

Statistical Review and Evaluation

DRAFT

NDA20-998

Name of Drug: SC-58635

Applicant: G. D. Searle and Co.

Indication: Treatment of Signs and Symptoms of Osteoarthritis and Rheumatoid Arthritis, Management of Pain, and Improvement of Gastrointestinal Safety

Documents Reviewed: RA Part of Statistical Section (Vol.258-Vol.339) of NDA20-998
Dated 6/30/98 by CDER

Reviewer: Laura Lu, Ph.D.

Date of Review: 10/30/98

I. Introduction

NDA20-998 has been submitted for approval of SC-58635 for treatment of signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), management of pain, and improvement of gastrointestinal (GI) safety. This review focuses on the indications of treatment of RA and GI safety.

Two pivotal studies and five supportive studies were conducted in patients with RA. The two phase-III pivotal studies (022, 023) were double blind, placebo-controlled trials of 12 weeks duration. Among the 5 supportive studies, Study 012 was a Phase-II study; Studies 041, 062, and 071 were double blind Phase-III studies; and Study 024 was an open labeled phase-III study. For efficacy results, this reviewer will focus on Studies 022 and 023. For Gastrointestinal (GI) safety results, this reviewer will focus on Studies 022 and 041. GI Studies 062 and 071 were conducted in both OA and RA patients and are reviewed by Dr. Ping Gao.

II. Efficacy Studies in RA patients

1. Study 022

1). Protocol

This was a double-blind, placebo-controlled, multi-center, parallel group, 12 weeks flared study for the comparison of the efficacy and UGI safety of SC-58635 (100 mg BID, 200 mg BID, 400 mg BID) versus placebo and Naproxen 500 mg BID in patients with RA.

A total of 1000 patients were to be recruited with 200 patients in each treatment group. Primary measures of arthritis efficacy were the ACR-20 Responder Index, Patient's Global Assessment of Arthritic Condition, Number of Tender/Painful Joints, Number of Swollen Joints, and Physician's Global Assessment of Arthritic Condition. Secondary measures of arthritis efficacy were Patient's Assessment of Pain-Visual Analog Scale (VAS), Tender/Painful Joints Score, Swollen Joints Score, Duration of Morning Stiffness, Health Assessment Questionnaire (HAQ) Functional Disability Index,

measurement of C-Reactive Protein (CRP), Incidence of Withdrawal Due to Lack of Arthritis Efficacy, Time to Withdrawal Due to Lack of Arthritis Efficacy, and the ACR-50 Responder Index. The above arthritis assessments were performed at the screening and baseline visits and at Weeks 2, 6 and 12 (or Early Termination) follow-up visits. The UGI safety of SC-58635 was assessed with endoscopies performed at baseline and Week 12 (or Early Termination). Quality of Life analysis consisted of the SF-36 Health Survey which was performed at baseline and Week 12 (or Early Termination Visit).

Physician's and Patient's Global Assessments of Arthritic Condition were graded on the following scale: 1 = very good; 2 = good; 3 = fair; 4 = poor; and 5 = very poor. A patient was classified as "improved" if a reduction of at least two grades from baseline for grades 3 to 5 or a change in grade 2 to 1 was observed. A patient was classified as "worsened" if an increase of at least two grades from baseline for grades 1 to 3 or a change in grade 4 to 5 was observed. The 'improved' rates and 'worsened' rates were analyzed by the CMH Test stratified by center. The linear trend test (Naproxen group excluded) and pairwise comparisons were performed based on the above CMH tests.

Mean change analyses, including the linear trend test for all SC-58635 and placebo groups and overall and pairwise comparisons for all five treatment groups, were performed on all primary measures of efficacy with the exception of the ACR-20 responder index, using an analysis of covariance (ANCOVA) with treatment and center as factors, and the corresponding baseline value as a covariate. ACR-20 Responder Index was analyzed by the CMH Test stratified by center. The results of the pairwise comparisons for the SC-58635 200 mg BID and 400 mg BID treatment groups versus placebo for the ITT Cohort were interpreted using Hochberg's step-up procedure.

2). Study Results

Patient Disposition

A total of 1149 patients were enrolled into the study and 1148 received treatment for up to 12 weeks as follows: 231 patients in the placebo group, 240 patients in the SC-58635 100 mg BID group, 235 patients in the SC-58635 200 mg BID group, 217 patients in the SC-58635 400 mg BID group, and 225 patients in the Naproxen 500 mg BID group.

Of the 1148 patients in the ITT Cohort, 698 (61%) completed the study: 101 (44%) in the placebo group, 154 (64%) in the SC-58635 100 mg BID group, 158 (67%) in the SC-58635 200 mg BID group, 137 (63%) in the SC-58635 400 mg BID group, and 138 (61%) in the Naproxen 500 mg BID group. The main reasons for study termination were treatment failure and adverse events. Placebo group had noticeably more patients withdrew due to treatment failure (45%) than other treatment groups (28% in SC-58635 100 mg BID, 21% in SC-58635 200 mg BID, 27% in SC-58635 400 mg BID, and 29% in Naproxen 500 mg BID.). The reasons for study termination, groups by treatment, for all randomized patients are summarized in Table 1 of Appendix A.

Demographics and Baseline Characteristics

The distributions of patients in age, race, gender, height, weight, vital signs, and systolic and diastolic blood pressures at baseline were similar among the treatment groups ($p \geq 0.1$).

Efficacy Results

The following results are for the intent-to-treat cohort.

APPEARS THIS WAY
ON ORIGINAL

ACR Response Index

The results for ACR Response Index described below are also listed in Table 2 of Appendix A.

SC58635 vs. placebo: Based on the ACR-20 Responder Index, more patients in the SC-58635 treatment groups were classified as 'improved' (responders) compared to the placebo group at Weeks 2, 6, and 12. After adjusted for multiple comparison, the results showed that the number of patients classified as 'improved' were statistically significantly higher in both SC-58635 200 mg BID and SC-58635 400 mg BID than in placebo at Weeks 2, 6, and 12 ($p \leq 0.012$). In addition, the number of patients classified as improved in the SC-58635 100 mg BID group was also statistically significantly higher than in placebo at Weeks 2, 6, and 12 ($p \leq 0.008$).

Naproxen vs. placebo and SC-58635: More patients in the Naproxen 500 mg BID group improved at Weeks 2, 6, and 12 compared to placebo and this difference in the distribution of patients who improved was statistically significant at each of these time points ($p \leq 0.049$). At Weeks 2 and 6, there were statistically significantly fewer patients who improved in the Naproxen 500 mg BID group versus the SC-58635 200 mg BID group ($p \leq 0.028$). There were no other statistically significant differences in the distribution of patients who improved between the Naproxen group and the SC-58635 treatment groups ($p \geq 0.076$).

Among SC-58635 groups: SC-58635 groups were generally comparable in ACR improvement rate except that the 200 mg BID group showed statistically significantly higher improvement rate than the 100 mg BID group and 400 mg BID group at Week 6 ($p = .038, .047$, respectively).

ACR Individual Components

The results of the comparison between SC-58635, placebo and Naproxen in ACR individual components described below are also listed in Tables 3-9 of Appendix A.

SC58635 vs. placebo: After adjusted for multiple comparison, the results showed that SC-58635 200 mg BID and 400 mg BID were statistically superior to placebo at all post-baseline time points (Weeks 2, 6, and 12) by both categorical change and mean change analyses in all ACR individual components except CRP. In addition, SC-58635 100 mg BID were statistically superior to placebo at all post-baseline time points by both categorical change and mean change analyses in all ACR individual components except CRP and HAQ.

No statistical significance was found between SC-58635 (100 mg BID, 200 mg BID, and 400 mg BID) and placebo in CRP measurements at any time points (week 2, week 6, and week 12). Also, no statistical significance was found between SC-58635 100 mg BID and placebo at Week 12 ($p=0.088$) in HAQ.

Naproxen vs. placebo and SC-58635: Except for Number of Tender/Painful Joint at Week 12 and CRP at all post-baseline time points, ACR individual components of Naproxen 500 mg BID were statistically superior to placebo at all post-baseline time points. In general, Naproxen 500 mg BID and SC-58635 (100 mg BID, 200 mg BID, and 400 mg BID) were not statistically significantly different in ACR individual components. Two noticeable patterns were that Naproxen 500 mg BID had statistically significantly more (or less deterioration) improvement in CRP than SC-58635 400 mg BID at Week 2 and Week 6 ($p=.007$ and $.021$, respectively), and more improvement in Physician's Global than SC-58635 200 mg BID at Week 2, Week 6 and Week 12 ($p=.003$, $.023$ and $.034$, respectively). _

Among SC-58635 groups: The results for ACR individual components were comparable for the SC-58635 200 mg BID and 400 mg BID. SC-58635 200 mg BID was numerically better than SC-58635 100 mg BID at all time points in all ACR individual components, and SC-58635 200 mg BID was also statistically superior to SC-58635 100 mg BID in Patients Global and Physician's Global at Week 2 and Week 6 ($p\leq.048$), and in HAQ score at Week 6 and Week 12 ($p=.026$ and $.008$, respectively).

ACR 50

A patient was classified as improved if there was at least a 20% improvement from baseline in the number of tender/painful joints and in the number of swollen joints and a 50% improvement from Baseline in at least three of the following: Physician's Global Assessment of Arthritic Condition, Patient's Global assessment of Arthritic Condition, Patient's Assessment of Pain, C-Reactive Protein, and HAQ Functional Disability Index.

The results of the analysis of the ACR-50 Responder Index are presented in Table 10 of Appendix A. The trend in ACR-50 Responder Index among treatment groups were similar to that in ACR-20 Responder Index with the pairwise comparison showing superiority of SC-58635 200 mg BID and 400 mg BID groups over the placebo group, and no statistically significantly difference between the SC-58635 groups and Naproxen group.

Quality of Life Measurements

After adjusted for multiple comparison, the results showed that SC-58635 200 mg BID and 400 mg BID were statistically superior to placebo at Week 12 in all domains of SF-36 (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health) ($p \leq 0.047$). SC-58635 100 mg BID was statistically superior to placebo at Week 12 only in Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional ($p \leq 0.027$).

Naproxen 500 mg BID was statistically superior to placebo at Week 12 in all domains of SF-36 ($p \leq 0.024$) except Role-Physical ($p = 0.097$).

Naproxen 500 mg BID was comparable to SC-58635 (100 mg BID, 200 mg BID, and 400 mg BID) in all SF-36 domains.

APPEARS THIS WAY
ON ORIGINAL

Safety Results

Tables 11-14 of Appendix A listed the pooled (Studies 022 and 023) incidences of adverse events that are statistically significantly different among treatment groups. If the total incidences of adverse events in a body system are statistically significantly different among treatment groups, the individual terms of adverse events in that body system are also listed. Tables 11, 12, 13 and 14 listed the incidences of all adverse events, adverse events that are treatment-related, severe adverse events and treatment-related severe adverse events, respectively, that are statistically significantly different across treatment groups by treatment group, body system and ICD-9 Code. Although the statistical significance were caused mainly by the higher adverse event rates in SC-58635 groups and Naproxen group, placebo had higher incidences in Back Pain, Pain and Nausea, which might be disease related instead of treatment related.

2. Study 023

APPEARS THIS WAY
ON ORIGINAL

1). Protocol

The protocol of Study 023 was identical to that of Study 022 except that UGI safety was not evaluated.

2). Study Results

APPEARS THIS WAY
ON ORIGINAL

Patient Disposition

A total of 1103 patients were enrolled at 75 sites in this study and were randomized to receive one of the five treatments for 12 weeks: placebo, 221 patients; SC-58635 100 mg BID, 228 patients; SC-58635 200 mg BID, 219 patients; SC-58635 400 mg BID, 217 patients; Naproxen 500 mg BID, 218 patients. Of the 1103 patients enrolled, a total of 1102 patients received at least one dose of study drug and were included in the ITT

Cohort. Of the 1102 patients in the ITT Cohort, 578 (52%) completed the study: 78 (35%) in the placebo group, 117 (51%) in the SC-58635 100 mg BID group, 124 (57%) in the SC-58635 200 mg BID group, 126 (58%) in the SC-58635 400 mg BID group, and 133 (61%) in the Naproxen 500 mg BID group. Placebo group had noticeably more patients withdrew due to treatment failure (57%) than other treatment groups (40% in SC-58635 100 mg BID, 34% in SC-58635 200 mg BID, 32% in SC-58635 400 mg BID, and 32% in Naproxen 500 mg BID.). Table 1 of Appendix A presents the reasons for study termination, grouped by treatment, for all randomized patients.

Demographics and Baseline Characteristics

There was a statistically significant difference in mean age across treatment groups ($p=0.017$), but further exploratory analysis did not indicate a statistically significant age by treatment interaction. The treatment groups were comparable in gender, height, weight, vital signs, and systolic and diastolic blood pressures at baseline.

Efficacy Results

The following results are for the intent-to-treat cohort.

**APPEARS THIS WAY
ON ORIGINAL**

ACR Response Index

The results for ACR Responder Index described below are also listed in Table 2 of Appendix A.

SC-58635 vs. placebo: Based on the ACR-20 Responder Index, more patients in the SC-58635 treatment groups were classified as improved compared to the placebo group at Weeks 2, 6, and 12. After adjusted for multiple comparison, the results showed that the differences in the distribution of patients classified as improved were statistically significant for both SC-58635 200 mg BID and SC-58635 400 mg BID compared to placebo at Weeks 2, 6, and 12 ($p\leq 0.002$). In addition, the percentage of patients classified as improved in the SC-58635 100 mg BID group was statistically significantly higher than placebo at Weeks 2, 6, and 12 ($p\leq 0.015$).

Naproxen vs. placebo and SC-58635 groups: More percentage of patients in the Naproxen 500 mg BID group improved at Weeks 2, 6, and 12 compared to placebo and this difference was statistically significant at each of these time points ($p\leq 0.001$). With the exception of Naproxen compared to SC-58635 100 mg BID at Week 12 ($p=0.011$), there were no statistically significant differences between the Naproxen group and the SC-58635 treatment groups in the percentage of patients classified as improved ($p\geq 0.096$).

Among SC-58635 groups: SC-58635 groups were generally comparable in ACR improvement rate except that the 200 mg BID group showed statistically significantly higher improvement rate than the 100 mg BID group at Week 12 ($p=.038$).

ACR Individual Components

The results of the comparison between SC-58635, placebo and Naproxen in ACR individual components described below are also list in Tables 3-9 of Appendix A.

SC-58635 vs. placebo: Except for CRP and Number of Swollen Joints, the results in ACR individual components of SC-58635 100 mg BID, 200 mg BID and 400 mg BID were statistically superior to placebo at all post-baseline time points by both categorical change and mean change analyses ($p \leq .103$). In CRP, no statistical significance was found between SC-58635 (100 mg BID, 200 mg BID, and 400 mg BID) and placebo at any post-baseline time points ($p > .06$) by mean change analyses. In Number of Swollen Joints, statistical significance were only found between SC-58635 100 mg BID and placebo by categorical change analysis at Week 2 ($p = .003$) and Week 12 ($p = .002$).

Naproxen vs. placebo and SC-58635: The results in all ACR individual components of Naproxen 500 mg BID were statistically superior to placebo at all post-baseline time points (week 2, week 6, and week 12). Naproxen 500 mg BID was statistically superior ($p \leq 0.042$) to SC-58635 100 mg BID at all time points in Patient's Global Assessment, Physician's Global Assessment, and at Week 2 and Week 12 in Patient's Assessment of Arthritis Pain, and at Week 12 in HAQ score. Naproxen 500 mg BID was also statistically superior ($p \leq 0.018$) to SC-58635 400 mg BID at all time points in CRP.

Among SC-58635 groups: The results in ACR individual components were comparable for SC-58635 200 mg BID and 400 mg BID except that the 200 mg BID had significantly more improvement in CRP ($p = .008$) than the 400 mg BID group at Week 6. SC-58635 200 mg BID was numerically better than SC-58635 100 mg BID at all time points in all ACR individual components, and SC-58635 200 mg BID was also statistically superior to SC-58635 100 mg BID in Patients Global, Patient's Assessment of Arthritis Pain at Week 2 and Week 12 ($p \leq .042$), HAQ score at Week 6 and Week 12 ($p \leq .031$), and Physician's Global and Number of Tender/Painful Joint at Week 2 ($p \leq .046$).

ACR 50

The results of the analysis of the ACR-50 Responder Index are presented in Table 10 of Appendix A. The trend in ACR-50 Responder Index among treatment groups were similar to that in ACR-20 Responder Index with the pairwise comparison showing superiority of SC-58635 200 mg BID and 400 mg BID groups over the placebo group, and no statistically significant difference between the SC-58635 200 mg BID, SC-58635 400 mg BID groups and Naproxen group.

Quality of Life Measurements

All three SC-58635 treatment groups showed statistically significantly more improvement than placebo in Physical Functioning, Role Physical, Bodily Pain, Vitality,

Social Functioning, and Mental Health domains ($p \leq 0.033$), but none of them showed statistically significantly more improvement than placebo in General Health and Role-Emotional. Placebo showed numerically more improvement in Role-Emotional than SC-58635 100 mg BID.

Naproxen 500 mg BID showed statistically significantly more improvement than placebo in Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, and Mental Health domains ($p \leq 0.004$).

No statistically significant differences were found between Naproxen 500 mg BID and SC-58635 groups in all quality of life domains. ($p \geq 0.074$).

Safety Results

See the discussion in Study 22 in page 5.

III. GI Studies in RA patients

APPEARS THIS WAY
ON ORIGINAL

1. GI Endpoints and Analyses Plan

1). Study 022

The UGI safety of SC-58635 was evaluated with endoscopies performed at baseline and exit time (Week 12 or early termination). Separate gastric and duodenal mucosal scores were assigned to each patients at each visit (0: no visible lesions (normal mucosa); 1: 1-10 petechiae; 2: >10 petechiae; 3: 1-5 erosions; 4: 6-10 erosions; 5: 11-25 erosions; 6: >25 erosions; 7: Ulcer).

A 'Week 12' analysis and a 'Final' analysis were done for the crude rates of gastroduodenal ulcers (i.e., a gastric or duodenal score of 7), gastric ulcers, and duodenal ulcers with CMH tests stratified by baseline status. In the 'Week 12' analysis, only patients undergoing endoscopy at Week 12 and patients found to have an ulcer before Week 12 were included, and last-observation-carried-forward approach was used in calculating the Week 12 ulcer rates among these patients. Patients were categorized as unknown and not included in the Week 12 analysis when they did not undergo an endoscopy at Week 12 and no ulcer was found before Week 12. In the 'Final' analysis, all patients who underwent endoscopy at a scheduled visit or an early termination visit were included and last-observation-carried-forward approach was used in calculating the final ulcer rates. Only those patients who did not undergo a final endoscopy were categorized as unknown and therefore not include in the "Final' analysis.

Time to ulcer was analyzed by log-rank tests. Cumulative ulcer rate based on Kaplan-Meier methods was calculated at Week 12. Patients who withdrew from the study because of reasons other than the development of gastric, duodenal or pyloric channel ulcer were censored at withdrawal time. Patients who completed the study without an

ulcer were censored at the final visit.

2). Study 041

Study 041 was a randomized, double-blind, multi-center, parallel trial designed to evaluate the efficacy and GI safety of SC-58635 200 mg BID as compared to Diclofenac SR 75 mg BID in treating the signs and symptoms of RA. For this study, this reviewer concentrates on the review of GI safety.

A total of 430 patients (212 in the SC-58635 200 mg BID group and 218 in the Diclofenac SR 75 mg BID group), instead of 288 patients as planned in the protocol, were scheduled for endoscopy examination at baseline and Week 24 (or Early Termination). Only a 'Final' analysis was done for the ulcer rate.

2. GI Safety Results

1). Study 022

**APPEARS THIS WAY
ON ORIGINAL**

Gastroduodenal Endoscopy Results

The gastroduodenal endoscopy results by 'Final' and 'Week 12' analyses described below are also presented in Table 15 of Appendix A.

Based on the 'Final' analysis, ulcers developed in 4 (2%) placebo patients, 9 (4%) SC-58635 100 mg BID patients, 6 (3%) SC-58635 200 mg BID patients, 8 (4%) SC-58635 400 mg BID patients and 37 (18%) Naproxen 500 mg BID patients. The incidence of ulceration was significantly greater in the Naproxen 500 mg BID group than all other treatment groups ($p < 0.001$) and there were no statistically significant differences between placebo and any of the SC-58635 groups ($p \geq 0.200$). Further, there was no statistically significant difference in the incidence of ulceration between any of the SC-58635 groups ($p \geq 0.526$).

Based on the 'Week 12' analysis, ulcers developed in 4 (4%) placebo patients, 9 (6%) SC-58635 100 mg BID patients, 6 (4%) SC-58635 200 mg BID patients, 8 (6%) SC-58635 400 mg BID patients and 36 (26%) Naproxen 500 mg BID patients. Results of pairwise comparisons were consistent with that of the 'Final analysis.

Based on the Kaplan-Meier estimator, the rate of developing gastroduodenal ulceration was greater for Naproxen than for placebo or any of the SC-58635 treatment groups and this difference was statistically significant ($p < 0.001$). There were no statistically significant differences between placebo and any of the SC-58635 groups ($p \geq 0.487$) and there were no statistically significant differences among any of the SC-58635 groups ($p \geq 0.348$). The estimated cumulative ulcer rates at Week 12 were: 4.2% for placebo, 11.5% for SC-58635 100 mg BID, 7.5% for SC-58635 200 mg BID, 9.9% for SC-58635 400 mg BID, and 37.4% for Naproxen 500 mg BID (Figure 1).

Gastric Endoscopy Results

The gastric endoscopy results by 'Final' and 'Week 12' analyses described below are also presented in Table 16 of Appendix A.

Based on the 'Final' analysis, ulcers developed in 3 (2%) placebo patients, 6 (3%) SC-58635 100 mg BID patients, 4 (2%) SC-58635 200 mg BID patients, 7 (4%) SC-58635 400 mg BID patients and 30 (14%) Naproxen 500 mg BID patients developed an ulcer. The incidence of ulceration was significantly greater in Naproxen 500 mg BID compared with all other treatment ($p < 0.001$) and there were no statistically significant differences between placebo and any SC-58635 groups ($p \geq 0.254$). Further, there was no statistically significant difference in the incidence of ulceration between any of the SC-58635 groups ($p \geq 0.404$).

Based on the 'Week 12' analysis, ulcers developed in 3 (3%) placebo patients, 6 (4%) SC-58635 100 mg BID, 4 (3%) SC-58635 200 mg BID patients, 7 (5%) SC-58635 400 mg BID patients and 29 (22%) Naproxen 500 mg BID patients. The results of the pairwise comparisons were consistent with that of the 'Final' analysis.

Based on the Kaplan-Meier estimator, the rate of developing gastric ulceration was greater for Naproxen than for placebo or any of the SC-58635 groups and this difference was statistically significant ($p < 0.001$). There were no statistically significant differences between placebo and any of the SC-58635 groups ($p \geq 0.394$) and there were no statistically significant differences among any of the SC-58635 groups ($p \geq 0.201$).

Duodenal Endoscopy Results

The duodenal endoscopy results by 'Final' and 'Week 12' analyses described below are also presented in Table 17 of Appendix A.

Based on the 'Final' analysis, 1 (<1%) placebo patients, 3 (1%) SC-58635 100 mg BID patients, 2 (<1%) SC-58635 200 mg BID patients, 1 (<1%) SC-58635 400 mg BID patients and 8 (4%) Naproxen 500 mg BID patients developed an ulcer. The incidence of ulceration was significantly greater in Naproxen 500 mg BID compared with all treatment groups including placebo ($p \leq 0.039$) except for Naproxen compared to SC-58635 100 mg BID ($p = 0.107$) and there were no statistically significant differences between placebo and any SC-58635 groups ($p \geq 0.297$). Further, there was no statistically significant difference in the incidence of ulceration between any of the SC-58635 groups ($p \geq 0.346$).

Based on the 'Week 12' analysis, ulcers developed in 1 (1%) placebo patients, 3 (2%) SC-58635 100 mg BID patients, 2 (1%) SC-58635 200 mg BID patients, 1 (1%) SC-

58635 400 mg BID patients, and 8 (6%) Naproxen 500 mg BID patients. The results of the pairwise comparisons were consistent with that of the 'Final' analysis.

Based on the Kaplan-Meier estimator, the rate of developing duodenal ulceration was greater for Naproxen than for placebo or any of the SC-58635 groups and this difference was statistically significant compared to the SC-58635 200 mg BID and 400 mg BID treatment groups ($p \leq 0.033$). There were no statistically significant differences between placebo and any of the SC-58635 groups ($p \geq 0.520$) and there were no statistically significant differences among any of the SC-58635 groups ($p \geq 0.383$).

2). Study 041

Gastroduodenal Endoscopy Results

The gastroduodenal endoscopy results described below are also presented in Table 18 of Appendix A.

Based on the 'Final' analysis, ulcers developed in 8 (4%) SC-58635 200 mg BID patients and 33 (15%) Diclofenac SR 75 mg BID patients. The comparison between the two treatments showed a statistically significant treatment difference ($p \leq 0.001$).

Based on the Kaplan-Meier estimator, the rate of developing gastroduodenal ulceration over 24 weeks was greater for Diclofenac SR 75 mg BID than for the SC-58635 200 mg BID group, and this difference was statistically significant ($p \leq 0.001$).

Gastric Endoscopy Results

The gastric endoscopy results described below are also presented in Table 19 of Appendix A.

Based on the 'Final' analysis, gastric ulcers developed in 5 (2%) SC-58635 200 mg BID patients and 24 (11%) Diclofenac 75 SR mg BID patients. The comparison between the two treatments showed a statistically significant treatment difference ($p = 0.002$).

Based on the Kaplan-Meier curves, the rate of developing gastric ulceration over 24 weeks was greater for Diclofenac SR 75 mg BID-treated patients than for SC-58635 200 mg BID patients and this difference was statistically significant ($p \leq 0.001$).

Duodenal Endoscopy Results

The duodenal endoscopy results described below are also presented in Table 20 of Appendix A.

Based on the 'Final' analysis, ulcers developed in 4 (2%) SC-58635 200 mg BID patients and 15 (7%) Diclofenac SR 75 mg BID patients. The comparison between the two treatments showed a statistically significant treatment difference ($p=0.003$).

Based on the Kaplan-Meier estimator, the rate of developing duodenal ulceration over 24 weeks was greater for the Diclofenac SR group than for the SC-58635 group and this difference was statistically significant ($p=0.007$).

III. Reviewer's Comments

1. Improvement Rates for ACR Individual Components

Since the ACR Index is a composite measurement of the improvement of the ACR individual components, it is also of interest to know the improvement rate of each component. This reviewer classifies a patient 'Improved' in an ACR individual component if he/she has a 20% improvement from baseline in that component at Week 12. The results of improvement rate for each ACR component are presented in Tables 21-22 of Appendix A.

Recall that, in Study 022, the ACR improvement rates for placebo, SC-58635 100 mg BID, SC-58635 200 mg BID, SC-58635 400 mg BID and Naproxen 500 mg BID at Week 12 were 29%, 40%, 44%, 39% and 36%, respectively. Table 21 shows that the improvement rates for Patient's Global, Number of Tender/Painful Joints, Number of Swollen Joints, Physician's Global and Patient's Assessment of Pain are higher than and are with similar trend to ACR responder rate in all treatment arms. The improvement rates for HAQ Score are similar to the ACR improvement rates in all treatment arms. The improvement rates for CRP are lower than the ACR improvement rates in all treatment arms, and they are close to each other (16.0%-23.8%) with a numerically higher improvement rate in the placebo group.

Recall that, in Study 023, the ACR improvement rates for placebo, SC-58635 100 mg BID, SC-58635 200 mg BID, SC-58635 400 mg BID and Naproxen 500 mg BID at Week 12 were 23%, 30%, 39%, 36% and 42%, respectively. Table 22 shows that the improvement rates for Patient's Global, Number of Tender/Painful Joints, Number of Swollen Joints, Physician's Global, Patient's Assessment of Pain and HAQ Score are higher than and are with similar trend to the ACR improvement rates in all treatment arms. The improvement rates for CRP are lower than the ACR improvement rates in all treatment arms, and are close to each other (19.0%-23.8%) with a numerically higher improvement rate in the Naproxen group.

The fact that, in both Studies 022 and 023, the improvement rates of CRP are lower than the ACR Response Index, and are close to each other in all treatment arms shows that the CRP level was not responding to the treatments.

2. 'Week 12' Analysis vs. 'Final' Analysis for UGI Event Rates

As described in the 'GI Endpoints and Analyses Plan' on page 8, both 'Week 12' analysis and 'Final' analysis were done for the crude rates of gastroduodenal ulcers in Study 022. The 'Week 12' analysis only included patients who either finished the 12 weeks treatment or developed ulcer before 12 weeks. Since there were less patients in the placebo group finished the 12 weeks study than in other treatment groups, the ulcer rate in the placebo arm was 'inflated' compared to that in other treatments. So the 'Week 12' analysis is biased against placebo. The 'Final' analysis is a last-observation-carried-forward analysis for all patients who underwent an endoscopy evaluation, so it is statistically and clinically more valid than the 'Week 12' analysis.

3. Patient Over-Enrollment in Study 041

APPEARS THIS WAY
ON ORIGINAL

In Study 041, the 49% over enrollment of patients (430 vs. 288) caused the Agency's concern. Per medical reviewer (GI part) Dr. Larry Goldkind's request, the Sponsor redid the GI analysis based on the first 288 patients recruited in the GI study, and the results were similar in terms of statistical significance to the original results based on the 430 patients. Please refer to Dr. Larry Goldkind's review for detailed results.

4. Ulcer Incidence along Time

In Study 022, the SC-58635 groups and Naproxen group showed a trend that gastroduodenal ulcer incidences were higher in the later stage than that in the beginning of the trial (Table 15 of Appendix A, Part 3), but there was no such a trend in the placebo group. This is also reflected by that the estimated ulcer incidences at Week 12 for the SC-58635 groups and Naproxen group (11.5% for SC-58635 100 mg BID, 7.5% for SC-58635 200 mg BID, 9.9% for SC-58635 400 mg BID, and 37.4% for Naproxen 500 mg BID (Figure 1)) were higher than the overall ulcer incidence (4% for SC-58635 100 mg BID, 3% for SC-58635 200 mg BID, 4% for SC-58635 400 mg BID and 18% for Naproxen 500 mg BID (Table 15 of Appendix A)). This would suggest that SC-58635 associated ulcers are less symptomatic than ulcers in patients not on any therapy, and a longer duration might be necessary to detect these ulcers.

IV. Final Conclusion

APPEARS THIS WAY
ON ORIGINAL

1. Efficacy in Treatment of RA

- a. SC-58635 100 mg BID, SC-58635 200 mg BID and SC-58635 400 mg BID are efficacious in treating RA signs and symptoms. The ACR improvement rates in the three SC-58635 groups are statistically significantly higher than that in the placebo group in both Study 022 and Study 023.
- b. Naproxen 500 mg BID is efficacious in treating RA signs and symptoms. The ACR improvement rate of Naproxen 500 mg BID is statistically higher than that in placebo

and not statistically different from SC-58635 200 mg BID and SC-58635 400 mg BID in both Study 022 and Study 023.

- c. Although, in general, there were no statistically significant differences between SC-58635 100 mg BID, SC-58635 200 mg BID and SC-58635 400 mg BID, SC-58635 200 mg BID was numerically superior than SC-58635 100 mg BID in ACR improvement rate and all ACR individual components in both Study 022 and Study 023.

