONE			
Baseline (30 mins Predose)			
Mean±SD	0.3157±0.17	0.3145±0.12	0.3217±0.21
Range	0.097 – 0.816	0.093 – 0.516	0.122 – 1.049
PRE-DOSE DAY SEVEN			
Baseline (30 mins Predose)			
Mean±SD	0.3729±0.22	0.3016±0.17	0.5814±0.58
Range	0.061 – 0.784	0.059 – 0.761	0.145 – 2.251
DIFFERENCE FROM DAY 7 TO PRE-DOSE DAY 1^b			
Mean±SD	-0.0111±0.11	+0.0503±0.15	0.1102±0.34
P-value ^c	0.571	0.372	0.139

a. Data from NDA volume 1.139, tables 16 and 17.

b. Data from Pre-dose Day 1 and Day 7 (0 – 1 hour postdose).

c. Using paired T-test, per the sponsor. Note that difference not calculated from pre-dose values on Days 1 and 7 above.

6. Changes in creatinine clearances between celecoxib and naproxen treatment groups predose and postdose on Day 1 and Day 7.

The table below summarizes the estimated creatinine clearance data from pre-dose Day one and 7, as well as the post-dose day 7, and a comparison of the changes in creatinine clearance from pre-dose day 1 to post-dose day 7. Note the large variability, both between subjects and from time point to time point (e.g.; from 60 minutes pre-dose to 30 minutes pre-dose). Note also that some of the estimated creatinine clearance values are supra-physiologic (e.g.; one subject had an estimated clearance of 323 at 60 minutes pre-dose on day 1). These problems confound interpretation of the data from the study.

Overall, there were no significant differences between treatment groups with regard to changes in creatinine clearance from pre-dose day 1 to day 7. The sponsor also looked at the short-term (hour to hour) effects of celecoxib and naproxen administration. In data not shown, there were no significant and clinically consistent effects detected.

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4.3.12.2d Analyses of Study 036 Trial Results

Table 4.3.12.2d.9 Effect of celecoxib and naproxen on creatinine clearance in study 036^a.

	Placebo N=23	Celecoxib 200 BID N=22	Naproxen 500 BID N=26
PRE-DOSE DAY ONE Baseline (60 mins Predose) Mean±SD Range	78.3±49 25 to 227	85.5±65 13 to 323	81.9±37 29 to 222
PRE-DOSE DAY ONE Baseline (30 mins Predose) Mean±SD Range	61.9±31 28 to 165	65.1±31 8 to 127	62.3±17 32 to 91
PRE-DOSE DAY ONE Baseline (0 mins Predose) Mean±SD Range	54.1±21 14 to 173	53.5±26 2 to 106	56.7±25 14 to 126
PRE-DOSE DAY SEVEN Baseline (60 mins Predose) Mean±SD Range	73.9±36 14 to 174	66.0±36 9 to 162	69.6±34 24 to 157
PRE-DOSE DAY SEVEN Baseline (30 mins Predose) Mean±SD Range	63.9±39 14 to 168	63.7±25 24 to 113	62.0±28 10 to 135
PRE-DOSE DAY SEVEN Baseline (0 mins Predose) Mean±SD Range	58.2±28 17 to 130	60.4±29 6 to 142	59.0±25 15 to 123
DIFFERENCE FROM DAY 7 TO PRE-DOSE DAY 1^b Mean±SD Range P-value ^c	-9.6±41 -83.7 to +115.5 0.289	-8.0±33 -99.8 to +53.6 0.280	-10.3±29 -105.9 to +59 0.086

a. Data from NDA volume 1.139, tables 16 and 17.

b. Data from Pre-dose Day 1 and Day 7 (0 – 1 hour postdose).

c. Using paired T-test, per the sponsor, using average of pre-dose values on Days 1 and 30 minute post-dose Day 7.

7. Safety and pharmacokinetics of celecoxib in subjects with stable chronic renal insufficiency.

The reader is referred to the pharmacologist's review for the examination of the pharmacokinetics of celecoxib.

4.3.13 Safety Outcomes

The adverse events, serious adverse events, and subject discontinuations are included in sections 8.1 and 8.2.

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below.

Table 4.3.13.1 Summary of subjects entered into study 036^a.

	Placebo	Celecoxib 200 BID	Naproxen 500 BID
Entered	25	23	27
Completed	23 (92%)	22 (96%)	26 (96%)
Discontinued: Total	2 (8%)	1 (4%)	1 (4%)
Protocol Non-compliance	0 (0%)	1 (4%)	0 (0%)
AEs	2 (8%)	0 (0%)	1 (4%)
Other	0 (0%)	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)
Serious Adverse Events	0 (0%)	0 (0%)	0 (0%)
Adverse Events^b	11 (44%)	9 (39%)	15 (56%)

a. Data from NDA volume 1.139, table 3 and table 25.

b. Counts all subjects who had at least one AE.

4.3.13.1 Comparisons of Defined Safety Endpoints

Due to the small sample size, no formal comparisons are performed. The adverse events are included in the overall safety analysis in section 8.1.

4.3.13.2 Comments on Specific Safety Parameters

Deaths

There were no deaths during the study.

Serious Adverse Events

There were no Serious Adverse Events reported during the study.

Discontinuations due to Adverse Events

Three patients withdrew from the study due to at least one adverse event: 2 (8%) placebo patients and 1 (4%) naproxen 500 mg BID patient. One placebo patient (0004-0051) withdrew from the study due to tinnitus, headache, and asthenia. One placebo patient (0007-0084) withdrew from the study due to confusion. One naproxen 500 mg BID patient (0007-0139) withdrew from the study due to urinary retention.

4.3.14 Study 036 Efficacy Summary

This study investigated the short-term effects of celecoxib and naproxen on several parameters of renal function and on the excretion of prostaglandins. The population studied were otherwise healthy individuals with stable, chronic renal insufficiency.

1. After 6 days, no effect of naproxen or celecoxib on GFR was detected (table 4.3.12.2d.1).
2. After 6 days, both celecoxib and naproxen inhibited urinary PGE₂ excretion. Due to wide patient variability, the effect of celecoxib was non-significant (table 4.3.12.2d.2).
3. After 6 days, both celecoxib and naproxen significantly inhibited urinary 6-keto-PGF₁-alpha excretion (table 4.3.12.2d.3). There was no significant difference between the effects of celecoxib and naproxen.
4. After 6 days, both celecoxib and naproxen significantly decreased urinary 11-dehydro-thromboxane A₂ excretion. With wide subject variability, only the naproxen effect achieved nominal significance (table 4.3.12.2d.4).
5. Naproxen caused an immediate and sustained decrease in serum thromboxane levels (table 4.3.12.2d.5). Celecoxib had no significant effect on serum thromboxane levels.
6. Between days one and day seven, serum renin activity fell in the naproxen group, but rose slightly in both the celecoxib and placebo groups. These changes were non-significant (table 4.3.12.2d.6).
7. Regarding the excretion of sodium and potassium, both tended to rise between days one and 7 in both celecoxib and naproxen-treated subjects.
8. Broad variability complicates interpretation of the GFR results (see table 4.3.12.2d.9). There was no trend towards any consistent effect.

4.3.15 Study 036 Safety Summary

1. There were no deaths and no Serious Adverse Event.
2. There were no incidences of acute renal failure.

4.3.16 Study 036 Reviewer's Conclusions

With regard to efficacy, this trial in subjects with stable, mild, renal insufficiency demonstrates that both naproxen and celecoxib inhibit the excretion of urinary prostaglandins (PGE₂, 6-keto-PGF₁) and thromboxanes (urinary 11-dehydro-thromboxane A₂). Naproxen also appears to decrease serum thromboxane levels. Both celecoxib and naproxen tended to increase sodium and potassium-excretion slightly. No significant effects of either naproxen or celecoxib on GFR were detected, in part due to wide subject variability.

As regards safety, the trial is underpowered to comment on the occurrence of common renal adverse events. No unexpected toxicities were detected.

5.0 to 5.2 Integrated Renal and Cardiac Safety Review for Celecoxib

The safety review is broken into three logical sections:

- 5.0 Methodologies used for Safety Review
- 5.1 Background Database for Safety Review
- 5.2 Summary of Safety Review

5.0 Methodologies Used for Renal and Cardiac Safety Review

5.0.1 Subsections of the Integrated Safety Review and Preliminary Comments

Section 4.0 will use the following outline:

- 1) Source materials for the safety review, including the numbers of subjects exposed in each of the treatment groups, along the extent of exposure;
- 2) General methodologies used to elicit adverse events within the database;
- 3) Specific search strategies used in the celecoxib database. This will include a discussion of the sponsor's decision to split the subjects receiving heparin into two groups for purposes of safety event comparison.

5.0.2 Source Materials and Methods for the Renal/ Cardiac Safety Review

The celecoxib NDA database includes a total of 29 clinical pharmacology and 22 phase II/III clinical efficacy trials. Of these, 13 clinical trials were performed to compare celecoxib with other NSAIDs. Three of these latter studies focused on the renal effects of celecoxib: study 010 (Renal effects in the elderly); study 033 (Na⁺/volume depletion and renal effects); and study 036 (Renal effects in chronic renal insufficiency). Detailed reviews of these three trials can be found elsewhere in this review/ consultation. Other individuals reviewed the remainder of the studies, and the reader is referred to those reviews for details on their efficacy results.

The database primarily used for the celecoxib renal/ cardiac safety review is drawn from the studies in OA and RA listed below. Less attention will be paid in this review to the data available from short-term administration of celecoxib in the post-surgical and dental pain trials. Where relevant the short-term database, including the surgical/ dental studies) will be specifically referred to. Additionally, the safety portions of the three 'renal' studies were reviewed individually above. Any pertinent findings from those safety reviews will be integrated into the discussion of individual adverse events in the relevant sections below.

No information from the long-term safety update was available for this review.

The next table summarizes the trials that will be emphasized for purposes of this review.

Table 5.0.2.1 Celecoxib phase II-III efficacy studies for OA and RA^a.

Study # /Duration	Short Title of Study	Included in N.A. Safety Database for Renal ISS ^b	Included in N.A. Controlled Trials ^c
020/ 12 weeks	Pivotal efficacy in knee OA	X	X
021/ 12 weeks	Pivotal efficacy/ UGI safety in knee OA	X	X
054/ 12 weeks	Pivotal efficacy in hip OA	X	X
060/ 6 weeks	Qday vs. BID efficacy	X	
087/ 6 weeks	QDay vs. BID efficacy	X	
013/ 2 weeks	Pilot OA efficacy	X	
047/ 4 weeks	Dose Ranging OA efficacy	X	
042/	International OA efficacy		
062/ 12 weeks	UGI safety vs. naproxen in OA & RA	X	
071/ 12 weeks	UGI safety vs. diclofenac and ibuprofen in OA & RA	X	
024	Long-term safety in OA & RA		
022/ 12 weeks	Pivotal efficacy/ UGI safety in RA	X	X
023/ 12 weeks	Pivotal efficacy in RA	X	X
012/ 4 weeks	Pilot RA efficacy	X	
041	International RA efficacy		
062/ 12 weeks	UGI safety vs. naproxen in OA & RA	X	
071/ 12 weeks	UGI safety vs. diclofenac and ibuprofen in OA and RA	X	
024	Long-term safety in OA and RA		

a. Data from NDA volume 1.3, table 2 and 125.

b. Database used for the sponsor's assessment of renal adverse event rates in the celecoxib database (NDA table 31.3.1).

c. Database used for the sponsor's assessment of laboratory changes in the controlled arthritis group (NDA table 25.1.1).

5.0.3 Extent of Subject Exposure to Study Drug

The dose and duration of exposure to celecoxib was discussed in section 3.1.1 above. Two of the summary tables from that section are included below, showing the numbers of subjects exposed to a given dose and time of celecoxib administration.

Dose and Duration Exposure to Celecoxib

As discussed above, the chronic exposure data comes from the trials in osteoarthritis (OA) or rheumatoid arthritis (RA). This will be the database used primarily for the assessment of renal and cardiac safety. The table below summarizes the duration of patient exposure in the OA/ RA database, broken into three categories: 0-6 weeks; 6 weeks to 6 months; and greater than 6 months. Note that there are very few subjects who received celecoxib with long-term (>180 days) exposure to celecoxib in a controlled trial (n=39). A larger number received celecoxib in open-label trials for >180 days (n=1809). This absence of long-term controlled data will limit the detection of AEs resulting from chronic exposure to celecoxib.

Table 5.0.3.1 (from table 3.1.3.2) Exposure to celecoxib, arranged by time-interval and dose in the NDA 20-998 OA/ RA database^a.

	25-50 mg	100 mg	200 mg	300 mg	400 mg	Total ^b
OR-RA Controlled Trials						
1-42 days	462	888	818	0	308	2476
32-180 days	481	1237	1836	0	307	3861
>180 days	0	0	39	0	0	39
OA-RA Uncontrolled (Open-Label) Trials						
1-42 days	110	1689	1527	768	200	4294
32-180 days	310	970	1509	451	489	3729
>180 days	0	236	941	222	410	1809
Total	1363	5020	6670	1441	1714	16208

a. Data from NDA 20-998, vol. 1.426, Table 3.4

b. There were 18 additional patients who received other doses (i.e., 200 mg in am, 300 mg in pm). These are included in the safety review but not this table.

The sponsor also summarized exposure to celecoxib in patient-years of exposure for all subjects in the arthritis trials through the NDA cutoff date of 11.21.97. The results are shown below.

Table 5.0.3.2 Duration of OA/ RA patient exposure to celecoxib, arranged by patient-years and dose, in the NDA 20-998 database^a.

	50 mg	100 mg	200 mg qD	200 mg BID	300 mg	400 mg	Any Dose ^b
OR-RA Controlled Trials	116	289	47	466	0	87	1020
OA-RA Uncontrolled (Open-Label) Trials	75	518	0	1271	340	465	2672
OA-RA Controlled & Uncontrolled Trials	117	680	47	1567	340	499	3267

a. Data from NDA 20-998, Integrated Summary of Safety, Table 4.3. Patients are counted only once per treatment group.

b. There were 18 additional patients who received other doses (i.e., 200 mg in am, 300 mg in PM). These are included in the safety review but not this table.