2. UGI Ulcer Rates

APPEARS THIS WAY
ON ORIGINAL

Study 022

- a. The incidence of **gastroduodenal** ulceration were statistically significantly higher in the Naproxen 500 mg BID group than that in the placebo, 58635 100 mg BID, SC-58635 200 mg BID and SC-58635 400 mg BID groups. The incidences of **gastroduodenal** ulcer for the three SC-58635 groups were numerically higher than that of the placebo group, although the differences were not statistically significant. There was no statistically significant difference between any of the SC-58635 groups in the incidence of **gastroduodenal** ulceration. There was a trend that the incidences of **gastroduodenal** ulcers in the SC-58635 groups and Naproxen group were higher at the later stage than that in the beginning of the trial.
- b. The incidences of **gastric** ulceration were statistically significantly higher in the Naproxen 500 mg BID group than that in the placebo, 58635 100 mg BID, SC-58635 200 mg BID and SC-58635 400 mg BID groups. There were no statistically significant differences in the incidence of **gastric** ulceration between placebo and the three SC-58635 groups. There was no statistically significant difference between any of the SC-58635 groups in the incidences of **gastric** ulceration.
- c. The incidences of **duodenal** ulceration was statistically significantly greater in the Naproxen 500 mg BID group than the placebo, SC-58635 200 mg BID and SC-58635 400 mg BID groups, but no statistically significant difference was found between Naproxen 500 mg BID and SC-58635 100 mg BID. There were no statistically significant differences in the incidence of duodenal ulceration between placebo and the three SC-58635 groups. Also, there was no statistically significant difference between any of the SC-58635 groups.

Study 041

APPEARS THIS WAY
ON ORIGINAL

The incidences of gastroduodenal, gastric and duodenal ulceration of Diclofenac 75 mg BID group were statistically significantly higher than that in the SC-58635 200 mg BID group.

APPEARS THIS WAY
ON ORIGINAL

Laura Lu, Ph.D.
Mathematical Statistician

Concur:

Stan Lin, Ph.D.
Team Leader

**APPEARS THIS WAY
ON ORIGINAL**

CC:

HFD-550/MO/Witter
HFD-550/PM/Lutwak
HFD-550/MO/Hyde
HFD-550/Div. File
HFD-725/Lu
HFD-725/Lin ST.
HFD-725/Huque
HFD-725/Div. File

Appendix A. Tables

Table 1. Reasons for Study Termination (All Randomized Patients: 12-Week Pivotal Studies 022 and 023 and 12-Week Pooled Pivotal Studies)

Study	Number of Rheumatoid Arthritis Patients by Treatment Group				
	Placebo	SC-58635			Naproxen
		100 mg BID	200 mg BID	400 mg BID	500 mg BID
Study 022	(n=231)	(n=240)	(n=235)	(n=218)	(n=225)
Total Completed	101 (44%)	154 (64%)	158 (67%)	137 (63%)	138 (61%)
Total Withdrawn	130 (56%)	86 (36%)	77 (33%)	81 (37%)	87 (39%)
Lost to Follow-up	3 (1%)	1 (<1%)	3 (1%)	1 (<1%)	1 (<1%)
Pre-Existing Violation	2 (<1%)	1 (<1%)	3 (1%)	2 (<1%)	0 (0%)
Protocol Non-Compliance	10 (4%)	4 (2%)	4 (2%)	7 (3%)	9 (4%)
Treatment Failure	104 (45%)	67 (28%)	50 (21%)	59 (27%)	65 (29%)
Adverse Event	11 (5%)	13 (5%)	17 (7%)	12 (6%)	12 (5%)
Study 023	(n=221)	(n=228)	(n=219)	(n=217)	(n=218)
Total Completed	78(35%)	117 (51%)	124 (57%)	126 (58%)	133(61%)
Total Withdrawn	143 (65%)	111 (49%)	95 (43%)	91 (42%)	85(39%)
Lost to Follow-up	0 (0%)	0 (0%)	0 (0%)	2 (<1%)	0 (0%)
Pre-Existing Violation	2(<1%)	2 (<1%)	3 (1%)	2 (<1%)	0 (0%)
Protocol Non-Compliance	4 (2%)	5 (2%)	2 (<1%)	2 (<1%)	0 (0%)
Treatment Failure	125 (57%)	92 (40%)	74 (34%)	69 (32%)	69(32%)
Adverse Event	12 (5%)	12 (5%)	16 (7%)	16 (7%)	16 (7%)
Pooled^a	(n=452)	(n=468)	(n=454)	(n=435)	(n=443)
Total Completed	179 (40%)	271 (58%)	282 (62%)	263 (60%)	271 (61%)
Total Withdrawn	273 (60%)	197 (42%)	172 (38%)	172 (40%)	172 (39%)
Lost to Follow-up	3 (<1%)	1 (<1%)	3 (<1%)	3 (<1%)	1 (<1%)
Pre-Existing Violation	4 (<1%)	3 (<1%)	6 (1%)	4 (<1%)	0 (0%)
Protocol Non-Compliance	14 (3%)	9 (2%)	6 (1%)	9 (2%)	9 (2%)
Treatment Failure	229 (51%)	159(34%)	124 (27%)	128 (29%)	134 (30%)
Adverse Event	23 (5%)	25 (5%)	33 (7%)	28 (6%)	28 (6%)

a) Pooled represents data from combined pivotal Studies 022 and 023.

APPEARS THIS WAY
ON ORIGINAL

Table 2. ACR-20 Responders Index: Categorical Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022, 023, and Pooled Pivotal Studies)

Treatment Group	Variable	Percent of Patients Who Improved or Did Not Improve		
		Study 022	Study 023	Pooled(a)
Baseline to Week 2				
Placebo	%Improved	22	25	23
	%Not Improved	78	75	77
SC-58635 100 mg BID	%Improved	40*	42*	41*
	%Not Improved	60	58	59
SC-58635 200 mg BID	%Improved	49* **	46*	48*
	%Not Improved	51	54	52
SC-58635 400 mg BID	%Improved	41*	43*	42*
	%Not Improved	59	57	58
Naproxen 500 mg BID	%Improved	40	44*	42*
	%Not Improved	60*	56	58
Baseline to Week 6				
Placebo	%Improved	28	27	27
	%Not Improved	72	73	73
SC-58635 100 mg BID	%Improved	39*	38*	38*
	%Not Improved	61	62	62
SC-58635 200 mg BID	%Improved	49* **	41*	45*
	%Not Improved	51	59	55
SC-58635 400 mg BID	%Improved	40*	43*	42*
	%Not Improved	60	57	58
Naproxen 500 mg BID	%Improved	37*	46*	42*
	%Not Improved	63	54	58
Baseline to Week 12				
Placebo	%Improved	29	23	26
	%Not Improved	71	77	74
SC-58635 100 mg BID	%Improved	40*	30 **	35*
	%Not Improved	60	70	65
SC-58635 200 mg BID	%Improved	44*	39*	42*
	%Not Improved	56	61	58
SC-58635 400 mg BID	%Improved	39*	36*	38*
	%Not Improved	61	64	62
Naproxen 500 mg BID	%Improved	36*	42*	39*
	%Not Improved	64	58	61

a) Pooled represents data combined from pivotal Studies 022 and 023.

* Indicates a statistically significant difference (p<0.05) from placebo.

** Indicates a statistically significant difference (p<0.05) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Table 3. Patient's Global Assessment of Arthritic Condition: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	3.8	3.7	3.7
SC-58635 100 mg BID	3.8	3.7	3.7
SC-58635 200 mg BID	3.8	3.7	3.7
SC-58635 400 mg BID	3.8	3.7	3.7
Naproxen 500 mg BID	3.7	3.7	3.7
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	3.3(-0.4)	3.4(-0.3)	3.3(-0.4)
SC-58635 100 mg BID	2.8(-0.9)*	2.9(-0.8)* **	2.9(-0.8)*
SC-58635 200 mg BID	2.7(-1.1)* **	2.8(-1.0)*	2.7(-1.0)*
SC-58635 400 mg BID	2.8(-1.0)*	2.8(-1.0)*	2.8(-1.0)*
Naproxen 500 mg BID	2.9(-0.9)*	2.7(-1.0)*	2.8(-0.9)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	3.3(-0.5)	3.4(-0.3)	3.3(-0.4)
SC-58635 100 mg BID	2.9(-0.8)*	3.0(-0.7)* **	3.0(-0.7)*
SC-58635 200 mg BID	2.8(-1.0)*	2.9(-0.8)*	2.8(-0.9)*
SC-58635 400 mg BID	2.8(-0.9)*	2.9(-0.8)*	2.9(-0.9)*
Naproxen 500 mg BID	2.9(-0.8)*	2.8(-0.9)*	2.9(-0.9)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	3.2(-0.5)	3.4(-0.3)	3.3(-0.4)
SC-58635 100 mg BID	2.9(-0.8)*	3.2(-0.6)* **	3.1(-0.7)* **
SC-58635 200 mg BID	2.8(-0.9)*	3.0(-0.8)*	2.9(-0.8)*
SC-58635 400 mg BID	2.9(-0.8)*	3.0(-0.7)*	3.0(-0.8)*
Naproxen 500 mg BID	3.0(-0.8)*	2.9(-0.9)*	2.9(-0.8)*

- a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference ($p < 0.05$) from placebo.
** Indicates a statistically significant difference ($p < 0.05$) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Text Table 4. Number of Tender/Painful Joints: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	29.2	30.1	28.7
SC-58635 100 mg BID	30.0	28.5	28.2
SC-58635 200 mg BID	31.4	29.7	29.6
SC-58635 400 mg BID	28.4	31.3	28.8
Naproxen 500 mg BID	28.9	29.8	28.2
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	21.7(-7.5)	23.2(-5.0)	22.5(-6.3)
SC-58635 100 mg BID	17.9(-11.3)*	17.7(-10.5)*	17.9(-10.9)*
SC-58635 200 mg BID	17.2(-12.0)*	16.2(-12.0)*	16.8(-12.0)*
SC-58635 400 mg BID	17.2(-12.0)*	16.5(-11.7)*	16.9(-11.8)*
Naproxen 500 mg BID	18.4(-10.8)*	16.5(-11.7)*	17.4(-11.3)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	21.0(-8.2)	23.0(-5.2)	21.8(-7.0)
SC-58635 100 mg BID	17.9(-11.3)*	17.7(-10.5)*	17.8(-10.9)*
SC-58635 200 mg BID	17.3(-11.9)*	17.6(-10.6)*	17.3(-11.4)*
SC-58635 400 mg BID	17.0(-12.2)*	16.9(-11.3)*	16.7(-12.0)*
Naproxen 500 mg BID	18.7(-10.5)*	16.7(-11.6)*	17.4(-11.3)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	21.0(-8.2)	22.7(-5.5)	21.9(-6.8)
SC-58635 100 mg BID	17.2(-12.0)*	18.2(-10.0)*	17.8(-10.9)*
SC-58635 200 mg BID	16.9(-12.3)*	18.0(-10.2)*	17.6(-11.2)*
SC-58635 400 mg BID	16.8(-12.4)*	17.1(-11.1)*	16.9(-11.8)*
Naproxen 500 mg BID	19.1(-10.1)	17.1(-11.2)*	18.1(-10.7)*

a) Pooled represents data combined from pivotal Studies 022 and 023.

b) Values are least square mean change. Negative values signify improvement.

* Indicates a statistically significant difference ($p < 0.05$) from placebo.

** Indicates a statistically significant difference ($p < 0.05$) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Table 5. Number of Swollen Joints: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	22.2	21.3	20.8
SC-58635 100 mg BID	21.0	21.4	20.5
SC-58635 200 mg BID	22.1	22.6	21.7
SC-58635 400 mg BID	20.8	22.3	20.7
Naproxen 500 mg BID	20.8	22.1	20.6
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	16.7(-4.6)	16.5(-3.9)	16.6(-4.2)
SC-58635 100 mg BID	14.3(-7.0)*	14.1(-6.3)*	14.2(-6.7)*
SC-58635 200 mg BID	13.3(-8.0)*	13.3(-7.1)*	13.2(-7.7)*
SC-58635 400 mg BID	14.4(-6.9)*	13.8(-6.6)*	14.2(-6.7)*
Naproxen 500 mg BID	14.5(-6.8)*	13.5(-6.8)*	14.0(-6.9)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	16.0(-5.4)	16.6(-3.8)	16.1(-4.8)
SC-58635 100 mg BID	13.7(-7.6)*	14.4(-5.9)*	14.0(-6.8)*
SC-58635 200 mg BID	12.4(-9.0)*	14.2(-6.2)*	13.1(-7.8)*
SC-58635 400 mg BID	13.3(-8.0)*	14.0(-6.4)*	13.5(-7.3)*
Naproxen 500 mg BID	13.4(-7.9)*	14.0(-6.4)*	13.5(-7.3)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	15.9(-5.5)	16.7(-3.7)	16.2(-4.6)
SC-58635 100 mg BID	13.3(-8.0)*	14.5(-5.9)*	14.0(-6.9)*
SC-58635 200 mg BID	12.2(-9.2)*	14.3(-6.0)*	13.2(-7.7)*
SC-58635 400 mg BID	13.7(-7.6)*	14.0(-6.4)*	13.9(-7.0)*
Naproxen 500 mg BID	13.8(-7.6)*	14.3(-6.1)*	14.0(-6.9)*

- a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference ($p < 0.05$) from placebo.
** Indicates a statistically significant difference ($p < 0.05$) from active comparator.

**APPEARS THIS WAY
ON ORIGINAL**

Table 6. Physician's Global Assessment of Arthritic Condition: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	3.7	3.6	3.6
SC-58635 100 mg BID	3.6	3.6	3.6
SC-58635 200 mg BID	3.8	3.6	3.7
SC-58635 400 mg BID	3.7	3.6	3.7
Naproxen 500 mg BID	3.6	3.7	3.6
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	3.2(-0.4)	3.3(-0.3)	3.2(-0.4)
SC-58635 100 mg BID	2.8(-0.8)*	2.9(-0.8)* **	2.8(-0.8)*
SC-58635 200 mg BID	2.6(-1.0)* **	2.7(-1.0)*	2.6(-1.0)*
SC-58635 400 mg BID	2.7(-0.9)*	2.8(-0.9)*	2.7(-0.9)*
Naproxen 500 mg BID	2.8(-0.8)*	2.7(-1.0)*	2.7(-0.9)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	3.1(-0.5)	3.3(-0.4)	3.2(-0.5)
SC-58635 100 mg BID	2.9(-0.8)*	3.0(-0.7)* **	2.9(-0.7)* **
SC-58635 200 mg BID	2.7(-1.0)* **	2.8(-0.8)*	2.7(-0.9)*
SC-58635 400 mg BID	2.7(-0.9)*	2.8(-0.8)*	2.8(-0.9)*
Naproxen 500 mg BID	2.9(-0.8)*	2.7(-0.9)*	2.8(-0.9)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	3.1(-0.5)	3.3(-0.3)	3.2(-0.4)
SC-58635 100 mg BID	2.9(-0.8)*	3.0(-0.6)* **	3.0(-0.7)*
SC-58635 200 mg BID	2.7(-0.9)* **	2.9(-0.8)*	2.8(-0.8)*
SC-58635 400 mg BID	2.8(-0.9)*	2.9(-0.8)*	2.8(-0.8)*
Naproxen 500 mg BID	2.9(-0.7)*	2.8(-0.9)*	2.9(-0.8)*

a) Pooled represents data combined from pivotal Studies 022 and 023.

b) Values are least square mean change. Negative values signify improvement.

* Indicates a statistically significant difference ($p < 0.05$) from placebo.

** Indicates a statistically significant difference ($p < 0.05$) from active comparator.

**APPEARS THIS WAY
ON ORIGINAL**

Table 7. Patient's Assessment of Pain-Visual Analog Scale (VAS): LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	70.2	68.5	68.5
SC-58635 100 mg BID	68.1	66.6	66.4
SC-58635 200 mg BID	69.8	68.3	68.1
SC-58635 400 mg BID	67.3	68.3	66.8
Naproxen 500 mg BID	68.1	67.2	66.6
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	59.8(-7.5)	58.5(-8.8)	59.3(-8.0)
SC-58635 100 mg BID	44.5(-22.7)*	46.6(-20.7)* **	45.9(-21.4)*
SC-58635 200 mg BID	40.1(-27.2)* **	41.3(-26.0)*	40.8(-26.5)*
SC-58635 400 mg BID	43.3(-24.0)*	42.3(-25.1)*	42.9(-24.4)*
Naproxen 500 mg BID	44.6(-22.7)*	41.2(-26.1)*	43.1(-24.2)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	58.4(-8.9)	61.2(-6.1)	59.4(-7.9)
SC-58635 100 mg BID	49.4(-17.9)*	49.0(-18.3)*	49.1(-18.2)*
SC-58635 200 mg BID	43.3(-24.0)* **	47.0(-20.4)*	44.8(-22.5)*
SC-58635 400 mg BID	47.2(-20.1)*	46.2(-21.1)*	46.5(-20.8)*
Naproxen 500 mg BID	48.2(-19.1)*	44.8(-22.5)*	46.2(-21.1)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	58.0(-9.3)	61.8(-5.5)	60.1(-7.2)
SC-58635 100 mg BID	49.0(-18.2)*	51.8(-15.5)* **	50.9(-16.4)*
SC-58635 200 mg BID	46.2(-21.1)*	46.9(-20.4)*	46.9(-20.4)*
SC-58635 400 mg BID	47.6(-19.7)*	48.9(-18.5)*	48.5(-18.8)*
Naproxen 500 mg BID	49.1(-18.2)*	45.3(-22.0)*	47.5(-19.8)*

a) Pooled represents data combined from pivotal Studies 022 and 023.

b) Values are least square mean change. Negative values signify improvement.

* Indicates a statistically significant difference ($p < 0.05$) from placebo.

** Indicates a statistically significant difference ($p < 0.05$) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Table 8. Health Assessment Questionnaire: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	1.45	1.42	1.39
SC-58635 100 mg BID	1.43	1.44	1.38
SC-58635 200 mg BID	1.52	1.38	1.40
SC-58635 400 mg BID	1.44	1.35	1.35
Naproxen 500 mg BID	1.51	1.43	1.43
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	1.38(-0.04)	1.29(-0.07)	1.34(-0.04)
SC-58635 100 mg BID	1.19(-0.23)*	1.12(-0.24)*	1.17(-0.22)*
SC-58635 200 mg BID	1.14(-0.28)* **	1.05(-0.31)*	1.11(-0.28)*
SC-58635 400 mg BID	1.11(-0.30)* **	1.06(-0.30)*	1.10(-0.29)* **
Naproxen 500 mg BID	1.22(-0.20)*	1.08(-0.28)*	1.16(-0.23)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	1.31(-0.11)	1.30(-0.06)	1.31(-0.08)
SC-58635 100 mg BID	1.22(-0.20)*	1.18(-0.18)*	1.21(-0.18)* **
SC-58635 200 mg BID	1.12(-0.30)*	1.08(-0.28)*	1.11(-0.28)*
SC-58635 400 mg BID	1.13(-0.29)*	1.10(-0.26)*	1.12(-0.26)*
Naproxen 500 mg BID	1.17(-0.25)*	1.10(-0.26)*	1.14(-0.25)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	1.32(-0.10)	1.29(-0.07)	1.32(-0.07)
SC-58635 100 mg BID	1.24(-0.17)	1.22(-0.14) **	1.25(-0.14)* **
SC-58635 200 mg BID	1.12(-0.30)*	1.12(-0.24)*	1.14(-0.25)*
SC-58635 400 mg BID	1.13(-0.29)*	1.11(-0.25)*	1.14(-0.25)*
Naproxen 500 mg BID	1.20(-0.22)*	1.11(-0.25)*	1.17(-0.22)*

- a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference ($p < 0.05$) from placebo.
** Indicates a statistically significant difference ($p < 0.05$) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Table 9. C-Reactive Protein: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	16901	15894	15986
SC-58635 100 mg BID	15532	16922	15857
SC-58635 200 mg BID	17214	18470	17310
SC-58635 400 mg BID	16705	16011	15792
Naproxen 500 mg BID	15248	16090	15051
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	16240(433.3)	15905(-300.7)	15965(-38.6)
SC-58635 100 mg BID	15642(-165.2)	16909(703.6)	16206(202.3)
SC-58635 200 mg BID	15516(-290.6)	16580(374.8)	15879(-124.3)
SC-58635 400 mg BID	18027(2220.3) **	17741(1535.4) **	17824(1820.0)* **
Naproxen 500 mg BID	14526(-1281)	14958(-1247)	14676(-1328)
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	16304(497.3)	17625(1420.0)	16814(810.1)
SC-58635 100 mg BID	17356(1548.8)	18312(2106.5)	17784(1780.7) **
SC-58635 200 mg BID	16039(232.1)	16601(395.5)	16211(206.9)
SC-58635 400 mg BID	19073(3266.2) **	20077(3871.3) **	19386(3382.8)* **
Naproxen 500 mg BID	15545(-261.7)	15865(-340.8)	15623(-380.7)
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	16788(981.3)	18984(2778.4)	17863(1858.9)
SC-58635 100 mg BID	17102(1294.9)	17442(1236.1)	17123(1119.7)
SC-58635 200 mg BID	16943(1135.6)	16243(37.6)	16454(450.2)
SC-58635 400 mg BID	19382(3574.8)	19195(2990.0) **	19165(3161.7) **
Naproxen 500 mg BID	16691(884.3)	14936(-1270)*	15761(-243.1)

- a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference (p<0.05) from placebo.
** Indicates a statistically significant difference (p<0.05) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Table 10. ACR-50 Responders Index: Categorical Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022, and 023)

		Percent of Patients Who Improved or Did Not Improve	
Treatment Group	Variable	Study 022	Study 023
Baseline to Week 2			
Placebo	%Improved	6	5
	%Not Improved	94	95
SC-58635 100 mg BID	%Improved	9	11*
	%Not Improved	91	89
SC-58635 200 mg BID	%Improved	15*	17*
	%Not Improved	85	83
SC-58635 400 mg BID	%Improved	16*	12*
	%Not Improved	84	88
Naproxen 500 mg BID	%Improved	12*	15*
	%Not Improved	88	85
Baseline to Week 6			
Placebo	%Improved	8	7
	%Not Improved	92	93
SC-58635 100 mg BID	%Improved	12	10
	%Not Improved	88	90
SC-58635 200 mg BID	%Improved	17*	16*
	%Not Improved	83	84
SC-58635 400 mg BID	%Improved	17*	12
	%Not Improved	83	88
Naproxen 500 mg BID	%Improved	13*	15*
	%Not Improved	87	85
Baseline to Week 12			
Placebo	%Improved	7	6
	%Not Improved	93	94
SC-58635 100 mg BID	%Improved	11	10**
	%Not Improved	89	90
SC-58635 200 mg BID	%Improved	17*	17*
	%Not Improved	83	83
SC-58635 400 mg BID	%Improved	17*	12*
	%Not Improved	83	88
Naproxen 500 mg BID	%Improved	13	18*
	%Not Improved	87	82

* Indicates a statistically significant difference (p<0.05) from placebo.

** Indicates a statistically significant difference (p<0.05) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Table 11. Number of Subjects in Pivotal Studies Reporting All-Causalities Adverse Events for Only Adverse Events Not Associated With Medical History Events --RA studies 22 and 23

Body System ICD-9 Term	Placebo N = 452		100mg BID N = 468		200mg BID N = 454		400mg BID N = 435		Naproxan N = 443		P-Value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
APPLICATION SITE DISORDERS											
CELLULITIS	0	(0.0)	0	(0.0)	1	(0.2)	4	(0.9)	2	(0.5)	0.029
BODY AS A WHOLE - GENERAL DISORDERS											
BACK PAIN	17	(3.8)	12	(2.6)	11	(2.4)	4	(0.9)	4	(0.9)	0.001
EDEMA GENERALIZED	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.2)	5	(1.1)	0.006
PAIN	6	(1.3)	4	(0.9)	4	(0.9)	2	(0.5)	1	(0.2)	0.045
PERIPHERAL PAIN	6	(1.3)	7	(1.5)	4	(0.9)	2	(0.5)	2	(0.5)	0.052
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS											
ALL TERMS IN BODY SYSTEM	118	(26.1)	102	(21.8)	95	(20.9)	84	(19.3)	85	(19.2)	0.008
APHASIA	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.160
ATAXIA	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
CONVULSIONS	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
CRAMPS LEGS	1	(0.2)	2	(0.4)	4	(0.9)	3	(0.7)	5	(1.1)	0.086
DIZZINESS	10	(2.2)	6	(1.3)	9	(2.0)	9	(2.1)	15	(3.4)	0.149
DYSKINESIA	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.160
DYSPHONIA	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.160
HEADACHE	100	(22.1)	78	(16.7)	77	(17.0)	66	(15.2)	62	(14.0)	0.002
HYPERTONIA	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0.467
HYPERTONIA	4	(0.9)	5	(1.1)	3	(0.7)	2	(0.5)	0	(0.0)	0.042
HYPOESTHESIA	1	(0.2)	3	(0.6)	2	(0.4)	1	(0.2)	0	(0.0)	0.303
MIGRAINE	6	(1.3)	8	(1.7)	0	(0.0)	2	(0.5)	2	(0.5)	0.022
NEURALGIA	2	(0.4)	3	(0.6)	4	(0.9)	4	(0.9)	4	(0.9)	0.353
NEURITIS	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0.467
NEUROPATHY	0	(0.0)	0	(0.0)	2	(0.4)	1	(0.2)	0	(0.0)	0.662
PARESTHESIA	5	(1.1)	5	(1.1)	1	(0.2)	3	(0.7)	2	(0.5)	0.174
VERTIGO	1	(0.2)	1	(0.2)	1	(0.2)	1	(0.2)	0	(0.0)	0.498
VISUAL FIELD DEFECT	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0.487
GASTRO-INTESTINAL SYSTEM DISORDERS											
ALL TERMS IN BODY SYSTEM	84	(18.6)	118	(25.2)	110	(24.2)	109	(25.1)	130	(29.3)	0.001
ABDOMINAL PAIN	12	(2.7)	19	(4.1)	13	(2.9)	15	(3.4)	26	(5.9)	0.042
BOWEL DISEASE	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.160
CHEILITIS	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
COLITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
CONSTIPATION	13	(2.9)	7	(1.5)	8	(1.8)	3	(0.7)	13	(2.9)	0.746
DIARRHEA	18	(4.0)	26	(5.6)	24	(5.3)	28	(6.4)	18	(4.1)	0.755
DIVERTICULITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
DYSPEPSIA	29	(6.4)	47	(10.0)	40	(8.8)	38	(8.7)	55	(12.4)	0.014
DYSPHAGIA	2	(0.4)	1	(0.2)	1	(0.2)	1	(0.2)	1	(0.2)	0.589
ERUCTATION	1	(0.2)	0	(0.0)	1	(0.2)	2	(0.5)	0	(0.0)	0.974
ESOPHAGITIS	1	(0.2)	1	(0.2)	1	(0.2)	1	(0.2)	0	(0.0)	0.498
FLATULENCE	3	(0.7)	13	(2.8)	10	(2.2)	8	(1.8)	8	(1.8)	0.511

BEST POSSIBLE COPY

Table 11. (Continue) Number of Subjects in Pivotal Studies Reporting All-Causalities Adverse Events for Only Adverse Events Not Associated With Medical History Events --RA studies 22 and 23

Body System ICD-9 Term	Placebo N = 452 N (%)	100mg BID N = 468 N (%)	200mg BID N = 454 N (%)	400mg BID N = 435 N (%)	Naproxan N = 443 N (%)	P-Value
GASTRO-INTESTINAL SYSTEM DISORDERS						
GASTRIC ULCER	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0.305
GASTRITIS	0 (0.0)	1 (0.2)	2 (0.4)	4 (0.9)	0 (0.0)	0.397
GASTROENTERITIS	4 (0.9)	5 (1.1)	2 (0.4)	4 (0.9)	2 (0.5)	0.426
GASTROESOPHAGEAL REFLUX	0 (0.0)	3 (0.6)	4 (0.9)	3 (0.7)	4 (0.9)	0.114
GI NEOPLASM BENIGN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0.150
GINGIVITIS	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0.305
H PYLORI	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0.631
HEMORRHAGE RECTUM	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0.150
HEMORRHOIDS	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)	0.497
HEMORRHOIDS BLEEDING	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0.150
HERNIA	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.047
HIATAL HERNIA	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0.599
HICCUP	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.5)	0 (0.0)	0.304
MELENA	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0.632
NAUSEA	23 (5.1)	18 (3.8)	15 (3.3)	18 (4.1)	18 (4.1)	0.550
SALIVARY GLAND ENLARGEMENT	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0.467
STOMATITIS	4 (0.9)	7 (1.5)	4 (0.9)	1 (0.2)	11 (2.5)	0.237
STOOLS ABNORMAL	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.304
TONGUE DISORDER	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0.487
TOOTH CARIES	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0.600
TOOTH DISORDER	6 (1.3)	9 (1.9)	9 (2.0)	8 (1.8)	5 (1.1)	0.799
VOMITING	5 (1.1)	4 (0.9)	4 (0.9)	11 (2.5)	6 (1.4)	0.207
LIVER AND BILIARY SYSTEM DISORDERS						
HEPATIC FUNCTION ABNORMAL	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.047
REPRODUCTIVE DISORDERS, FEMALE						
DYSMENORRHEA	5 (1.1)	4 (0.9)	2 (0.4)	3 (0.7)	0 (0.0)	0.042
REPRODUCTIVE DISORDERS, MALE						
INFECTION SOFT TISSUE	1 (0.2)	1 (0.2)	4 (0.9)	2 (0.5)	6 (1.4)	0.032

BEST POSSIBLE COPY

Table 12. Number of Subjects in Pivotal Studies Reporting Treatment-Related Adverse Events
RA studies 22 and 23

Body System ICD-9 Term	Placebo N = 452 N (%)	100mg BID N = 468 N (%)	200mg BID N = 454 N (%)	400mg BID N = 435 N (%)	Naproxan N = 443 N (%)	P-Value
BODY AS A WHOLE - GENERAL DISORDERS						
BACK PAIN	4 (0.9)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0.010
EDEMA GENERALIZED	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	5 (1.1)	0.001
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS						
HEADACHE	39 (8.6)	34 (7.3)	31 (6.8)	24 (5.5)	25 (5.6)	0.040
GASTRO-INTESTINAL SYSTEM DISORDERS						
ALL TERMS IN BODY SYSTEM						
ABDOMINAL PAIN	60 (13.3)	81 (17.3)	79 (17.4)	70 (16.1)	97 (21.9)	0.004
BOWEL DISEASE	11 (2.4)	16 (3.4)	10 (2.2)	11 (2.5)	21 (4.7)	0.151
COLITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.160
CONSTIPATION	6 (1.3)	3 (0.6)	5 (1.1)	2 (0.5)	11 (2.5)	0.150
DIARRHEA	12 (2.7)	21 (4.5)	17 (3.7)	17 (3.9)	12 (2.7)	0.858
DIVERTICULITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0.150
DYSPEPSIA	24 (5.3)	39 (8.3)	34 (7.5)	30 (6.9)	44 (9.9)	0.049
DYSPHAGIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0.150
ERUCTION	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.5)	0 (0.0)	0.974
ESOPHAGITIS	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0.498
FLATULENCE	3 (0.7)	8 (1.7)	7 (1.5)	6 (1.4)	8 (1.8)	0.271
GASTRIC ULCER	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0.305
GASTRITIS	0 (0.0)	1 (0.2)	2 (0.4)	3 (0.7)	0 (0.0)	0.536
GASTROENTERITIS	1 (0.2)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	0.302
GASTROESOPHAGEAL REFLUX	0 (0.0)	3 (0.6)	3 (0.7)	2 (0.5)	2 (0.5)	0.469
HEMORRHOIDS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0.150
HEMORRHOIDS BLEEDING	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.160
HIATAL HERNIA	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0.599
HICCUP	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.304
MELENA	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0.987
NAUSEA	16 (3.5)	13 (2.8)	11 (2.4)	14 (3.2)	12 (2.7)	0.626
STOMATITIS	3 (0.7)	3 (0.6)	3 (0.7)	0 (0.0)	9 (2.0)	0.115
STOOLS ABNORMAL	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0.304
VOMITING	2 (0.4)	3 (0.6)	3 (0.7)	5 (1.1)	1 (0.2)	0.952
LIVER AND BILIARY SYSTEM DISORDERS						
HEPATIC FUNCTION ABNORMAL	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.047
PSYCHIATRIC DISORDERS						
INSOMNIA	0 (0.0)	3 (0.6)	6 (1.3)	2 (0.5)	8 (1.8)	0.012
VISION DISORDERS						
BLURRED VISION	2 (0.4)	5 (1.1)	1 (0.2)	0 (0.0)	0 (0.0)	0.027