As discussed above, a subset of the OA/RA trials was used to construct the renal safety database prepared by the sponsor. In addition, a smaller # of the individuals were used for the detection of laboratory abnormalities (from the North American 12-week Arthritis Trials). The numbers of subjects for these two comparisons are listed below.

Table 5.0.3.3 Number of subjects in relevant subsets of the OA/ RA database for NDA 20-998^c.

Subset	Placebo	50 mg	100 mg	200 mg BID	400 mg BID	Active Control
12-Week N.A. Arthritis Trials^b	1080	658	1099	1087	419	1071
Renal Adverse Events Safety Database^a	1864	690	1779	1914	615	2098

a. Data from NDA 20-998, Renal Integrated Summary of Safety, Table 31.3.1. Includes studies 012, 013, 020, 021, 022, 023, 047, 054, 060, 062, 071, and 087. Additional subjects who received 25-50 mg are not shown in this table.

b. Data from NDA 20-998, Integrated Summary of Safety, Table 2.6. Includes studies 020, 021, 022, 023, and 054.

c. In many cases, the actual number of measurements available for a given measurement, especially a given laboratory measurement, is considerably less than the maximal number shown. See reviews of individual lab data for details.

5.0.4 General Methodologies Used for Safety Review

This section details the examination of AEs in the celecoxib safety database, with exclusive emphasis on the renal and cardiac AEs. In general, this was accomplished by examination of data from the Phase II-III trials, comparing the incidence of a given AE in the control group (either placebo or active control) with the group receiving celecoxib. Wherever possible, all AEs potentially linked to the administration of celecoxib are further examined for dose-, time-, sex-, age-, race-dependency. These examinations will be complicated by the different regimens employed in each of the trials for both the dose and duration of celecoxib. Due to time constraints, the majority of the datasets examined have been prepared by the sponsor, and no independent confirmation of their accuracy by this reviewer has been performed. Any primary analysis performed by FDA reviewers will be identified as such. Time constraints have also limited the examination of the individual Case Report Forms by this reviewer.

The time-dependency of an AE will be examined both in terms of the time of onset of a given AE, as well as the duration or severity of a given AE. When examining the association of drug administration to a given AE, increased significance will be given to AEs that occur during or shortly after study drug administration. For example, an AE that occurs 10 days after the end of celecoxib administration may be less likely to be related to drug administration than one that occurs during use of celecoxib.

5.0.4.1 Approach of the Sponsor to Eliciting Deaths and Serious Adverse Events

In the celecoxib NDA, an adverse experience (AE) was considered serious Adverse Events if it was fatal, life-threatening, permanently disabling, requiring prolonged hospitalization, was a congenital anomaly, a cancer, or an overdose.

Whether or not unexpected or considered to be associated with the use of the drug, were communicated to Searle or its designee immediately upon discovery of the event. The Searle monitor or designee then advised the Investigator regarding the nature of any further information or documentation that was required. The Investigator was instructed to promptly inform the Institutional Review Board of any adverse events that were considered to be serious and unexpected, and possibly related to the study drug.

Investigators were instructed to follow up all serious adverse events with appropriate medical management until they resolved.

Certain serious adverse events may not be reflected in the programmed tables or listings because, per protocol, they are not recorded in the clinical database. These include:

1. Events that occurred after a patient discontinued receiving study medication;
2. Events that were directly related to arthritis signs or symptoms that occurred in any study of arthritis patients. Investigators were instructed not to record such events as adverse events, since information related to signs and symptoms of arthritis was collected in the efficacy assessments. However, any such events that were serious were handled the same as any serious adverse event, and so narratives of these events are found in the relevant appendices.
3. Events occurring in the long-term open label trial between 11.21.97, and 5.1.98. The clinical database for this study includes only data from visits completed through 11.21.97. Therefore, serious adverse events occurring between this date and 5.1.98 are included in the appendix of MedWatch forms but not in the tables or listings.

5.0.4.2 Approach to Eliciting Adverse Events

1. General

Patients were evaluated at study visits, when they were assessed for adverse signs and symptoms that they had had since their last visit. All data on each treatment-emergent adverse event were recorded onto a case report form, along with the Investigator's opinions of:

1. whether there was a reasonable possibility that the event may have been caused by the drug (none, uncertain, or probable), and
2. the severity of the event: mild (causing no limitation of usual activities), moderate (causing some limitation of usual activities), and severe (causing inability to carry out usual activities).

In all studies, investigators were instructed to provide information concerning any findings that suggested significant hazards, contraindications, side effects, or precautions pertinent to the safety of celecoxib. In addition, Investigators were informed that an adverse event could include signs or symptoms, clinically significant laboratory abnormalities, or any abnormality detected during physical examination. In the arthritis studies, patients were asked whether they had any symptoms that were not related to their arthritis. Symptoms of arthritis of the type under study in a given trial were generally not considered as adverse events, since these findings were specifically addressed in the efficacy assessments. Any arthritis-related adverse events that met the criteria for a serious event, however, were handled and are summarized in this document the same way as other serious adverse events.

5.0.4.2 Approach to Eliciting Adverse Events (cont)

A note needs to be made regarding the detection of AEs that occur as the result of chronic exposure to study drug. As shown in section 4.0.3, there is very limited controlled data from subjects exposed to celecoxib for greater than 12 weeks. The incidence of common AEs that during long-term trials (i.e., myocardial infarction, elevated blood pressure), then, will be simply impossible to determine, since no comparison group is available. Uncommon severe AEs (i.e., vasculitis, pancytopenia) may be detected as occurring in the open-label data, although their incidence will likewise be impossible to determine.

A note also needs to be made concerning the choice of celecoxib dose used for the majority of the tables below. Given that this is a safety review, the strongest potential signal for drug toxicity is likely to be in the highest dose-group. This is particularly true in the controlled trials, where the duration of exposure is limited to 4-12 weeks. For this reason, the celecoxib 400 mg dose-group will be examined, as well as the data from the proposed doses for use (100 and 200 mg). Where relevant, the safety results from the lower doses will also be included. This will be especially important for any adverse events identified as potentially dose-related.

2. Laboratory Testing

Laboratory testing was performed according to standard laboratory practice; CLIA-approved central laboratories were used whenever possible. In all North American arthritis and analgesia studies, central laboratories analyzed all clinical laboratory samples (hematology, clinical chemistry, and urinalysis). Laboratory data were transferred to the sponsor electronically and merged into the study database. In the case of laboratory data that were obtained by a laboratory without the capacity to transmit data electronically, laboratory data were typed into databases from case report forms or from laboratory reports. All laboratory values were converted to SI units upon being entered into databases. For evaluation of clinical laboratory results, upper and lower limits representing values of potential clinical relevance were determined as were cutoff values considered to represent lower and upper extremes. These upper and lower mid-range and extreme values were developed following discussion with external safety consultants. The relevant values for this renal/ cardiac safety review are shown below. Note that there is no defined value for abnormal bicarbonate, as no bicarbonate levels were measured as part of the NDA.

Table 5.0.4.2.1 Cut-offs for abnormal lab detection in the NDA database^a.

Laboratory Test	Lower Extreme	Lower Mid-Range Limit	Higher Mid-Range Limit	Higher Extreme
Serum Chemistry				
Creatinine	N/A	N/A	176.8 µmol/L (2.0 mg/dl)	265.2 µmol/L (3 mg/dl)
BUN	N/A	N/A	9.3 mmol/L (28 mg/dl)	14.3 mmol/L (43 mg/dl)
Glucose	2.22 mmol/L	2.78 mmol/L	8.88 mmol/L	19.4 mmol/L
Uric Acid	119 µmol/L	148.7 µmol/L	475.8 µmol/L	713.8 µmol/L
Creatine Phosphokinase (CPK)	N/A	N/A	180 U/L	300 U/L
Sodium	120 mmol/L	135 mmol/L	145 mmol/L	160 mmol/L
Potassium	2.0 mmol/L	3.5 mmol/L	5.0 mmol/L	6.0 mmol/L
Chloride	75 mmol/L	90 mmol/L	110 mmol/L	130 mmol/L
Calcium	>15% below Baseline, or <1.7 mmol/L	2.0 mmol/L	2.74 mmol/L	3.74 mmol/L
Inorganic phosphorus	0.32 mmol/L	0.97 mmol/L	1.61 mmol/L	2.42 mmol/L
Cholesterol (total)	N/A	3.1 mmol/L	6.5 mmol/L	7.8 mmol/L
Urinalysis				
Protein	N/A	N/A	Trace	1+ (300 mg/24h)
Blood	N/A	N/A	Trace	1+
Glucose	N/A	N/A	Trace	1+ (1 g/24h)
pH	N/A	4.0	4.8	8.5
Specific gravity	N/A	1.003	1.030	1.040
RBC	N/A	0/hpf	5/hpf	10/hpf
WBC	N/A	0/hpf	10/hpf	20/hpf
Ketones	N/A	N/A	Trace	1+
Urine bilirubin	N/A	N/A	Trace	1+

a. Data from NDA Integrated Safety Summary, text table 3.

3. Extent of Laboratory Testing, Reporting and Follow-up for Abnormal Lab Values

Laboratory safety measurements (hematology, serum chemistry, urinalysis, and miscellaneous) were performed at intervals during the clinical trials reported in this submission. Since not all patients had all laboratory tests performed, the denominator for a laboratory adverse experience varies, and is the number of patients who had that laboratory test performed. The reporting of any laboratory adverse experience was always dependent on the individual investigator's assessment of its clinical importance. Thus, laboratory values within or outside the normal range could be interpreted as adverse by one investigator and not by another.

4. Vital Signs

The sponsor also established broad limits for abnormal vital signs, including weight. These are summarized below.

Table 5.0.4.2.2 Cut-offs for abnormal lab detection in the NDA database^a.

Laboratory Test	Lower Extreme	Higher Extreme
Systolic BP	15% decrease from Baseline	15% increase from Baseline
Diastolic BP	15% decrease from Baseline	15% increase from Baseline
Pulse rate	15% decrease from Baseline	15% increase from Baseline
Body weight	5% decrease from Baseline	5% increase from Baseline

a. Data from NDA Integrated Safety Summary, text table 4.

5.0.5 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

Adverse events were coded using the World Health Organization Adverse Reaction Terminology (WHOa.r.t.) dictionary. Conventions for assigning Included and Preferred Terms to certain events were adopted in order to ensure consistent coding of events among different studies and coders.

Included in this review of renal and cardiac safety will be all adverse events referable to either of those two body systems as mapped by WHO. In addition, adverse events related to the lab values listed above, as well as changes in vital signs (weight, pulse rate, blood pressure) will also be investigated.

5.0.6 Specific Search Strategies Unique to the Celecoxib Renal/ Cardiac Safety Review

This review will focus entirely on those adverse events, including deaths, SAEs and lab abnormalities, relevant to cardiac and/or renal safety.

The majority of the estimates of incidence of specific AEs will be based on the pooled data from the phase II-III studies done in OA and RA. This is based on the homogeneity of the patient population entered into those trials. The long-term open-label study will be critical in evaluating the occurrence of AEs that require longer periods of drug exposure, even though no placebo or control group is available. Time limitations will limit the exploration for drug-disease, drug-drug, and drug-demographic interactions with celecoxib as they concern renal and cardiac toxicity.

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5.1 Background Database for Safety Review

For the purposes of this section, the primary analysis will compare the incidence of AEs and SAEs in the database between three groups: celecoxib alone, active control, and placebo.

In the integrated safety summary, adverse events will be examined in the following order:

- 1) Deaths,
 - 2) Serious Adverse Events (SAEs),
 - 3) Adverse Events (AEs) related to clinical findings,
 - 4) Adverse Events related to laboratory findings and special examinations,
- and
- 5) Subject discontinuations.

Following this, the occurrence of AEs in subjects with pre-existing renal or cardiac disease will be examined, including the safety database from the three 'Renal' trials. The datatables below have been submitted to the sponsor to allow for correction of typographical or other errors of presentation.

5.1.1 Deaths in the celecoxib safety database

Deaths will be examined first in the overall database, and then in each trial as relevant.

5.1.1.1 Integrated data on deaths in the celecoxib database

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 one of this consult (section 6.1).

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. Based on review of the individual case report forms and summaries by the medical reviewer, and discussion with the sponsor, the individuals in bold letters died of cardiovascular disease.

Table 5.1.1.1.1 Deaths during controlled trials in the NDA 20-998 database^a.

Subject #	Age/ Sex	Treatment	Duration of Tx	Cause of Death
Deaths During Study Drug Administration				
071-US0382-65811310	78/M	Ibuprofen 800 mg TID	29	Obstructive pulmonary disease
062-US0117-46761235	68/M	Naproxen 500 mg BID	63	Brain-stem infarct
021-US0191-1334	67/M	Naproxen 500 mg BID	47	Pulmonary embolus
071-US0333-46521451	53/F	Diclofenac 75 mg BID	1	Hypertensive cardiovascular disease
041-BE0002-0010	70/M	Celecoxib 200 mg BID	81	Gallbladder carcinoma with liver metastasis
087-US0021-0182	56/M	Celecoxib 200 mg QD	30	Arteriosclerotic cardiovascular disease
Deaths After Study Drug Discontinuation				
020-US0052-0683	62/F	Celecoxib 100 mg BID	26/ 54	Pulmonary carcinoma
020-US0033-0768	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 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 5.1.1.1.2 Deaths during the long-term open-label trial prior to database cutoff date of Nov. 21, 1997^a.