BEST POSSIBLE COPY

Table 13. Number of Subjects in Pivotal Studies Reporting All-Causalities Adverse Events for Only Severe Adverse Events
RA studies 22 and 23

Body System ICD-9 Term	Placebo N = 452		100mg BID N = 468		200mg BID N = 454		400mg BID N = 435		Naproxan N = 443		P-Value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS											
ALL TERMS IN BODY SYSTEM											
ATAXIA	13	(2.9)	5	(1.1)	5	(1.1)	4	(0.9)	5	(1.1)	0.040
DIZZINESS	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
HEADACHE	12	(2.7)	4	(0.9)	2	(0.4)	3	(0.7)	2	(0.5)	0.147
MIGRAINE	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0.002
NEURALGIA	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0.487
PARESTHESIA	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.600
GASTRO-INTESTINAL SYSTEM DISORDERS											
ALL TERMS IN BODY SYSTEM											
ABDOMINAL PAIN	5	(1.1)	8	(1.7)	8	(1.8)	5	(1.1)	15	(3.4)	0.045
DIARRHEA	1	(0.2)	3	(0.6)	1	(0.2)	1	(0.2)	6	(1.4)	0.090
DYSPEPSIA	3	(0.7)	1	(0.2)	1	(0.2)	1	(0.2)	1	(0.2)	0.971
GASTRIC ULCER	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.5)	6	(1.4)	0.164
GASTROENTERITIS	1	(0.2)	2	(0.4)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
NAUSEA	0	(0.0)	1	(0.2)	3	(0.7)	1	(0.2)	2	(0.5)	0.497
STOMATITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.265
TOOTH CARIES	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.150
TOOTH DISORDER	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
VOMITING	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0.632
											0.600

BEST POSSIBLE COPY

Table 14. Number of Subjects in Pivotal Studies Reporting Treatment-Related Adverse Events for Only Severe Adverse Events
RA studies 22 and 23

Body System ICD-9 Term	Placebo N = 452		100mg BID N = 468		200mg BID N = 454		400mg BID N = 435		Naproxan N = 443		P-Value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
GASTRO-INTESTINAL SYSTEM DISORDERS											
ALL TERMS IN BODY SYSTEM											
ABDOMINAL PAIN	3	(0.7)	4	(0.9)	7	(1.5)	4	(0.9)	11	(2.5)	0.027
DIARRHEA	1	(0.2)	2	(0.4)	1	(0.2)	1	(0.2)	4	(0.9)	0.218
DYSPEPSIA	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	1	(0.2)	0.662
GASTRIC ULCER	2	(0.4)	1	(0.2)	2	(0.4)	2	(0.5)	6	(1.4)	0.067
NAUSEA	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
VOMITING	0	(0.0)	0	(0.2)	3	(0.7)	1	(0.2)	2	(0.5)	0.265
					1	(0.2)	0	(0.0)	0	(0.0)	0.987

BEST POSSIBLE COPY

Table 15. ANALYSIS OF GASTRODUODENAL CRUDE ULCER RATE (Study 022)

Part 1: Ulcer Rate

	Placebo (N=231)	SC-58635 100mg (N=240)	SC-58635 200mg (N=235)	SC-58635 400mg (N=217)	Naproxan 500mg (N=225)
Week12 Analysis					
Known Results					
No ulcer	95 (96%)	139 (94%)	139 (96%)	122 (94%)	101 (74%)
Ulcer	4 (4%)	9 (6%)	6 (4%)	8 (6%)	36 (26%)
Unknown Results (Without Endo /With Endo)	132 (36/96)	92 (22/70)	90 (28/62)	87 (24/63)	88 (22/66)
Final Analysis					
No Ulcer	196 (98%)	214 (96%)	213 (97%)	189 (96%)	173 (82%)
Ulcer	4 (2%)	9 (4%)	6 (3%)	8 (4%)	37 (18%)
Unknown	31 (31/0)	17 (17/0)	16 (16/0)	20 (20/0)	15 (15/0)

Part 2: p- VALUES FOR TREATMENT COMPARISONS (a):

	200mg vs. Placebo	400mg vs. placebo	100mg vs. placebo	200mg vs. 100mg	400mg vs. 100mg	400mg vs. 200mg	Naproxen vs. placebo	Naproxen vs. 100mg	Naproxen vs. 200mg	Naproxen vs. 400mg
Week12	0.829	0.434	0.482	0.554	0.883	0.666	<0.001	<0.001	<0.001	<0.001
Final	0.539	0.230	0.200	0.526	0.966	0.582	<0.001	<0.001	<0.001	<0.001

(a) Cochran- Mantel- Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis

Part 3: NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL

Study Days	Placebo (N=231)		SC-58635 100mg (N=240)		SC-58635 200mg (N=235)		SC-58635 400mg (N=217)		Naproxan 500mg (N=225)	
	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer
WK2 (2- 28)	64	1	31	1	28	1	28	0	27	8
WK6 (29- 76)	32	1	39	1	34	1	35	1	39	5
WK12 (77- 91)	95	2	139	7	139	4	122	7	101	23
>91	5	0	5	0	12	0	4	0	6	1
TOTAL	196	4	214	9	213	6	189	8	173	37

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 16. ANALYSIS OF GASTRIC CRUDE ULCER RATE (Study 022)

Part 1: Ulcer Rate

	Placebo	SC-58635 100mg	SC-58635 200mg	SC-58635 400mg	Naproxan 500mg
	(N=231)	(N=240)	(N=235)	(N=217)	(N=225)
Week12 Analysis					
Known Results					
Noulcer	96 (97%)	141 (96%)	140 (97%)	123 (95%)	105 (78%)
Ulcer	3 (3%)	6 (4%)	4 (3%)	7 (5%)	29 (22%)
Unknown Results (Without Endo /With Endo)	132 (36/96)	93 (22/71)	91 (28/63)	87 (24/63)	91 (22/69)
Final Analysis					
Noulcer	197 (99%)	217 (97%)	215 (98%)	190 (96%)	180 (86%)
Ulcer	3 (2%)	6 (3%)	4 (2%)	7 (4%)	30 (14%)
Unknown	31 (31/0)	17 (17/0)	16 (16/0)	20 (20/0)	15 (15/0)

Part 2: p- VALUES FOR TREATMENT COMPARISONS (a):

	200mg vs. Placebo	400mg vs. placebo	100mg vs. placebo	200mg vs. 100mg	400mg vs. 100mg	400mg vs. 200mg	Naproxen vs. placebo	Naproxen vs. 100mg	Naproxen vs. 200mg	Naproxen vs. 400mg
WEEK12	0.828	0.409	0.717	0.550	0.607	0.477	<0.001	<0.001	<0.001	<0.001
FINAL	0.861	0.254	0.412	0.570	0.710	0.404	<0.001	<0.001	<0.001	<0.001

(a) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis

Table 17. ANALYSIS OF DUODENAL CRUDE ULCER RATE (Study 022)

Part 1: Ulcer Rate

	Placebo	SC-58635 100mg	SC-58635 200mg	SC-58635 400mg	Naproxan 500mg
	(N=231)	(N=240)	(N=235)	(N=217)	(N=225)
Week12 Analysis					
Known Results					
Noulcer	96 (99%)	144 (98%)	142 (99%)	128 (99%)	120 (94%)
Ulcer	1 (1%)	3 (2%)	2 (1%)	1 (<1%)	8 (6%)
Unknown Results (Without Endo /With Endo)	134 (36/98)	93 (22/71)	91 (28/63)	88 (24/64)	97 (22/75)
Final Analysis					
Noulcer	199 (>99%)	220 (99%)	217 (99%)	196 (99%)	202 (96%)
Ulcer	1 (<1%)	3 (1%)	2 (<1%)	1 (<1%)	8 (4%)
Unknown	31 (31/0)	17 (17/0)	16 (16/0)	20 (20/0)	15 (15/0)

Part 2: p- VALUES FOR TREATMENT COMPARISONS (a):

	200mg vs. Placebo	400mg vs. placebo	100mg vs. placebo	200mg vs. 100mg	400mg vs. 100mg	400mg vs. 200mg	Naproxen vs. placebo	Naproxen vs. 100mg	Naproxen vs. 200mg	Naproxen vs. 400mg
WEEK12	0.583	0.789	0.428	0.574	0.360	0.534	0.026	0.084	0.033	0.019
FINAL	0.510	0.784	0.297	0.598	0.346	0.537	0.011	0.107	0.039	0.019

(a) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 18. GASTRODUODENAL ENDOSCOPY RESULTS by 'Final' Analysis (Study 041)

	SC-58635200mg	DICLOFENAC75MG	p-VALUE (a)
	(N=326)	(N=329)	
CRUDEULCERRATE:			<0.001
NOULCER	204 (96%)	185 (85%)	
ULCER	8 (4%)	33 (15%)	
TOTAL	212 (100%)	218 (100%)	

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

Table 19. GASTIC ENDOSCOPY RESULTS by 'Final' Analysis (Study 041)

	SC-58635200mg	DICLOFENAC75MG	p-VALUE (a)
	(N=326)	(N=329)	
CRUDEULCERRATE:			<0.002
NOULCER	207 (98%)	194 (89%)	
ULCER	5 (2%)	24 (11%)	
TOTAL	212 (100%)	218 (100%)	

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

Table 20. DUODENAL ENDOSCOPY RESULTS by 'Final' Analysis (Study 041)

	SC-58635200mg	DICLOFENAC75MG	p-VALUE (a)
	(N=326)	(N=329)	
CRUDEULCERRATE:			<0.003
NOULCER	208 (98%)	202 (93%)	
ULCER	4 (2%)	15 (7%)	
TOTAL	212 (100%)	217 (100%)	

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

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 21. Study 022: Number and Percent of Patients Improved in ACR Individual Components (a)

	Placebo N(%)	SC-58635 100 N(%)	SC-58635 200 N(%)	SC-58635 400 N(%)	Naproxan 500 N(%)
Patient's Global	109 (47.19)	144(60.00)	148(62.98)	133(61.29)	130(57.78)
No. of Tender Joints	125(54.11)	170(70.83)	168(71.49)	153(70.51)	152(67.56)
No. of Swollen Joints	128(55.41)	160(66.67)	170(72.34)	139(64.06)	146(64.89)
Physician's Global	107(46.32)	137(57.08)	154(65.53)	135(62.21)	126(56.00)
Assessment of Pain	90(38.96)	129(53.75)	130(55.32)	121(55.76)	111(49.33)
HAQ Score	84(36.36)	95(39.58)	113(48.09)	97(44.70)	78(34.67)
CRP	55(23.81)	56(23.33)	47(20.00)	38(17.51)	36(16.00)

(a) A patient is classified as 'Improved' in a ACR individual component if the patient had at least 20% improvement from baseline in that component

Table 22. Study 023: Number and Percent of Patients Improved in ACR Individual Components (a)

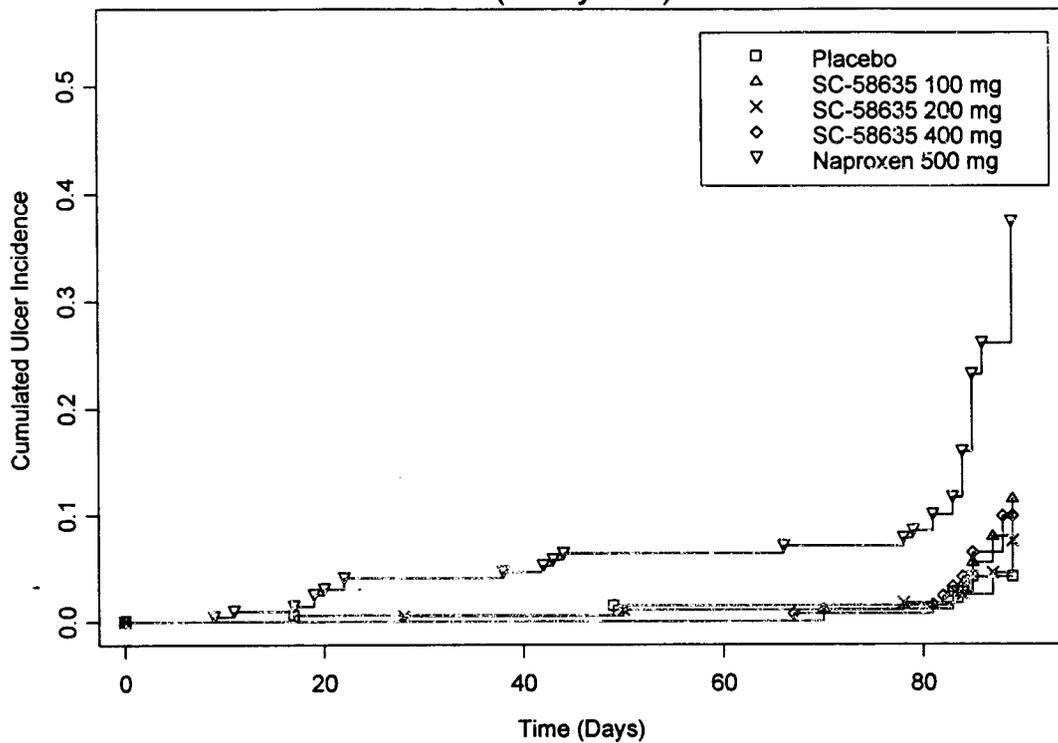
	Placebo N(%)	SC-58635 100 N(%)	SC-58635 200 N(%)	SC-58635 400 N(%)	Naproxan 500 N(%)
Patient's Global	88(39.82)	116(50.88)	126(57.80)	126(58.06)	139(63.76)
No. of Tender Joints	108(48.87)	146(64.04)	143(65.60)	156(71.89)	153(70.18)
No. of Swollen Joints	120(54.30)	129(56.58)	146(66.97)	137(63.13)	137(62.84)
Physician's Global	80(36.20)	123(53.95)	126(57.80)	135(62.21)	148(67.89)
Assessment of Pain	78(35.29)	116(50.88)	118(54.13)	115(53.00)	132(60.55)
HAQ Score	69(31.22)	89(39.04)	98(44.95)	91(41.94)	98(44.95)
CRP	42(19.00)	52(22.81)	46(21.10)	45(20.74)	52(23.85)

(a) A patient is classified as 'Improved' in a ACR individual component if the patient had at least 20% improvement from baseline in that component

APPEARS THIS WAY
ON ORIGINAL

Appendix B. Figures

Figure 1. Kaplan-Meier Estimates of Gastroduodenal Ulcer Rate (Study 022)



APPEARS THIS WAY
ON ORIGINAL

Arthritis Advisory Committee

December 1, 1998

NDA 20-998 Celebrex™ (celecoxib) Searle

Volume I: FDA Medical Reviews

Pain

Statistical Review

STATISTICAL EFFICACY AND SAFETY REVIEW

ALL ACUTE PAIN STUDIES

NDA: 20-998

Drug Class: Analgesic and Anti-inflammatory Agent

Name of Drug: Celecoxib (SC-58635) [Celebrex] Capsules 100 mg and 200 mg

Applicant: G.D. Searle
4901 Searle Parkway, Skokie, IL 60077
Contact: Winifred Begley (847) 982-8155

Indications: Management of Acute and Chronic Pain;
Treatment of Signs and Symptoms
Of Osteoarthritis and Rheumatoid Arthritis

**Controlled
Clinical Studies:** Pain - N49-96-02-005; -025; -027; -028; -029; -070; -080
Separate Review: RA-012; RA-022; RA-023; RA-041; OA-013;
OA-020; OA-021; OA-042; OA-047; OA-054; OA-060; OA-087;
GI-062; GI-071

Statistical Reviewer: Lillian Patrician, MS, MBA

Submission Date: June 29, 1998
Fileability Meeting Date: August 05, 1998
Review Date: October 24, 1998
User Fee Date: December 31, 1998

I. Background

On March 13, 1995, the sponsor began a clinical development program to investigate the efficacy and safety of SC-58635 Celecoxib as compared to placebo in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis, and in the management of pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) were included as positive control. The NDA was filed June 29, 1998. This drug has not been approved elsewhere in the world.

SC-58635 Celecoxib is a new molecular entity that is an analgesic and anti-inflammatory agent. It selectively inhibits cyclooxygenase-2 (COX-2), thereby reducing the formation of prostaglandins that are involved in inflammation. NSAIDs are the currently used analgesic and anti-inflammatory agents, referred to as COX-1 agents. They have a recognized degree of adverse effects including upper gastrointestinal (UGI) mucosal injury, impairment of renal function, exacerbation of hypertension, and alteration of platelet function.

This review is an evaluation of the performance of Celecoxib (Celebrex) as studied for the management of acute pain in studies using postsurgical pain models. A total of 1,347 patients with postsurgical pain were randomized to seven placebo-controlled clinical trials of up to five days treatment duration (Studies N49-96-02-005; 025; 027; 028; 029; 070; and 080).

Measurements of analgesic efficacy included time-specific pain assessments of Pain Intensity Difference or Change from Baseline (PID), Pain Relief (PR) and Sum of Pain Intensity Difference and Pain Relief (PRID), as well as Median Time to Perceptible Pain Relief.

[Attachment # 1 - Page 25]

The analgesic effect on pain experienced by Osteoarthritis and Rheumatoid Arthritis patients was evaluated under separate statistical review for studies conducted for the treatment of the signs and symptoms of OA and RA (OA studies -020; -021; -042; -047; -054; -060; -087, and RA studies -022; -023). During a Pre-NDA meeting on 12-FEB-98 between the FDA and sponsor, the concept of a general chronic pain claim was discussed. A chronic pain claim and the types of studies needed to support such a claim was not determined. The sponsor planned to propose a labeling with the NDA.

II. Overall Safety Summary in Acute Pain Studies [Attachments # 2 A-B-C - Pages 26-28]

1. Patient Disposition: There were 1,347 patients enrolled in the six acute pain studies, 005, 025, 027, 028, 029, and 070 in which 305 were randomized to placebo, and 294 to active control agents: 50 to Ibuprofen 400 mg; 50 to Aspirin 650 mg; 89 to Naproxen 550 mg; and 105 to Darvocet 100 mg. There were 748 Celecoxib patients: 50 were in the 25 mg; 85 in the 50 mg; 268 in the 100 mg; 260 in the 200 mg; and 85 in the 400 mg dosage groups. Nine hundred fifty-four (954) or 71% of the patients were Caucasian; 257 or 19% were Hispanic; and the remaining 136 or 10% were of other racial origins. More females than males participated; 816 or 61% were female and 531 or 39% were male. **[Attachment # 2A - Page 26]**

2. Safety Profile: The overall safety profile for Celecoxib use in these short-term acute pain studies was comparable to placebo and the positive control agents. Throughout all acute pain studies, no deaths and no serious adverse experiences were reported. Nine hundred twenty-five (925) or 69% of the patients completed study by definition of "completion" established in the study reports. Across treatment groups, a comparable percentage of patients discontinued due to adverse reactions: placebo (3%); Celecoxib groups (2%); and active comparator agents (2%). More placebo patients discontinued due to treatment failure (26%) as compared to Celecoxib (20%) and active control agents (22%). However, fewer placebo patients discontinued for reasons of noncompliance (3%) as compared to Celecoxib (6%) and active control (11%).

3. Adverse Reactions: Seven Hundred ninety-five or 59% of the patients had no concurrent adverse experiences. Five hundred fifty-two (552) or 41% reported reactions: 124 or 9% noted at least one severe reaction; 255 or 19% had no higher than moderate reactions; and 173 or 13% had no higher than mild. By the investigators' opinions regarding relation to treatment, 17 or 1% of the patients had adverse reactions that were considered probably related, and 301 or 22% were patients whose relation to drug was deemed uncertain. The sponsor included a secondary review of these adverse experiences and determined according to their medical opinion that 248 or 18% of the patients had adverse reactions that were related to treatment.

The percentage of patients reporting reactions was comparably distributed among treatment groups. While 40% of placebo patients reported adverse experiences, 41% of all Celecoxib patients did so, and 43% of the patients in the active control groups also reported adverse experiences. There was also a comparable distribution of patients experiencing severe adverse reactions: 10% of placebo patients; 9% of Celecoxib patients; and 11% of active comparator patients reported severe adverse reactions.

Five hundred fifty-two (552) of the 1,347 patients enrolled in the acute pain program reported a total of 995 adverse reactions. The incidence of reaction per patient was higher in the active comparator group. Two hundred fourteen (214) reactions were experienced by 305 placebo patients resulting in 0.70 reactions per patient, and a comparable 0.71 for the 531 experiences reported by the 748 Celecoxib patients. However, the 294 active control patients taken as a group reported 250 reactions resulting in 0.85 reactions per patient.

The highest incidence of reactions was nausea; headache; alveolar osteitis; vomiting; and dizziness. Celecoxib patients had a lower percentage incidence of nausea (12%) than those taking active control agents (16%), although both groups were higher than placebo (8%). Celecoxib patients also had a lower percentage incidence of headache (8%) compared to active control (12%) and placebo (13%). However, the percentage incidence of alveolar osteitis was higher in the Celecoxib group (8%) than in active control (5%) and placebo (6%). There was comparable percentage incidence of vomiting (5% to 6%) and dizziness (4% to 5%) in all three treatment groups. There was also a comparable incidence of severe adverse reactions reported across the placebo (11% of all reactions were severe), Celecoxib (12% were severe), and active comparator groups (14% were severe). There was no prevalence of specific adverse reaction per sex or racial group. [Attachment # 2B - Page 27]

Patients in the Celecoxib group and not those in the placebo and active control groups experienced a low incidence of certain adverse reactions. These are noted in the event that they may represent a safety signal regarding use of this investigational drug. They include reports of anxiety; arthrosis; asthenia; epistaxis; fatigue; hypokinesia; ileus; influenza-like symptoms; LDH increase; menorrhagia; pallor; pneumothorax; abnormal stools; stupor; and vasodilation. Additionally, even though the incidence rate is again very low, there was a higher incidence of confusion; diarrhea; dyspepsia; hot flushes; oral hemorrhage; somnolence; and upper respiratory tract infection reported by patients in the Celecoxib group than by placebo and active control. [Attachment # 2C - Page 28]

III. Protocol Considerations

1. Intent-to-Treat Analysis (ITT): The sponsor analyzed all pain management studies by using an ITT Cohort defined as "all randomized patients (with two exceptions) who took at least one dose of study drug. One exception was exclusion from the efficacy analysis for patients who required rescue medication prior to the one-hour assessment. Additionally, if two consecutive scheduled pain assessments in the first two hours were missed, and therefore obtained by interpolation from the same two observed data points for any patient, that patient was excluded from the analyses". Time-specific pain measurements were analyzed at all defined time points.
2. Missing Values: As per the 12-FEB-98 Pre-NDA meeting, the sponsor decided to consider 2 approaches to missing values, that of using both the LOCF (last observation carried forward) and BOCF (baseline observation carried forward) for imputing pain intensity and pain relief data after the patient took rescue medication.
3. Measures of Analgesic Efficacy in Post-surgical Pain Studies: Time-Specific Pain Intensity (Categorical) was assessed as pain at this time is 0=none; 1=mild; 2=moderate; 3=severe. Time-Specific Pain Relief (PR) assessed by relief from starting pain of 0=none; 1=little; 2=some; 3=lot; 4=complete. Time to Rescue Medication was calculated as the difference between the start time for the rescue medication and time the first dose was taken.

Time to Onset of Perceptible Pain Relief (Studies 025, 027, 070 only) was assessed by instructing the patient to click a stopwatch at the time of perceptible pain relief. Each patient was instructed: "I would like you to stop the stopwatch when you first feel any pain-relieving effect whatsoever from the drug. This does not necessarily mean you feel completely better, although you might, but when you first feel any differences in the pain that you have had."

Time-Specific Pain Intensity (VAS) was assessed by asking the patient to place a mark on the 100 mm VAS [ranging from 0 mm (no pain) to 100 mm (worst pain)] to indicate pain magnitude.

Time to Onset of Meaningful Pain Relief (025, 027, 070 only) was assessed by instructing the patient to stop a stopwatch at the time when he or she first experienced meaningful pain relief. Each patient was given the following instruction: "I would like you to stop the stopwatch when you have meaningful pain relief. That is, when the relief from the pain is meaningful to you."

4. Primary Efficacy Measures:

- 1) Time-Specific Pain Intensity Difference (PID) (Categorical), derived by subtracting from the Baseline pain intensity score the pain intensity score at the post-dose time points (emphasis in the ISE at the time points up to eight hours). Time-Specific Pain Intensity was assessed as a categorical scale of 0=none; 1=mild; 2=moderate; 3=severe.
- 2) Time-Specific Pain Relief (PR), measured at the post-dose time points (emphasis in the ISE at the time points up to eight hours). Time-Specific Pain Relief (PR) was assessed as 0=none; 1=little; 2=some; 3=lot; 4=complete.
- 3) Time-Specific Sum of PID on categorical scale and PR (PRID), at the post-dose time points (emphasis in the ISE at the time points up to eight hours);
- 4) Time to Onset of Perceptible Pain Relief.

Mean Pain Intensity Difference and Pain Relief (PRID) Scores were calculated as the sum of the Pain Relief (PR) Score and Pain Intensity Difference (PID) Score. The best possible score was 7 (complete pain relief [PR=4] and change from severe pain at Baseline to no pain [PID=3]). The worst possible score was -1 (no pain relief [PR=0] and change from moderate pain at Baseline to severe pain [PID= -1]). Mean Pain Relief (PR) scores were reported on a scale of 0 to 4 with 0 indicating no pain relief and 4 indicating complete pain relief. Mean PID (Categorical) Scores were calculated by subtracting the pain intensity at a specific assessment time from the Baseline pain intensity. Scores could range from -1 (worst possible score) to 3 (best possible score).

5. Secondary Efficacy Measures:

- 1) Time-Specific Pain Intensity Difference (VAS), derived by subtracting from the Baseline pain intensity score, the pain intensity score at the post-dose time points;
- 2) Summed Pain Intensity Difference, (SPID), for the sum of the PID scores through the first 3, 6, 8, 10 and 12 hours, respectively;
- 3) Total Pain Relief (TOTPAR) for the sum of the PR through hours 3, 6, 8, 10 and 12;
- 4) Summed PRID scores (SPRID) for the sum of the PRID scores through the first 3, 6, 8, 10 and 12 hours, respectively;
- 5) Time to First Experienced 50% Pain Relief;
- 6) Proportion of patients who experienced 50% pain relief;
- 7) Proportion of patients who experienced 100% pain relief defined as complete pain relief (PR=4) and pain intensity (categorical) rating of none (PI=0).

6. Statistical Assessment of Efficacy Variables: The sample size calculation was based on one primary efficacy variable (PID), and the comparison of each dose of Celecoxib versus

placebo. A sample size of 50 patients per treatment group was required to detect with at least 80% power and type I error at 0.0167 (for a two-sided test adjusted for three comparisons) a difference of at least 0.396 at 45 minutes in the PID score. The estimate of variability used for sample size calculations in the PID scores at 45 minutes is 0.60.

A one-way analysis of variance (ANOVA) was performed to determine whether the randomization was successful in creating treatment groups that exhibited only chance variations at Baseline with respect to age, height, weight, and vital signs. Homogeneity of treatment groups in terms of gender and race was examined by Pearson's Chi-square test. The summary of dental surgery and Baseline data (categorical variables including surgical trauma rating, maximum degree of impaction, Baseline pain intensity, and number of molars extracted) were analyzed with Pearson's Chi-square test. Other Baseline variables included the time from surgery until taking study medication, and the Baseline pain intensity (VAS). These variables were analyzed using ANOVA. Number of molars extracted was also analyzed using ANOVA.

Time-specific PID (Categorical and VAS), time-specific PR, time-specific PRID, SPID, TOTPAR, and SPRID were analyzed using ANOVA with treatment and patient's pain intensity at Baseline as factors. For time-specific PR, the analysis was also performed without patient's pain intensity at Baseline included as a factor. The Baseline pain intensity was treated as a categorical variable except for PID (VAS) where pain intensity at Baseline was treated as continuous. A p-value was provided for the treatment effect with treatment and Baseline being the factors in the ANOVA model. For subgroup analyses, a p-value provided age and gender effect by including these separately in the ANOVA model. Fisher's protected least significant difference (LSD) multiple comparison was applied to the model-adjusted treatment means.

Time to Onset of Perceptible Pain Relief, Time to Meaningful Pain Relief, Time First Experienced 50% Pain Relief and the Time to Rescue Medication were analyzed using survival analysis methods. The median time to event for each drug group was calculated using the Kaplan-Meier product limit estimator. Ninety-five percent confidence intervals on the median time to event were calculated using the method of Simon and Lee. An overall log-rank test comparing treatment groups was performed. If the overall test was significant, pairwise comparisons were made between treatment groups using pairwise log-rank tests as outlined below: For time to event variables: Time to Onset of Perceptible Pain Relief, Time to Meaningful Pain Relief, Time First Experienced 50% Pain Relief, if a patient took rescue medication before experiencing the event, the time to event variable was set to take an event time equal to $24.1 + (0.005 \times \text{Time to Rescue Medication})$ hours. The shorter the time to rescue, the longer the time to event.

For the Analysis of Post-General and Post-Orthopedic Surgery Studies, the single dose (Day 1) data were carried out in a manner analogous to that used in the single dose post-oral surgery studies. These analyses were based on the pain assessments before first remediation or rescue medication. The multiple dose data were analyzed and based on the pain assessments before rescue medication using similar statistical methodology.

Time to Onset of Perceptible Pain Relief and Meaningful Pain Relief Calculation: If a patient stopped the first stopwatch, then that time was taken as the Time to Onset of Perceptible Pain Relief. If a patient stopped the second stopwatch, that time was Time to Meaningful Pain Relief. If the patient stopped only the first stopwatch, and did not take rescue medication, Time to Meaningful Pain Relief was taken as a censored time equal to the lesser of 24 hours or the time to withdrawal. If the patient took rescue and stopped only the first stopwatch, then the Time to Meaningful Pain Relief was taken as an event time equal to $24.1 + (0.005 \times \text{Time to Rescue Medication})$ hours. If the patient stopped neither stopwatch and did not take rescue medication,

the Time to Onset of Perceptible Pain Relief and Time to Meaningful Pain Relief were taken as a censored time (24 hours or the time to withdrawal). If the patient took rescue and stopped neither stopwatch, the Time to Onset of Perceptible Pain Relief and Time to Meaningful Pain Relief were taken as an event time equal to $24.1 + (0.005 \div \text{Time to Rescue})$ hours.

Time First Experienced 50% Pain Relief: For patients not experiencing 50% pain relief and who took rescue medication, the Time to First Experienced 50% Pain Relief was taken as an event time equal to $24.1 + (0.005 \div \text{Time to Rescue Medication})$ hours. For patients not experiencing 50% pain relief and who did not take rescue medication, this time was taken as the lesser of 24 hours or the time to withdrawal. The percentage of patients with at least 50% pain relief was analyzed by pairwise Fisher's exact test.