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
Celecoxib 200 mg 024-US0023--0230020	76/M	Celecoxib 200 mg BID	45	MI, cardiac failure
024-US0053--0530001	80/M	Celecoxib 200 mg BID	159	Massive coronary
024-US0058--0580018	59/M	Celecoxib 200 mg BID	246	Ischemic heart disease
Celecoxib 300 mg 024-US0052--0520043	83/F	Celecoxib 300 mg BID	193	Coronary thrombosis
024-US0121--1210052	52/M	Celecoxib 300 mg BID	114	MI
024-US0066--0660004	60/M	Celecoxib 400 mg BID	155	Adenocarcinoma
Celecoxib 400 mg 024-US0073--0730060	84/F	Celecoxib 400 mg BID	243	Respiratory failure, CHF
024-US0024--0240004	58/M	Celecoxib 400 mg BID	273	MI
024-US0001-0010053	65/F	Celecoxib 400 mg BID	196	Myocardial rupture post-MI
024-CA0139--139009	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. All were due to cardiovascular disease (and are shown in bold letters).

Table 5.1.1.1.3 Deaths during the long-term open label trial after cutoff Date of Nov. 21, 1997^a.

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
024-US0116-1160042	78/F	Celecoxib 200 mg BID	88	Aortic Aneurysm
024-US0001-0010076	74/M	Celecoxib 400 mg BID	336	Heart block
024-US0024-0240024	71/M	Celecoxib 400 mg BID	32	Coronary artery disorder
024-US0073-0730189	71/F	Celecoxib 400 mg BID	37	MI
024-US0110-1100006	61/F	Celecoxib 400 mg BID	471	MI

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

Finally, there were five deaths that occurred more than 28 days after last dose in any study reported in this New Drug Application (note that the two patients in the 020 trial are included in table 5.1.1.1 above. Two of these patients died after participation in trial 020 and three died following participation in Study 024 (long-term, open-label trial). Of the five celecoxib subjects in this group, two died of cardiovascular disease (40%).

Table 5.1.1.1.4 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
020-US0052-0683	62/F	Celecoxib 100 mg BID	6	54	Pulmonary carcinoma
020-US0033-0768	80/F	Celecoxib 200 mg BID		45	MI
024-CA0087-0870100	66/M	Celecoxib 200 mg BID	73	29	Sepsis, pneumonitis
024-US0042- 0420004	77/F	Celecoxib 200 mg BID	11	36	Pulmonary carcinoma
024-US0027- 0270004	66/M	Celecoxib 400 mg BID	34		Anterior MI

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

5.1.1.2 Mortality Rate due to Cardiovascular Disease and for Total Mortality

1. Total Mortality

Depending on the population used for the denominator, mortality can be calculated in two ways using the information from the celecoxib database, summarized above.

The first way uses the number of subjects exposed to the drug in each treatment group, independent of the duration of that exposure.

Table 5.1.1.2.1 Calculation of crude mortality incidence in deaths per patients exposed in NDA 20-998^a.

Population	Number of Deaths	Number of Exposed Subjects	Crude Mortality Incidence
Controlled N.A. OA/RA Trials			
Deaths during trial			
Placebo	0	1864	0%
Celecoxib	2	6376 ^e	0.03%
Active Control	4	2768	0.14%
All known deaths^b			
Placebo	0	1864	0%
Celecoxib	4	6376 ^e	0.06%
Active Control	4	2768	0.14%
Long-term, Open-label Trial			
Deaths before cut-off date	10	5155	0.19%
Known deaths during celecoxib use	15 ^d	5155	0.29%
All known deaths^c	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 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after cut-off date (11.21.97).

e. Number equals the total number of individual patients in the OA and RA trials (4151 and 2086, see table 3.1.2.1).

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

Table 5.1.1.2.2 Calculation of mortality rate in deaths per patient-years of exposure in NDA 20-998^a.

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

c. 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 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97).

e. Data from table 3.1.3.3 and from sponsor at request of reviewer.

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2. Cardiovascular Mortality

In similar fashion, the mortality rate due to cardiovascular disease can be calculated. The deaths attributed to cardiovascular disease were highlighted in the tables of deaths above, as determined by review of the sponsor-generated narrative summaries and the case report forms.

Cardiovascular mortality per patients exposed

Table 5.1.1.2.3 Calculation of crude cardiovascular mortality incidence in deaths per patients exposed in NDA 20-998^a.

Population	# of Deaths	# of Exposed Subjects	Mortality Incidence
Controlled N.A. OA/RA Trials			
Cardiac deaths during trial			
Placebo	0	1864	0.00%
Celecoxib	1	6376 ^e	0.02%
Active Control	2	2768	0.07%
All known cardiac deaths^b			
Placebo	0	1864	0.00%
Celecoxib	2	6376 ^e	0.03%
Active Control	2	2768	0.07%
Long-term, Open-label Trial			
Cardiac deaths before cut-off date	9	5155	0.17%
Known deaths during celecoxib use	14 ^d	5155	0.27%
All known cardiac deaths ^c	15	5155	0.29%

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.

c. 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 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after cut-off date (11.21.97).

e. Number equals the total number of individual patients in the OA and RA trials (4151 and 2086, see table 3.1.2.1).

Cardiovascular mortality in deaths per patient-years of exposure

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

Table 5.1.1.2.4 Calculation of cardiovascular mortality rate in deaths per patient-years of exposure^a.

Population	# of Deaths	Patient-years of Exposure ^e	Mortality Rate
Controlled N.A. OA/RA Trials			
Cardiac deaths during trial			
Placebo	0	208	0.00%
Celecoxib	1	1020	0.10%
Active Control	2	535	0.37%
All Known Cardiac Deaths^b			
Placebo	0	208	0.00%
Celecoxib	2	1020	0.20%
Active Control	2	535	0.37%
Long-term, Open-label Trial			
Cardiac deaths before cut-off date	9	2672	0.33%
Known deaths during celecoxib use	14 ^d	4274	0.33%
All known cardiac deaths ^c	15	4274	0.35%

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.

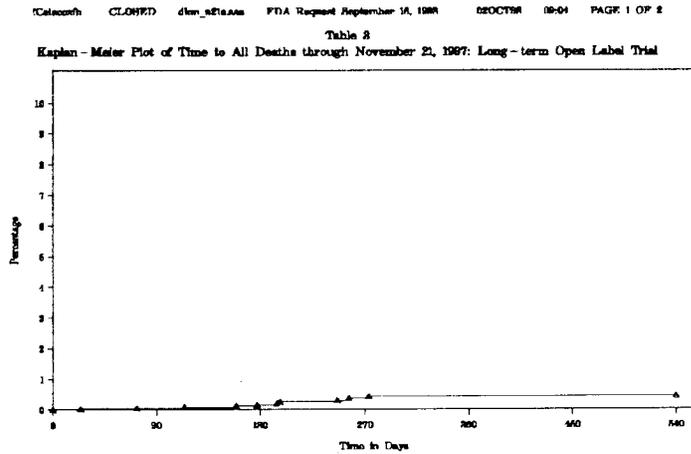
c. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97). Also includes three deaths that occurred >28 days after last reported use of celecoxib (see tables 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date (11.21.97).

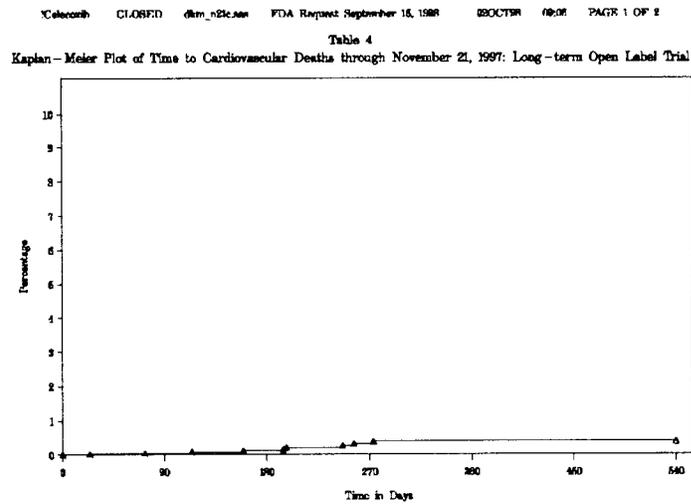
e. Data from table 3.1.3.3 and from sponsor at request of reviewer.

At this reviewer's request, the sponsor obtained Kaplan-Meier curves for both all-cause and cardiovascular mortality. These curves allow the reader to look at the relationship between duration of exposure to drug and time of death, to look for clustering of deaths, which might suggest a common etiology of death related to drug-exposure. Given the small number of deaths in the controlled-trial 12-week database, those curves are not enlightening and are not shown here.

The first curve below shows the survival analysis for all-cause mortality from the long-term trial, through November 22, 1997.



The next curve shows the Kaplan-Meier plot of time to death for the cardiovascular deaths in the open-label trial. Deaths were identified as cardiovascular by the Medical Reviewer through review of case report forms and discussion with sponsor.



Finally, the sponsor derived a Kaplan-Meier plot of all known and cardiovascular deaths, including those that occurred more than 28 days after discontinuation of celecoxib. These curves, like those above, show a broad scatter of time to death relative to the duration of exposure to celecoxib.

Table 7
Kaplan-Meier Plot of Time to All Deaths through May 1, 1998: Long-term Open Label Trial
Includes death occurred greater than 28 days after last dose

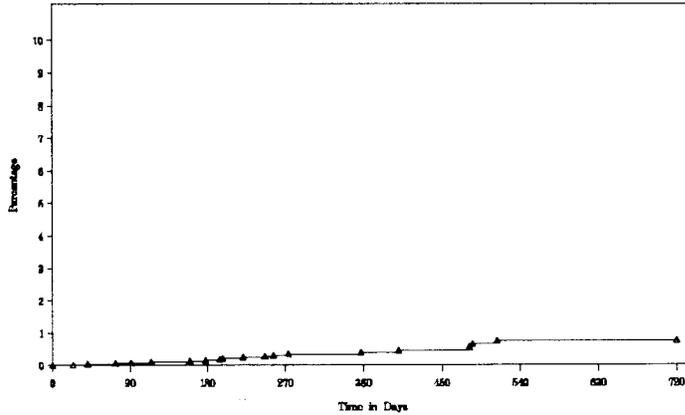
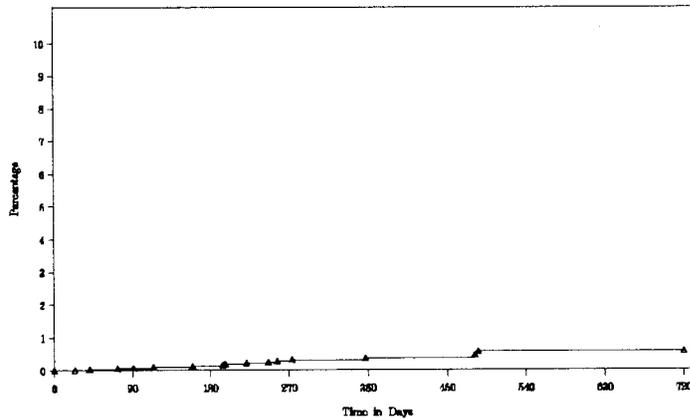


Table 8
Kaplan-Meier Plot of Time to Cardiovascular Deaths through May 1, 1998: Long-term Open Label Trial
Includes death occurred greater than 28 days after last dose



The Kaplan-Meier plots can also be used to derive cumulative incidence rates for all-cause and cardiovascular mortality (chosen at 24 and 52 weeks). The first table comes from the controlled-trial OA/RA database.

Table 5.1.1.2.5 Kaplan-Meier estimates for cumulative incidence rates for all mortality in the North American OA/ RA trials^a.

Controlled Studies (24 weeks)	All-Cause Deaths (n, %)	Cardiovascular Deaths (n, %)
Deaths ≤28 days after last dose of study drug		
Placebo	0 (0%)	0 (0%)
Celecoxib	2 (0.38)	1 (0.02%)
Active Control	4 (0.26%)	2 (0.12%)
All deaths		
Placebo	0 (0%)	0 (0%)
Celecoxib	4 (0.45%)	2 (0.05%)
Active Control	4 (0.22%)	2 (0.10%)

a. Data from sponsor-derived plots.

The next table comes from the long-term trials, using various cut-offs for inclusion.

Table 5.1.1.2.6 Kaplan-Meier estimates for cumulative incidence rates for cardiovascular mortality in the open-label, long-term trial (024)^a.

Long-term Open-Label Study(52 wks)	All-Cause Deaths (n, %)	Cardiovascular Deaths (n, %)
Deaths ≤28 days after last dose of study drug		
As of 11.21.97	10 (0.43%)	9 (0.39%)
As of 5.1.98	15 (0.38%)	14 (0.35%)
All deaths		
As of 5.1.98	18 (0.41%)	14 (0.35%)

a. Data from sponsor-derived plots.

Finally, it is possible to look at the mortality rate per patient-yr of exposure in the long-term trial, arranged by highest dose of celecoxib used by each patient prior to death. The small numbers of patients obviously make interpretation of such calculated rates difficult. Since all of the patients in this group died of cardiovascular causes, the total mortality and the cardiovascular mortality rates are the same.

Table 5.1.1.2.7 Calculation of cardiovascular mortality rates in deaths per patient-years of exposure, arranged according to highest dose of celecoxib received, from the long-term trial^{a,b}.

Celecoxib Dose	Number of Deaths	Patient-years of Exposure ^d	Crude Mortality Rate ^c
100 mg	0	519	0%
200 mg	4	1271	0.31%
300 mg	2	340	0.59%
400 mg	3	465	0.64%

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

b. Data shown for deaths that occurred prior to cut-off date 11.21.97.

c. Mortality (for both total and cardiovascular deaths) in deaths/pt-yrs (x100).

d. Data from ISS, Appendix table 4.3.

5.1.2 Other Serious Adverse Events (SAEs) in the Phase II-III Safety Database

The SAEs in the database were analyzed in several different ways by the sponsor. For the discussion below, the initial examination will be of the combined North American OA/RA trials. Next, the SAEs reported during the long-term, open-label trials will be summarized. Finally, the SAEs collected by the sponsor and felt to be related to renal AEs will be summarized.

Table 5.1.2.1 Serious cardiac and renal adverse events collected in the North American Arthritis trial database^a.

Body System/ SAE	Placebo N=1864	Celecoxib 25-400 mg N=5083	Active Controls N=2098
Total # with SAEs	30 (1.6%)	75 (1.5%)	39 (1.9%)
Body as a whole	3 (0.2%)	9 (0.2%)	5 (0.2%)
Sudden Death	0 (0%)	0 (0%)	1 (<0.1%)
Chest pain	0 (0%)	3 (<0.1%)	0 (0%)
Cardiovascular System	1 (<0.1%)	5 (0.1%)	2 (0.1%)
Angina, unstable	0 (0%)	1 (<0.1%)	1 (<0.1%)
Heart failure	1 (<0.1%)	3 (<0.1%)	0 (0%)
Myocardial infarction	2 (0.1%)	8 (0.1%)	2 (0.1%)
Rhythm Disturbances^b	1 (<0.1%)	5 (0.1%)	2 (0.1%)
Hypertension^c	0 (0%)	3 (<0.1%)	0 (0%)
Hypotension	0 (0%)	0 (0%)	1 (<0.1%)
Urinary System	2 (0.1%)	3 (<0.1%)	2 (0.1%)
Renal Failure	0 (0%)	0 (0%)	0 (0%)

a. Data from NDA Integrated Safety Summary, Appendix Table 22.1, 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 the following terms: arrhythmia; atrial arrhythmia; atrial fibrillation; heart block; palpitation; and supraventricular tachycardia.

c. Includes hypertension and aggravated hypertension.

The next table shows the incidence of relevant serious adverse events that occurred in the long-term, open-label celecoxib trials.

Table 5.1.2.2 Serious renal and cardiac adverse events collected in long-term, open-label database^a.

Body System/ SAE	Combined N=4499
Total # with SAEs	244 (5.4%%)
Body as a Whole	
Death	1 (<0.1%)
Chest pain	6 (0.1%)
Cardiovascular System	
Angina, unstable	5 (0.1%)
Heart failure (left or right)	6 (0.1%)
Cardiac Arrest	1 (<0.1%)
Myocardial infarction^b	16 (0.4%)
Bradycardia	2 (<0.1%)
Atrial Fibrillation	4 (<0.1%)
Ventricular Fibrillation	1 (<0.1%)
Urinary System	
Renal Failure	1 (<0.1%)
Bladder Carcinoma	3 (0.1%)
Renal Calculus	2 (<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.

The sponsor also collected those SAEs they felt potentially linked to renal disease. These are listed below. Note that several of the celecoxib events are primarily related to excess fluid retention. The relative incidence rates for the placebo, celecoxib and active control groups were 2/1864 (0.05%), 7/5083 (0.14%) and 1/2098 (0.05%). Narratives for all of the listed patients can be found Appendix two, section 10.1 of this review.

Examination of the SAEs from the International trials and from the Pain trials (not shown) revealed no unanticipated SAEs, or SAEs occurring at significantly different frequencies from those listed in the North American OA/RA trials. Time constraints prevented the reviewer from examining the Case Report Forms for each patient.

Table 5.1.2.3 Renal and Cardiac SAEs in the celecoxib database^a.

Serious Adverse Event	Patient #	Age/ Sex	Treatment	Stopped Tx?
Controlled Trials				
Aggravated hypertension	071-US0016-76132005	62/F	Celecoxib 200 mg BID	No
Aggravated Hypertension	062-US0265-54241602	40/F	Celecoxib 200 mg BID	No
Cardiac failure	021-US0113-0139	81/F	Celecoxib 200 mg BID	Yes
Cardiac failure	054-US0016-1467	66/F	Placebo	Yes
Cardiac failure	060-US0198-0214	76/M	Celecoxib 100 mg BID	Yes
Hypertension	022-US0114-0683	54/F	Celecoxib 400 mg BID	Yes
Renal calculus	022-US0114-0345	62/M	Placebo	Yes
Renal calculus	071-US0354-56553061	27/F	Celecoxib 200 mg BID	Yes
Pyelonephritis	071-US0267-77861660	51/F	Ibuprofen 800 mg BID	Yes
Uremia	047-US0033-0030	70/F	Celecoxib 400 mg BID	Yes
Long-term Open Label Trial				
Acute renal failure	024-US0149-1490002	65/M	Celecoxib 200 mg BID	Yes
Aggravated hypertension	024-US0005-0050022	71/F	Celecoxib 100 mg BID	No
Respiratory failure	024-US0006-0060001	71/M	Celecoxib 300 mg BID	Yes
Prostatic disorder	024-US0002-0020014	66/M	Celecoxib 300 mg BID	No
Hydronephrosis	024-US0074-0740011	71/F	Celecoxib 300 mg BID	Yes
Hypokalemia	024-US0013-0130009	78/F	Celecoxib 200 mg BID	No
Hyponatremia	024-US0033-0330007	72/F	Celecoxib 300 mg BID	Yes
Pyelonephritis	024-US0030-0300024	70/F	Celecoxib 200 mg BID	No
Pyelonephritis	024-US0007-0070058	55/F	Celecoxib 100 mg BID	Yes
Renal calculus	024-US0001-0010016	43/M	Celecoxib 200 mg BID	Yes
Renal calculus	024-US0009-009037	58/F	Celecoxib 200 mg BID	No
Renal colic	024-US0043-0430011	53/F	Celecoxib 100 mg BID	No

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

5.1.3 Clinical Adverse Events (AEs) from the Celecoxib Safety Database

The adverse experience tables below present the percentages of subjects having at least one adverse event on treatment during the adverse experience reporting period of each trial. A subject may be counted more than once if he/she had multiple adverse experiences classified in more than one body system. However, a given patient is counted only once in the overall total and once in any particular body system, regardless of how many clinical adverse experiences were reported in that body system. Similarly, a subject who reported multiple occurrences of the same adverse event appears only once for that particular adverse event.

The list of adverse events is, again, focused on cardiovascular and renal AEs. For some categories, this reviewer has combined more than one type of AEs (in particular, the AEs relating to edema). The shaded boxes represents AEs where there is $\geq 2X$ difference between the celecoxib groups and either of the placebo or active control groups, and where the minimal incidence rate was 0.1%. The celecoxib data are presented in two columns. First, the incidence of AEs from all subjects who received celecoxib in the database. The data focusing on the AEs in the 100-200 mg dose group are also presented. Examination of the AEs from the International trials and from the Pain trials revealed no unanticipated AEs, or AEs occurring at significantly different frequencies from those listed in the North American OA/RA trials below. The incidence of peripheral edema was significantly greater in the celecoxib when compared with placebo ($p=0.007$).

Table 5.1.3.1 Adverse events in the North American Arthritis trials of celecoxib from NDA 20-998^a. Part one: Cardiovascular AEs.

Clinical AE	Placebo N=1864	Celecoxib 25- 400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Subjects with an AE	1018 (55%)	3451 (63%)	2503 (60%)	1399 (67%)
Body as a Whole				
Chest Pain	14 (0.8%)	40 (0.7%)	33 (0.9%)	16 (0.8%)
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%)
Cardiovascular System				
Sudden Death	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)
Cardiac Failure ^b	1 (<0.1%)	5 (0.1%)	4 (0.1%)	2 (0.1%)
Heart Valve Disorder	0 (0%)	4 (<0.1%)	3 (0.1%)	3 (0.1%)
Hypertension ^c	12 (0.6%)	64 (1.1%)	55 (1.6%)	20 (1.0%)
Hypotension	1 (<0.1%)	1 (<0.1%)	0 (0%)	4 (0.2%)
Hypotension, Postural	0 (0%)	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Syncope	2 (0.1%)	3 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Arrhythmia ^d	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 (0.2%)
Tachycardia ^e	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%)
Myocardial, Pericardial and Valve Disorders				
Angina Pectoris ^f	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%)
Pericarditis	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)
Myocardial Infarction (MI) ^g	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.

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

c. Includes both undifferentiated hypertension and aggravated hypertension.

d. Includes undifferentiated arrhythmia, atrial and ventricular arrhythmia.

e. Includes undifferentiated and supraventricular tachycardia.

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

g. Includes 'Thrombosis, coronary'.

Table 5.1.3.1 (cont) Adverse events in the North American Arthritis trials of celecoxib from NDA 20-998^a
Part two: Renal AEs.

Clinical AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=3512	Active Controls N=2098
Renal System				
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%)
Renal Calculus	1 (<0.1%)	7 (0.1%)	5 (0.1%)	2 (0.1%)
Urinary Abnormalities				
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%)
Urinary Tract Infection	16 (0.9%)	63 (1.1%)	44 (1.1%)	27 (1.3%)
Urinary Incontinence	3 (0.2%)	5 (0.1%)	5 (0.1%)	3 (0.1%)
Metabolic Abnormalities				
Hypercalcemia	1 (<0.1%)	5 (0.1%)		1 (0.1%)
Hyperchloremia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hyperkalemia	0 (0%)	5 (0.1%)	3 (<0.1%)	0 (0%)
Hypernatremia	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)
Hyperuricemia	2 (0.1%)	6 (0.1%)	4 (0.1%)	0 (0%)
Hypocalcemia	0 (0%)	2 (<0.1%)		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%)
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.

The above table of AEs draws from the short-term arthritis trials. The table below summarizes the incidence data on AEs in the long-term open-label trial. The same conventions in the previous two tables apply.

Table 5.1.3.2 Renal and cardiovascular adverse events in the long-term, open-label trial of celecoxib (024) from NDA 20-998^a Part one: Cardiovascular AEs.

Clinical AE	Celecoxib 25-400 mg N=4499
Subjects with a clinical AE	3327 (73.9%)
Body as a Whole	
Chest Pain	70 (1.6%)
Edema, Generalized	26 (0.6%)
Edema, Facial	13 (0.3%)
Edema, Peripheral	172 (3.8%)
Edema, Tongue	4 (<0.1%)
Edema, All Categories	285 (6.3%)
Cardiovascular System	
Sudden Death	1 (<0.1%)
Cardiac Failure ^b	11 (0.2%)
Heart Valve Disorder	8 (0.2%)
Hypertension ^c	110 (2.4%)
Hypotension	4 (<0.1%)
Syncope	9 (0.2%)
Arrhythmia ^d	10 (0.2%)
Atrial fibrillation	9 (0.2%)
Bradycardia	3 (<0.1%)
Tachycardia ^e	24 (0.5%)
Palpitations	19 (0.4%)
Ventricular arrhythmia	1 (<0.1%)

Table 5.1.3.2 Adverse events in the long-term, open-label trial of celecoxib from NDA 20-998^a Part two: Cardiac and Renal AEs.

Clinical AE	Celecoxib 25-400 mg N=4499
Myocardial, Pericardial and Valve Disorders	
Angina Pectoris ^f	35 (0.8%)
Coronary Artery Disorder	16 (0.4%)
Pericardial Effusion	1 (<0.1%)
Myocardial Infarction (MI) ^g	19 (0.4%)
MI + Coronary Artery Disorder	35 (0.8%)
Renal System	
Uremia	0 (0%)
BUN Increased	14 (0.3%)
Nephritis	1 (<0.1%)
Cystitis	45 (1.0%)
Renal Calculus	11 (0.2%)
Urinary Abnormalities	
Albuminuria	23 (0.5%)
Hematuria	23 (0.5%)
Pyuria	8 (0.2%)
Urinary Tract Infection	142 (3.2%)
Urinary Incontinence	9 (0.2%)
Metabolic Abnormalities	
Hypercalcemia	4 (<0.1%)
Hyperchloremia	2 (<0.1%)
Hyperkalemia	6 (0.1%)
Hypernatremia	2 (<0.1%)
Hyperuricemia	14 (0.3%)
Hypocalcemia	2 (<0.1%)
Hypokalemia	16 (0.4%)
Hyponatremia	3 (<0.1%)
Hypophosphatemia	0 (0%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from trial 024.

5.1.4 Adverse Events Related to Laboratory Findings

5.1.4.1 Standard Analyses and Explorations of Laboratory Data

Laboratory data are presented in this section in three ways: 1) incidence of extreme laboratory values; 2) comparison of mean laboratory values; and 3) shifts of laboratory values among the five categories defined by the extreme and mid-range high and low values for each laboratory test. Shown are the incidence of extreme values at any time during the trial. In this short-term database, there were relatively few extreme values.

Incidence of extreme laboratory values

The summary data below comes from the North American OA/RA trials. An examination of the labs from the smaller International trials, comparing celecoxib with active control, and from the Pain trials revealed no lab abnormalities occurring at significantly different frequencies from those below.

Table 5.1.4.1.1 Incidence of extreme renal lab values in the controlled North American Arthritis trials of celecoxib from NDA 20-998^a.

	Placebo N=1080 ^b	Celecoxib 400 mg N=3250 ^c	Active Controls N=1060 ^d
Lab Test, Low Extreme Criteria			
Sodium <120 mmol/L	0 (0%)	0 (0%)	0 (0%)
Potassium <2 meq/L	0 (0%)	0 (0%)	0 (0%)
Chloride <75 mmol/L	0 (0%)	0 (0%)	0 (0%)
Calcium <1.7 or 15% decrease from baseline	0 (0%)	2 (0.1%)	1 (<0.1%)
Phosphate <0.32 mmol/L (<1 mg/dl)	0 (0%)	0 (0%)	0 (0%)
Lab Test, High Extreme Criteria			
Creatinine >265.2 mmol/L (. 3.0 mg/dl)	0 (0%)	0 (0%)	0 (0%)
BUN >14.3 mmol/l (42.7 mg/dl)	0 (0%)	6 (0.2%)	1 (<0.1%)
Chloride >130 mmol/L	0 (0%)	0 (0%)	0 (0%)
Calcium >3.74 mmol/l (>15 mg/dl)	0 (0%)	0 (0%)	0 (0%)
Phosphate >2.42 mmol/L (>7.5 mg/dl)	0 (0%)	0 (0%)	0 (0%)
Urinary Indices			
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, within the range of 1080.

c. The number of available subjects varied slightly from test to test, within the range of 3250.

d. The number of available subjects varied slightly from test to test, within the range of 1060.

Table 5.1.4.1.2 Incidence of extreme renal lab values in the open-label, long-term Arthritis trials (OA and RA) from NDA 20-998^a.