IV. Pain Study 005 - Postsurgical Dental Pain [Attachment # 3 - Page 29]

1. Study Design: Study 49-96-02-005 was a Phase 2, single-blind, placebo-controlled comparison of the safety and efficacy of 2 doses of Celecoxib (100 and 400 mg) with Placebo and Aspirin 650 mg in patients with moderate to severe postsurgical dental pain following extraction of third molar teeth (one of which must have been mandibular) requiring bone removal.

The study was conducted between 08/23/95 and 10/03/95. The protocol date is 6/22/95.

Amendment #1, dated 8/4/95, changed the comparator in the study from Ibuprofen to Aspirin.

Administrative Change #1, dated 8/14/95, reconciled data collection on the case report forms with the Searle database; and Administrative Change #2, dated 10/25/95 (almost 1 month after end-of-study), modified the statistical sections of the protocol to reflect the FDA draft guidance ("Presentation of Efficacy Results of Single-Dose Analgesics for Studies Using Acute Pain Models", Jan 1995) as recommended by the FDA Pilot Drug Evaluation Staff.

The sponsor's study report was revised in 12/97 after end-of-study for the following changes:

- 1) The definition of a patient who completed the study was changed from one who completed evaluations through 1 hour (as defined by protocol), to one who completed through 24 hours; and
- 2) The method of extrapolation for pain scores was changed to be consistent with the FDA draft guidance document (Presentation of Efficacy Results of Single-Dose Analgesics for Studies Using Acute Pain Models, Jan 1997) and with other analgesia studies conducted in the program. This change in methodology resulted in slight differences in the efficacy results.

There was a Pretreatment Visit, Surgical Procedure, a Baseline Visit, a 24-hour Treatment Period, and a Post-treatment Period. The Pretreatment Visit occurred within 14 days prior to the administration of study medication. At the Surgical Procedure, the molar(s) was extracted and an oral surgeon made a surgical trauma rating. At the Baseline assessment, only patients experiencing moderate to severe pain (greater than or equal to 50 mm on a VAS of 100 mm) within six hours of the completion of surgery were enrolled into the study.

The Treatment Period was the 8-hour period immediately following the administration of a single dose of study medication. Patients remained in the research unit for the 8-hour Treatment Period. Scheduled pain assessments were at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours post-dose. Assessments included Pain Intensity (Categorical Scale); Pain Relief; Pain at Least Half Gone; Pain Intensity (VAS); and Patient's Global Evaluation.

The use of potentially confounding medications in the post-surgical period was restricted as specified in the protocol. Patients were allowed to take rescue medication at any time in the study, if needed. Prior to taking the rescue medication, the patients completed a final pain assessment and were dropped from the study. For those patients who did not take rescue medication, the final pain assessments and end-of-study safety assessments were performed in the Post-treatment Period.

2. Patient Disposition: Using ANOVA and Pearson's Chi-square testing, the sponsor reports that the treatment groups were comparable for age, race, gender, and with respect to height, weight, and vital signs at Baseline. For all patients, the age range was 18 to 60 years. Across treatment groups, 36% to 50% of the patients were male and 70% to 84% were Caucasian. The degree of impaction and baseline pain intensity were comparable ($p \geq 0.966$) across all treatment groups. All treatment groups were comparable with respect to number of molars extracted ($p \geq 0.612$, continuous). All treatment groups were comparable with respect to time from surgery until taking study medication and baseline pain intensity on the VAS ($p \geq 0.069$). Mean pain intensity across treatment groups was 59.1 to 62.0 (0 to 100 scale) and mean time until taking study medication was 2:25 to 2:45 hours after surgery.

3. Sponsor's Evaluation: The sponsor reports, "The single Celecoxib doses of 100 and 400 mg were effective analgesic agents in the dental pain model; they were safe and efficacious in alleviating post-oral surgery pain. A nonefficacious dose was not identified. Based on these results, doses of 25 mg, 50 mg, 100 mg, 200 mg and 400 mg were studied in Phase III trials." [ISE - Page 339 of 355]

Fisher's protected LSD multiple comparison procedure was applied to the adjusted treatment means. The time to rescue medication was analyzed by pairwise log-rank tests. Patients not requiring rescue medication were considered censored at eight hours for the time to rescue medication analysis. The above pairwise multiple comparisons were done in the same fashion as Fisher's protected LSD. This means an overall log-rank test on the time to rescue medication was performed. If the overall test was significant, pairwise comparisons were made between the treatment groups using pairwise log-rank tests.

4. Reviewer's Evaluation: This single-blind study did not undergo a full efficacy review. The treatment medications were dispensed as bottles of 4 capsules for the placebo, 100 mg and 400 mg arms, and as bottles of 2 Nuprin caplets plus 2 placebo capsules for the positive control arm. Therefore, the secondary objective, "to compare the analgesic activity of aspirin 650 mg versus placebo in patients with moderate to severe pain in a postsurgical dental pain model and to assess the relationship between SC-58635 plasma concentrations and pain intensity difference (PID) scores 1 hour post-treatment" was not met under fully blinded conditions.

However, the sponsor's analyses indicate that both 400mg and 100mg SD Celecoxib groups showed statistically significant analgesic efficacy compared to placebo when used in a postsurgical dental pain model. For LOCF in both dosage groups, statistically superior mean Pain Relief (PR) and mean Pain Intensity Difference (PID) began 45 minutes postdose and continued through Hour 8. Positive control Aspirin 650mg was superior to placebo beginning 30 minutes postdose through Hour 8; to Celecoxib 400mg beginning 30 minutes postdose through Hour 1; and to Celecoxib 100mg beginning 45 minutes postdose through Hour 8.

V. Pain Study 025 - Postsurgical Dental Pain [Attachment # 4 - Page 30]

1. **Study Design:** Study 49-96-02-025 was a double-blind, placebo-controlled comparison of the safety and efficacy of 3 single doses (SD) of Celecoxib (25, 50, and 200 mg) with Placebo and Ibuprofen 400mg SD in patients with moderate to severe postsurgical dental pain following extraction of molar teeth involving mandibular bone removal. This study followed the same design and included the same patient population as that of Study N49-96-02-005, however, the study was double-blind and of 24-hour duration. Scheduled pain assessments were made at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours postdose. Additionally, patients were given 2 stopwatches to separately record Time to Perceptible and Time to Meaningful Pain Relief.

The study was conducted from 7/9/96 through 11/7/96. The protocol date is 6/3/96. One amendment is dated as 6/13/96. The sponsor's study report was revised after the end-of-study in 12/97 for the following: (1) The definition of a patient completing study was changed from completing evaluations through 1 hour (as defined by protocol), to completing through 24 hours; (2) The method of extrapolation for pain scores was changed to be consistent with the FDA draft guidance ("Presentation of Efficacy Results of Single-Dose Analgesics for Studies Using Acute Pain Models", Jan 1997) and with other analgesia studies conducted in the SC-58635 program. This change in methodology resulted in slight differences in the efficacy results. (3) Adverse events were recoded for consistency with other reports in the program.

2. **Patient Disposition:** Using ANOVA and Pearson's Chi-square testing, the sponsor reports that the treatment groups were comparable for age, race, gender, and with respect to height, weight, and vital signs at Baseline. For all patients, the age range was 18 to 50 years. Across treatment groups, 20% to 42% of the patients were male and 54% to 68% were Caucasian. The degree of impaction and baseline pain intensity were comparable ($p \geq 0.217$) across all treatment groups. All treatment groups were comparable with respect to number of molars extracted ($p \geq 0.927$, categorical and $p=0.756$, continuous). All treatment groups were comparable with respect to time from surgery until taking study medication and baseline pain intensity on the VAS ($p \geq 0.281$). Mean pain intensity across treatment groups was 59.8 to 63.6 (0 to 100 scale) and mean time until taking study medication was 2:27 to 2:38 hours after surgery.

3. **Sponsor's Evaluation:** The sponsor reports, "Celecoxib 25 mg and 50 mg were submaximally efficacious doses in Study 025 as higher doses of Celecoxib were associated with a greater degree of analgesic efficacy." It was also reported, "Across all efficacy measures there was a statistically significant increase in analgesic effectiveness with increasing doses of Celecoxib, with the 200 mg dose level providing the most rapid relief with the longest duration as compared to the Celecoxib 50 mg, 25 mg and placebo treatments". [ISE - Page 339 of 355]

"The results of this study demonstrate that, for all primary (PID, PR, PRID, Time to Onset of Perceptible Pain Relief, Time to Rescue Medication) and secondary (Time-Specific PID VAS, PPID, Peak Pain Relief, Time to Meaningful Pain Relief, Time to 50% Pain Relief, Percent of Patients Experiencing at Least 50% Pain Relief, Patient Global Evaluation, and the 6, 8, 10, 12, and 24 hour SPID, TOTPAR, and SPRID) measures of efficacy, single oral doses of SC-58635 at dose levels of 25 mg, 50 mg and 200 mg provided greater relief from moderate to severe postoperative dental pain than placebo."

"Across all efficacy measures there was a statistically significant increase in analgesic effectiveness with increasing doses of SC-58635, with the 200 mg dose level providing the most

rapid relief with the longest duration as compared to the SC-58635 25 mg, 50 mg and placebo treatments. The SC-58635 200 mg dose level demonstrated greater analgesic efficacy as compared to the SC-58635 25 mg, 50 mg and placebo treatments. This greater analgesic efficacy persisted throughout the 24 hour Posttreatment Period”.

“This difference in analgesic response was consistently numerically better than placebo for most assessment times after 0.5 hours postdose and was statistically significant for the SC-58635 200 mg dose as compared to placebo for all the summed efficacy measures at all assessment times. The increase in SC-58635 200 mg analgesic efficacy was also statistically significant for PID (1.0-24.0 hours), PR (0.75-24.0 hours), PRID (0.75-24.0 hours), and percent of patients experiencing at least 50% Pain Relief (1.0 - 9.0 hours). The SC-58635 200 mg dose level provided statistically significant more rapid onset of Time to Perceptible Pain Relief”.

4. Reviewer’s Evaluation : [Attachment # 9 A-B - Pages 37-38] A repeated analysis of primary efficacy parameters using the sponsor’s efficacy datasets for LOCF verified the results reported in the submission. These were again executed after modifying for baseline-observation-carried-forward (BOCF). The results for LOCF offer Celecoxib a slightly better advantage over those for BOCF primarily in that the duration of statistical significance is longer for LOCF than BOCF. [Missing Values - Page 3]

Celecoxib 200mg SD demonstrated analgesic efficacy compared to placebo when used in a postsurgical dental pain model. Using LOCF, statistically superior mean Pain Relief (PR) beginning 45 minutes postdose ($p=0.0173$) through Hour 24 ($p= 0.0004$). Mean Pain Intensity Difference (PID) began 1 hour postdose and continued through Hour 12. The Celecoxib 25mg and 50mg dosage levels also separated from placebo for these 2 efficacy measures, but the superiority only lasted for 2 hours duration. Ibuprofen 400mg, used as a positive control, demonstrated superiority to placebo from 45 minutes ($p=0.0001$) through Hour 11 ($p=0.0398$), and also to the 3 dosage levels of Celecoxib at varying assessment timepoints.

Using BOCF, statistically superior mean Pain Relief (PR) for the Celecoxib 200mg group compared to placebo began 45 minutes postdose and continued through Hour 10. The mean Pain Intensity Difference (PID) began 1 hour postdose and continued through Hour 9. The Celecoxib 25mg and 50mg dosage levels also separated from placebo for these 2 efficacy measures, but the superiority only lasted for 2 - 4 hours duration. Ibuprofen 400mg was superior to placebo from 45 minutes postdose through Hour 8 (PR) and Hour 9 (PID), and also to the 3 dosage levels of Celecoxib at varying assessment timepoints.

Mean Pain Intensity Difference (PID-LOCF) [Study Report Table 025-9 - Pages 39-41] or change from baseline for patients in all 3 Celecoxib dosage groups (25, 50, and 200 mg SD) showed a statistically significant difference from placebo beginning at Hour 1 and continuing up to Hour 3 following treatment. The 200mg and 50mg groups continued with statistically significant differences through Hour 12. At 45 minutes, 400mg SD Ibuprofen was statistically superior to all levels of Celecoxib, as well as placebo. Ibuprofen remained statistically superior to Celecoxib and placebo through Hour 5, and continued to be statistically superior to placebo and numerically superior to Celecoxib throughout the subsequent hourly assessments.

Mean Pain Relief (PR-LOCF) [Study Report Table 025-10 - Pages 44-46] for patients in all 3 Celecoxib dosage groups (25, 50, and 200 mg SD) showed a statistically significant difference from placebo beginning at Hour 1 and continuing up to Hour 3 postdose. The 200mg SD group showed a statistically significant difference beginning 45 minutes after treatment start and

continuing through Hour 24. At 45 minutes, positive control 400mg SD Ibuprofen was statistically superior to all levels of Celecoxib, as well as placebo. Ibuprofen remained statistically superior to Celecoxib and placebo through Hour 3, and continued to be statistically superior to placebo and numerically superior to Celecoxib throughout the subsequent hourly assessments.

Only patients in the Ibuprofen 400mg SD group achieved a meaningful level of analgesia (74% of Ibuprofen 400mg patients compared to 18% of placebo; 42% of 25mg; 46% of 50mg; and 54% of 200 mg Celecoxib patients). A higher percentage of Ibuprofen patients also achieved a perceptible level of pain relief (82% of Ibuprofen 400mg patients compared to 36% of placebo; 58% of 25mg; 64% of 50mg; and 70% of 200 mg Celecoxib patients). [*Study 025 App 2.3*]

Mean Sum of Pain Intensity Difference and Pain Relief (PRID-LOCF) [*Study Report Table 025-11 - Pages 49-51*] in all 3 Celecoxib dosage groups (25, 50, and 200 mg SD) showed a statistically significant difference from placebo beginning at Hour 0.75 and continuing up to Hour 10 following treatment. The 200mg group continued with statistically significant differences through Hour 24. At 45 minutes, positive control 400mg SD Ibuprofen was statistically superior to all levels of Celecoxib, as well as placebo. Ibuprofen remained statistically superior to Celecoxib and placebo through Hour 5, and continued to be statistically superior to placebo and numerically superior to Celecoxib throughout the subsequent hourly assessments.

Median Time to Onset of Perceptible Pain Relief - LOCF [*Study Report Table 025-12 - Pages 53-54*] for patients in all 3 Celecoxib dosage groups (25, 50, and 200 mg SD) showed a statistically significant difference from placebo. The positive control, 400mg SD Ibuprofen, was statistically superior to the 50 mg and 25 mg levels of Celecoxib, as well as placebo. The median time to onset was 0:33 for Ibuprofen; 0:38 for Celecoxib 200mg; 1:05 for Celecoxib 50mg; 0:53 for Celecoxib 25mg; and >24:00 for placebo.

Median Time to Administration of Rescue Medication - LOCF revealed that fewer patients in the 200mg Celecoxib group required rescue medication than in any other treatment group, including Ibuprofen (84% of Ibuprofen 400mg compared to 92% of placebo; 92% of 25mg; 86% of 50mg; and 74% of 200 mg Celecoxib patients). The median time to rescue medication was 3:05 for Celecoxib 200mg; 1:48 for Celecoxib 50mg; 1:32 for Celecoxib 25mg; and 1:17 for placebo. [*Study 025 Appendix 2.3*]

Duration of analgesic efficacy - LOCF was determined as the time for which a treatment group maintained a statistically significant difference from placebo. Ibuprofen 400mg SD resulted in statistically significant differences from placebo beginning 45 minutes postdose and continuing through Hour 24. Ibuprofen was also superior to 200mg Celecoxib beginning at 45 minutes postdose and continuing for 3 to 5 hours. It was superior to both 25mg and 50mg dosages from 45 minutes through Hour 24.

Peak analgesic effect - LOCF for Ibuprofen 400mg SD in PID score was 1.12 units, whereas Celecoxib 200mg peaked with a score of 0.58 and the 50mg dose with a score of 0.48. The peak scores in Pain Relief (PR) for these 3 treatment groups was 2.28 for Ibuprofen; 1.74 for Celecoxib 200mg; and 1.18 for Celecoxib 50mg. All groups achieved these maximum levels at Hour 3 postdose. The time to onset of perceptible pain relief was 33 minutes for Ibuprofen; 38 minutes for Celecoxib 200mg; and 1 hour 5 minutes for Celecoxib 50mg.

VI. Pain Study 027 - Postsurgical Dental Pain [Attachment # 5 - Page 31]

1. Study Design: Study 49-96-02-027 was a double-blind, placebo-controlled comparison of safety and efficacy of 2 doses of Celecoxib (100 and 200 mg SD) with Placebo and Anaprox 550mg SD in patients with moderate to severe postsurgical dental pain following extraction of 2 or more impacted third molar teeth. This study followed the same design and included the same patient population as that of Study N49-96-02-005, however, the study was double-blind and of 24-hour duration. Scheduled pain assessments were made at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours postdose. Additionally, patients were provided two stopwatches with which to record Time to Perceptible and Time to Meaningful Pain Relief.

The study was conducted between 03/04/97 and 07/25/97. The protocol date is 01/28/97. Amendment #1, dated 01/29/97, added the 200mg dose and increased the planned study size to 220. Amendment #2, dated 02/10/97, extended the posttreatment period to 24 hours. Administrative change dated 09/24/97 (2 months following end-of-study) modified the analysis plan based on communications with the FDA. The modifications (1) changed the extrapolation method for missing values to the LOCF method; (2) changed the time windows used in linear interpolation of missing values; (3) added exploratory analysis of time to onset of analgesia; and (4) clarified the name of one of the primary measures of efficacy. The medical monitor for this study was also changed.

2. Patient Disposition: Using ANOVA and Pearson's Chi-square testing, the sponsor found treatment groups comparable for age, race, gender, as well as height, weight, and vital signs at Baseline. Of the 220 patients enrolled, none required rescue medication throughout the first hour postdose (ITT cohort period), and 81 completed the Hour 24 assessment without rescue.

The age range of patients in all treatment groups was 18 to 52 years, with the majority less than 30 years old. Across treatment groups, 45% of the patients were male and 36% were Caucasian. The degree of impaction and baseline pain intensity were comparable ($p \geq 0.322$) across all treatment groups. All treatment groups were comparable with respect to number of molars extracted ($p \geq 0.718$, categorical). All treatment groups were comparable with respect to time from surgery until taking study medication and baseline pain intensity on the VAS ($p \geq 0.061$). Mean pain intensity across treatment groups was 61.2 to 65.9 (0 to 100 scale) and mean time until taking study medication was 3:00 to 3:10 hours after surgery.

3. Sponsor's Evaluation: The sponsor reports, "Single oral doses of SC-58635 100 mg and 200 mg were safe and well tolerated; and Single oral doses of SC-58635 100 mg and 200 mg provided greater analgesic relief than placebo". [Study Report 027- Page 103]

4. Reviewer's Evaluation: [Attachment # 9 A-B - Pages 37-38] Both 100mg and 200mg SD Celecoxib showed statistically significant analgesic efficacy compared to placebo when used in a postsurgical dental pain model. For LOCF, statistically superior mean Pain Relief (PR) began Hour 1 postdose ($p=0.0001$ for 200mg and $p=0.0034$ for 100mg) and continued through Hour 24 ($p=.0001$ for 200mg and $p=0.0206$ for 100mg). Adjusting for multiplicity of multiple comparisons reduces the time length for significance of Celecoxib 100mg to Hour 8 ($p=0.0115$). The mean Pain Intensity Difference (PID) also began 45 minutes postdose and continued through Hour 24. The NSAID agent, Anaprox 550mg, used as a positive control, was not only superior to placebo, but also to the 100mg and 200mg dosage levels of Celecoxib at varying assessment time points. As was seen in the review of Study 025, the results for LOCF offer Celecoxib a slightly better advantage over those for BOCF primarily in that the duration of

The age range of patients in all treatment groups was 19 to 87 years, with the majority less than 30 years old. Across treatment groups, 50-55% of the patients were male and 83-95% were Caucasian. The type of surgical procedure performed and baseline pain intensity were comparable ($p \geq 0.548$ and $p \geq 0.297$ respectively); and duration of surgery, time from end of anesthesia until taking study medication and Baseline Pain Intensity (Visual Analog Scale) were also comparable across all treatment groups ($p \geq 0.279$). Mean duration of surgery across treatment groups was 1:45 to 1:60 (hour:minutes). Mean time from end of anesthesia until taking study medication was 30:03 to 33:54 (hour:minutes). Mean Baseline Pain Intensity (VAS) across treatment groups was 57.4 mm to 61.0 mm (0 to 100 mm scale).

3. Sponsor's Evaluation: The sponsor reports issuing a protocol amendment and interim analysis plan before the interim data set closed, but the analysis, dated December, 1997, appears to have been performed without an *a priori* plan. This was labeled as an administrative change dated 12/22/97, 8 months into study and 3 months before end-of-study. This also changed the Clinical Monitor; outlined the rationale and objective of the interim analysis; and defined the study's stopping rule. The sponsor also reports that an independent Data Monitoring Committee conducted the interim efficacy analysis and made the recommendation to continue the trial as planned. The results of the interim analysis were not disseminated to non-committee members and the study blind was maintained for non-committee members.

The sponsor reports, "In Study 028, the sensitivity of the model to detect statistically significant differences from placebo was limited by the unexpectedly large placebo response at the early assessment times. Nevertheless, the proportion of patients not requiring rescue medication or remediation during the eight hours after dosing was only 2% with placebo contrasted to 10% and 22% ($p < 0.05$) with the 100 mg and 200 mg doses, respectively. The PPID (categorical) scores with Celecoxib 100 mg and 200 mg were similar to values observed in the post-oral surgery studies. However, the lack of statistical significance compared to placebo in Study 028 was due to the larger than expected placebo response in that study."

"Over a 24 hour period patients randomized to Celecoxib received the compound BID PRN, with a minimum dosing interval of 4 hours. Patients randomized to Darvocet-N50 (2 tablets) received medication QID PRN with a minimum dosing interval of 4 hours. The median time to rescue medication or remediation was 04:01 hours for the Celecoxib 100mg BID PRN treatment group and 03:52 hours for the Celecoxib 200mg BID PRN treatment group. These results are similar to the median time to rescue medication (03:48 hours for Celecoxib 100mg SD and 06:03 hours for 200mg SD) derived from the pooled analysis of the post-oral surgery studies. Additional evidence of the analgesic efficacy of this regimen was provided by the proportion of patients remaining in the study at 24 hours after the first dose. At 24 hours after the first dose of study medication the proportion of patients remaining in the study in the Celecoxib 100mg BID PRN treatment group (16/67 or 24%) and the Celecoxib 200mg BID PRN (11/58 or 19%) treatment group was similar to the Darvocet-N50 (2X) QID PRN group (17/62 or 27%). All 3 groups had more patients remaining at 24 hours than in the placebo QID PRN group (4/59 or 7%)". [ISE]

4. Reviewer's Evaluation: As used in this postsurgical orthopedic pain study, the assessment of analgesic efficacy of the 100mg and 200mg Celecoxib BID PRN doses did not demonstrate a particularly convincing performance as compared to placebo, although the pain assessment scores were numerically greater than those of placebo. For both the single dose and multiple dose analyses of mean Pain Intensity Difference (PID) using BOCF, Celecoxib 200mg BID PRN only showed statistically significant analgesic efficacy compared to placebo during the Hour 6 and Hour 7 assessment periods, however, Celecoxib 100mg and 200mg were

statistical significance is longer for LOCF than BOCF. [*Missing Values - Page 3*]

Mean Pain Intensity Difference (PID-LOCF) [*Study Report Table 027-9 - Pages 39-41*] or change from baseline for patients in the 2 Celecoxib dosage groups (100 and 200 mg SD) showed a statistically significant difference from placebo beginning 45 minutes postdose and continuing through Hour 24. At 30 minutes, Anaprox 550 was statistically superior to all levels of Celecoxib, as well as placebo. Anaprox remained statistically superior to Celecoxib and placebo through Hour 4, and continued to be statistically superior to placebo and Celecoxib 100mg, and numerically superior to Celecoxib 200mg throughout subsequent assessments.

Mean Pain Relief (PR-LOCF) [*Study Report Table 027-10 - Pages 43-45*] for patients in all 2 Celecoxib dosage groups (100 and 200 mg SD) showed a statistically significant difference from placebo beginning 45 minutes postdose and continuing through Hour 24. At 30 minutes, positive control Anaprox 550mg was statistically superior to all levels of Celecoxib, as well as placebo. Anaprox remained statistically superior to Celecoxib and placebo through Hour 5, and continued to be statistically superior to placebo and Celecoxib 100mg, and numerically superior to Celecoxib 200mg throughout the subsequent hourly assessments.

A higher percentage of Anaprox patients achieved a perceptible level of pain relief (93% of Anaprox 550mg patients compared to 51% of placebo; 69% of 100mg; and 79% of 200 mg Celecoxib patients). [*Study 027 Appendix 2.3*]

Mean Sum of Pain Intensity Difference and Pain Relief (PRID-LOCF) [*Study Report Table 027-11 - Pages 47-49*] in the 2 Celecoxib dosage groups (100 and 200 mg SD) showed a statistically significant difference from placebo beginning 30 minutes postdose and continuing through Hour 24. At 30 minutes, positive control Anaprox 550mg was statistically superior to all levels of Celecoxib, as well as placebo. It remained statistically superior to Celecoxib 100mg and placebo through Hour 5, and continued to be statistically superior to Celecoxib 100mg and placebo, and numerically superior to Celecoxib 200mg throughout subsequent assessments.

Median Time to Onset of Perceptible Pain Relief - LOCF [*Study Report Table 027-12 - Pages 51-52*] for patients in the Celecoxib 200mg dosage group showed a statistically significant difference from placebo. The positive control, Anaprox 550mg SD, was statistically superior to both the Celecoxib 100 and 200mg levels, as well as placebo. The median time to onset was 0:24 for Anaprox; 0:30 for Celecoxib 200mg; 0:45 for Celecoxib 100mg; and 0:58 for placebo.

Median Time to Administration of Rescue Medication - LOCF [*Study Report - Page 53*] revealed that fewer patients in the Anaprox 550mg group required rescue medication than in any other treatment group, followed by those in the Celecoxib 200mg group (46% of Anaprox 550mg compared to 84% of placebo; 69% of 100mg; and 52% of 200 mg Celecoxib patients). The median time to rescue medication was 10:02 for Celecoxib 200mg; 4:17 for Celecoxib 100mg; and 1:20 for placebo.

Duration of analgesic efficacy - LOCF was determined as the time for which a treatment group maintained a statistically significant difference from placebo. Anaprox 550mg SD resulted in statistically significant differences from placebo beginning 30 minutes postdose and continuing through Hour 24. Anaprox was also superior to 100mg and 200mg Celecoxib beginning at 30 minutes postdose and continuing for 4 to 5 hours. It continued to demonstrate a statistically significant difference with Celecoxib 100mg from 30 minutes through Hour 24.

Peak analgesic effect - LOCF for Anaprox 550mg SD in PID score was 1.28 units, whereas Celecoxib 200mg peaked with a score of 0.82 and the 100mg of 0.58. The peak scores in Pain Relief (PR) for these 3 treatment groups was 2.72 for Anaprox; 2.07 for Celecoxib 200mg; and 1.62 for Celecoxib 100mg. All groups achieved these maximum levels at Hours 2 to 3 postdose.

VII. Pain Study 028 - Postsurgical Orthopedic Pain [Attachment # 6A-B-C - Pages 32-34]

1. **Study Design:** Study 49-96-02-028 was a double-blind, placebo-controlled comparison of safety and efficacy of 2 doses of Celecoxib (100 mg and 200 mg BID PRN) with Placebo and Propoxyphene napsylate naprox 100 mg with acetaminophen 650 mg (Darvocet-N50 2X) QID PRN in patients with moderate to severe postsurgical orthopedic pain (baseline pain intensity on categorical scale). The orthopedic procedure required open manipulation of bone with periosteal elevation that was expected to require administration of analgesics for management of pain for 3-5 days. Patients were to have received administration of the first dose of study medication within 54 hours after the end of anesthesia.

The study was conducted between 5/6/97 and 3/10/98 by 12 investigators, 11 of whom enrolled at least one patient. The protocol was dated 2/7/97.

Amendment #1 dated 3/4/97, added the treatment group SC-58635 100 mg BID PRN, increased the sample size to 240 patients, added clarification to the evaluation of 3 efficacy measures, "SPID, TOTPAR and SPRID, will be weighted by time intervals between successive evaluations" and changed measurement of vital signs from sitting or supine to supine position only.

Amendment # 2, dated 5/12/97, added clinical laboratory tests, including bleeding time and urine collection, for one study site (SCIREX), and allowed for the collection of screening laboratory test data at all sites.

Administrative Change # 1, dated 6/16/97, removed 12 hour urine collection section on CRFs and added sodium, potassium, chloride, osmolality and creatinine clearance to the normal laboratory values form.

Amendment # 3, dated 7/22/97, increased the time frame from end of anesthesia to first dose of study medication from 48 to 54 hours; added shoulder reconstruction and laminectomy to inclusion criterion #4; added an exclusion criterion #11, which modified the wording of existing exclusion criterion #8, regarding lactose-intolerant patients; and changed the Medical Monitor.

Amendment # 4, dated 11/3/97, allowed patients to continue in the study as outpatients for up to five days; changed the minimum hospital stay after study drug dosing from 24 hours to 12 hours; redefined criteria for "completed patient"; changed exclusion criterion from "has been treated" to "had treatment initiated" for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to receiving the first dose of study medication; changed exclusion criterion from is willing to abstain from alcohol 24 hours "prior to" surgery to "from" surgery; added exclusion criterion "the patient has cancer and has been in remission, and off any treatment for less than 2 years prior to study enrollment"; added CRFs to capture additional pain assessments at the time of rescue or remedication; and modified the analysis plan based on communications with the FDA, i.e. changed the extrapolation method for missing values to LOCF and changed the time windows used in linear interpolation of missing values.

Administrative Change # 2, dated 12/22/97 (8 months into study and 3 months before end-of-study), changed the Clinical Monitor, outlined the objective of the interim analysis conducted December, 1997 and defined the study's stopping rule. The objectives were to: (1) evaluate the feasibility of the pain model for the study; (2) evaluate the analgesic effect of SC-58635; (3) drop the low dose of SC-58635 100 mg if not efficacious; and (4) re-estimate the variation of the primary efficacy variables for future study design. The active control will be compared to placebo for validation of the pain model. Each of the SC- 58635 100 mg and 200 mg dose groups will be compared to placebo to evaluate the analgesic effect of the study drug. The standard deviation of the primary efficacy variables will be calculated. The study may be stopped for any one the following reasons: (1) Lack of efficacy of SC-58635. An alpha-spending function corresponding to a linear low boundary will be applied for accepting H_0 . A significance level of 0.32 (z-value=1.004, two-sided) will be used for accepting H_0 .

Patients were allowed to receive analgesic medications such as Patient Controlled Analgesia (PCA) in the postsurgical period prior to first dose of study medication. If they were administered PCA during the postsurgical period, they must have tolerated and received pain relief from an oral analgesic medication prior to receiving study medication.

The Pretreatment Period included the Screening Visit, Surgery, and Baseline. Screening occurred up to 14 days prior to surgery. The Baseline assessment was within 54 hours after the end of anesthesia. The clinical laboratory tests at Screening were repeated. Immediately prior to study drug administration, each patient was asked to record the severity of his or her starting pain and only patients indicating moderate or severe pain were enrolled in the study.