	Celecoxib 100-400 mg ^b
Lab Test, Low Extreme Criteria	
Sodium <120 mmol/L	0/4197 (0%)
Potassium <2 meq/L	0/4186 (0%)
Chloride <75 mmol/L	0/4199 (0%)
Calcium <1.7 or 15% decrease from baseline	N/A
Phosphate <0.32 mmol/L	0/4190 (0%)
Lab Test, High Extreme Criteria	
Creatinine >265.2 mmol/L (. 3.0 mg/dl)	1/4376 (<0.1%)
BUN >14.3 mmol/l (42.7 mg/dl)	12/4372 (0.3%)
Chloride >130 mmol/L	0/4199 (0%)
Calcium >3.74 mmol/l	N/A
Phosphate >2.42 mmol/L	0/4190 (0%)
Urinary Indices	
Urine pH >8.5	6/4085 (0.1%)
Urine Protein >1+	91/ 4049 (2.2%)
Urine Glucose >1+	127/ 4023 (3.2%)
Urine Ketones >1+	5/4082 (0.1%)
Urine RBCs >10 per HPF	330/ 3979 (8.3%)
Urine WBCs >20 per HPF	282/ 3971 (7.1%)

a. Data from NDA Integrated Safety Summary, table 24.7, shown for all subjects with OA and RA. The database used is from study 024. The number shown reflects the incidence of any extreme value at any time during the trial. The incidence of extreme values at last visit were, in general, lower.

b. The number of available subjects with data varied broadly, and are shown for each lab individually.

Comparison of mean laboratory values

The sponsor also analyzed the labs according to changes in mean values. The table below will focus on the celecoxib 400 mg dose, and will show only the final measurements. Where appropriate, references to other celecoxib doses and time of measurement will be added. Each mean represent data from 400 to 450 subjects. Labs that are not shown found no significant differences between any of the three groups (i.e., calcium, urinary indices).

Table 5.1.4.1.3 Changes in final measured mean labs in the controlled North American Arthritis trials of celecoxib from NDA 20-998^a.

Changes in Final Visit Lab Values from Baseline	Placebo	Celecoxib 400 mg	Active Controls	P-value Celecoxib vs. Placebo	P-value Celecoxib vs. Active Control	P-value Active Control vs. Placebo
Creatinine (µmol/l)	-1.3±0.54	-1.8±0.54	-0.8±0.56	NS	NS	NS
BUN (mmol/l)	-0.57±0.061	0.27±0.063	0.55±0.071	<0.001	0.003	<0.001
Potassium (mmol/l)	-0.03±0.02	0.05±0.02	-0.01±0.02	<0.001	0.013	NS
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).

These same labs were also examined for the long-term, open-label trial.

Table 5.1.4.1.4 Changes in final measured mean labs in the open-label, long-term Arthritis trials (OA and RA) from NDA 20-998^a.

Changes in Final Visit Lab Values from Baseline	Celecoxib
Creatinine (µmol/l)	0.5±0.18
BUN (mmol/l)	0.28±0.023
Potassium (mmol/l)	0.04±0.006
Chloride (mmol/l)	-0.3±0.05
Phosphate (mmol/l)	0.005±0.0029

a. Data from NDA Integrated Safety Summary, table 25.4. The database used is from trial 024, and includes between 2300 and 2400 subjects (see table 25.4r details).

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Shifts of laboratory values among the five categories defined by the extreme and mid-range high and low values for each laboratory test

Finally, the sponsor analyzed the change in lab values within the five defined lab ranges (extremely low, low, normal, high, and extremely high). The table below shows the incidence of maximal shifts from baseline for selected renal labs in the 400 mg BID group. Similar patterns were seen in the 100-200 mg celecoxib group (see NDA Integrated Safety Summary, Appendix 5.1.2 for details).

Table 5.1.4.1.5 Shift in serum lab values in the 12-week, controlled North American Arthritis trials of celecoxib for 400 mg from NDA 20-998^a.

Maximal Change in Lab Value	Placebo	Celecoxib 400 mg	Active Controls
Creatinine (µmol/l) High (176.8-265.2 mmol/l) Extreme high	None None	None None	None None
BUN (mmol/l) High (9.3-14.3 mmol/l) Extreme high	5/420 from Normal 3/11 from High None	17/409 from Normal 8/10 from High None	21/423 from Normal 6/11 from High 0/1 from Extreme High
Sodium (mmol/l) Low (120-135 mmol/l) High (140-160 mmol/l) Extreme High or Low	11/29 from Low 12/398 from Normal 17/398 from Normal 1/3 from High None	9/27 from Low 26/385 from Normal 12/385 from Normal 1/6 from High None	7/21 from Low 27/401 from Normal 23/401 from Normal 3/12 from High None
Potassium (mmol/l) Low (2-3.5 mmol/l) High (5-6 mmol/l) Extreme High (>6 mmol/l)	3/6 from Low 12/406 from Normal 1/8 from High 8/416 from Normal 2/8 from High None	4/6 from Low 8/399 from Normal 0/12 from High 20/399 from Normal 5/12 from High None	2/4 from Low 20/419 from Normal 0/9 from High 20/419 from Normal 3/9 from High None
Chloride Low (75-90 mmol/l) High (110-130 mmol/l) Extreme High or Low	0/0 from Low 0/413 from Normal 19/413 from Normal 4/17 from High None	0/0 from Low 2/408 from Normal 40/406 from Normal 3/13 from High None	0/0 from Low 5/407 from Normal 45/407 from Normal 12/27 from High None
Phosphate Low (0.32-0.97 mmol/l) (1.0 to 3.0 mg/dl) High (1.61-2.42 mmol/l) (5.0 to 7.5 mg/dl) Extreme High or Low	31/63 from Low 55/366 from Normal 3/366 from Normal 2/2 from High None	42/70 from Low 61/348 from Normal 2/348 from Normal 0/0 from High None	62/75 from Low 117/358 from Normal 2/358 from Normal 0/0 from High None

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.

Table 5.1.4.1.6 Shift in urine lab values in the 12-week, controlled North American Arthritis trials of celecoxib from NDA 20-998^a.

Maximal Change in Urine Lab Value	Placebo	Celecoxib 400 mg BID	Active Controls
Urine Protein High (trace to 1+)	11/395 from Normal 0/8 from High 0/8 from Extreme High	10/389 from Normal 2/11 from High 0/5 from Extreme High	16/409 from Normal 1/8 from High 0/3 from Extreme High
Extreme High (above limit of 1+)	5/395 from Normal 2/8 from High 6/8 from Extreme High	5/389 from Normal 0/11 from High 2/5 from Extreme High	3/409 from Normal 0/8 from High 2/3 from Extreme High
Urine Glucose High (trace to 1+)	3/405 from Normal 0/2 from High 0/4 from Extreme High	2/396 from Normal 0/4 from High 0/5 from Extreme High	0/412 from Normal 0/1 from High 1/7 from Extremely High
Extreme High (above limit of 1+)	6/405 from Normal 1/2 from High 2/4 from Extreme High	7/396 from Normal 2/4 from High 3/5 from Extreme High	2/412 from Normal 0/1 from High 2/7 from Extreme High
Urine RBCs High (5-10 per HPF)	7/382 from Normal 0/9 from High 3/20 from Extreme High	10/388 from Normal 0/6 from High 0/10 from Extreme High	11/394 from Normal 0/12 from High 0/14 from Extreme High
Extreme High (>10 per HPF)	17/382 from Normal 2/9 from High 8/20 from Extreme High	24/388 from Normal 3/7 from High 2/10 from Extreme High	15/394 from Normal 1/12 from High 5/14 from Extreme High
Urine WBCs High (10-20 per HPF)	10/383 from Normal 4/15 from High 3/13 from Extreme High	12/390 from Normal 1/7 from High 1/8 from Extreme High	13/402 from Normal 3/6 from High 3/12 from Extreme High
Extreme High (>20 per HPF)	16/383 from Normal 4/15 from High 8/13 from Extreme High	16/390 from Normal 2/7 from High 2/8 from Extreme High	22/402 from Normal 0/6 from High 4/12 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.

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A similar analysis was performed for the subjects in the long-term, open-label study.

Table 5.1.4.1.7 Incidence of extreme renal serum lab values in the open-label trial from NDA 20-998^a.

Maximal Change in Lab Value	Celecoxib
Creatinine (µmol/l)	
High (176.8-265.2 mmol/l)	5/4376 from Normal 0/0 from High 0/0 from Extreme High
Extreme high	1/4376 from Normal 0/0 from High 0/0 from Extreme High
BUN (mmol/l)	
High (9.3-14.3 mmol/l)	298/4251 from Normal 82/121 from High 1/4 from Extreme High
Extreme high	5/4251 from Normal 7/121 from High 2/4 from Extreme High
Sodium (mmol/l)	
Low (120-135 mmol/l)	109/173 from Low 395/3935 from Normal 1/89 from High
High (140-160 mmol/l)	4/173 from low 346/3935 from Normal 29/89 from High
Extreme High or Low	None
Potassium (mmol/l)	
Low (2-3,5 mmol/l)	48/91 from Low 174/3976 from Normal 0/119 from High
High (5-6 mmol/l)	3/91 from Low 329/3976 from Normal 59/119 from High
Extreme High (>6 mmol/l)	1/3976 from Normal 1/119 from Extreme High
Chloride	
Low (75-90 mmol/l)	0/1 from Low 4/4027 from Normal 0/171 from High
High (90-110 mmol/l)	599/4027 from Normal 60/171 from High
Extreme High or Low	None
Phosphate	
Low (0.32-0.97 mmol/l) (1.0 to 3.0 mg/dl)	466/643 from Low 1069/3538 from Normal 1/9 from High
High (1.61-2.42 mmol/l) (5.0 to 7.5 mg/dl)	2/643 from Low 68/3538 from Normal 2/9 from High
Extreme High or Low	None

a. Data from NDA Integrated Safety Summary, table 5.4. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

Table 5.1.4.1.8 Incidence of extreme urine lab values in the long-term, open-label trial from NDA 20-998^a.

Maximal Change in Urine Lab Value	Celecoxib
Urine Protein High (trace to 1+)	179/3970 from Normal 15/79 from High 5/37 from Extreme High
Extreme High (above limit of 1+)	79/3970 from Normal 12/79 from High 22/37 from Extreme High
Urine Glucose High (trace to 1+)	50/3989 from Normal 4/34 from High 1/63 from Extreme High
Extreme High (above limit of 1+)	107/3989 from Normal 20/34 from High 54/63 from Extreme High
Urine RBCs High (5-10 per HPF)	141/3926 from Normal 2/53 from High 9/108 from Extreme High
Extreme High (>10 per HPF)	313/3926 from Normal 17/53 from High 47/108 from Extreme High
Urine WBCs High (10-20 per HPF)	189/3892 from Normal 21/79 from High 17/116 from Extreme High
Extreme High (>20 per HPF)	265/3892 from Normal 17/79 from High 60/116 from Extreme High

a. Data from NDA Integrated Safety Summary, table 5.4. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

5.1.4.2 Special Investigations Related to Renal and Cardiac AEs

The sponsor investigated the association of several AEs related to renal and cardiac events as part of the NDA submission. Others were performed at the request of this reviewer. Overall, these were aimed at exploring potential patterns of renal or cardiac injury.

As will be discussed below, there is an apparent link between celecoxib (or active control) administration and an increased incidence of edema, when compared with placebo. This was especially true for ‘peripheral edema’ as described by the investigators (see also the listing of adverse events, table 5.1.3. above). The sponsor investigated the association of this increased edema with other renal and cardiovascular AEs.

First, few individuals developed both edema and had worsening of their hypertension (as marked by a 5 mm Hg increase in diastolic BP). There was a non-significant trend towards a larger group of such patients in the celecoxib population, as compared with placebo. There was no similar trend in the active control group. The shaded boxes represent a difference at a nominally significant level of <0.05.

Table 5.1.4.2.1 Occurrence of HTN and edema in the North American Arthritis trials^a.

Syndrome	Placebo N=1136	Celecoxib N=2690	Placebo N=1136	Active Control N=1099
Adverse Events				
Any of the 4 AEs below	31 (1.7%)	116 (3.3%)	19 (1.7%)	41 (3.7%)
HTN	5 (0.3%)	22 (0.6%)	5 (0.4%)	7 (0.6%)
HTN Aggravated	7 (0.4%)	20 (0.6%)	4 (0.4%)	5 (0.5%)
Edema, Generalized	0 (0%)	4 (0.1%)	0 (0%)	9 (0.8%)
Edema, Peripheral	12 (1.2%)	52 (2.3%)	12 (1.1%)	21 (1.9%)
Diastolic BP Rise^b	35 (1.9%)	87 (2.5%)	20 (1.8%)	23 (2.1%)
Both AE and Increased BP	2 (0.1%)	11 (0.3%)	1 (<0.1%)	0 (0%)

a. Data from Integrated Safety Summary, table 31.3.4.

b. >95 mm Hg and >5 mm Hg from baseline).

Next, there was a trend towards an association between the development of edema and renal insufficiency.

Table 5.1.4.2.2 Occurrence of edema and renal insufficiency in the North American Arthritis trials^a.

AEs, both clinical and lab	Placebo N=1864	Celecoxib N=3512	Placebo N=1136	Active Control N=1099
Edema, Generalized	0 (0%)	4 (0.1%)	0 (0%)	9 (0.8%)
Edema, Peripheral	12 (12%)	52 (2.3%)	12 (1.1%)	21 (1.9%)
BUN >14.3 mmol/l^b	0 (0%)	5 (0.2%)	0 (0%)	2 (0.2%)
Creatinine >159 mmol/l^c	0 (0%)	4 (0.2%)	0 (0%)	0 (0%)
Chloride >110 mmol/l	60 (3.2%)	209 (6.0%)	55 (4.8%)	97 (8.8%)
Both AEs and Labs	0 (0%)	4 (0.2%)	0 (0%)	2 (0.2%)

a. Data from corrected tables from the Integrated Safety Summary, table 3.1.3.6, dated 9.16.98.

b. 43 mg/dl.

c. 1.8 mg/dl.

Next, the sponsor examined the association between weight gain and edema formation. Using only the subset of patients with both sets of data available, the sponsor reported that there was no association between weight gain and edema formation. Note that the incidence of edema in this table differs from that in the AE table above (5.1.3.1 and shown as top line in table below), where all reported incidence of edema (irregardless of the collection of weights) is included. Shaded boxes are nominally significant.

Table 5.1.4.2.3 Occurrence of edema and weight gain in the North American Arthritis trials^a.

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

a. Data from corrected tables from the Integrated Safety Summary, table 3.1.3.6, dated 9.16.98. Edema includes 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.

In data not shown, there was no association between the development of edema and the development of hyponatremia or the development of urine protein >1+.

The sponsor also looked at the association between the presence of back pain and hematuria (as occurred following the administration of specific NSAIDs). For celecoxib, there was no trend towards such an association (data not shown). The reader is referred to the Integrated Safety Summary, tables 31.3.3-14 for details.

At the request of this reviewer, the sponsor also performed a series of analyses looking for associations between specific lab abnormalities and adverse events. The laboratory values and the AEs used for the analysis are first presented below, taken from the North American Arthritis trials and then Long-term open-label trial. A subset of the trials used in table 5.1.4.1.2 were used, including only those trials where celecoxib was directly compared with both active control and placebo, and where serum chloride was measured.

Table 5.1.4.2.3 Incidence of selected AEs and lab abnormalities in the controlled U.S. 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
Serum Labs					
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%)
BUN >6.7 mmol/l ^b	140 (12.3%)	296 (26.2%)	379 (33.7%)	147 (33.9%)	482 (43.9%)
BUN >14.3 mmol/l ^c	0 (0%)	1 (<0.1%)	4 (0.4%)	0 (0%)	2 (0.2%)
Creatinine >132 µmol/l ^d	6 (0.5%)	7 (0.6%)	15 (1.3%)	2 (0.5%)	14 (1.3%)
Creatinine >159 µmol/l ^e	0 (0%)	1 (<0.1%)	3 (0.3%)	0 (0%)	0 (0%)
PO ₄ <0.97 mmol/l ^f	195 (17.2%)	233 (20.6%)	237 (21.1%)	83 (19.1%)	351 (31.9%)
Ca ²⁺ <1.7 mmol/l	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Urine Labs					
Urine Glucose >trace	30 (2.6%)	46 (4.1%)	34 (3.0%)	13 (3.0%)	22 (2.0%)
Urine Glucose >1+	21 (1.8%)	36 (3.2%)	26 (2.3%)	11 (2.5%)	17 (1.5%)
Urine Glucose >trace, Non-diabetics	25 (2.4%)	20 (2.0%)	26 (2.5%)	12 (3.0%)	23 (2.3%)
Urine Protein >Trace	43 (3.8%)	41 (3.6%)	44 (3.9%)	15 (3.5%)	48 (4.4%)
Urine pH >7.5	10 (0.9%)	13 (1.1%)	12 (1.1%)	2 (0.5%)	13 (1.3%)
Adverse Events					
Fracture, Accidental	3 (0.3%)	6 (0.5%)	4 (0.4%)	4 (0.9%)	4 (0.4%)
Fracture, Pathological	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Myalgias	23 (2.0%)	24 (2.1%)	21 (1.9%)	6 (1.4%)	8 (0.7%)
Osteoporosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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.

d. 1.5 mg/dl.

e. 1.8 mg/dl

f. 3.0 mg/dl.

Similar data was summarized for the long-term, open-label trial.

Table 5.1.4.2.4 Incidence of selected AEs and lab abnormalities in the controlled U.S arthritis trials.

AE/ Lab Value	Celecoxib N=4499
Serum Labs	
Chloride >110 mmol/l	593 (13.2%)
Chloride >120 mmol/l	0 (0%)
BUN >6.7 mmol/l ^b	1995 (44.3%)
BUN >14.3 mmol/l ^c	14 (0.3%)
Creatinine >132 µmol/l ^d	53 (1.2%)
Creatinine >159 µmol/l ^e	10 (0.2%)
PO ₄ <0.97 mmol/l ^f	1361 (30.3%)
Ca ²⁺ <1.7 mmol/l	1 (<0.1%)
Urine Labs	
Urine Glucose >trace	200 (4.4%)
Urine Glucose >1+	150 (3.3%)
Urine Protein >Trace	274 (6.1%)
Urine pH >7.5	68 (1.5%)
Urine pH >8.5	6 (0.1%)
Adverse Events	
Fracture, Accidental	63 (1.4%)
Fracture, Pathological	5 (0.1%)
Myalgias	14 (0.3%)
Osteoporosis	113 (2.5%)

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.

Using the abnormalities identified above, the sponsor performed a series of analyses searching for associations between one or more of these abnormalities. Shading indicates that the treatment group (either celecoxib or active control) differed significantly from placebo (nominal $p < 0.05$).

1a. Association between hyperchloremia and abnormalities in serum BUN/ Cr/ PO₄ and/or urine Glucose/ protein/ pH. Controlled Trials.

First, the sponsor looked for an association between hyperchloremia and other renal lab abnormalities. A significantly higher percentage of patients in the celecoxib and active control groups had hyperchloremia and one or more of these abnormalities. Note also that there was a significantly higher incidence of elevated BUN, and decreased PO₄ in the celecoxib and active control groups, relative to placebo. While there was a trend towards an increased incidence of glycosuria in the celecoxib group, the sponsor reports that if the diabetics are excluded from the analysis, this difference disappears.

Table 5.1.4.2.5 Hyperchloremia and other renal lab abnormalities in the controlled NA trials^a.

Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
Chloride >110 mmol/l	60 (3.2%)	209 (6.0%)	97 (8.8%)
BUN >6.7 mmol/l	140 (12.3%)	675 (29.9%)	482 (43.9%)
Cr >132 mmol/l	6 (0.5%)	22 (1.0%)	14 (1.3%)
PO ₄ <0.97 mmol/l	195 (17.2%)	470 (20.8%)	351 (31.9%)
Urine Glucose >trace	30 (2.6%)	80 (3.5%)	22 (2.0%)
Urine Protein >trace	43 (3.8%)	85 (3.8%)	48 (4.4%)
Urine pH >7.5	10 (0.9%)	25 (1.1%)	14 (1.3%)
Any of the above Lab Abnormalities	356 (31.3%)	1084 (48.0%)	702 (63.9%)
Both Hyperchloremia and one or more other lab abnormality	27 (2.4%)	95 (4.2%)	65 (5.9%)
Both Hyperchloremia and one or more other lab abnormality at last clinic visit	8 (0.70%)	21 (0.93%)	9 (0.82%)

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

This nominally significant association between hyperchloremia and abnormalities in renal labs for patients taking celecoxib (or the active control) persisted if one examined only those subjects with more pronounced elevations in serum BUN, creatinine, and urine glucose/pH (data not shown).

The individual patient records were reviewed for those patients who had both hyperchloremia and one or more other lab abnormalities at the last available visit, and the results are shown in the last row above. There was no clear difference between treatment groups, there was a higher % of such patients in the celecoxib and active treatment groups, relative to placebo.

Among these patients, there were five in the celecoxib group whose last Cl⁻ was >113mmol/l, 2 in the active control group, and none in the placebo. These patients are listed below. The peak Cl⁻ at last visit for the celecoxib group was 116 mmol/l. If one assumes an average Anion Gap of 6-13 (avg. 8) and a serum Na⁺ of 140, this Cl⁻ of 116 would correspond to a HCO₃ of 16 meq/l.

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

Patient #	Days on Study Drug	Baseline/ Final PO ₄ ⁻ (mmol/l and mg/dl)	Baseline/ Final Cl ⁻ (mmol/l)
Placebo (none)			
Celecoxib			
022-0861	87	1.16/ 0.81	107/ 115
054-1137	12	0.84/ 0.74 ^b	109/ 115
020-0357	85	1.07/ 0.84	112/ 114 ^b
023-1358	43	0.97/ 0.94	109/ 116 ^c
Active Control			
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 HCO₃ or PO₄ was abnormally elevated at time of entry.

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

1b. Association between hyperchloremia and abnormalities in serum BUN/ Cr/ PO₄ and/or urine Glucose/ protein/ pH. Long-term open-label trial.

In addition, almost 10% of the subjects in the long-term open-label trials had a similar association between hyperchloremia and other renal lab abnormalities.

Table 5.1.4.2.7 Hyperchloremia and other renal lab abnormalities in the long-term trial^a.

Abnormality	Celecoxib N=4499
Chloride >110 mmol/l	593 (13.2%)
BUN >6.7 mmol/l	1995 (44.3%)
Cr >132 mmol/l	53 (1.2%)
PO ₄ <0.97 mmol/l	1361 (30.3%)
Urine Glucose >trace	200 (4.4%)
Urine Protein >trace	274 (6.1%)
Urine pH >7.5	68 (1.5%)
Any of the above Lab Abnormalities	2853 (63.4%)
Both Hyperchloremia and one or more other lab abnormality	444 (9.9%)
Both Hyperchloremia & one or more other lab abnormality at last lab visit	26 (0.6%)

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

The individual patient records were reviewed for those patients who had both hyperchloremia and one or more other lab abnormalities at the last available visit, and the results are shown in the last row above.

Among these patients, there were four patients whose last Cl⁻ was >113mmol/l, who had other abnormalities (2 hypo-phosphatemia, one proteinuria). These patients are listed below. The peak Cl⁻ at last visit for the celecoxib group was 115 mmol/l. If one assumes an average Anion Gap of 6-13 (avg. 8) and a serum Na⁺ of 140, this Cl⁻ of 116 would correspond to a HCO₃⁻ of 17 meq/l. There were no patients found who had a steadily increasing chloride concentration measured over several lab values. There was also no apparent association (in this long-term dataset) between glycosuria and hyperchloremia.

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

Patient #	Days on Study Drug	Baseline/ Final PO ₄ ⁻ (mmol/l and mg/dl)	Baseline/ Final Cl ⁻ (mmol/l)
012-0504 ^c	366	1.0/ 1.13	112/ 114
022-1433	83	1.10/ 0.90	109/ 114
022-0861	87	1.16/ 0.81	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.

Finally, there were two patients with notable abnormalities in renal labs in this set, which are summarized below. One had a persistently, severely, low serum PO₄ associated with hyperchloremia. The other patient developed significant proteinuria associated with decreased serum PO₄.

Table 5.1.4.2.9. Patients receiving celecoxib in the long-term, open-label trial with other notable renal lab abnormalities^a.

Patient #	Days on Study Drug	Baseline/ Final PO ₄ ⁻ (mmol/l and mg/dl)	Baseline/ Final Cl ⁻ (mmol/l)
022-0622	92	0.55/ 0.42	109/ 113
013-0401 ^c	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.

2a. Association of urinary abnormalities in the controlled North American trials.

The sponsor also searched for a clustering of the urinary abnormalities described in the controlled trials. The three urinary labs that were measured that might occur as a part of a proximal renal tubular injury are proteinuria, glycosuria, and changes in urinary pH. Of these, the pH is the most variable, and of the least use diagnostically. There was an increased incidence of glycosuria in the celecoxib group relative to placebo, but the incidence of proteinuria was similar in all treatment groups. As shown in the table below, there was no trend detected towards an increased association between these urinary abnormalities in the celecoxib group.

Table 5.1.4.2.10. Association between glycosuria and other urinary abnormalities in controlled trials^a.

Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
Urine Glucose >1+	21 (1.8%)	62 (2.7%)	17 (1.5%)
Urine Protein >trace	43 (3.8%)	85 (3.8%)	48 (4.4%)
Urine pH >8.5	0 (0%)	0 (0%)	2 (0.2%)
Any of the above Lab Abnormalities	43 (3.8%)	85 (3.8%)	50 (4.5%)
Both Glycosuria and one or more other lab abnormality	4 (0.4%)	3 (0.1%)	6 (0.5%)

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

3a. Hyperchloremia and serum Ca²⁺/ PO₄ abnormalities in controlled NA OA/RA trials.

There was also an association between low serum PO₄ and elevated serum Cl⁻ in the subjects who received celecoxib and the active control, with the active control group being nominally significant versus placebo. There was no link with alterations in change in serum Ca²⁺, however.

Table 5.1.4.2.11. Association between Ca²⁺, PO₄³⁻, and Cl⁻ abnormalities in controlled trials^a.

Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
PO ₄ <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%)
Calcium <1.7 mmol/l	0 (0%)	0 (0%)	0 (0%)
Calcium >2.74 mmol/l	1 (<0.1%)	2 (<0.1%)	2 (0.2%)
Any of the above Lab Abnormalities	227 (20%)	597 (26.5%)	399 (35.3%)
Both low PO ₄ and high Cl ⁻	16 (1.4%)	51 (2.3%)	34 (3.1%)
Both low PO ₄ and high Cl ⁻ 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.

The number of patients who had at least two of the labs abnormal on their last clinic visit were tabulated, and are shown in the last row above. There was no difference between treatment groups. As discussed above in section 1.2, the severity of the PO₄/ Cl abnormalities were, however, greater in the celecoxib and active control groups. While no placebo patient had a Cl >113 at last clinic visit (associated with abnormal PO₄³⁻), there were 4 such patients in the celecoxib group, and 3 in the active control group. Their baseline and final lab values are summarized in table 5.1.4.1.6 above.

In the long-term, open-label database, 247 (5.5%) of the celecoxib patients developed both hypophosphatemia and hyperchloremia during the study. Of these, 13 (0.3%) had both abnormalities at the end of the study.

4a. Proteinuria and development of elevated BUN/ Creatinine

The association between the development of trace proteinuria or greater and abnormally elevated BUN/ Creatinine (Cr_t) were examined using two levels of BUN/ Cr_t. For the patients with less marked elevations there was a nominally significant association between the development of proteinuria and elevated BUN/Cr_t in the celecoxib and active control groups.

Table 5.1.4.2.12. Association between proteinuria and elevated BUN/ Crt in controlled trials^a.

<i>Abnormality</i>	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%)	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.