The Treatment Period was defined as up to a 5-day period after the first dose of study medication. Day 1 was defined as the 24-hour period beginning with the date and time of the first dose of study medication. Patients received the second dose not less than four hours after the first dose. Subsequent doses of study medication were administered as needed, no closer than 2 hours apart, and could not exceed 4 doses in 24 hours. In the Celecoxib groups, only the first 2 doses were active; doses 3 and 4 were matching placebo. All 4 doses of Darvocet-N50 (2 tablets) were active. Patients received study medication for up to 5 days maximum.

Patients underwent the following assessments at 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, and 24 hours post-dose: Pain Intensity (Categorical Scale); Pain Relief; Pain at Least Half Gone; and Pain Intensity (VAS). They were also provided with a stopwatch to record Meaningful Pain Relief. Additionally, the APS Pain Measure was completed by each patient every 24 hours after the first dose of study medication. Final pain assessments were performed at the last hourly observation; just prior to rescue analgesia or just prior to hospital discharge.

2. Patient Disposition: Using ANOVA and Pearson's Chi-square testing, the sponsor reports that the treatment groups were comparable for age, race, gender, and with respect to height, weight, and vital signs at Baseline. Of the 255 patients enrolled in 11 centers, only 3 completed the study as per definition in the protocol, i.e. remained in study for 5 full days. Since many of the patients were discharged from the hospital prior to the 5 days, they were ruled noncompliant premature terminations. Because 9 patients [13-0185; 4-0225; 9-0490; and 9-0605 (took rescue medication before the 1-hour pain assessment); 2-0011 and 2-0315 (2 consecutive pain assessments interpolated by the same 2 values within the first 2 hours); 5-0039 (withdrew at Time 0 [spit out study medication]); 9-0135 (predose pain assessments only), and 9-0167 (did not have any pain assessments) were excluded from the ITT cohort for Day 1, the efficacy analysis was based on the remaining sample size of 246.

numerically superior to placebo beginning 45 minutes postdose and continuing through Hour 24. For the BOCF (single dose and multiple dose) and LOCF (single dose and multiple dose) analyses, the Celecoxib 100mg BID PRN and 200mg BID PRN doses yielded numerically greater mean PR scores, as well as sporadic statistically significant differences, over placebo. Darvocet N50 (2 tablets) QID PRN used as a positive control, was not only statistically superior to placebo, but also to the 100mg and 200mg dosage levels of Celecoxib at varying assessment timepoints.

Mean Pain Intensity Difference (PID) [Study Report Table 028-9-12 - Pages 50-61] or change from baseline for patients in all 2 Celecoxib dosage groups (100 and 200 mg BID PRN) showed a statistically significant difference from placebo only during Hours 6 through 7 using single dose analyses for BOCF, and Hours 6 through 8 for LOCF, with statistical significance extending into Hours 10 through 12 using multiple dose analyses. With few exceptions, the mean scores for Celecoxib 200mg were greater than those of Celecoxib 100mg. Darvocet N50 (2X) QID PRN was statistically superior to Celecoxib 200mg between Hours 2 and 4 for BOCF (single dose analyses) and at varying timepoints from Hours 2 through 11 for BOCF (multiple dose analyses). Darvocet was also statistically superior to Celecoxib 100mg between Hours 1 through 5 for BOCF (single dose analyses) and between Hours 1 and 18 for BOCF (multiple dose analyses).

There were statistically significant effects for center and surgery type as well as a treatment by center interaction at various timepoints. Further subgroup analyses were performed for the time-specific primary efficacy measures by center and surgery type. These analyses did not reveal any consistent pattern across timepoints.

Mean Pain Relief (PR) [Study Report Table 028-13-16 - Pages 64-75] scores (extrapolated for baseline values factored into the analyses) for BOCF showed a statistically significant difference between Celecoxib 100mg and placebo only at Hours 4 or 5 for single and multiple dose analyses; Celecoxib 200mg was statistically superior to placebo only at Hours 6 or 9 for single and multiple dose analyses. The 100mg and 200mg Celecoxib doses were numerically greater than placebo beginning 45 minutes postdose and continuing through Hour 24. Relatively similar results were seen for the LOCF.

Mean PR scores for Darvocet-N50 (2X) QID PRN were statistically superior to placebo at Hours 2 through 6 for BOCF single dose analysis; at Hours 2 through 18 for BOCF multiple dose analysis; at Hours 2 through 7 and 24 for LOCF single dose analysis; and at Hours 1.5 through 24 for LOCF multiple dose analysis ($p=0.0105$ at Hour 1.5 and $p=0.0068$ at Hour 24). For the BOCF single dose analysis, the mean PR scores for Darvocet-N50 were statistically superior to Celecoxib 200mg BID PRN at Hour 5, and Celecoxib 100mg BID PRN at Hours 2 and 5. For the BOCF multiple dose analysis, Darvocet-N50 (2 tablets) QID PRN demonstrated a statistically significant difference from Celecoxib 200mg at Hours 5, 10, 11, and 18; and from Celecoxib 100mg at Hours 2, 3, and 6 through Hours 11 and 18. For LOCF, the mean PR scores for Darvocet-N50 (2X) QID PRN were statistically superior to Celecoxib 100mg at Hours 6 and 18.

VIII. Pain Study 029 - Postsurgical General Nonorthopedic Pain [Attachment # 7 - Pg 35]

1. **Study Design:** Study 49-96-02-029 was a double-blind, placebo-controlled comparison of safety and efficacy of 2 doses of Celecoxib (100 and 200 mg) BID PRN with Placebo and Propoxyphene napsylate 100 mg with acetaminophen 650 mg (Darvocet-N50) QID PRN in patients with moderate to severe post-general (non-orthopedic) surgical pain (baseline pain intensity on categorical scale). The general surgical procedure was expected to require

administration of analgesics for management of pain for 3 - 5 days. This study followed the same design as that of Post-surgical Orthopedic Pain Study N49-96-02-028.

The study was conducted between 05/12/97 and 01/18/98 by 13 U.S. and 1 New Zealand investigator, 12 of whom enrolled at least one patient. The protocol date is 02/07/97.

Amendment #1, dated 03/04/97 before start-of-study, added the treatment group SC-58635 100 mg PRN up to BID; increased the sample size to 240; added clarification to the evaluation of efficacy; and changed the measurement of vital signs from sitting or supine to supine only.

Amendment #2, dated 05/09/97, added clinical laboratory tests, bleeding time, and urine collection for 1 study site (SCIREX) and allowed for the collection of screening laboratory test data at all sites.

Administrative change dated 06/16/97 (1 month into study) removed the 12-Hour Urine Collection section on 3 CRFs; added sodium, potassium, chloride, osmolality, and creatinine clearance to the Normal Lab Values Form; and corrected the spelling of the laboratory name.

Amendment #3, dated 07/22/97 (2 months into study) increased the time frame from end of anesthesia to first dose of study medication from 48 to 54 hours; added an exclusion criterion #12 which modified the wording of the exclusion criteria regarding lactose intolerant patients; and changed the Medical Monitor.

Amendment #4, dated 11/03/97 (1 month before end-of-study), allowed patients to continue in the study-as outpatients for up to five days; changed the minimum hospital stay after study drug dosing from 24 hours to 12 hours; redefined the criteria for a "completed patient"; modified exclusion criteria #2, #4, #5 and #8; captured additional pain assessments on the CRFs at time of rescue or remediation; and modified the analysis plan for the study based on communications with the FDA. The modifications consisted of: changing the extrapolation method for missing values to the last observation carried forward (LOCF) method; and changing the time windows used in linear interpolation of missing values.

Administrative change #2, dated 12/22/97 (1 month before end-of-study), outlined the rationale and objective of the interim analysis conducted in December 1997; defined the study's stopping rule; and changed the Clinical Monitor and the Statistician.

2. Patient Disposition: Across all groups, there were 19 patients who violated one or more entry criteria. These included 6 patients in the placebo group, 4 patients in the SC-58635 100 mg BID PRN group, 6 patients in the SC-58635 200 mg BID PRN group, and 3 patients in the Darvocet-N 100mg QID PRN group.

A total of 167 patients were enrolled in this study before the study was discontinued. All randomized patients received at least one dose of study medication. Of the 167, only 2 (1%) completed the study as per definition in the protocol, i.e. remained in study for 5 full days. The remaining 165 (99%) withdrew prior to completing the full five days of the study. Since many of the patients were discharged from the hospital prior to completion of the 5 days, they were ruled noncompliant premature terminations.

3. Sponsor's Evaluation: Out of the 167 patients, 7 were excluded from the efficacy analysis. Six of these (patients NZ0007-0448, US0004-0404 and US0011-0474 in the Darvocet-N 100 mg

QID PRN treatment group; patients US0008-0478 and US0009-0129 in the SC-58635 200 mg BID PRN treatment group; and patient US0011-0527 in the SC-58635 100 mg BID PRN treatment group) terminated from the study prior to the one hour assessment.

4. Reviewer's Evaluation: This review did not perform an efficacy analysis on this study, which was discontinued prior to full enrollment. Across all groups, there were 19 patients who violated one or more entry criteria. Of the 167 patients enrolled, only 2 (1%) completed the study as per definition in the protocol, i.e. remained in study for 5 full days. The remaining 165 (99%) withdrew prior to completing the full five days of the study.

IX. Pain Study 070 - Postsurgical Dental Pain [Attachment # 8 - Page 36]

1. Study Design: Study 49-96-02-070 was a double-blind, placebo-controlled comparison of safety and efficacy of 4 doses of Celecoxib (50, 100, 200, and 400 mg) with Placebo and Anaprox 550 mg in patients with moderate to severe postsurgical dental pain following extraction of 1 or more impacted third molar teeth involving mandibular bone removal.

The study was conducted between 4/17/97 and 7/1/97. The protocol was dated 12/30/97. Administrative Change # 1, dated 9/24/97 (3 months after end-of-study), modified the analysis plan based on communications with the FDA. The modifications consisted of: (1) changing the extrapolation method for missing values to the last observation carried forward (LOCF) method; (2) changing the time windows used in linear interpolation of missing values; (3) adding exploratory analysis of time to onset of analgesia; and (4) clarifying the name of one of the primary measures of efficacy. The medical monitor for this study was also changed.

2. Patient Disposition: Forty-nine (49) patients completed the 24-hour assessment period without taking rescue medication and completed the scheduled 24.0 hour assessments. Two hundred and six (206) patients took rescue medication during the 24 hour assessment period. One Celecoxib 50 mg patient (#539), who took rescue medication, withdrew from the study due to an adverse event (alveolar osteitis on Day 21 post-treatment).

The treatment groups were comparable for age, race, and gender. For all treatment groups, the age range was 19 to 47 years (majority less than 30 years old). Across treatment groups, 60% to 63% of the patients were female and 51% to 66% were Caucasian ($p \geq 0.960$). All treatment groups were comparable ($p \geq 0.318$) with respect to height, weight, and vital signs at Baseline.

The treatment groups were comparable ($p \geq 0.072$) for surgical trauma rating, degree of impaction, and number of molars extracted. There was a slightly greater percentage of Placebo, Celecoxib 100mg and 200mg patients with severe pain intensity (52%, 58% and 44%, respectively) than in the naproxen sodium 550 mg, Celecoxib 50 mg, and 400 mg treatment groups (29%, 40% and 23%, respectively). Although this difference was statistically significant ($p=0.010$), the sponsor did not consider it clinically relevant for purposes of this study. All treatment groups were comparable with respect to time from surgery until taking study medication ($p \geq 0.115$). The mean time until study medication was 2:26 to 2:56. The mean Baseline pain intensity across treatment groups was 61.3 to 68.3 (0 to 100 scale).

3. Sponsor's Evaluation: The sponsor reports, " Celecoxib 50 mg was a submaximally efficacious dose as higher doses of Celecoxib were associated with a greater degree of analgesic efficacy ... demonstrated and replicated in Studies 027 and 070. In Study 070, the

responses to these doses provided similar efficacy while in Study 027 the magnitude of the response was greater with 200 mg. As shown in Study 070, a dose of 400 mg offered some improved analgesic efficacy when compared to 100 mg or 200 mg." [ISE]

The sponsor summarized "Results of this study were comparable to those seen in 3 previous postsurgical dental pain studies. In these studies, SC-58635 (100, 200, and 400 mg) provided statistically significant greater analgesic efficacy than placebo during most of the treatment periods. In general, greater efficacy (earlier onset of relief and greater duration of relief) has been observed with increasing doses of SC-58635 with this difference reaching statistical significance at the 8 hour through 24 hour assessment times. It is therefore concluded that in this study: Single oral doses of SC-58635 50 mg, 100 mg, 200 mg, and 400 mg were safe and well tolerated; Single oral doses of SC-58635 50 mg, 100 mg, 200 mg, and 400 mg provided greater analgesic activity than placebo in patients with moderate to severe postsurgical dental pain; and SC-58635 50 mg was a submaximally effective therapeutic dose." [Study Report 070 - Page 4]

4. Reviewer's Evaluation: [Attachment # 9 A-B - Pages 37-38] The ITT Cohort was the entire patient enrollment of 255 randomized to single doses of Placebo; Naproxen sodium 550 mg; and 3 Celecoxib arms at 50mg, 100mg, 200mg, and 400mg.

With varying onset time and duration of effect, all SD dosage groups of Celecoxib (400mg, 200mg, 100mg, and 50mg) showed statistically significant analgesic efficacy compared to placebo when used in a postsurgical dental pain model. For LOCF in the 400mg, 200mg, and 100mg dosage groups, statistically superior mean Pain Relief (PR) began 1 hour postdose ($p=.0210$ for 400mg; $p=0.0080$ for 200mg; and $p=0.0036$ for 100mg) and continued through Hour 24 ($p=.0001$ for 400mg; $p=0.0026$ for 200mg; and $p=0.0103$ for 100mg). The mean Pain Intensity Difference (PID) began 1 to 1.5 hours postdose and continued through Hour 24. Although the 50mg SD Celecoxib group also demonstrated statistical superiority over placebo, the separation began at a later postdose timepoint (1.5 hours) and only continued through Hour 6 for PID and Hour 8 for PR. However, positive control Anaprox 550mg was superior to placebo beginning 45 minutes postdose through Hour 24, and superior to all 4 dosage levels of Celecoxib beginning 45 minutes postdose through Hours 4 to 6, depending on the dosage level.

Mean Pain Intensity Difference (PID-LOCF) [Study Report Table 070-9 Pages 39-41] or change from baseline for patients in 3 Celecoxib dosage groups (100, 200, and 400 mg SD) showed a statistically significant difference from placebo beginning 1 hour postdose and continuing through Hour 24. At 45 minutes, positive control Anaprox 550mg was statistically superior to all levels of Celecoxib, as well as placebo. Anaprox remained statistically superior to placebo through Hour 24. It was statistically superior to Celecoxib 400mg through Hour 4; to Celecoxib 200 mg through Hour 5; and to Celecoxib 100 mg and 50 mg through Hour 6.

Mean Pain Relief (PR-LOCF) [Study Report Table 070-10 - Pages 44-46] for patients in 3 Celecoxib dosage groups (100, 200, and 400 mg SD) showed a statistically significant difference from placebo beginning 1 hour postdose and continuing through Hour 24. At 45 minutes, positive control Anaprox 550mg was statistically superior to all levels of Celecoxib, as well as placebo. Anaprox remained statistically superior to placebo through Hour 24. It was statistically superior to Celecoxib 400mg through Hour 3; to Celecoxib 200 and 100 mg through Hour 4; and to Celecoxib 50 mg through Hour 8.

X. Pain Study 080 - Postsurgical Orthopedic Pain

Study 49-96-02-080 was a double-blind, placebo-controlled comparison of safety and efficacy of 1 dose of Celecoxib (200 mg) with Placebo and Naproxen 500 mg in patients with moderate to severe postsurgical orthopedic pain.

The sponsor reports, "Study 080 had only one patient enrolled when a decision was made to discontinue the study because the comparator selected was not considered to be suitable for the pain model. Because there was only one patient enrolled and that patient had been randomized to the active control, the results from Study 080 are not included in the discussions of the efficacy results for the management of pain". [*Index ISE Page 236 of 1256*]

XI. Overall Review Conclusions [*Attachments # 9 - 13 - Pages 37 - 46*]

The sponsor conducted 7 studies to investigate the analgesic efficacy of Celecoxib as an agent for acute pain. Results and data from 5 of these were reviewed under this submission. The seventh study (080) was terminated after enrolling 1 patient in the positive control arm, which was deemed an inappropriate control agent for a postsurgical orthopedic pain model. Another study (029) using a postsurgical general nonorthopedic model, was terminated after the sponsor's interim analysis. Of the 5 studies reviewed, 4 used postsurgical dental pain models (005; 025; 027; 070); and one used a postsurgical orthopedic model (028).

With regard to postsurgical dental pain, this review is in agreement with the sponsor's conclusions regarding the management of pain **associated with postoperative dental procedures**. "In summary, studies conducted in multiple clinical settings support the analgesic efficacy of the following dosing regimen in the management of pain: Celecoxib 100 mg or 200 mg as needed every 4-6 hours, up to a maximum total daily dose of 400 mg. Some patients may derive additional efficacy from an initial dose of 200 mg. The active controls were included in the postsurgical pain studies to validate the sensitivity of the model in assessing analgesic efficacy. In general, in the single dose post-oral surgery studies, the NSAID comparators demonstrated a more rapid onset of analgesia and a greater peak response than Celecoxib at the doses studied (25 mg SD, 50 mg SD, 100 mg SD, 200 mg SD, 400 mg SD." [*ISE*]

1. Efficacy: [*Attachments # 9 - 13 A-B - Pages 37 - 46*]

Postsurgical Dental Pain: The evaluation of Celecoxib's analgesic efficacy is based on only 1 acute pain model, that of postsurgical dental pain or third molar extraction during oral surgery. Celecoxib 100 mg was found to be statistically superior to placebo in 3 of these dental pain studies (005; 027; 070). The 200 mg dose was also found to be statistically superior to placebo in 3 dental pain studies (025; 027; 070). And the 400 mg dose was found to be statistically superior to placebo in 2 postsurgical dental pain studies (005; 070) although Study 005 was a Phase 2, single-blind study and may not constitute an adequate and well-controlled trial. The 25 mg and 50 mg doses used in postsurgical dental pain studies did not show sufficiently efficacious analgesic effect, most especially with respect to duration of effect. Statistically significant differences in primary efficacy measures for the Celecoxib dose groups from those of the placebo groups are seen in graphical representation for Mean Pain Relief and Mean Pain Intensity Difference presented in *Attachments*

10A (LOCF) and 10B (BOCF) on Pages 39 - 40, and Attachments 12A (LOCF) and 12B (BOCF) on Pages 43 - 44.

The robustness of study results is evidenced by the graphical summary of mean Pain Relief for each Celecoxib dose level (placebo included as a reference measure) in **Attachments 11A (LOCF) and 11B (BOCF) on Pages 41 - 42.**

Onset: The post dose time at which Celecoxib demonstrated statistically significant differences from placebo with regard to pain relief (PR) and pain intensity difference (PID) was 45 minutes to 1 hour. The positive control Ibuprofen 400mg demonstrated a comparable onset in Study 025, whereas Naproxen 550 mg in Study 027 separated from placebo earlier, beginning 30 minutes postdose. In Study 070 the time for both positive control and Celecoxib was later perhaps due to the particular patient sample of this study. Naproxen demonstrated statistically significant differences from placebo at 45 minutes, and Celecoxib at 1 hour postdose. Patients in both the NSAID and Celecoxib 100 mg, 200 mg, and 400 mg dose groups maintained a statistically significant separation from placebo throughout the remaining assessments, including the final Hour 24 time point. This time to onset of statistically significant differences is tabulated and graphically presented in **Attachments # 13 A-B - Pages 45 - 46.**

The significant p-values (both adjusted and nonadjusted for the multiplicity of multiple comparisons) of pairwise Treatment Mean comparisons are tabulated in **Attachments 9A (LOCF) and 9B (BOCF) - Pages 37 - 38.** The more conservative BOCF method yielded shorter durations for which statistical separation from placebo can be maintained. However, as was described by the sponsor, "with the BOCF method, the estimated missing pain assessments, using the patient's baseline pain intensity, may reflect the patient's status hours before termination from the study. This method does not account for partial improvement at the time of discontinuation. It could potentially create a bias against the treatment group in which patients discontinue with improvement from baseline, however, it is included to provide an additional frequently used method of imputing missing data. On the other hand, the LOCF method, which estimates the missing value by using the observation obtained at the nearest time point, may better reflect reality and patient experiences. It has the closest temporal relation to the patient's status at the time of discontinuation".

The actual efficacy parameter, "time to onset of perceptible pain relief" yielded more favorable results. The median time to onset of perceptible pain relief was slightly shorter than that of demonstrating statistical significance with regard to PR and PID. Ibuprofen 400 mg had a median onset time of 33 minutes, and Naproxen 550mg had onsets of 24 minutes in Study 027 and 36 minutes in Study 070. Celecoxib 400 mg patients had median onset time of 43 minutes; Celecoxib 200 mg patients had median onset times of 38 minutes (Study 025), 30 minutes (Study 027), and 44 minutes (Study 070). Celecoxib 100 mg patients had median onset times of 45 minutes (Study 027) and 39 minutes (Study 070).

Peak: The examination of peak pain relief found that patients in the positive control NSAID groups attained a greater level of pain relief at an earlier post dose time than did those in the Celecoxib and placebo groups. [**Attachment # 13 A - Page 45**]

Naproxen 550mg patients realized a mean peak pain relief of 2.72 units at Hour 2 (Study 027) and 2.5 at Hour 3 (Study 070). These peak scores translate between the pain relief scores of

"some" and "lot" with scores of 0=none; 1=little; 2=some; 3=lot; 4=complete. However, at best, Celecoxib provided no more than "some" pain relief at its peak. The Celecoxib mean scores for peak pain relief occurred at later postdose times and at lower levels: Celecoxib 400 mg peaked at 1.94 PR units at Hour 4 (Study 070). Celecoxib 200 mg peaked at 2.05 PR units at Hour 4 (Study 027); at 1.74 PR units at Hour 2 (Study 025); and at 1.64 PR units at Hour 2 (Study 070). Celecoxib 100 mg peaked at 1.62 PR units at Hour 4 (Study 027) and at 1.64 PR units at Hour 3 (Study 070). The 50 mg and 25 mg Celecoxib groups peaked at even lower levels: Celecoxib 50 mg peaked at 1.22 PR units at Hour 4 (Study 025) and Celecoxib 25 mg peaked at 1.11 PR units at Hour 1.5 (Study 025). Peak pain relief for placebo patients was 0.4 to 0.6 at Hour 24.

Duration: The length of time for which each treatment group maintained a statistically significant separation from Placebo with regard to Pain Relief (using BOCF) was greatest for patients in the Naproxen treatment groups, followed by those in the 200 mg and 400 mg Celecoxib groups. Patients in Celecoxib 200 mg and 400 mg dose groups maintained a statistically significant separation from placebo beginning 45 minutes (Study 027) to 1 hour (Study 070) and continued throughout the remaining assessments, including the final Hour 24 time point. The 100 mg Celecoxib group began at Hour 1 post dose but only continued to separate statistically from placebo through Hour 6 (Study 027) and Hour 12 (Study 070). Naproxen demonstrated statistically significant differences from placebo at 30 minutes (Study 027) and 45 minutes (Study 070) post dose and continued through Hour 24. Ibuprofen 400mg demonstrated statistically significant differences beginning 30 minutes into Study 025 and only continuing through Hour 8. [Attachments 9A (LOCF) and 9B (BOCF) - Pages 37 - 38; tabulated in Attachment 13A (BOCF) - Page 45; and graphically shown by Attachment 13B - Page 46].

Evaluating duration by the median time to Rescue Medication found slightly shorter times than that of demonstrating statistical significance with regard to Pain Relief. Ibuprofen 400 mg had a median rescue time of 7 hours, and Naproxen 550mg had rescue times of > 24 hours in Study 027 and 7 hours in Study 070. Celecoxib 400 mg patients had median time to rescue of 8 hours and 13 minutes; Celecoxib 200 mg patients had median rescue times of 3 hours and 5 minutes (Study 025), 10 hours and 2 minutes (Study 027), and 4 hours and 15 minutes (Study 070). Celecoxib 100 mg patients had median rescue times of 4 hours and 17 minutes (Study 027) and 2 hours and 36 minutes minutes (Study 070).

Postsurgical Orthopedic Pain: The results from only 1 postsurgical orthopedic study (Study 028) demonstrate marginal analgesic efficacy that might be considered supportive to a second study using the same model if that study were to show positive results regarding analgesic efficacy for this indication. The sponsor reports that the PPID efficacy responses for the 100 mg and 200 mg arms of Study 028 were comparable to those found in the postsurgical dental pain studies, however, there was no consistent evidence of statistically significant differences as compared to placebo. The sponsor believes this was due to an unusually high placebo response in this study, but did not pursue a second study using this pain model. [Attachments # 6 A-B-C - Pages 32 - 34]

**APPEARS THIS WAY
ON ORIGINAL**

2. **Safety:** [Attachments # 2 A-B-C - Pages 26 - 28] Safety comparisons of Celecoxib with active comparators should have been made at comparable efficacious doses, i.e. in order to compare safety profiles, the doses of Celecoxib as compared to that of active comparators should be delivering at least the same level of efficacy to the patients in the study. Even though the efficacy levels of Celecoxib are shown to be lower than those of the active control agents, the overall safety profiles appear similar, with the exception of a higher percentage incidence of alveolar osteitis reported by the Celecoxib group.

3. **Other Reviewer Comments:** In Study 005, Administrative Change #2, dated 10/25/95 (almost 1 month after end-of-study), modified the statistical sections of the protocol. The sponsor reports that this was done to reflect the FDA draft guidance ("Presentation of Efficacy Results of Single-Dose Analgesics for Studies Using Acute Pain Models", Jan 1995).

In 4 studies, the sponsor changed Clinical Monitors and appears to have performed 2 interim analyses without a *priori* planning as per protocol:

In Study 027, an Administrative change dated 09/24/97 (2 months following end-of-study) modified the analysis plan based on communications with the FDA. The modifications (1) changed the extrapolation method for missing values to the LOCF method; (2) changed the time windows used in linear interpolation of missing values; (3) added exploratory analysis of time to onset of analgesia; and (4) clarified the name of one of the primary measures of efficacy. The medical monitor for this study was also changed.

Study 028 had a protocol amendment and detailed interim analysis plan issued before the interim data set closed, but the analysis (dated December, 1997) appears to have been performed without an a priori interim analysis plan. This was labeled as an administrative change dated 12/22/97, 8 months into study and 3 months before end-of-study. The Administrative change also changed the Clinical Monitor, outlined the rationale and objective of the interim analysis and defined the study's stopping rule. The sponsor also reports that an independent Data Monitoring Committee conducted the interim efficacy analysis and made the recommendation to continue the trial as planned. The results of the interim analysis were not disseminated to non-committee members and the study blind was maintained for non-committee members. More may be learned by a DSI examination of this study. The stated objectives of the interim analysis were to: (1) evaluate the feasibility of the pain model for the study; (2) evaluate the analgesic effect of SC-58635; and (3) re-estimate the variation of the primary efficacy variables for future study design.

Study 029 also had an administrative change with the very same date of 12/22/97 (1 month before end-of-study), which outlined the rationale and objective of an interim analysis also conducted in December 1997; defined the study's stopping rule; and also changed the Clinical Monitor and the Statistician.

Study 070 also had an Administrative change that was dated the same as that of Study 027, 9/24/97 (3 months after end-of-study). It modified the analysis plan based on

communications with the FDA. The modifications consisted of: (1) changing the extrapolation method for missing values to the last observation carried forward (LOCF) method; (2) changing the time windows used in linear interpolation of missing values; (3) adding exploratory analysis of time to onset of analgesia; and (4) clarifying the name of one of the primary measures of efficacy. The medical monitor for this study was also changed.

**APPEARS THIS WAY
ON ORIGINAL**

Lillian Patrician, MS, MBA
Mathematical Statistician

cc: Orig. NDA 20-998
HFD-550
HFD-550/Dr. DeLap
HFD-550/Dr. Hyde
HFD-550/Dr. Witter
HFD-550/Dr. Averbuch
HFD-550/Ms. Lutwak
HFD-725/File
HFD-725/Ms. Patrician
Chron.

Draft

This review has forty-six [46] pages including thirteen [13] attachments.