Next the individual labs from patients who developed proteinuria plus Crt >132 and BUN >6.7 mmol/l were reviewed, to see if there was a temporal association between the lab abnormalities. The number of patients who had at least two of the labs abnormal on their last clinic visit were tabulated, and are shown in the last row of the table above. As can be seen, a higher number of celecoxib and active control subjects in the controlled trials ended the trial with abnormal elevations in two of the three lab values.

Another measure of severity is to look at how significant the proteinuria was. In the celecoxib patients, 2 with no proteinuria at trial entry ended the trial with at least 2+ proteinuria and abnormally elevated BUN, compared with no such patients in the placebo group, and 3 patient in the active control group.

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.

5.1.4.2.13 Patients with marked abnormalities in final BUN/Crt from proteinuria/BUN/Crt cluster^a.

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 ^b (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.

4b. Association between hyperchloremia and bony/ muscular abnormalities. Long-term open-label trial.

Finally, the potential consequences of prolonged acidosis were examined by looking for an association between hyperchloremia and the development of bony fractures. These fractures occur in untreated metabolic acidosis as a consequence of loss of HCO₃ and PO₄ from the bone in an attempt to buffer the acidosis.

In the short-term controlled data, there was no significant increase in the frequency of this combination in the celecoxib or active control groups.

Table 5.1.4.2.14. Association between hyperchloremia and bony AEs in controlled trials^a.

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.

In the long-term trial, there were 5 pathological fractures, and 32 patients who had one or more bony AE in addition to hyperchloremia.

Table 5.1.4.2.15. Association between hyperchloremia and bony AEs in long-term open-label trial^a.

Abnormality	Celecoxib N=4499
Chloride >110 mmol/l	593 (13.2%)
Fractures, Accidental	63 (1.4%)
Fractures, Pathologic	5 (0.1%)
Myalgias	113 (2.5%)
Both Chloride and one AE	32 (0.7%)

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

5.1.5 Vital Signs

Data on the incidence of abnormal heart rates were collected during both the controlled and the open-label trials. The sponsor summarized the data in two ways: 1) the incidence of 'extreme' changes in BP, heart rate or weight; and 2) mean changes in the same parameters. In addition, changes in blood pressure (i.e., hypotension, hypertension) and pulse rate (i.e., bradycardia, tachycardia, asystole) were included in both the AEs and the SAEs collected in all trials.

Incidence of Extreme Changes in BP, Heart Rate or Weight

In the controlled North American OA/RA trials, there was no clinically significant differences between placebo and celecoxib in the incidence of any of these parameters. The reader is referred to the Integrated Safety Summary, Text table 85 for details.

In the long-term, open-label trial, again, there was wide variability in patient responses, and no clinically relevant pattern to suggest a consistent effect of celecoxib on BP, heart rate, or weight.

Mean Changes in BP, Heart Rate or Weight

In the controlled North American trials, several small, nominally significant differences were found between celecoxib and placebo. These are summarized below. Overall, no clinically significant effects were detected. Importantly, no significant effect on BP was detected. In data not shown, a similar pattern was seen for the 100-200 mg celecoxib dose-group. Shaded boxes differed from placebo with nominal significance ($p < 0.05$).

Table 5.1.5.1 Changes in mean vital signs in the 12-week, controlled North American Arthritis trials of celecoxib from NDA 20-998^{a,b}.

Vital Sign Measured (Change from baseline)	Placebo	Celecoxib 400 mg BID	Active Controls
Systolic BP	-2.1±0.5	-0.5±0.5*	-0.3±0.6*
Diastolic BP	-0.6±0.3	-0.5±0.3	-0.5±0.3
Pulse Rate	0.8±0.3	-0.4±0.3*	0.3±0.4
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.

In the long-term, open-label trials, vital signs were measured at each office visit (weeks 2, 6 and 12, then months 6, 9, 12, 15, and final). Overall, there was no discernable, consistent effect of celecoxib detected (see ISS, Table 30.4 for details).

Adverse Events and Serious Adverse Events Related to Vital Signs

Changes in blood pressure (i.e., hypotension, hypertension) and pulse rate (i.e., bradycardia, tachycardia, asystole) were included in both the AEs and the SAEs collected in all trials.

AEs

See section 4.1.3 above for details of the incidence of rhythm disturbances as AEs in the celecoxib database.

SAEs

For the controlled North American arthritis trials, the following rhythm disturbances (WHO classification) as SAEs occurred in single patients in one of the dose groups (placebo, celecoxib or active control): arrhythmia; arrhythmia (atrial); fibrillation (atrial); heart block; palpitation; syncope; and tachycardia (both atrial and ventricular). Hypertension, or aggravated hypertension, occurred in three subjects in the celecoxib group, and in no placebo or active control patients.

In the open-label trial, the following rhythm disturbances (WHO classification) as SAEs occurred in single patients: hypotension; arrhythmia; AV block; cardiac arrest; extrasystoles; fibrillation (ventricular); and heart block. There were four episodes of atrial fibrillation, 2 episodes of supraventricular tachycardia, and 2 episodes of bradycardia.

ECGs and Special Examinations

No long-term data on the effect of celecoxib on the incidence of ECG abnormalities were collected. During the short-term phase I-II trials, only study 071 collected baseline and follow-up ECGs. No significant findings were reported by the sponsor in this study.

5.1.6 Discontinuations

The next table shows a summary of the disposition of subjects in the phase II-III trials of celecoxib, including the dropouts. Note that a smaller % of the placebo patients completed the trial, primarily due to drop-outs from therapeutic failure.

Table 5.1.6.1 Disposition of subjects randomized in the combined North American controlled OA/RA trials^a.

Patient Disposition	Placebo N=1864	Celecoxib 50-400 mg BID N=5704	Active Control N=2098
Randomized	1864	5704	2098
Completed	970 (52%)	3971 (69.6%)	1480 (70.5%)
Discontinued (Total)	894 (48.0%)	1733 (30.3%)	618 (9.5%)
Therapeutic Failure	680 (36.5%)	1119 (19.6%)	316 (15.1%)
Adverse Event	114 (6.1%)	398 (7.0%)	203 (9.7%)
Patient noncompliance	58 (3.1%)	135 (2.4%)	76 (3.6%)
Lost to Follow-Up	17 (0.9%)	36 (0.6%)	14 (0.7%)

a. Data from Integrated Safety Summary, Appendix Table 5.8.

Table 5.1.6.2 Disposition of subjects randomized in the long-term, open-label combined OA/RA trial^a.

Patient Disposition	Celecoxib
Randomized	4499
Completed	3317 (73.7%)
Discontinued (Total)	1182 (26.3%)
Therapeutic Failure	639 (14.2%)
Adverse Event	296 (6.6%)
Patient noncompliance	165 (3.7%)
Lost to Follow-Up	46 (1.0%)

a. Data from Integrated Safety Summary, Appendix Table 5.9.

Discontinuations associated with Adverse Events (AEs)

The next table summarizes the subjects who were withdrawn from study drug prematurely due to one or more adverse events related to the cardiac or renal systems.

Table 5.1.6.3 Cardiovascular adverse events leading to subject discontinuation collected in the North American OA/RA trials^a.

Body System/ AE	Placebo N=1864	Celecoxib 50-400 mg BID N=5704	Active Control N=2098
Total # with AEs leading to discontinuation	114 (6.1%)	298 (7.0%)	203 (9.7%)
Hypertension^b	0 (0%)	6 (0.1%)	1 (<0.1%)
Hypotension, includes postural	0 (0%)	1 (<0.1%)	2 (<0.1%)
Edema, peripheral	1 (<0.1%)	4 (<0.1%)	1 (<0.1%)
Edema, facial	3 (0.2%)	7 (0.1%)	2 (0.1%)
Edema, Generalized	0 (0%)	1 (<0.1%)	2 (0.1%)
Arrhythmia^c	1 (<0.1%)	9 (0.16%)	3 (0.14%)
Arteritis/ Vasculitis	0 (0%)	1 (<0.1%)	0 (0%)
Angina^d	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..

b. Includes hypertension, aggravated hypertension.

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

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

Table 5.1.6.4 Renal adverse events leading to subject discontinuation collected in the North American OA/RA trials^a.

Body System/ AE	Placebo N=1864	Celecoxib 50-400 mg BID N=5704	Active Control N=2098
Total # with AEs leading to discontinuation	114 (6.1%)	298 (7.0%)	203 (9.7%)
Uremia	0 (0%)	1 (<0.1%)	0 (0%)
Abnormal renal function	1 (<0.1%)	0 (0%)	0 (0%)
Renal calculus	1 (<0.1%)	1 (<0.1%)	0 (0%)

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

Table 5.1.6.5 Cardiovascular adverse events leading to subject discontinuation, collected in the long-term, open-label trial^a. Shown according to the date of last celecoxib dose.

Body System/ AE	1-90 Days	91-180	181-270	271-360	361-450	451-540
# of Subjects Total	4499	3540	2373	1576	970	294
Total # with AEs leading to discontinuation	147 (3.3%)	99 (2.8%)	34 (1.4%)	21 (1.3%)	6 (0.6%)	2 (0.7%)
Hypertension^b	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)
Edema, generalized	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Edema, facial	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Edema, peripheral	4 (0.1%)	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)
Fibrillation, Atrial	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	2 (0.1%)	0 (0%)	0 (0%)
Palpitation	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fibrillation, Ventricular	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cardiac Failure	1 (<0.1%)	1 (<0.1%)	3 (0.1%)	(<0.1%)	0 (0%)	0 (0%)
Unstable Angina^d	0 (0%)	2 (0.1%)	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)
Myocardial Infarction^c	4 (0.1%)	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	1 (0.1%)	0 (0%)
Arteritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from Integrated Safety Summary, Appendix table 9.6.

b. Includes hypertension, aggravated hypertension.

c. Includes coronary thrombosis.

d. Includes 'angina pectoris.'

Table 5.1.6.6 Renal adverse events leading to subject discontinuation, collected in the long-term, open-label trial^a. Shown according to the date of last celecoxib dose^a.

Body System/ AE	1-90 Days	91-180	181-270	271-360	361-450	451-540
# of Subjects Total	4499	3540	2373	1576	970	294
Total # with AEs leading to discontinuation	147 (3.3%)	99 (2.8%)	34 (1.4%)	21 (1.3%)	6 (0.6%)	2 (0.7%)
BUN Increased	1 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Acute Renal Failure	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from Integrated Safety Summary, Appendix table 9.6. Other events, including albuminuria, bladder carcinoma, hematuria, and UTI, led to discontinuation of single subjects in the database.

Per the sponsor, twenty-five (25) patients were withdrawn from the controlled OA/RA trial due to renal adverse events. A total of four patients (0.2%) withdrew from placebo treatment. For the celecoxib 50 mg BID to 400 mg BID treatment groups combined, 16 patients (0.3%) withdrew as a result of an adverse event associated with renal function. In the active control group, five patients (0.2%) withdrew from treatment for a renal adverse event. Note that the incidence of withdrawal for hypertension and for edema were higher in both the celecoxib and active control groups than in the placebo group. Time constraints precluded review of the individual Case Report Forms.

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

Treatment Group/ Patient #	Preferred Term for AE
<i>Placebo</i>	
020-880	Hematuria
021-0445	Edema, Peripheral
022-0345	Renal Calculus
060-0441	Renal Function, Abnormal
<i>Celecoxib 50-400 mg</i>	
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
<i>Active Control</i>	
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.

Per the sponsor, twenty-five (39) patients were withdrawn from the long-term open-label trial due to renal and/or cardiac adverse events. Within this list, 22 subjects, listed below, were withdrawn for renal AEs. The remaining 17 had cardiac AEs, including 6 with cerebrovascular accidents, 8 with acute myocardial infarctions, and 3 with angina pectoris.

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

Celecoxib Dose ^b / Patient #	Final Dose	Adverse Event	Days on Celecoxib
<u>Celecoxib 100 mg</u>			
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
<u>Celecoxib 200 mg</u>			
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
<u>Celecoxib 300 mg</u>			
023-1173	300	Edema, facial	N/A
023-0671	300	'Urine abnormal' & 'Urine smells'	N/A, ongoing at day 310
		Edema, generalized	
<u>Celecoxib 400 mg</u>			
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 .

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5.2 Integrated Summary of Renal and Cardiac Safety

This section will summarize the critical renal and cardiac safety issues identified by this reviewer. Each will be discussed in turn, followed by an opinion regarding the association between celecoxib administration and each particular adverse event. An adverse event has been included either because, in the opinion of this reviewer, it is significantly more or less common in the celecoxib-treated patients when compared with the placebo group, or because it is a critical aspect of usual cardiac/renal safety review. Those adverse events that are not listed in this section are interpreted as either occurring too rarely to determine their association with celecoxib use or occurred with no evidence of specific association with celecoxib use.

In reviewing the database summarized above, this reviewer was careful to examine the data for evidence of events occurring more frequently in the placebo group relative to celecoxib, in addition to searching for events linked to celecoxib use. This is important so as to avoid the bias potentially present in any analysis that includes multiple analyses such as the safety review. It is also important to remember that the use of statistics to examine the incidence of rare and unusual events in a safety database is flawed with the same difficulties inherent to multiple looks. The intent of the following sections is to look for trends suggesting an increased incidence of a given adverse event, based on multiple lines of (indirect) evidence. This is, of course, the nature of a safety review.

Before listing the adverse renal and cardiac safety events, the limitations of the available safety database need to be reviewed.

5.2.1 Limitation of NDA Dataset for Detecting Renal and Cardiovascular AEs

There are two limiting factors that an NDA places on the detection of renal and cardiac adverse events (AEs): 1) the extent of patient exposure in both controlled and uncontrolled trials; and 2) the potential absence of relevant data.

Patient Exposure

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 the drug for <180 days. Long-term, open-label exposure data (>180 days) was collected for 1809 patients, (see Table 3.1.3.2).

The number of patient-years of exposure puts absolute limits on detecting and characterizing the renal and cardiac safety of celecoxib. Using the number 6376, and not taking into account the duration of exposure, we can estimate a 95% likelihood of detecting at least one occurrence of adverse events occurring at a rate of between 1/1000 and 1/2500. Less information, obviously, will be available regarding the relative rates for adverse events (i.e., celecoxib vs. placebo). Comparative rates between celecoxib and placebo (or active control) will be limited by the fact that the placebo-controlled trials were limited to 12 weeks or less of exposure. Using 1809 as the number of patients in the long-term exposure data yields a 95% likelihood of detecting at least one occurrence of an adverse event related to chronic exposure (>12 weeks) that occurs at a frequency of approximately 1/600. In terms of known renal toxicities of NSAIDs, such database would likely detect the occurrence of fluid and electrolyte disturbances (especially edema and worsened hypertension), which is the most common 'renal' toxicity of NSAIDs. It is less likely to detect other rare toxicities that occur at a frequency <1/1000 (nephrotic syndrome, papillary necrosis). The incidence of 'acute renal failure' due to NSAIDs is difficult to estimate, but if it occurs at a frequency of 1/500 to 1/1000, then we might expect the celecoxib database to detect at least one such event.

It is also relevant to discuss the uncontrolled aspect of the long-term safety database. As shown in table 5.03.1, the chronic exposure data is almost exclusively uncontrolled and open-label. Some adverse events occur predominately after long periods of exposure to study drug (>180 days). For example, the effect of a study drug on cardiac mortality would likely require long periods of exposure to become manifest. Without a direct comparator group within the long-term trials, the reviewer is forced to make assumptions about the expected rate of a given adverse event occurring in an untreated population at large from other sources (i.e., publication of other trials, epidemiology data). The approach limits the power to strongly associate such an adverse event with celecoxib with any confidence. Obviously, if detection of adverse mortality effects is difficult, it also be more difficult to discern associations between study drug and less severe adverse events in an uncontrolled database. For these adverse events (i.e., liver function abnormalities, acute renal failure) weight will of necessity be given to withdrawals due to a given adverse event, SAEs, and other indirect markers of incidence.

Data Collection

There is obviously a trade-off between the desire on the part of the FDA for complete safety information and the practicalities of performing large clinical trials. For the development of celecoxib, the sponsor did not collect serum bicarbonate data, normally a routine part of serum electrolytes. One possible explanation was the use of central lab facilities, which precludes the accurate measurement of HCO₃, unless labor-intensive steps are taken. As is clear from the above analyses, this omission, in association with the significantly increased incidence of hyperchloremia, forces the use of other, less clear-cut, markers for acid-base balance. Ultimately, this decision means that the data needed to resolve questions related to the effect of celecoxib on acid-base balance will simply not be available.

5.2.2 Occurrence of Significant Cardiovascular AEs and SAEs

The following Cardiovascular adverse events will be examined individually: cardiovascular mortality, blood pressure effects, edema formation, rhythm disturbances, and heart failure.

5.2.2a Cardiovascular Mortality

1. The crude rates of death due to cardiovascular disease in both the celecoxib and in the active control groups were higher than in the placebo group. For each of these analyses, the mortality rate for the active control group was numerically greater than the celecoxib group.

Mortality in deaths per patients exposed

Table 5.1.1.2.3 Calculation of crude cardiovascular mortality incidence in deaths per patients exposed in NDA 20-998^a.

Controlled N.A. OA/RA Trials	# of Deaths	# of Exposed Subjects	Mortality Incidence
<u>Cardiac deaths during trial</u>			
Placebo	0	1864	0.00%
Celecoxib	1	6376 ^e	0.02%
Active Control	2	2768	0.07%
<u>All known cardiac deaths^b</u>			
Placebo	0	1864	0.00%
Celecoxib	2	6376 ^e	0.03%
Active Control	2	2768	0.07%

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 in deaths per patient-years of exposure

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

Table 5.1.1.2.4 Calculation of cardiovascular mortality rate in deaths per patient-years of exposure in NDA 20-998^a.

Controlled N.A. OA/RA Trials	# of Deaths	Patient-years of Exposure ^e	Mortality Rate
<u>Cardiac deaths during trial</u>			
Placebo	0	208	0.00%
Celecoxib	1	1020	0.10%
Active Control	2	535	0.37%
<u>All Known Cardiac Deaths^b</u>			
Placebo	0	208	0.00%
Celecoxib	2	1020	0.20%
Active Control	2	535	0.37%

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.

Cardiovascular mortality derived from Kaplan-Meier Plot

Table 5.1.1.2.5 Kaplan-Meier estimates for cumulative incidence rates for all mortality in the North American OA/ RA trials^a.

Controlled Studies, 24 week	All-Cause Deaths (n, %)	Cardiovascular Deaths (n, %)
Deaths ≤28 days after last dose of study drug		
Placebo	0 (0%)	0 (0%)
Celecoxib	2 (0.38)	1 (0.02%)
Active Control	4 (0.26%)	2 (0.12%)
All deaths		
Placebo	0 (0%)	0 (0%)
Celecoxib	4 (0.45%)	2 (0.05%)
Active Control	4 (0.22%)	2 (0.10%)

a. Data from sponsor-derived plots.

2. In the long-term, open-label trial, the cumulative incidence of cardiovascular death was between 0.17% and 0.35%.

Mortality in deaths per patients exposed

Table 5.1.1.2.3 Calculation of crude cardiovascular mortality in deaths/pts exposed^a.

Long-term, Open-label Trial	# of Deaths	# of Exposed Subjects	Mortality Incidence
Cardiac deaths before cut-off date	9	5155	0.17%
Known deaths during celecoxib use	14 ^d	5155	0.27%
All known cardiac deaths^c	15	5155	0.29%

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

c. 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 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97).

Mortality in deaths per patient-years of exposure

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

Table 5.1.1.2.4 Calculation of cardiovascular mortality rate in deaths per pt-years of exposure^a.

Long-term, Open-label Trial	# of Deaths	Patient-years of Exposure^e	Mortality Rate
Cardiac deaths before cut-off date	9	2672	0.33%
Known deaths during celecoxib use	14 ^d	4274	0.33%
All known cardiac deaths^c	15	4274	0.35%

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

c. 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 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date (11.21.97).

Cardiovascular mortality derived from Kaplan-Meier Plot

The next table comes from the long-term trials, using various cut-offs for inclusion.

Table 5.1.1.2.6 Kaplan-Meier estimates for cumulative incidence rates for cardiovascular mortality in the open-label, long-term trial^a.

Long-term Open-Label Study (52 wk)	All-Cause Deaths (n, %)	Cardiovascular Deaths (n, %)
Deaths ≤28 days after last dose of study drug		
As of 11.21.97	10 (0.43%)	9 (0.39%)
As of 5.1.98	15 (0.38%)	14 (0.35%)
All deaths		
As of 5.1.98	18 (0.41%)	14 (0.35%)

a. Data from sponsor-derived plots.

3. Arranged according to last dose of celecoxib received, there was an apparent relationship between dose of celecoxib and mortality rate.

Table 5.1.1.2.7 Calculation of cardiovascular mortality rates in deaths per patient-years of exposure, arranged according to highest dose of celecoxib received, from the long-term trial^{a,b}.

Celecoxib Dose	Number of Deaths	Patient-years of Exposure ^d	Crude Mortality Rate ^c
100 mg	0	519	0%
200 mg	4	1271	0.31%
300 mg	2	340	0.59%
400 mg	3	465	0.64%

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

b. Data shown for deaths that occurred prior to cut-off date 11.21.97.

c. Mortality (for both total and cardiovascular deaths) in deaths/pt-yrs (x100).

d. Data from ISS, Appendix table 4.3.

4. In the long-term trial, the predominate (90% +) cause of death for patients taking celecoxib at any dose was cardiovascular (see tables 5.1.1.2 and 5.1.1.3). The majority of these deaths represented progression of previously known cardiac disease (see individual narrative summaries, appendix one).

5. Examining the Kaplan-Meier survival curves for both controlled and long-term trials, there was no apparent relationship between any given duration of exposure and increased mortality (see sponsors figure 3, 4 and 5).

6. The demographics of the subjects in the controlled trials were estimated from the ICD-9 codes. Overall, 35-40% of the subjects had hypertension, 15% had a history of significant cardiac disease (i.e., MI, angina pectoris), 7-8% were diabetic, 7-10% were hyperlipidemic, and 3-4% had significant renal disease. No information about smoking history is available.

From Table 3.1.3.5 Significant cardiac and renal past medical history in the celecoxib North American controlled trials^a.

	Placebo N=1864 ^b	Celecoxib 25-400 mg N=5704 ^c	Active Controls N=2098 ^d
Cardiovascular Disease			
Angina Pectoris	57 (3.1%)	194 (3.4%)	75 (3.6%)
Coronary Atherosclerosis	70 (3.8%)	201 (3.5%)	82 (3.9%)
Congestive Heart Failure	24 (1.3%)	63 (1.1%)	25 (1.2%)
Hypertension (not otherwise specified)	732 (39.3%)	2172 (38.1%)	749 (35.7%)
CABG	31 (1.7%)	118 (2.1%)	39 (1.8%)
Myocardial Infarction (not otherwise specified)	54 (2.9%)	167 (2.9%)	74 (3.5%)
Endocrine Disease			
Diabetes Type I (uncomplicated)	26 (1.4%)	89 (1.5%)	34 (1.6%)
Diabetes Type II (uncomplicated)	114 (6.1%)	408 (7.2%)	156 (7.4%)
Hypothyroid	234 (12.6%)	659 (11.6%)	241 (11.5%)
Hyperlipidemia	108 (5.8%)	376 (6.6%)	137 (6.5%)
Obesity	131 (7.0%)	389 (6.8%)	148 (7.1%)
Renal/ GU Disease			
Renal calculus	64 (3.4%)	206 (3.6%)	93 (4.4%)
Hematuria	29 (1.6%)	65 (1.1%)	17 (0.8%)
UTI	95 (5.1%)	231 (4.0%)	76 (3.6%)

a. Data from NDA Integrated Safety Summary, Appendix 8.2. The database used includes studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Collected ICD-9 codes were used to calculate incidence rates for each group.

Conclusion regarding cardiovascular mortality

There are aspects of the dataset above that could suggest an association between celecoxib (and active control) use and increased cardiovascular mortality:

- 1) the increased relative rate of cardiovascular death in the celecoxib and active control groups during the controlled trials (0% for placebo, 0.02% for celecoxib, 0.12% for active control, see table 5.1.1.2.5),
- 2) the apparent relationship between dose of celecoxib and rate of cardiovascular death in the long-term, open-label trial (table 5.1.1.2.7), and
- 3) the preponderance of deaths due to cardiovascular disease in the open-label trial (tables 5.1.1.1.1 through 5.1.1.1.4).

Based on the demographics of the enrolled population, this interpretation would imply some effect of the drugs to accelerate cardiovascular disease in a population already at risk for it. The problems with this interpretation can be summarized as follows:

1) The overall small number of deaths that occurred in the controlled database (table 5.1.1.2.4). The occurrence of only 8 deaths during the controlled phase of the trials severely limits interpretation of the calculated mortality rates from these trials. The occurrence of a single death in the placebo group would eliminate the apparent discrepancy in the mortality rates in this population.

2) We don't have good comparator data to know what the 'expected' rate of cardiovascular death is in the OA/RA population, and we lack a control group for the long-term trial. Extrapolation from other population at low risk for cardiovascular disease, such as the primary prevention trials using Aspirin or cholesterol-lowering agents, is difficult because of differences in the clinical characteristics of the patient populations studied (see table 3.1.3.5). The ongoing Women's Health study may give some data in this regard, but has not yet released the pertinent data.

3) The lack of information about the sub-populations within the long-term database. While the apparent relationship between dose of celecoxib and rate of cardiovascular death is provocative (Table 5.1.1.2.7), patients who received higher doses of celecoxib could also have more advanced osteoarthritis and rheumatoid disease, and may have had it for a longer duration. If this were true, they might also be more likely to have received steroids and other potent medications, more likely to be hypertensive, and more likely to have other clinical illness that confounds the analysis. While the large majority of the deaths were cardiovascular, this might be expected in a population selected to exclude those with significant other medical disease, as was done in this case. The deaths, where examined by this reviewer, were also largely a progression of previously known cardiovascular disease.

The available data are inadequate either to exclude or confirm a link between celecoxib administration and cardiovascular death.

5.2.2b Blood Pressure Effects

1. The blood pressure (BP) effects of the study drugs were measured both during the trials and BP readings, and in the form of AEs and SAEs (tables 5.1.5.1, 5.1.2.1, 5.1.2.1, 5.1.2.3, 5.1.3.1). The reasons for withdrawal from the open-label trial also included hypertension (table 5.1.6.2 5.1.6.3, and 5.1.6.7). Blood pressures were also measured during each clinic visit, and those data summarized as change from baseline (table 5.1.5.1).

2. With regard to changes in measured BPs, administration of celecoxib and active control were associated with a nominally significantly higher mean systolic BP at the end of the trial, compared with placebo. While all three groups had a decrease in their mean systolic BP, the greatest decrease occurred in the placebo group compared with celecoxib and active control. No effect of celecoxib or active control on diastolic BP was detected.

From Table 5.1.5.1 Mean changes in blood pressure in the 12-week, controlled North American Arthritis trials of celecoxib from NDA 20-998^{a,b}.

Vital Sign Measured (Change from baseline)	Placebo	Celecoxib 400 mg BID	Active Controls
Systolic BP	-2.1±0.5	-0.5±0.5*	-0.3±0.6*
Diastolic BP	-0.6±0.3	-0.5±0.3	-0.5±0.3

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.

3. There was a higher incidence of 'hypertension' as an AE in the celecoxib and active control groups, relative to placebo (table 5.1.3.1).

Table 5.1.3.1 Adverse events in the North American Arthritis trials of celecoxib from NDA 20-998^a Part one: Cardiovascular AEs.

Hypotension as an AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Hypertension ^c	12 (0.6%)	64 (1.1%)	55 (1.6%)	20 (1.0%)
Hypotension	1 (<0.1%)	1 (<0.1%)	0 (0%)	4 (0.2%)
Hypotension, Postural	0 (0%)	2 (<0.1%)	1 (<0.1%)	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.

c. Includes both undifferentiated hypertension and aggravated hypertension.