**APPEARS THIS WAY
ON ORIGINAL**

**Study Description for Post-Surgical Pain Studies
N49-96-02- 005 / 025 / 027 / 028 / 029 / 070 / 080**

Study	Noteworthy Actions	Study Dates	Title of Protocol	Regimen: Enrollment
005	Adm Change #2 of 10/25/95 (1 month after end-of-study), modified stat sections of protocol to reflect the FDA draft guidance ("Presentation of Efficacy Results of Single-Dose Analgesics for Acute Pain Models", Jan 1995).	8/23/95 to 10/3/95	<u>Single-blind</u> , Placebo-controlled Comparison of Safety and Efficacy of 2 Doses of Celecoxib with Placebo and Aspirin 650 mg in Patients with moderate to severe <u>postsurgical dental pain</u> following extraction of third molar teeth.	n=50 Celecoxib 100 mg SD n=50 Celecoxib 400 mg SD n=50 Aspirin 650 mg SD n=50 Placebo
025		7/9/96 to 11/7/96	<u>Double-blind</u> , Placebo-controlled Comparison of Safety and Efficacy of 3 Doses of Celecoxib with Placebo and Ibuprofen 400 mg in Patients with moderate to severe <u>postsurgical dental pain</u> following extraction of molar teeth involving mandibular bone removal.	n=50 Celecoxib 25 mg SD n=50 Celecoxib 50 mg SD n=50 Celecoxib 200 mg SD n=50 Ibuprofen 400 mg SD n=50 Placebo
027	Admin change of 09/24/97 (2 months following end-of-study) modified analysis plan based on communications with the FDA and changed the Medical Monitor.	3/4/97 to 7/25/97	<u>Double-blind</u> , Placebo-controlled Comparison of Safety and Efficacy of 2 Doses of Celecoxib with Placebo and Anaprox 550 mg in Patients with moderate to severe <u>postsurgical dental pain</u> following extraction of 2 or more impacted third molar teeth.	n=55 Celecoxib 100 mg SD n=56 Celecoxib 200 mg SD n=54 Naproxen Na 550 mg SD n=55 Placebo
028	Admin Change # 2 of 12/22/97 (8 months into study and 3 months before end-of-study), changed the Clinical Monitor, outlined the rationale for 12/97 interim analysis, and defined stopping rule.	5/6/97 to 3/10/98	<u>Double-blind</u> , Placebo-controlled Comparison of Safety and Efficacy of 2 Doses of Celecoxib with Placebo and Propoxyphene napsylate naprox 100 mg with acetaminophen 650 mg (Darvocet-N50) in Patients with mod to severe <u>postsurgical orthopedic pain</u> .	n=68 Celecoxib 100 mg BID PRN n=62 Celecoxib 200 mg BID PRN n=65 Darvocet-N50 (2X) QID PRN n=60 Placebo
029	Admin change of 12/22/97 (1 month before end-of-study), outlined the rationale for 12/97 interim analysis; defined stopping rule; and changed the Clinical Monitor and the Statistician. <u>Study terminated</u> .	5/12/97 to 1/18/98	<u>Double-blind</u> , Placebo-controlled Comparison of Safety and Efficacy of 2 Doses of Celecoxib BID PRN with Placebo and Propoxyphene napsylate 100 mg with acetaminophen 650 mg (Darvocet-N50) QID PRN in Patients with mod to severe <u>post-general (non-orthopedic) surgical pain</u> .	n=45 Celecoxib 100 mg BID PRN n=42 Celecoxib 200 mg BID PRN n=40 Darvocet-N50-2X QID PRN n=40 Placebo
070	Admin change of 9/24/97 (3 months after end-of-study) changed analysis plan and Medical Monitor.	8/23/95 to 10/3/95	<u>Double-blind</u> , Placebo-controlled Comparison of Safety and Efficacy of 4 Doses of Celecoxib with Placebo and Anaprox 550 mg in Patients with moderate to severe <u>postsurgical dental pain</u> following extraction of 1 or more impacted third molar teeth involving mandibular bone removal.	n=35 Celecoxib 50 mg SD n=50 Celecoxib 100 mg SD n=50 Celecoxib 200 mg SD n=35 Celecoxib 400 mg SD n=35 Naproxen Na 550 mg SD n=50 Placebo
080	<u>Study terminated</u> after 1 Naproxen patient enrolled due to inappropriate control for model.	8/23/95 to 10/3/95	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of 1 Dose of Celecoxib with Placebo and Naproxen 500 mg in Patients with moderate to severe <u>postsurgical orthopedic pain</u> .	n=50 Celecoxib 200 mg BID PRN n=51 Naproxen 500 mg BID PRN n=50 Placebo

**** Dose Level Summary of Adverse Experiences Reported in All Acute Pain Studies**

Reviewer's Results	Placebo	Cele 25 mg	Cele 50 mg	Cele 100 mg	Cele 200 mg	Cele 400 mg	IBU 400 mg	Aspirin 650 mg	Naproxen 550 mg	Darvocet 100 mg	Total
# Enrolled (Safety Evaluable)	305	50	85	268	260	85	50	50	89	105	1347
# Pats with No AE (%)	182 (60%)	27 (54%)	45 (53%)	174 (65%)	143 (55%)	55 (65%)	27 (54%)	33 (66%)	54 (61%)	55 (52%)	795
# Pats with Any AE (%)	123 (40%)	23 (46%)	40 (47%)	94 (35%)	117 (45%)	30 (35%)	23 (46%)	17 (34%)	35 (39%)	50 (48%)	552
# Pats w Trt-rel AE (%) -- Investigator: Uncer/Probable	71 (23%)	05 (10%)	16 (19%)	64 (24%)	71 (27%)	17 (20%)	06 (12%)	12 (24%)	18 (20%)	38 (36%)	318
# Pats w Trt-rel AE (%) -- Sponsor's Medical Opinion	54 (18%)	03 (06%)	11 (13%)	55 (21%)	57 (22%)	12 (14%)	02 (04%)	06 (12%)	13 (15%)	35 (33%)	248
Incidence of Adv Reactions	214	44	58	172	211	46	36	39	68	107	995
Maj Incidence - Nausea	23	07	12	30	34	08	04	11	16	15	160 (12%)
Maj Incidence - Headache	40	07	07	21	22	06	07	03	18	08	139 (10%)
Maj Incidence - Alv Osteitis	18	09	15	10	20	08	06	0	10	0	96 (7%)
Maj Incidence - Vomiting	14	04	03	12	13	04	02	05	06	06	69 (5%)
Maj Incidence - Dizziness	11	03	06	11	14	0	03	05	01	04	58 (4%)

**** Doses were primarily single dose in postsurgical dental pain studies.
The maximum dosage from remaining postsurgical studies was BID for 5 days duration.**

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

NDA 20-998 Celebrex (Celecoxib)

Attachment # 2 B

Summary of Adverse Experiences Reported in All Acute Pain Studies

Reviewer's Results	Placebo	All Celecoxib Dosage Groups (1- 5 days single dose)	Positive Control Dosage Groups	Total
# Enrolled (Safety Evaluable)	305	748	294	1347
# Completed Study (%)	205 (67%)	531 (71%)	189 (64%)	925 (69%)
# Discontinued Due to AE (%)	08 (03%)	16 (02%)	06 (02%)	30 (02%)
# Disc Due to Trmnt Failure (%)	78 (26%)	147 (20%)	66 (22%)	291 (22%)
# Disc Due to Noncompl (%)	08 (03%)	48 (06%)	32 (11%)	88 (07%)
# Disc Due to Protl Violation (%)	04 (01%)	05 (01%)	0 (0%)	09 (01%)
# Disc by Lost-to-Follow-up (%)	02 (01%)	01 (00%)	01 (0%)	04 (0%)
# Pats with Any AE (%)	123 (40%)	304 (41%)	125 (43%)	552 (41%)
# Pats w Severe AE (%)	29 (09%)	64 (09%)	31 (11%)	124 (09%)
# Adv Reactions (per patient)	214 (0.70)	531 (0.71)	250 (0.85)	995 (0.74)
Incidence of Severe AE (%)	34 (11%)	88 (12%)	41 (14%)	163 (12%)
Major Incidence - Nausea	23 (08%)	91 (12%)	46 (16%)	160 (12%)
Major Incidence - Headache	40 (13%)	63 (08%)	36 (12%)	139 (10%)
Major Incidence - Alv Osteitis	18 (06%)	62 (08%)	16 (05%)	96 (07%)
Major Incidence - Vomiting	14 (05%)	36 (05%)	19 (06%)	69 (05%)
Major Incidence - Dizziness	11 (04%)	34 (05%)	13 (04%)	58 (04%)

APPEARS THIS WAY
ON ORIGINAL

Low Incidence Adverse Experiences Reported in All Acute Pain Studies

Adverse Experience	Placebo n=305	Celecoxib n=748	Active Controls n=294
Anxiety	0 (0%)	2 (< 1%)	0 (0%)
Confusion	1 (< 1%)	5 (1%)	0 (0%)
Diarrhea	2 (< 1%)	7 (1%)	2 (1%)
Dyspepsia	5 (2%)	14 (2%)	4 (> 1%)
Epistaxis	0 (0%)	3 (< 1%)	0 (0%)
Fatigue	0 (0%)	2 (< 1%)	0 (0%)
Glycosuria	0 (0%)	1 (< 1%)	0 (0%)
Gout	0 (0%)	1 (< 1%)	0 (0%)
Hot Flushes	0 (0%)	5 (1%)	2 (1%)
Hyperkalemia	0 (0%)	1 (< 1%)	0 (0%)
Hyperkinesia	0 (0%)	1 (< 1%)	0 (0%)
Hypokinesia	0 (0%)	1 (< 1%)	0 (0%)
Ileus	0 (0%)	1 (< 1%)	0 (0%)
Influenza-like Symptoms	0 (0%)	3 (< 1%)	0 (0%)
Increased LDH	0 (0%)	1 (< 1%)	0 (0%)
Menorrhagia	0 (0%)	1 (< 1%)	0 (0%)
Myalgia	0 (0%)	2 (< 1%)	0 (0%)
Oral Hemorrhage	0 (0%)	6 (1%)	1 (< 1%)
Pallor	0 (0%)	2 (< 1%)	0 (0%)
Pneumothorax	0 (0%)	1 (< 1%)	0 (0%)
Somnolence	5 (2%)	22 (3%)	8 (3%)
Abnormal Stools	0 (0%)	1 (< 1%)	0 (0%)
Stupor	0 (0%)	1 (< 1%)	0 (0%)
Upper Respiratory Tract Infection	1 (< 1%)	6 (1%)	2 (1%)

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

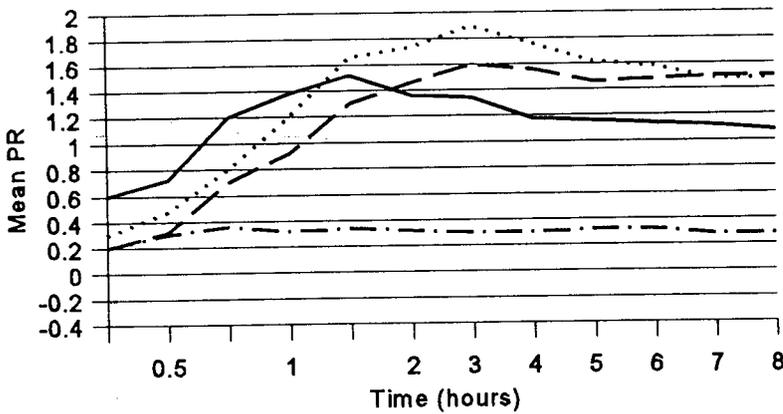
Demographic Summary for PostSurgical Dental Pain Study

Phase 2 Study 49-96-02-005

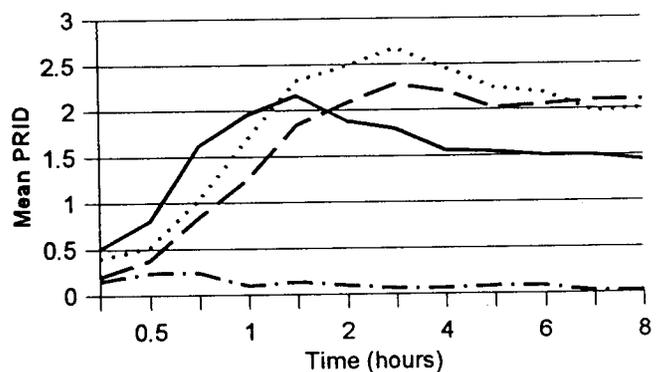
Reviewer's Results - Study 005	Placebo	Cele 100mg SD	Cele 400mg SD	Aspirin 650mg SD
# Enrolled (Safety Evaluable)	50	50	50	50
# Completed Study (%)	48 (96%)	50 (100%)	49 (98%)	49 (98%)
# Terminations (%)	47 (94%)	30 (60%)	28 (56%)	36 (72%)
- Due to Lost-to-follow-up	2 (04%)	0 (0%)	1 (02%)	1 (02%)
* - Due to Trt Fail/Resc Med	0 (0%)	0 (0%)	0 (0%)	0 (0%)
*- Due to Trt Fail/Resc	45 (90%)	30 (60%)	27 (54%)	35 (70%)
- Due to Adverse Reaction	0 (0%)	0 (0%)	0 (0%)	0 (0%)
# Pats with Any AE (%)	12	13	15	17
# Pats w Trt-rel AE (%)	10	06	12	12
# Males (%)	18 (36%)	22 (44%)	25 (50%)	21 (42%)
# Females (%)	32 (64%)	28 (56%)	25 (50%)	29 (58%)
# Caucasian (%)	35 (70%)	42 (84%)	41 (82%)	39 (78%)
# Hispanic (%)	06 (12%)	05 (10%)	06 (12%)	09 (18%)
# Other (%)	09 (18%)	03 (06%)	03 (06%)	02 (04%)

** Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

Study 005 PR **



Study 005 PRID



— ASP 650mg - - - CEL 400mg
 CEL 100mg - · - · PBO

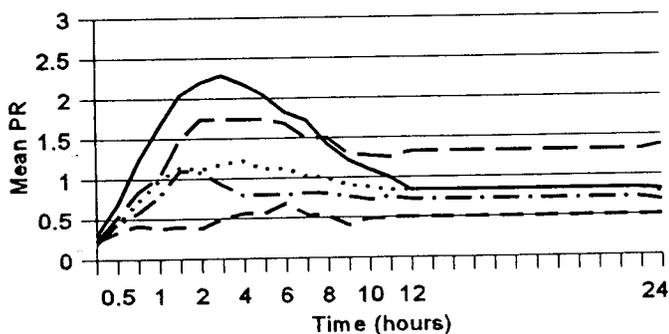
BEST POSSIBLE COPY

Demographic Summary for PostSurgical Dental Pain Study 49-96-02-025

Reviewer's Results - Study 025	Placebo	Cele 25mg SD	Cele 50mg SD	Cele 200mg SD	Ibuprofen 400 SD
# Enrolled (Safety Evaluable)	50	50	50	50	50
# Completed Study (%)	04 (08%)	04 (08%)	07 (14%)	13 (26%)	08 (16%)
# Req Rescue Meds (%)	46 (92%)	46 (92%)	43 (86%)	37 (74%)	42 (84%)
# Terminations (%)					
- Due to Lost-to-follow-up	0	0	0	0	0
* - Due to Trt Fail/Resc Med	0	0	0	0	0
* - Due to Trt Fail/Resc	46 (92%)	46 (92%)	43 (86%)	37 (74%)	42 (84%)
- Due to Adverse Reaction	0	0	0	0	0
# Pats with Any AE (%)	20 (40%)	23 (46%)	20 (40%)	24 (48%)	23 (46%)
# Pats w Trt-rel AE (%)	07 (14%)	05 (10%)	08 (16%)	09 (18%)	06 (12%)
# Males (%)	21 (42%)	18 (36%)	19 (38%)	17 (34%)	10 (20%)
# Females (%)	29 (58%)	32 (64%)	31 (62%)	33 (66%)	40 (80%)
# Caucasian (%)	27 (54%)	32 (64%)	34 (68%)	27 (54%)	32 (64%)
# Hispanic (%)	18 (36%)	14 (28%)	08 (16%)	17 (34%)	15 (30%)
her (%)	05 (10%)	04 (08%)	08 (16%)	06 (12%)	03 (06%)
Age Range in Years	18 - 38	18 - 46	18 - 45	18 - 46	18 - 50
# Pats Achieving Analgesia	9 (18%)	21 (42%)	23 (46%)	27 (54%)	37 (74%)
# Pats Achieving Perceptible Pain Relief (%)	18 (36%)	29 (58%)	32 (64%)	35 (70%)	41 (82%)

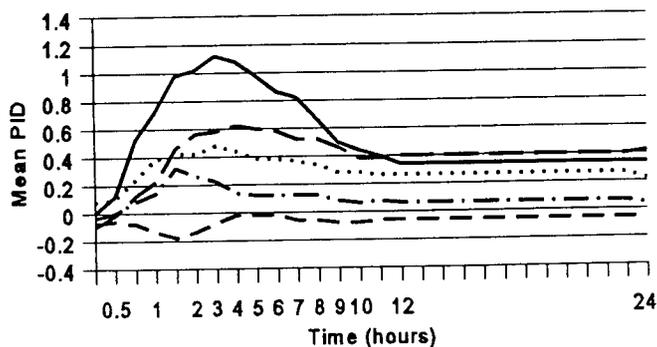
** Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

Study 025 PR **



— IBU 400mg - - - CEL 200mg
 . . . CEL 50mg - . - CEL 25mg
 - - - PBO

Study 025 PID



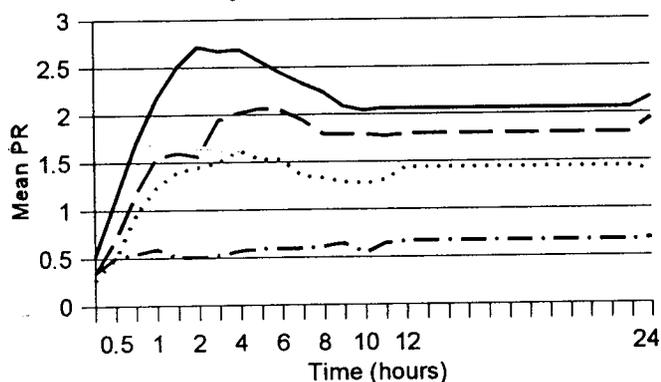
— IBU 400mg - - - CEL 200mg
 . . . CEL 50mg - . - CEL 25mg
 - - - PBO

Demographic Summary for PostSurgical Dental Pain Study 49-96-02-027

Reviewer's Results - Study 027	Placebo	Cele 100 SD	Cele 200 SD	Naproxen NA 550 SD
# Enrolled (Safety Evaluable)	55	55	56	54
# Efficacy Eval - ITT (%)	55 (100%)	55 (100%)	56 (100%)	54 (100%)
# Completed Study (%)	09 (16%)	17 (31%)	27 (48%)	28 (52%)
# Req Rescue Meds (%)	46 (84%)	38 (69%)	29 (52%)	26 (48%)
# Terminations - Trt Fail/Resc Med	46 (84%)	38 (69%)	29 (52%)	26 (48%)
# Pats with Any AE (%)	27 (48%)	24 (44%)	29 (52%)	25 (46%)
# Pats w Trt-rel AE (%)	12 (22%)	10 (18%)	14 (25%)	13 (24%)
# Males (%)	25 (45%)	25 (45%)	26 (46%)	24 (44%)
# Females (%)	30 (55%)	30 (55%)	30 (54%)	30 (56%)
# Caucasian (%)	36 (65%)	34 (62%)	39 (70%)	35 (65%)
# Hispanic (%)	05 (09%)	03 (05%)	03 (05%)	01 (02%)
# Other (%)	14 (25%)	18 (33%)	14 (25%)	18 (33%)
# Age Range in Years	18 - 32	18 - 50	18 - 45	18 - 52
# Pats Achieving Perceptible Pain Relief (%)	28 (51%)	38 (69%)	44 (79%)	50 (93%)

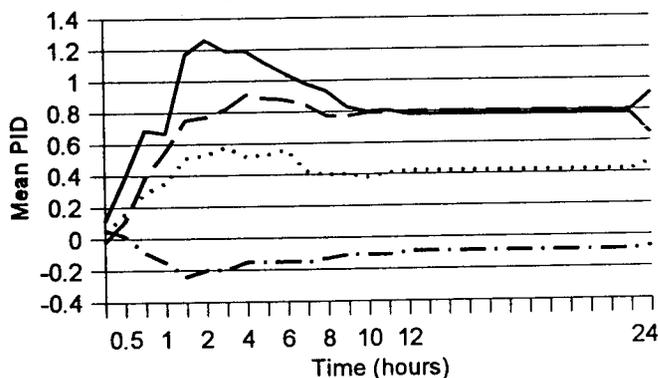
** Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

Study 027 PR (LOCF)



_____ NAP 550mg - - - - CEL 200mg
 CEL 100mg - · - · PBO

Study 027 PID (LOCF)



_____ NAP 550mg - - - - CEL 200mg
 CEL 100mg - · - · PBO

BEST POSSIBLE COPY

Demographic Summary for PostSurgical Orthopedic Pain Study 49-96-02-028

Reviewer's Results - Study 028	Placebo	Cele 100mg BID PRN	Cele 200mg BID PRN	Darvocet N50 (2X) QID PRN
# Enrolled (Safety Evaluable)	60	68	62	65
# Completed Study (%)	01	01	0	01
# Terminations (%)	59 (98%)	67 (99%)	62 (100%)	64 (98%)
- Due to Trt Fail/Resc Med	51	47	43	44
- Due to Adverse Reaction	03	01	09	01
- Due to Noncompliance	03	16	10	19
- Due to Protocol Violation	02	03	0	0
# Pats with Any AE (%)	23	25	25	28
# Pats w Trt-rel AE (%)	16	19	19	21
# Males (%)	30 (50%)	37 (54%)	34 (55%)	36 (55%)
# Females (%)	30 (50%)	31 (46%)	28 (45%)	29 (45%)
# Caucasian (%)	51 (85%)	60 (88%)	59 (95%)	54 (83%)
# Hispanic (%)	02 (03%)	03 (04%)	02 (03%)	03 (05%)
# Other (%)	07 (12%)	05 (07%)	01 (02%)	08 (12%)
# Age Range in Years	23 - 87	19 - 82	21 - 86	27 - 84

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Mean Pain Relief in PostSurgical Orthopedic Pain Study 49-96-02-028

Last Observation Carried Forward (LOCF)

- Single (SD) and Multiple Dose (MD)

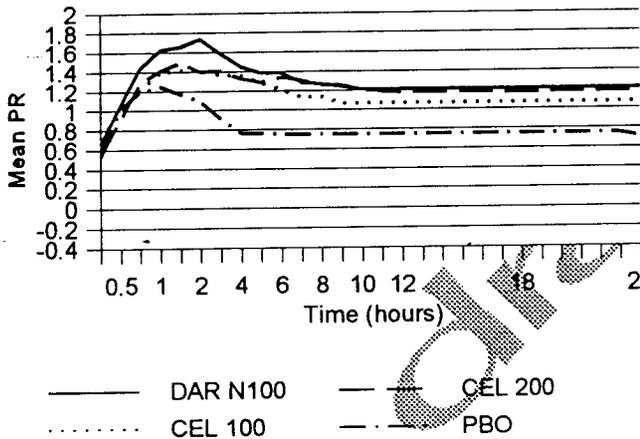
Baseline Observation Carried Forward (BOCF)

- Single (SD) and Multiple Dose (MD)

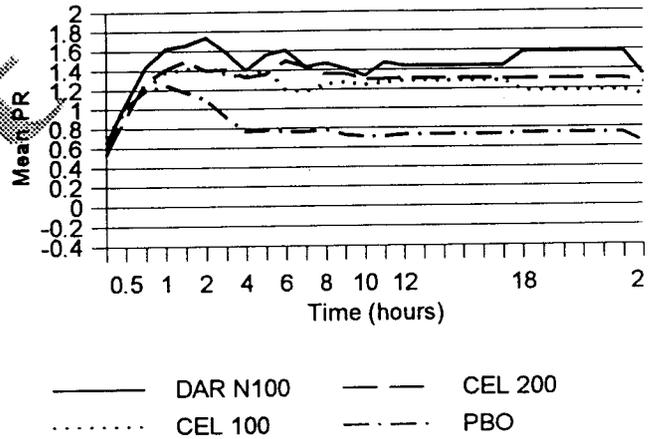
DAR N100 = Darvocet N100 QID PRN
 CEL 200 = Celecoxib 200 mg BID PRN
 CEL 100 = Celecoxib 100 mg BID PRN

** Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

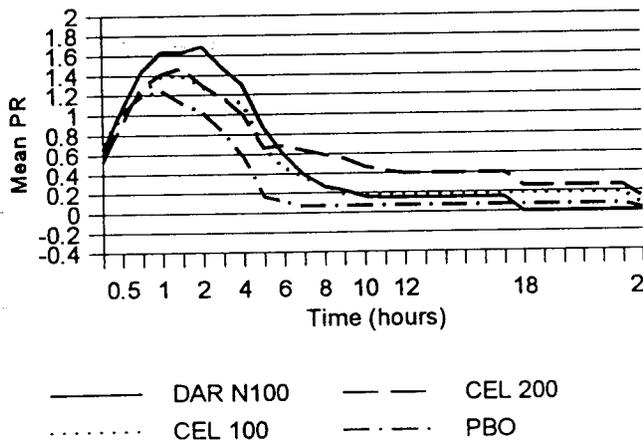
Study 028 PR
LOCF (SD)



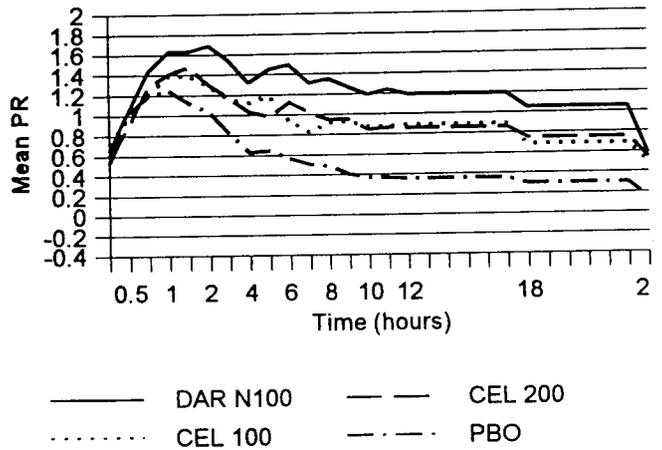
Study 028 PR
LOCF (MD)



Study 028 PR
BOCF (SD)



Study 028 PR
BOCF (MD)



BEST POSSIBLE COPY

Mean Pain Intensity Difference in PostSurgical Orthopedic Pain Study 49-96-02-028

Last Observation Carried Forward (LOCF)

- Single (SD) and Multiple Dose (MD)

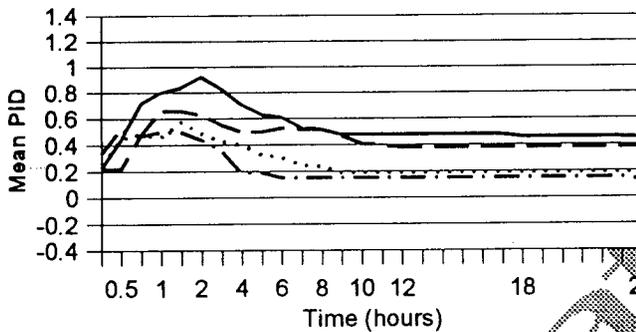
Baseline Observation Carried Forward (BOCF)

- Single (SD) and Multiple Dose (MD)

DAR N100 = Darvocet N100 QID PRN
 CEL 200 = Celecoxib 200 mg BID PRN
 CEL 100 = Celecoxib 100 mg BID PRN

Study 028 PID

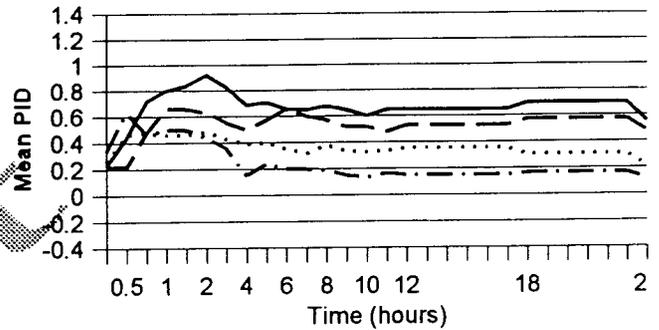
LOCF (SD)



— DAR N100 - - - CEL 200
 CEL 100 - · - · PBO

Study 028 PID

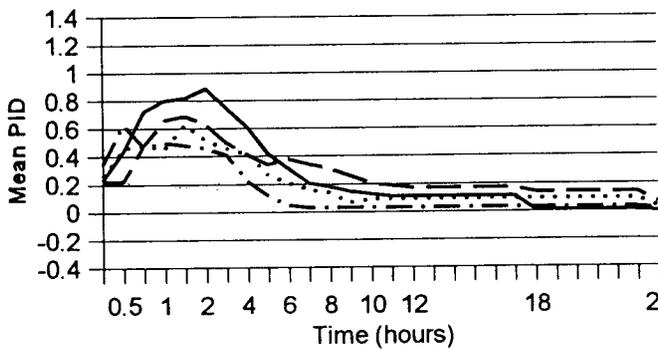
LOCF (MD)



— DAR N100 - - - CEL 200
 CEL 100 - · - · PBO

Study 028 PID

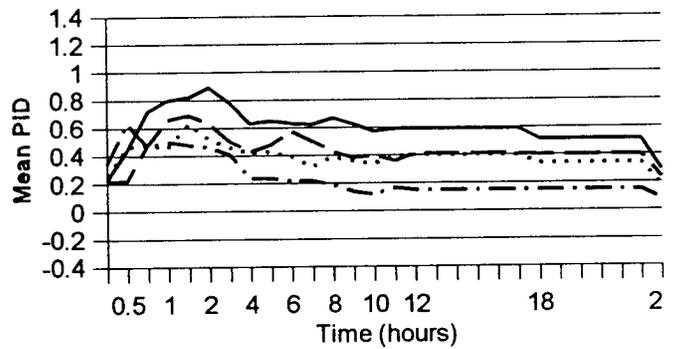
BOCF (SD)



— DAR N100 - - - CEL 200
 CEL 100 - · - · PBO

Study 028 PID

BOCF (MD)



— DAR N100 - - - CEL 200
 CEL 100 - · - · PBO

BEST POSSIBLE COPY

Demographic Summary for PostSurgical Non-Orthopedic Pain Study 49-96-02-029

Reviewer's Results - Study 029	Placebo	Cele 100mg BID PRN	Cele 200mg BID PRN	Darvocet N50 (2X) QID PRN
# Enrolled (Safety Evaluable)	40	45	42	40
# Completed Study (%)	1	1	0	0
# Terminations (%)	39 (98%)	45 (98%)	42 (100%)	40 (100%)
- Due to Adverse Reaction	5	2	3	5
- Due to Trt Fail/Resc Med	27	29	28	22
- Due to Noncompliance	5	13	9	13
- Due to Protocol Violation	2	0	2	0
# Pats with Any AE (%)	17 (43%)	20 (44%)	21 (50%)	22 (55%)
# Pats w Trt-rel AE (%)	12 (30%)	20 (44%)	17 (40%)	17 (43%)
# Males (%)	04 (10%)	06 (13%)	07 (17%)	05 (13%)
# Females (%)	36 (90%)	39 (87%)	35 (83%)	35 (88%)
# Caucasian (%)	28 (70%)	40 (89%)	29 (69%)	30 (75%)
# Black (%)	03 (08%)	04 (09%)	09 (21%)	03 (08%)
# Other (%)	09 (23%)	04 (09%)	04 (09%)	07 (18%)

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

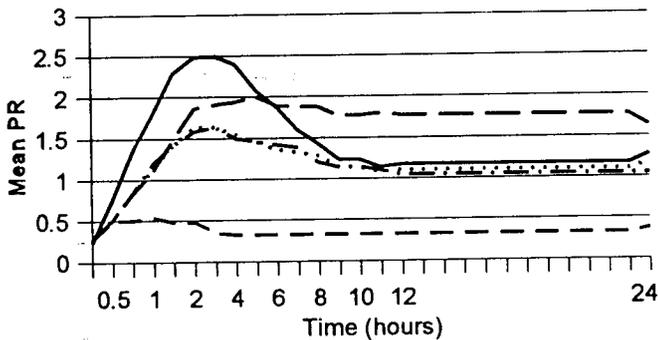
Demographic Summary for PostSurgical Orthopedic Pain Study 49-96-02-070

Reviewer's Results - Study 070	Placebo	Cele 50mg BID PRN	Cele 100mg BID PRN	Cele 200mg BID PRN	Cele 400mg BID PRN	Naproxen 550 QID PRN
# Enrolled (Safety Evaluable)	50	35	50	50	35	35
# Completed Study (%)	50 (100%)	34 (97%)	50 (100%)	50 (100%)	35 (100%)	35 (100%)
# Terminations (%)	0	1	0	0	0	0
- Due to Adverse Reaction	0	1 (#539)	0	0	0	0
- Due to Trt Fail/Resc Med	0	0	0	0	0	0
- Due to Lost-to-follow-up	0	0	0	0	0	0
# Pats with Any AE (%)	24 (48%)	20 (57%)	12 (24%)	18 (36%)	15 (43%)	10 (29%)
# Pats w Trt-rel AE (%)	14 (28%)	8 (23%)	9 (18%)	12 (24%)	5 (14%)	5 (14%)
# Males (%)	20 (40%)	13 (37%)	20 (40%)	20 (40%)	14 (40%)	14 (40%)
# Females (%)	30 (60%)	22 (63%)	30 (60%)	30 (60%)	21 (60%)	21 (60%)
# Caucasian (%)	32 (64%)	18 (51%)	28 (56%)	27 (54%)	23 (66%)	22 (63%)
# Hispanic (%)	13 (26%)	12 (34%)	14 (28%)	16 (32%)	08 (23%)	08 (23%)
# Other (%)	15 (30%)	05 (14%)	08 (16%)	07 (14%)	04 (11%)	05 (14%)

** Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

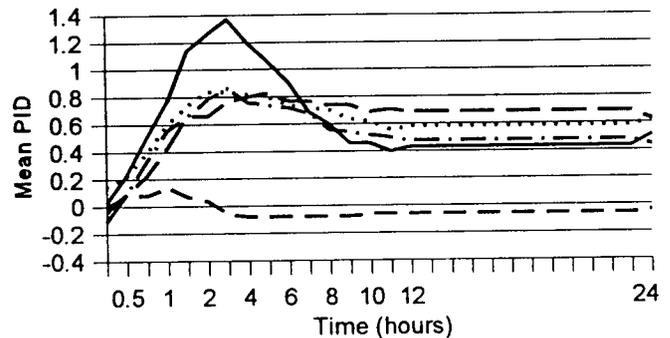
BEST POSSIBLE COPY

Study 070 PR



——— NAP 550mg - - - CEL 400mg
 CEL 200mg - · - · CEL 100mg
 - - - - PBO

Study 070 PID



——— NAP 550mg - - - CEL 400mg
 CEL 200mg - · - · CEL 100mg
 - - - - PBO

Treatment Pairwise Comparisons of Mean Pain Relief (PR) in PostSurgical Dental Pain Studies
Last Observations Carried Forward (LOCF)

LOCF Comparisons	H0.75	H1.0	H1.5	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H24
Study 025															
Ibuprofen 400 vs Placebo	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0005	.0008	.0030	.0096	.0398		
Ibuprofen 400 vs Celecoxib 200	.0335	.0157													
Celecoxib 200 vs Placebo	.0173	.0012	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0003	.0002	.0009	.0014	.0007	.0004
Study 027															
Naproxen 550 vs Placebo	.0003	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001
Naproxen 550 vs Celecoxib 200	.0112	.0037	.0037	.0007	.0064	.0149									
Naproxen 550 vs Celecoxib 100	.0019	.0001	.0001	.0001	.0001	.0001	.0003	.0013	.0005	.0013	.0048	.0070	.0078	.0128	.0128
Celecoxib 200 vs Placebo	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001
Celecoxib 100 vs Placebo	.0034	.0002	.0002	.0002	.0001	.0002	.0009	.0011	.0078	.0115	.0240	.0280	.0220	.0245	.0206
Study 070															
Naproxen 550 vs Placebo	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0010	.0010	.0023	.0016	.0020
Naproxen 550 vs Celecoxib 400	.0245	.0112	.0087	.0117	.0404										
Naproxen 550 vs Celecoxib 200	.0171	.0081	.0021	.0053	.0020	.0057	.0530								
Naproxen 550 vs Celecoxib 100	.0171	.0180	.0021	.0029	.0020	.0038	.0530								
Celecoxib 400 vs Placebo		.0210	.0004	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001
Celecoxib 200 vs Placebo		.0080	.0003	.0001	.0001	.0001	.0001	.0001	.0002	.0001	.0015	.0011	.0019	.0014	.0026
Celecoxib 100 vs Placebo		.0036	.0003	.0001	.0001	.0001	.0001	.0001	.0001	.0003	.0008	.0011	.0015	.0019	.0103

** The above are p-values (2-sided testing at alpha level of 5%) for statistically noteworthy comparisons ONLY, i.e. for postdose assessment times of statistically significant differences in mean pain relief between treatment groups (not adjusting for multiplicity of multiple comparisons).

** Shaded cells represent statistical significance adjusted for multiplicity (at alpha level of 1.25%).

BEST POSSIBLE CO

Treatment Pairwise Comparisons of Mean Pain Relief (PR) in PostSurgical Dental Pain Studies
Baseline Observations Carried Forward (BOCF)

BOCF Comparisons	H0.5	H0.75	H1.0	H1.5	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H24
Study 025																
Ibuprofen 400 vs Placebo	.0110	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0046	.0216				
Ibu 400 vs Celecoxib 200	.0327	.0019	.0127	.0226												
Celecoxib 200 vs Placebo	.0184	.0014	.0001	.0001	.0001	.0001	.0002	.0003	.0007	.0034	.0029	.0037	.0110	.0140	.0078	.0069
Celecoxib 50 vs Placebo		.0027	.0022	.0079	.0257	.0372										
Study 027																
Naproxen 550 vs Placebo	.0003	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0005
Napr 550 vs Celecoxib 200	.0112	.0051	.0037	.0039	.0005	.0053	.0107									
Napr 550 vs Celecoxib 100	.0019	.0001	.0001	.0001	.0001	.0001	.0001	.0002	.0012	.0006	.0020	.0021	.0070	.0057	.0092	.0329
Celecoxib 200 vs Placebo		.0007	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0002	.0007	.0004	.0008	.0010	.0005
Celecoxib 100 vs Placebo	.0195	.0034	.0003	.0002	.0005	.0002	.0005	.0025	.0060	.0307	.0501					
Study 070																
Naproxen 550 vs Placebo	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0011	.0031	.0063	.0063	.0070
Napr 550 vs Celecoxib 400	.0245	.0112	.0065	.0064	.0213							.0449	.0461	.0205	.0259	
Napr 550 vs Celecoxib 200	.0171	.0061	.0019	.0043	.0025	.0046		.0372	.0469							
Napr 550 vs Celecoxib 100	.0171	.0160	.0019	.0019	.0011	.0014	.0168	.0168	.0543							
Celecoxib 400 vs Placebo		.0210	.0004	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001
Celecoxib 200 vs Placebo		.0080	.0002	.0001	.0001	.0001	.0001	.0001	.0001	.0002	.0003	.0019	.0032	.0067	.0064	.0123
Celecoxib 100 vs Placebo		.0036	.0002	.0001	.0001	.0001	.0001	.0001	.0001	.0002	.0013	.0019	.0032	.0042	.0067	.0315

** The above are p-values (2-sided testing at alpha level of 5%) for statistically noteworthy comparisons ONLY, i.e. for postdose assessment times of statistically significant differences in mean pain relief between treatment groups (not adjusting for multiplicity of multiple comparisons).

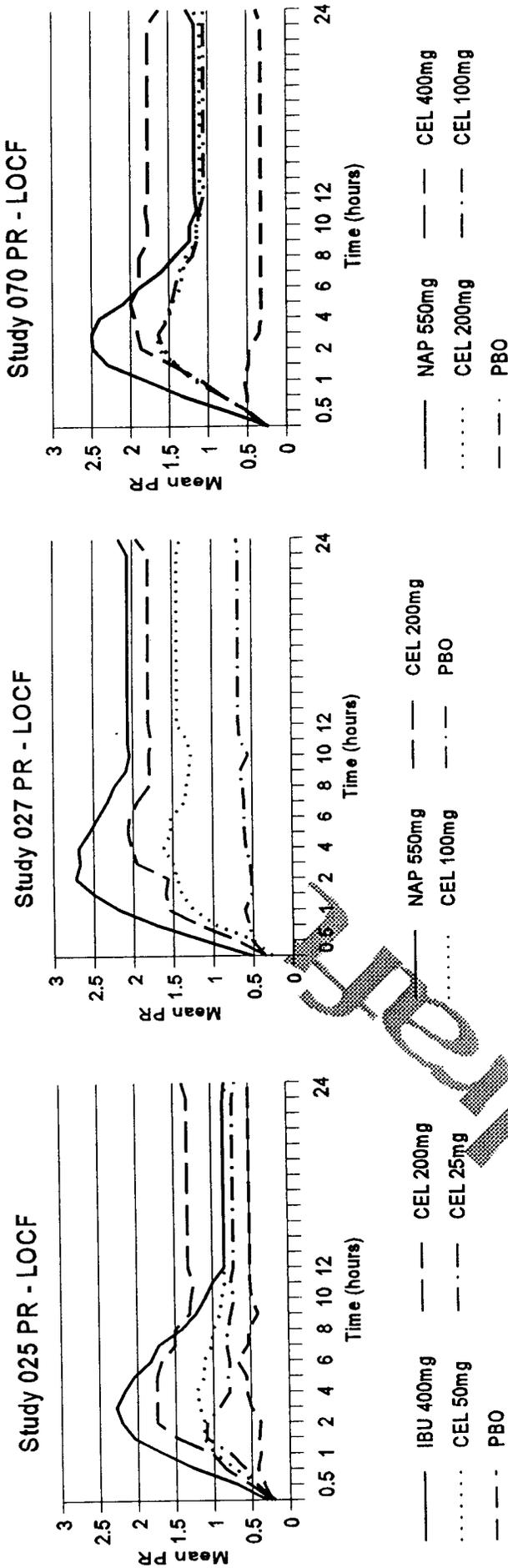
** Shaded cells represent statistical significance adjusted for multiplicity (at alpha level of 1.25%).

Mean Pain Relief (PR) in PostSurgical Dental Pain Studies

Last Observation Carried Forward (LOCF)

Pain Relief Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

BEST POSSIBLE COPY



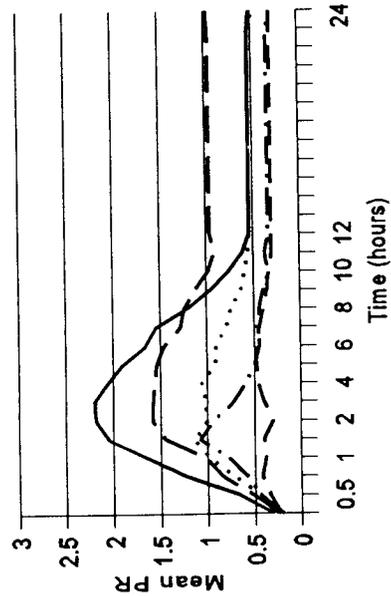
APPEARS THIS WAY
ON ORIGINAL

Mean Pain Relief (PR) Summarized by Dose PostSurgical Dental Pain Studies

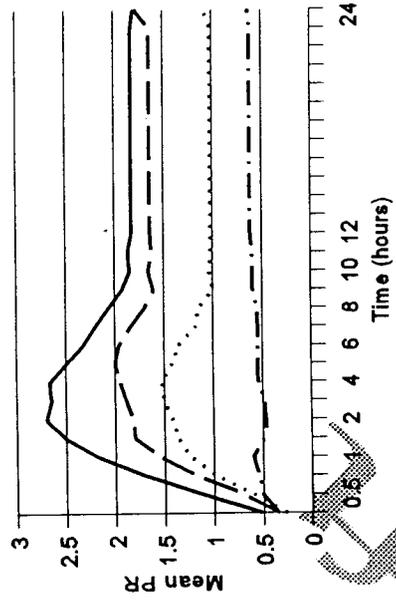
Baseline Observation Carried Forward (BOCF)

Pain Relief Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

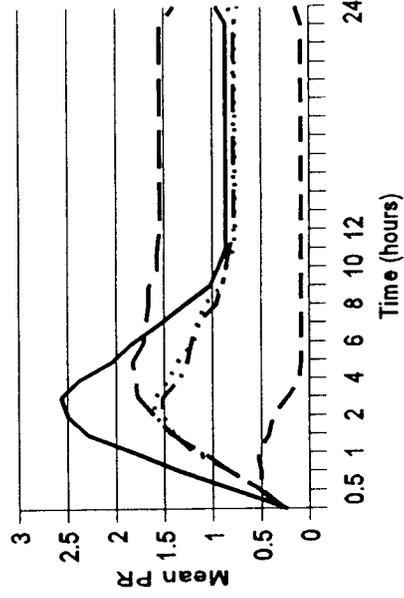
Study 025 PR - BOCF



Study 027 PR - BOCF



Study 070 PR - BOCF



IBU 400mg — CEL 200mg
CEL 50mg CEL 25mg
PBO - - - - - PBO

NAP 550mg — CEL 200mg
CEL 100mg - - - - - PBO

NAP 550mg — CEL 400mg
CEL 200mg CEL 100mg
PBO - - - - - PBO

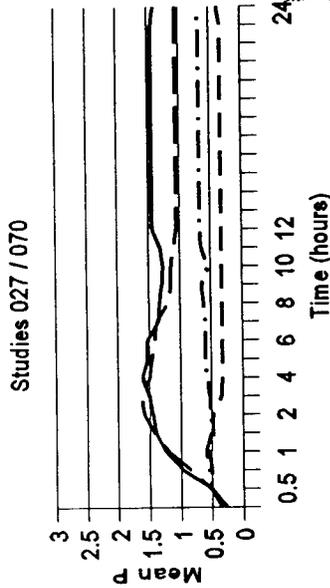
APPEARS THIS WAY
ON ORIGINAL

Mean Pain Relief (PR) Summarized by Dose PostSurgical Dental Pain Studies

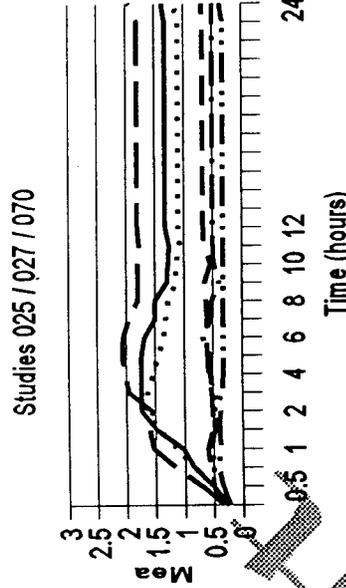
Last Observation Carried Forward (LOCF)

Pain Relief Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

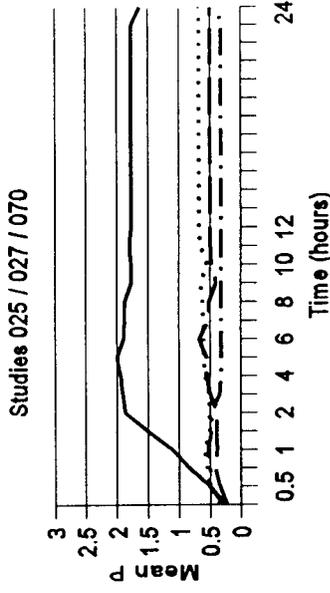
Celecoxib 100mg & Placebo - LOCF



Celecoxib 200mg & Placebo - LOCF



Celecoxib 400mg & Placebo - LOCF



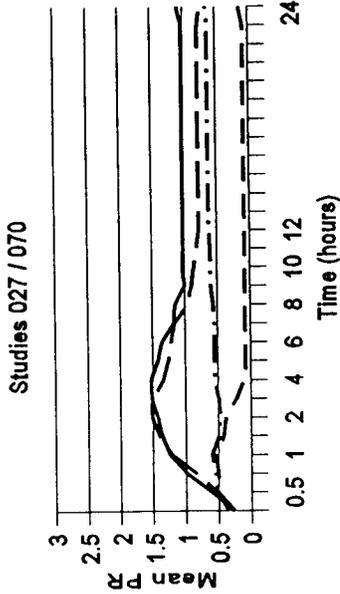
APPEARS THIS WAY ON ORIGINAL

Mean Pain Relief (PR) Summarized by Dose PostSurgical Dental Pain Studies

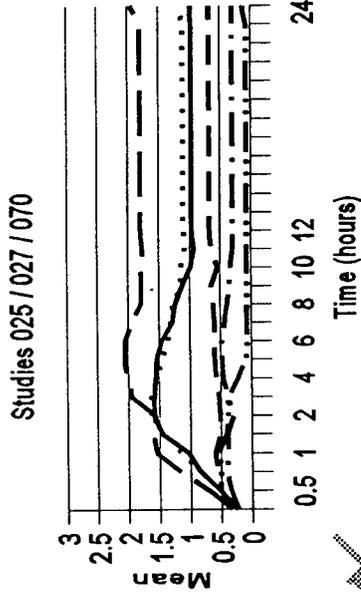
Baseline Observation Carried Forward (BOCF)

Pain Relief Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

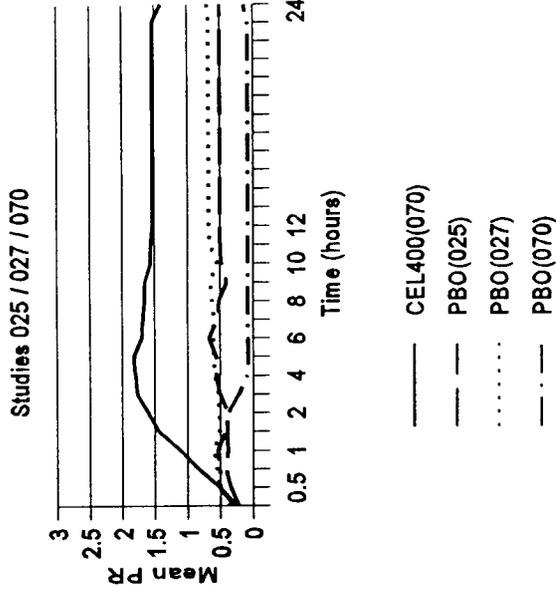
Celecoxib 100mg & Placebo - BOCF



Celecoxib 200mg & Placebo - BOCF



Celecoxib 400mg & Placebo - BOCF



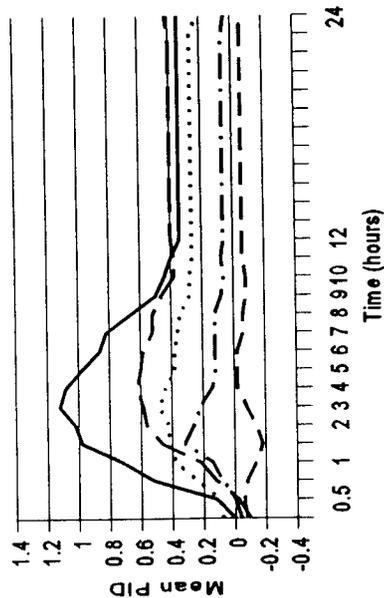
DRAFT

APPEARS THIS WAY
ON ORIGINAL

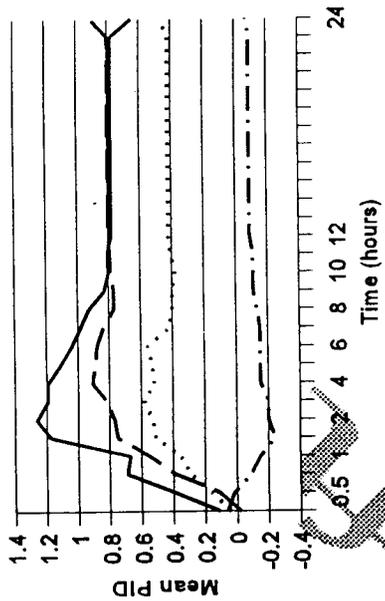
Mean Pain Intensity Difference (PID) in PostSurgical Dental Pain Studies

Last Observation Carried Forward (LOCF)

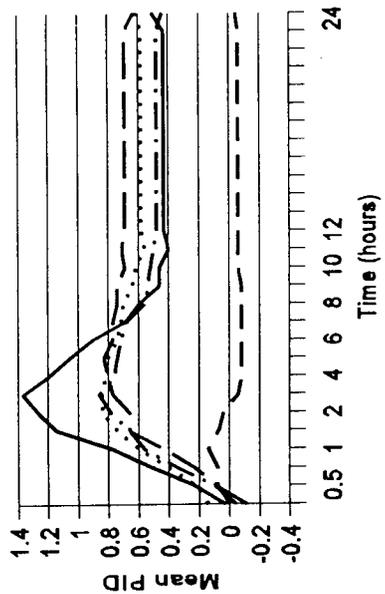
Study 025 PID - LOCF



Study 027 PID - LOCF



Study 070 PID - LOCF



— IBU 400mg — CEL 200mg
 CEL 50mg — CEL 25mg
 - - - - - PBO

— NAP 550mg — CEL 200mg
 CEL 100mg — PBO

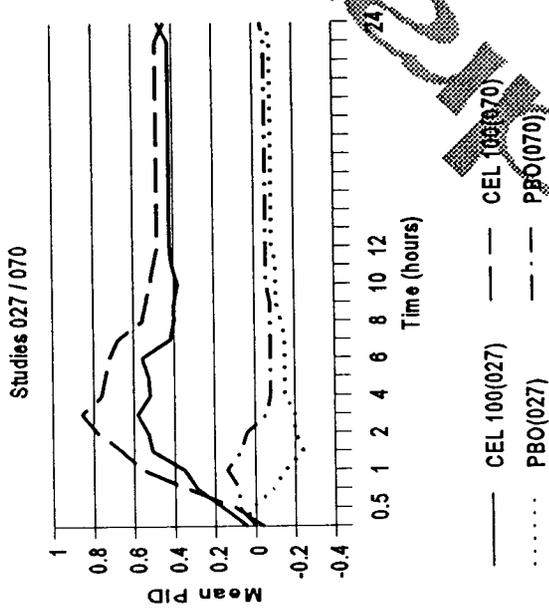
— NAP 550mg — CEL 400mg
 CEL 200mg — CEL 100mg
 - - - - - PBO

APPEARS THIS WAY ON ORIGINAL

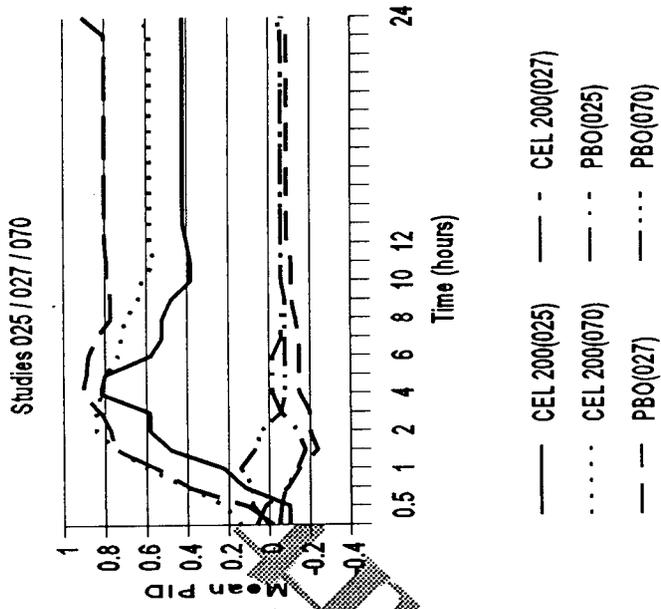
Mean Pain Intensity Difference (PID) Summarized by Dose PostSurgical Dental Pain Studies

Last Observation Carried Forward (LOCF)

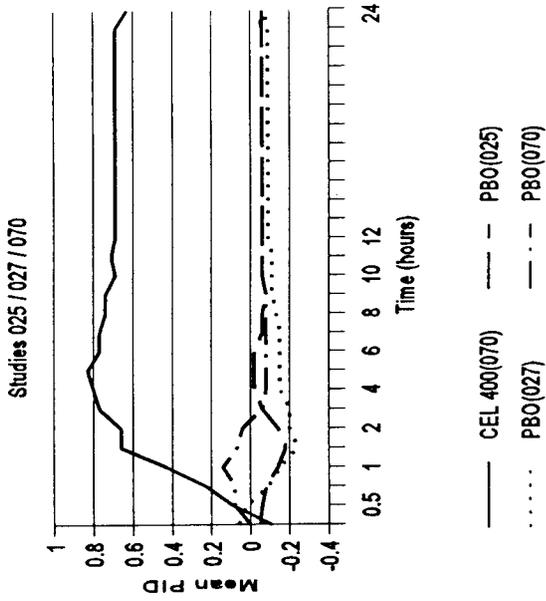
Celecoxib 100mg & Placebo - LOCF



Celecoxib 200mg & Placebo - LOCF



Celecoxib 400mg & Placebo - LOCF

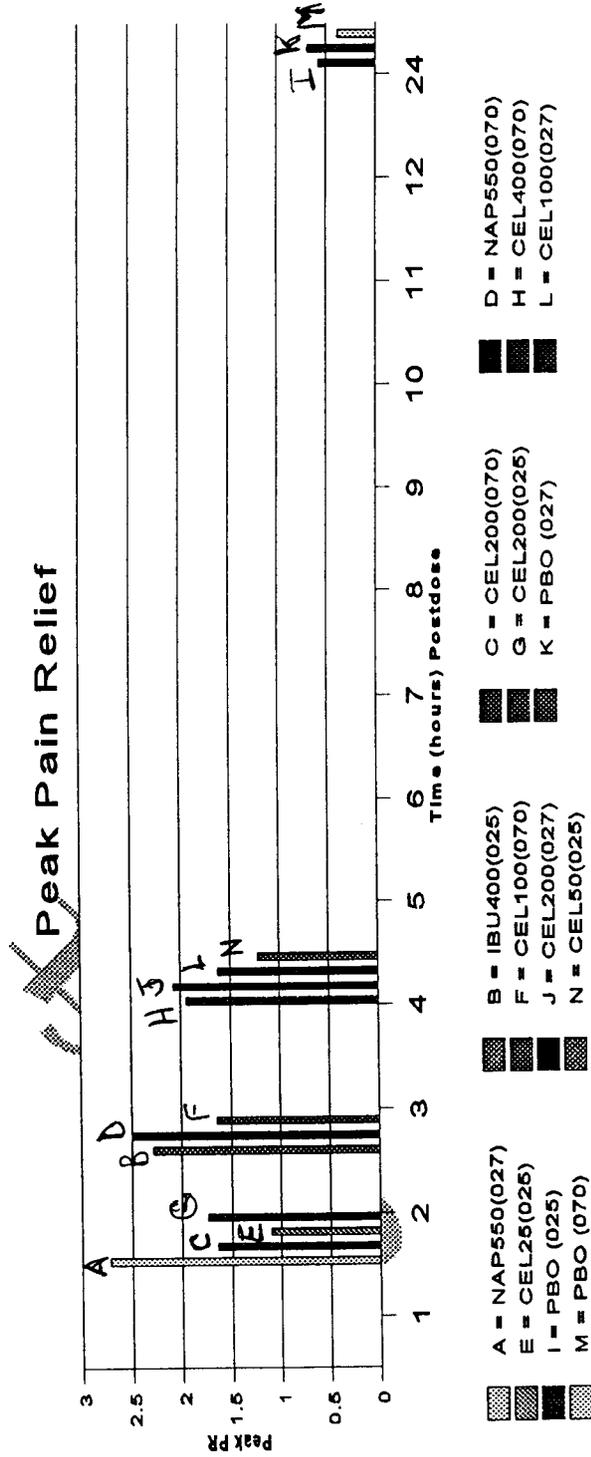


APPEARS THIS WAY
ON ORIGINAL

Dose Level Summary of Mean and Peak Pain Relief (PR) in PostSurgical Dental Pain Studies
Baseline Observations Carried Forward (BOCF)

Study	Celecoxib 25	Celecoxib 50	Celecoxib 100	Celecoxib 200	Celecoxib 400	Ibuprofen 400	Naproxen 550
025 PR Onset	H0.75 → H3	H1 → H2				H0.5 → H8 (PBO)	
PR Peak (hour)	1.1 at H2	1.22 at H4	H1 → H24 1.74 at H2			H0.5 → H8 (25/50) H0.5 → H4 (200) 2.28 at H3	
027 PR Onset			H1 → H6				H0.5 → H24 (PBO)
PR Peak (hour)			1.62 at H4	H0.75 → H4 2.07 at H4			H0.5 → H24 (100) H0.5 → H4 (200) 2.72 at H2
070 PR Onset			H1 → H12		H11.5 → H24		H0.75 → H24 (PBO)
PR Peak (hour)			1.64 at H3	1.64 at H2	1.94 at H4		H0.75 → H8 (50) H0.75 → H4 (100/200) H0.75 → H3 (400) 2.5 at H3

** "Onset Hx → Hy" is Time (Hour x through y) of Statistically Significant Differences in Mean Pain Relief from that of Placebo.
"Peak at Hour x" is Peak Pain Relief Score Attained at Hour x.

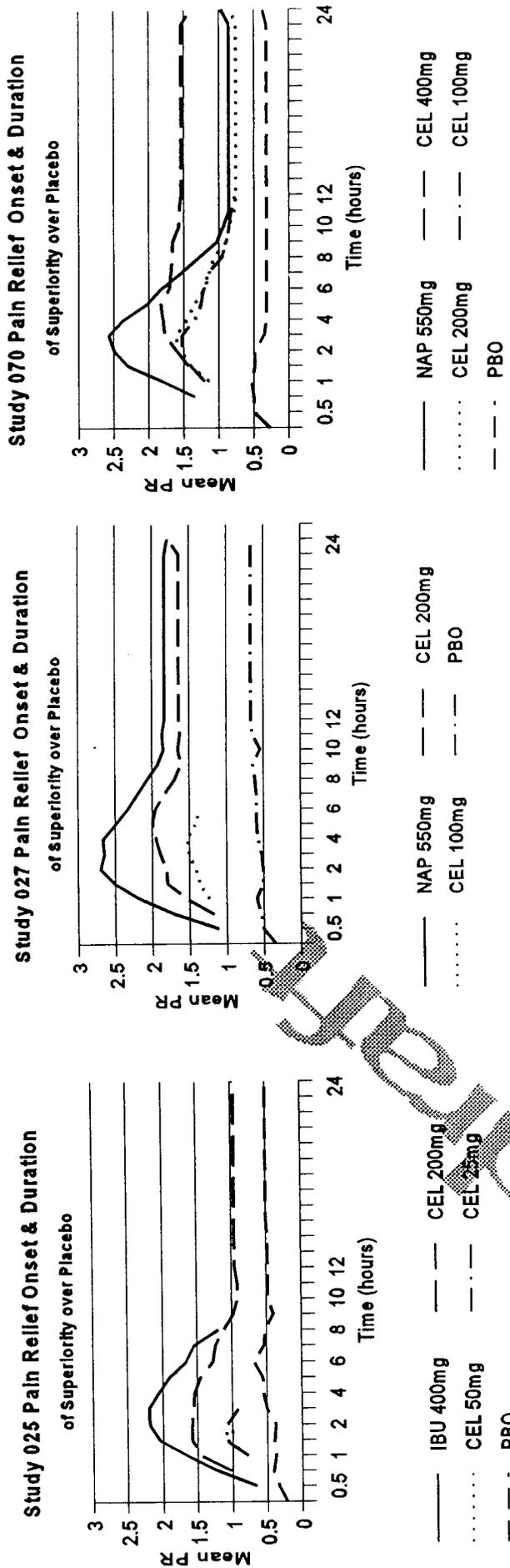


BEST POSSIBLE COPY

Onset and Duration of Statistically Significant Differences in Mean Pain Relief (PR)

PostSurgical Dental Pain Studies

Baseline Observations Carried Forward (BOCF)



BEST POSSIBLE COPY

I Kalam

Arthritis Advisory Committee

Food and Drug Administration
Center for Drug Evaluation and Research

December 1, 1998

Town Center Hotel
8727 Colesville Road, Silver Spring, MD

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

Contents

Agenda and Questions

Volume I

Medical Reviews

Primary Medical Review

Secondary Medical Review

Safety Review

Gastrointestinal Review

Renal Review

Volume II

Statistical Reviews

Osteoarthritis

Rheumatoid Arthritis

Pain

Volume III

Pharmacology Reviews

Biopharmaceutics

Pharmacology/Toxicology

NDA: 20-998**SUBMISSION DATES:** 6/29/98,**PRODUCT:** Celebrex™ (celecoxib) Capsules, 100 mg & 200 mg 8/24/98, 9/3/98, 10/1/98**SPONSOR:** Searle

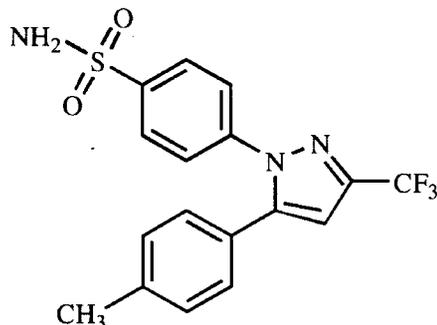
4901 Searle Parkway

Skokie, IL 60077

TYPE OF SUBMISSION: Original, 1P**REVIEWER:** Sue-Chih Lee, Ph.D.

1. Synopsis

Celecoxib (SC-58635), a diarylsubstituted pyrazole compound, is a member of a novel class of agents that selectively inhibits cyclooxygenase-2 (COX-2). It is intended for use as an oral anti-inflammatory and analgesic agent for the acute or chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), and management of pain.



In support of this application, the sponsor has submitted a total of 30 pharmacokinetic studies. Out of these, 2 studies (one single dose and one multiple dose studies) were conducted in Japanese healthy subjects and were not reviewed in full length because they did not add new information to this application. It was noted that results from additional studies were used to support the labeling and were included in the summary section but the individual reports were not provided in Section 6. This reviewer has since requested and reviewed these individual reports except for the study in renal insufficiency patients which is currently under review. The following is a brief summary of the pharmacokinetic study results.

Pharmacokinetic characteristics of celecoxib

Absorption: Following a single dose under fasted conditions, peak plasma celecoxib concentrations (C_{max} ~ 600-900 ng/mL for a 200 mg dose) occur at approximately 3 hours postdose. Relative to an oral suspension, Celebrex capsules have a relative bioavailability of 99%. Because of the low aqueous solubility of celecoxib, absolute bioavailability studies have not been conducted. Multiple dose pharmacokinetics of celecoxib can generally be predicted from the single dose pharmacokinetics.

Effects of food and antacid: When Celebrex capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in C_{max} of 39% (200 mg capsules) to 62% (100 mg capsules) and total absorption (AUC) of 10% to 20% (for both strengths). Coadministration of Celebrex with an aluminum and magnesium containing antacid resulted in a reduction in plasma celecoxib concentrations (C_{max}: ↓ 37%; AUC: ↓ 10%).

Dose proportionality: Both AUC and C_{max} are not dose proportional. The dose adjusted parameter values reduce with an increase in dose due to the poor solubility of the drug. However, the AUC is roughly dose proportional between the 100 mg and 200 mg doses. The deviation from dose proportionality is reduced under fed conditions.

Distribution: Celecoxib is highly plasma protein bound and the binding is linear within clinical dose range (~97%). In vitro studies indicate it binds to human plasma albumin and, to a lesser extent, α₁-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into tissues.

Metabolism: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors in the in vitro models.

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite with low amounts of the glucuronide also appearing in the urine. The low solubility of the drug prolongs the absorption process making terminal half-life (t_{1/2}) determinations more variable. The overall effective half-life, based on a single dose of celecoxib, is approximately 11 hours. The apparent plasma clearance (CL/F) is about 500 mL/min.

Special populations

Effects of age, gender and race: At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} (1363 vs. 973 ng/mL) and a 70% higher AUC compared to the young subjects. In elderly females celecoxib C_{max} and AUC are 20-25% higher than those for elderly males but these increases are thought to be due to lower body weight in elderly females. There are no studies conducted in pediatric subpopulation.

Effects of gender: A meta analysis did not show any difference in celecoxib AUC between genders. A (14%) lower C_{max} in female subjects was found to be statistically significant after a single dose of celecoxib. On the other hand, there was no difference in C_{max} between genders after multiple dosing. Therefore, there is no consistent evidence of gender differences in celecoxib pharmacokinetics.

Effects of race: A meta analysis of pharmacokinetic studies suggested a (30%) higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this difference is unknown.

Hepatic insufficiency: A pharmacokinetic study showed that steady state celecoxib AUC increased (~30%) in volunteers with mild hepatic impairment (Child-Pugh Class I) and more than doubled (270%) in volunteers with moderate hepatic impairment (Child-Pugh Class II) when compared to the matching control group. Patients with severe hepatic impairment have not been studied.

Renal insufficiency: In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic moderate renal insufficiency (GFR 35-60 mL/min/1.73 m) than that seen in subjects with normal renal function. No significant relationship was found between serum creatinine or estimated creatinine clearance and celecoxib clearance. Further, patients with severe renal insufficiency have not been studied.

Drug interactions

In vitro studies: In vitro studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4. Although not a substrate, in vitro studies indicate that celecoxib is a moderately potent inhibitor of cytochrome P450 2D6. (The K_i value for inhibition of bufuralol 1'-hydroxylation was $\sim 4.2 \mu\text{M}$, which is approximately 10-fold weaker than quinidine.) This finding suggests that there is a potential for an in vivo drug interaction with CYP2D6 substrate.

In vivo studies:

Glyburide, ketoconazole, phenytoin and tolbutamide: The effect of celecoxib on the pharmacokinetics of these drugs has been studied in vivo and clinically important interactions have not been found.

Fluconazole: Concomitant administration of fluconazole resulted in an increase of 68% in C_{max} and 134% in AUC. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole.

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with Celebrex 200 mg BID as compared to subjects receiving lithium alone, which is similar to previous findings with other NSAIDs.

Methotrexate: In an interaction study of rheumatoid arthritis patients taking methotrexate, Celebrex did not have significant effect on the pharmacokinetics of methotrexate.

Warfarin: The effect of celecoxib on the anti-coagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time.

Bioequivalence of commercial formulations:

The sponsor has shown bioequivalence between the 100 mg and 200 mg commercial capsules. The 100 mg capsules are bioequivalent to the 100 mg Phase III capsules in terms of AUC but the C_{max} is lower for the commercial capsules. A study was conducted to demonstrate the bioequivalence of the 200 mg commercial capsules to the 200 mg Phase III capsules. Because of the design and analysis method used, this study is currently evaluated by Dr. Shan Sun of QMRS/FDA.

II. Recommendation

The sponsor has adequately characterized the pharmacokinetics and pharmacodynamics of the subject drug. From the biopharmaceutic standpoint, the application is approvable provided that the sponsor addresses the issues as listed under “Comments to be Conveyed to the Sponsor.”

III. Comments

A. General Comments:

1. Celecoxib has two important characteristics: (a) low aqueous solubility and high permeability, and (b) extensively metabolized in the liver which is predominantly mediated via CYP2C9; elimination through renal excretion of the parent compound is negligible.
2. The low aqueous solubility of celecoxib contributed to the high variability in absorption after oral administration.
3. In patients with chronic moderate renal insufficiency (GFR: 34-48 mL/min/1.73 m²), the apparent clearance (CL/F) appears higher resulting in a 40% lower AUC when compared to studies in healthy subjects. This may be due to an increase in the unbound drug in renal impairment patients. However, this study is still under review as the individual report was not provided to this reviewer in the original submission.
4. A population PK analysis in OA and RA patients has been performed by the sponsor to characterize celecoxib pharmacokinetics in these patients and to identify possible covariates. However, due to the inappropriate study design, the analysis is deemed unreliable.
5. A population PK/PD analysis of four dental pain trials was included in the original submission. After receiving comments from this reviewer, the sponsor submitted a revised analysis which is currently under review.

B. Comments to be Communicated to the Sponsor:

1. It seems that low solubility prolonged absorption process making the terminal half-life appear longer than the true half-life of the drug. This is based on the much shorter terminal half-life seen in subjects taking the drug immediately after a high fat meal. It

- follows that the amount of water taken by a subject may also affect the absorption and apparent terminal half-life of the drug. The sponsor should comment on this.
2. Very high plasma celecoxib concentrations (3-10 times of mean values) were observed in 6 out of several hundred subjects exposed to the 200 mg dose. These may be poor metabolizers but more information is needed from the sponsor. These subjects were on single dose or short term multiple dose use of celecoxib and no serious adverse events occurred during the study. However, Dr. Maria Villalba, Medical Officer of HFD-550, indicated that many lab tests were performed several days after the last dose.
 3. We have requested the following information but have not received a response from the sponsor:
 - a. Effective half-life of the drug
 - b. Volume of distribution at steady state
 - c. Genotyping information for subjects with very high plasma celecoxib concentrations.
 4. Regarding study 004: Values for CL/F and V_z/F in the individual report (Vol. 1.85, pp. 43, 47) differ from those in the summary (Vol. 1.81, p. 166). Discrepancies were also observed with Study 003. The sponsor should clarify.

**APPEARS THIS WAY
ON ORIGINAL**

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD Initialed by Dennis Bashaw, Pharm.D. _____

FT Initialed by Dennis Bashaw, Pharm.D. _____

CPB Briefing (Date: 11/24/98; Attendees: and Lee)

CC:
NDA 20-998
HFD-550 (Div.File)
HFD-550 (CSO/Lutwak)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

**APPEARS THIS WAY
ON ORIGINAL**

Table of Contents:

Page no.

I.	Synopsis	1
II.	Recommendation	4
III.	Comments	4
IV.	Background	7
V.	Formulation	7
VI.	Analytical	8
VII.	Summary of Bio/PK/PD Characteristics	9
A.	Metabolism	
a.	Evaluation of total radioactivity in biological samples	9
b.	Metabolic profiles in biological samples	10
c.	Proposed metabolic pathway	11
d.	Cytochrome P450 isoforms in the metabolism of celecoxib	12
B.	Protein Binding	13
C.	Single Dose Pharmacokinetics: Dose escalation study	14
D.	Multiple Dose Pharmacokinetics	
a.	In healthy subjects (17-44 yrs)	16
b.	In healthy subjects & OA patients (40-58 yrs)	17
E.	Relative Bioavailability	19
F.	Dose Proportionality of Commercial Capsules	20
G.	Effect of Food and Antacid	
a.	200 mg celecoxib commercial capsules	21
b.	100 mg celecoxib commercial capsules	22
H.	Effect of Dosage Regimen and Dosing Time	
a.	Dosage regimen: 200 mg bid vs. 400 mg qd	24
b.	Dosing time: AM vs PM	25
I.	Special Populations	
a.	Age effect (Healthy young vs. elderly)	26
b.	Gender Effect..	29
c.	Effect of Race	29
d.	Reduced Renal Function	30
e.	Hepatic Impairment Study	32
J.	Drug-Drug Interactions	
a.	In vitro studies	34
b.	In vivo studies	
	Fluconazole (p. 35), ketoconazole (p. 37), methotrexate (p. 39), lithium (p. 41), tolbutamide (p. 42), warfarin (p. 44), glyburide (p. 46), phenytoin (p. 49)	
K.	Population PK Analysis	50
L.	Population PK/PD Analysis	51
M.	Bioequivalence	
a.	Commercial capsules (100 mg & 200 mg) and	

	Phase III 100 mg capsules	56
	b. 200 mg Phase III capsules vs. 200 mg commercial capsules	58
N.	In Vitro Dissolution	59
Appendix 1:	Individual Studies (study design, data, tables & figures)	61

IV. Background

Celecoxib (SC-58635), is a specific COX-2 inhibitor intended for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis and management of pain. Cyclooxygenase (COX) is present in at least two forms in human cells. One form is constitutive (COX-1) and is widely expressed in nearly all tissues throughout the body, including gastric and renal epithelial cells, and platelets. The other form (COX-2) is inducible and is generally expressed in very low amounts in normal tissues, but is prominently expressed in inflamed tissues. Currently available NSAIDs are considered non-specific COX inhibitors. The sponsor claims that celecoxib inhibits COX-2 approximately 300-fold more effectively than COX-1 in in vitro studies. It is thought that COX-2 specific inhibitors will provide efficacy as an antiinflammatory and analgesic agent while minimizes adverse events associated with COX-1 inhibition (gastrointestinal ulceration, platelet dysfunction and nephrotoxicity).

Celecoxib has an aqueous solubility of about 5 µg/mL at between 5 and 40°C, which is pH independent below pH 9. It is freely soluble in methanol, ethanol, PEG 400 and acetone and very slightly soluble to practically insoluble in oils (< 3 mg/mL in corn oil) and non-polar hydrocarbons. Its pK_a of 11.1 is associated with ionization of the sulfonamide moiety. The apparent octanol/water partition coefficient for celecoxib is above 10³ at pH 7. Therefore, it is a low solubility, high permeability drug.

V. Formulation

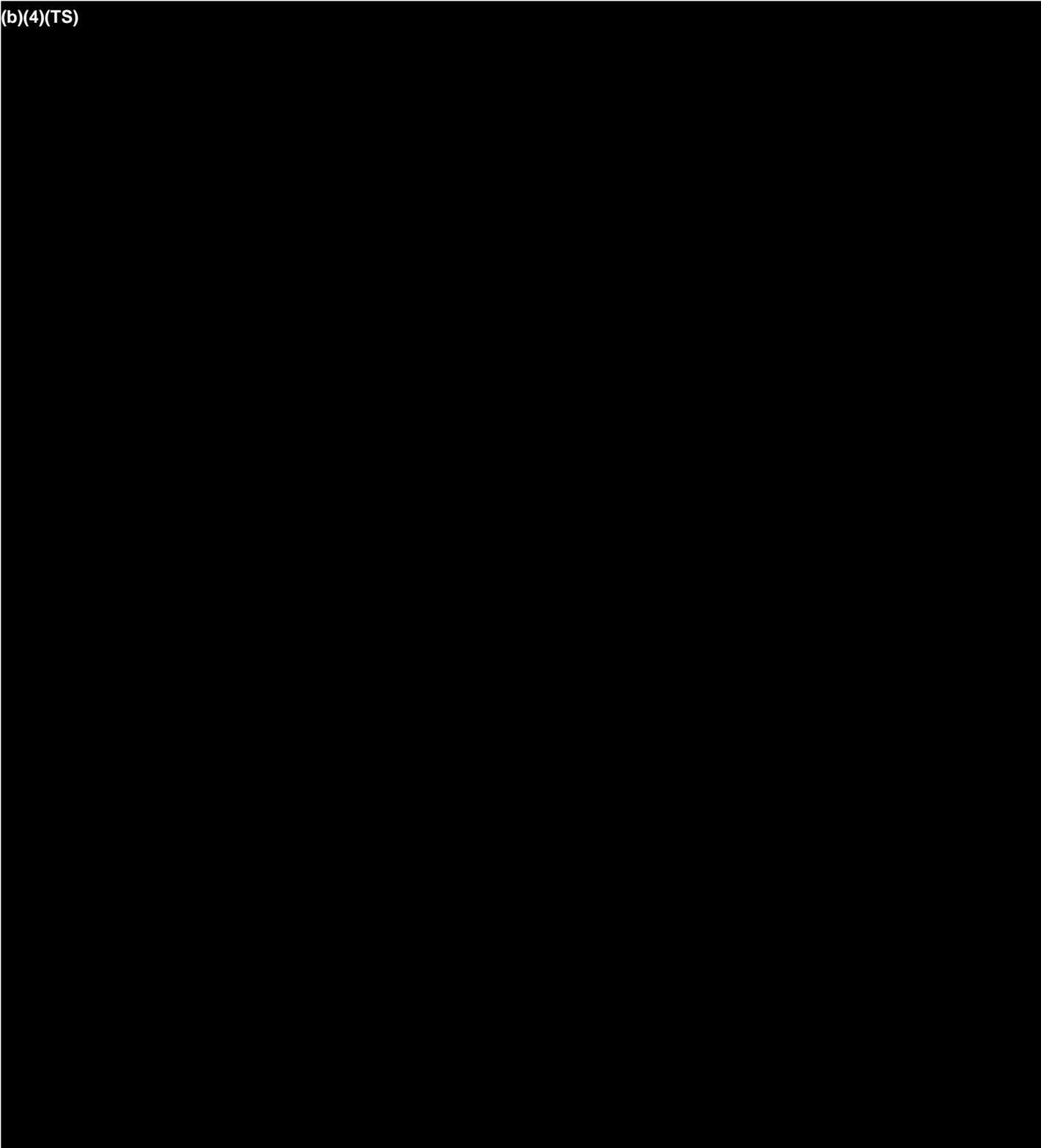
The sponsor intends to market both the 100 mg (blue) and 200 mg (gold) capsules. As shown in the table below, the formulations for these two strengths are not proportionally similar.

Ingredient	mg/Capsule		Function
	100 mg Capsules	200 mg Capsules	
SC-58635, Milled	100.0	200.0	Active Ingredient
Lactose, Monohydrate	(b)(4)(TS)		
Sodium Lauryl Sulfate			
Povidone			
Croscarmellose Sodium			
Magnesium Stearate			
Purified Water*			
Total Capsule Fill Weight	270	270	-

DRAFT

VI. Analytical Methods

(b)(4)(TS)



VII. Summary of Bio/PK/PD Characteristics

(Note: For easy reference, the study number cited in this section corresponds to the last three digits of protocol numbers given in Appendix 1.)

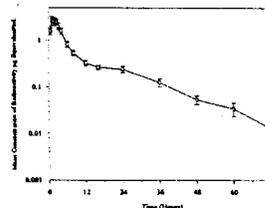
METABOLISM

a. Evaluation of Total Radioactivity in Human Biological Samples (Study 006)

This study was conducted (1) to determine the ADME profile (mass balance) of an oral fine suspension of [¹⁴C]celecoxib and (2) to estimate the bioavailability of an oral capsule relative to the fine suspension. Each subject received a single 300-mg dose of suspension (containing radiolabeled drug; ~100 μ Ci) and capsule (containing cold drug) formulations. The detailed study design is given in Appendix 1 (p. 62). This section discusses the results from the suspension formulation as related to the first objective.

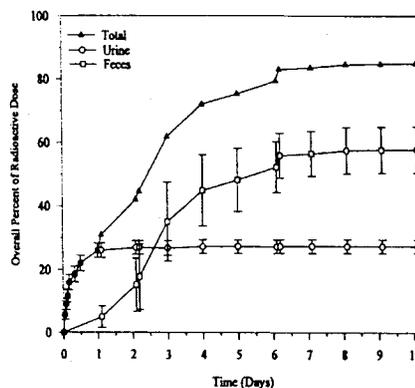
Eight healthy male subjects (2 in pilot phase and 6 in definitive phase) completed the study. Concentrations of total radioactivity in plasma, red blood cells, saliva, urine, and fecal samples collected at specified time intervals after dose administration were determined.

Plasma concentration of total Radioactivity: The mean plasma concentration of total radioactivity reached a maximum of 2.75 ± 1.29 μ g equivalents/mL at 1.75 hr postdose. Radioactivity in plasma obtained 72 hours after dose administration was not detectable in most subjects. The elimination half-life of total radioactivity was approximately 17.0 ± 4.0 hrs.



Distribution into red blood cells: Celecoxib concentrations in plasma and RBC were compared at 1 and 4 hours postdose. The mean concentration of radioactivity was slightly lower in red blood cells than in plasma at 1 and 4 hours postdose (RBC: 2.33 ± 0.34 and 1.26 ± 0.22 μ g/mL; plasma: 2.43 ± 0.49 and 1.57 ± 0.17 μ g/mL, respectively). The mean of individual ratios of RBC/plasma concentrations of total radioactivity were 1.02 ± 0.3 and 0.80 ± 0.29 at 1 and 4 hours postdose, respectively.

Excretion in urine and feces: Radioactivity was excreted in urine and feces following oral administration of celecoxib. The mean percent of total radioactivity excreted was $27.1 \pm 2.2\%$ in the urine samples (0-144 hrs) and $57.6 \pm 7.3\%$ in fecal samples. As shown in the figure, most (95.6%) of the urinary excretion occurred within the first 24 hours postdose while ~78% of the fecal excretion occurred within 96 hours postdose.



Saliva: The concentration of radioactivity in saliva was very low at the time periods examined. Most of the saliva samples had no quantifiable concentrations of radioactivity. The amount of radioactivity secreted into the saliva up to 24 hours postdose was negligible.

Total recovery: Recovery from saliva and fecal wipes were very small (~0.14%). The total mean percent of the radioactive dose recovered ($84.8 \pm 4.9\%$) were mostly from urine and feces.

Conclusion:

- Celecoxib was not preferentially bound to erythrocytes.
- Secretion of celecoxib into saliva was negligible.
- After oral administration of 300 mg celecoxib, approximately 85% of the dose was recovered from urine and feces ($27.1 \pm 2.2\%$ of the dose from urine and $57.6 \pm 7.3\%$ of the dose from feces).

b. Metabolic Profiles in Biological Samples

Plasma: Plasma samples obtained at 0.5, 3, 4 and 12 hours after oral administration of celecoxib at 300 mg were analyzed using (b)(4)(CC). The findings were:

- The parent compound was the major species present in plasma. (*Reviewer's note:* In a drug interaction study with fluconazole, the AUC of M2 was found to be comparable to that of the parent compound when celecoxib was administered alone.)
- Three metabolites of celecoxib were found in plasma: SC-60613, SC-62807 and the glucuronide conjugate of SC-62807. Note: These metabolites were shown to be inactive as COX inhibitors in in vitro models.
- SC-60613 is the product of partial oxidation of the methyl moiety of celecoxib to a hydroxyl group and is a minor circulating metabolite as indicated in the table below.
- SC-62807 (M2) is the result of complete oxidation of the methyl moiety of celecoxib to a carboxyl group. Glucuronidation of the carboxyl metabolite forms M1. (See next page for chemical structures.)

Celecoxib and Metabolites in Plasma (in terms of % total radioactivity in plasma samples)

Time ,hr postdose	M1	M2	SC-60613	Celecoxib
0.5 (n=8)	1.10 ± 0.60	12.1 ± 2.6	2.43 ± 0.89	84.4 ± 3.6
3 (n=8)	21.0 ± 4.9	21.2 ± 1.9	0.217 ± 0.182	57.6 ± 6.5
4 (n=2)	13.5	21.0	0.00	65.6
12 (n=6)	23.2 ± 4.1	27.0 ± 5.9	0.00 ± 0.0	49.9 ± 4.5

Urine: Urine samples collected up to 12 hours postdose were analyzed (b)(4)(CC)

- No unchanged drug was detected in the urine.
- The species present in these samples were metabolites M1 and M2. The mean (n=8) cumulative amount of metabolites excreted in the urine within 12 hours postdose was equivalent to $18.8 \pm 2.1\%$ of the dose for M2 and $1.48 \pm 0.15\%$ of the dose for M1.

Feces: Analysis of fecal samples collected over 8-10 days after dosing gave the following results:

- The radioactivities in fecal samples were associated with metabolite M2 and the parent drug.
- The mean cumulative amount excreted in the feces were equivalent to $54.4 \pm 6.8\%$ (M2) and $2.56 \pm 1.09\%$ (celecoxib) of the dose, respectively.

Mean Percent of Dose Excreted In Urine and Feces

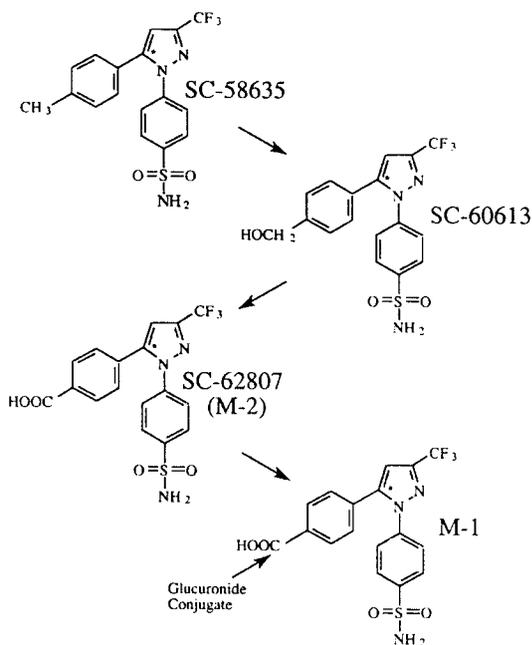
	Glucuronide of SC-62807 (M1)	SC-62807 (M2)	SC-60613	Celecoxib
Urine (0-12 hrs)	1.48 ± 0.15	18.8 ± 2.1	-	-
Feces	-	54.4 ± 6.8	-	2.56 ± 1.09

Conclusion:

- Urinary radioactivity was associated with M1 and M2. No unchanged drug was detected in the urine.
- Fecal radioactivity was associated with unchanged drug and M2.
- Metabolism of celecoxib was extensive. After oral administration, only approximately $2.56 \pm 1.09\%$ of the recovered total radioactivity in urine and feces was unchanged drug.

c. Proposed Metabolic Pathway

The sponsor proposed that celecoxib first undergoes partial oxidation of the methyl group to form a hydroxymethyl derivative (SC-60613), which was further oxidized to a carboxylic acid compound (SC-62807; M2). Glucuronidation of the carboxylic acid forms M1. (See figure below.)



Chemical structure and metabolic pathways of SC-58635. Asterisks indicate the position of the labeled carbon atoms.

BEST POSSIBLE COPY

d. In Vitro Studies: Determination of P450 Isoforms in the Metabolism of Celecoxib

The in vitro metabolism of ^{14}C -celecoxib was investigated using human liver microsomes and cDNA-expressed human cytochrome P450 enzymes. The major metabolites of celecoxib generated by human liver microsomes, SC-60613 and SC-62807, are the same as the major (unconjugated) metabolites found in vivo. The apparent K_m and V_{max} for celecoxib metabolism by a pool of human liver microsomes were estimated to be $49.3 \mu\text{M}$ ($18.8 \mu\text{g/mL}$) and 735 pmole/min/mg , respectively. The following studies were conducted using a protein concentration of 1.0 mg/mL .

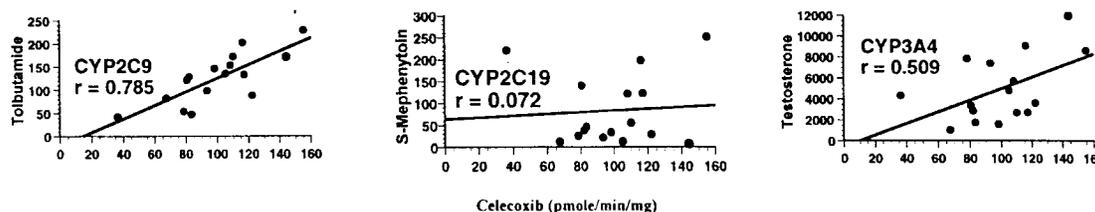
Celecoxib metabolism by cDNA-expressed human P450 enzymes: As shown in the table below, human recombinant CYP2C9, CYP2C19 and CYP3A4 were each found to be capable of metabolizing ^{14}C -celecoxib (at $10 \mu\text{g/mL}$ or $26 \mu\text{M}$) to ^{14}C -SC-60613 in vitro. Metabolism of ^{14}C -celecoxib was not detectable with human recombinant CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 and CYP3A5.

Table: Percent of Celecoxib Converted to SC-60613

1A2	2A6	2B6	2C9	2C19	2D6	2E1	3A4	3A5	PHM ¹
<0.5	<0.5	<0.5	38.7	64.4	<0.5	<0.5	2.1	<0.5	48.2

¹Pooled human liver microsomes

Correlation of celecoxib metabolism with metabolism of P450 isoform-specific substrates by human liver microsomes: Specific enzymatic activities for ^{14}C -celecoxib metabolism at the celecoxib substrate concentrations of 2.6 and $10 \mu\text{M}$ (~ 1.0 and $3.81 \mu\text{g/mL}$) were determined for 16 individual human microsome samples and compared to the known (phenotyped) specific enzymatic activities of the same microsomes for a series of cytochrome P450 isoform-specific substrates. The figures below present the correlation between isoform specific substrate metabolism and celecoxib metabolism at $2.6 \mu\text{M}$ celecoxib substrate concentration. Celecoxib metabolism correlated strongly with CYP2C9 (tolbutamide hydroxylase; $p < 0.001$). The correlation was weaker for CYP3A4 (testosterone 6β -hydroxylase; $p < 0.05$), and there was no correlation for CYP2C19 (S-mephenytoin 4'-hydroxylase). Similar results were obtained at the higher celecoxib substrate concentration ($10 \mu\text{M}$).



Inhibition of celecoxib metabolism by known cytochrome P450 inhibitors: The experiments with known inhibitors of P450 were performed at a ^{14}C -celecoxib substrate concentration of $10 \mu\text{g/mL}$ and inhibitor concentrations of $20 \mu\text{M}$ furafylline, $0.3 - 100 \mu\text{M}$ sulfaphenazole, $0.3 - 30 \mu\text{M}$ omeprazole, $20 \mu\text{M}$ mephenytoin, $20 \mu\text{M}$ quinidine, $20 \mu\text{M}$ DDTC, $20 - 100 \mu\text{M}$ TAO or $0.5 - 1.0 \mu\text{M}$ ketoconazole.

Further evidence for the importance of CYP2C9 in ¹⁴C-celecoxib metabolism by human liver microsomes was provided by the finding that sulfaphenazole, a potent and specific CYP2C9 inhibitor, inhibited both ¹⁴C-celecoxib and tolbutamide to the same extent (80-90%) in six individual human microsome samples. Other cytochrome P450 isoform selective inhibitors were less effective (omeprazole/CYP2C19; troleandomycin/CYP3A4; ketoconazole/CYP3A4), or ineffective (furafylline/CYP1A; quinidine/CYP2D6; DDTC/CYP2E1) as inhibitors of ¹⁴C-celecoxib metabolism by human liver microsomes.

Table: Percent Inhibition of Celecoxib Metabolism by Various Inhibitors

1A	2C9	2C19	2C19	2D6	2E1	3A4	3A4
furafylline	sulfa-phenazole	omeprazole	mephenytoin	quinidine	DDTC	TAO	ketoconazole
10.0	80.0	57.3	4.3	0	0	0	-
-	70.4 (10 μ M)	27.5 (10 μ M)	-	-	-	14.7 (100 μ M)	36.9 (1.0 μ M)

*Inhibitor concentration at 20 μ M unless otherwise specified.

Conclusion:

- Human recombinant CYP2C9, CYP3A4 and CYP2C19 were each found to be capable of metabolizing celecoxib.
- CYP2C9 is judged to be most important in human metabolism of celecoxib based on correlation analysis using a series of characterized human microsome samples (high correlation found between celecoxib and tolbutamide metabolism) and the strong inhibition of celecoxib metabolism by the specific CYP2C9 inhibitor, sulfaphenazole.

Reviewer's comment:

All the above in vitro metabolism studies were performed at a high celecoxib concentration (10 μ g/mL) except for the correlation study which used a celecoxib concentration (1 μ g/mL) within the range found at the recommended dose (steady state Cmax: < 2 μ g/mL after 200 mg BID).

PROTEIN BINDING

a. Report MRC-94S-0136

- In an in vitro protein binding study using plasma sample from one subject and employing a (b)(4)(CC) method, celecoxib was found to be highly protein bound at ¹⁴C-celecoxib concentrations of 0.3 μ g/mL (97.3% bound) and 3.0 μ g/mL (90.6% bound), respectively.

b. The Binding of SC-58635 to Mouse, Rat, Dog and Human Plasma Proteins

(Report # M3097065)

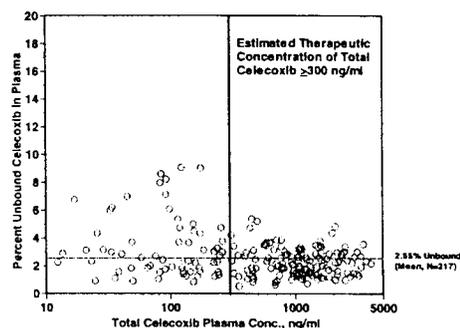
An (b)(4)(CC) method was employed in this study. ¹⁴C-celecoxib concentrations of 0.1, 0.3, 1.0, 3.0 and 10 μ g/mL were evaluated. Only the results related to human plasma protein binding is summarized here. (Note: The human plasma was obtained from only one subject.)

- The percentages of binding of ^{14}C -celecoxib to human plasma in vitro at total celecoxib plasma concentrations of 0.1, 0.3, 1.0, 3.0 and 10.0 $\mu\text{g}/\text{ml}$ were 98.2%, 97.9%, 96.5%, 96.7% and 96.3%, respectively.
- Celecoxib binds in vitro to both human albumin and α_1 -acid glycoprotein.
- The percentages of binding of ^{14}C -celecoxib to human albumin in vitro at celecoxib concentrations of 0.1, 0.3, 1.0, 3.0 and 10 $\mu\text{g}/\text{mL}$ were 100, 100, 99.8, 99.9 and 99.8, respectively.
- The percentages of binding of ^{14}C -celecoxib to human α_1 -acid glycoprotein in vitro at celecoxib concentrations of 0.1, 0.3, 1.0, 3.0 and 10 $\mu\text{g}/\text{mL}$ were 92.4, 91.6, 91.0, 88.4 and 78.6, respectively.

c. Study 032

This study was conducted to evaluate the effects of 600 mg celecoxib BID versus 500 mg naproxen BID on platelet function in normal healthy subjects. Eight volunteers (3 male, 5 female, 20 to 39 years) received a single oral dose of celecoxib 600 mg with food, followed by celecoxib 600 mg BID with food for seven days. Blood samples for total and unbound celecoxib plasma assays were collected for up to 48 hours after single dose and last BID dose, in addition to trough plasma samples on predetermined days.

The dose of celecoxib in this study was higher than the anticipated therapeutic dose for treatment of osteoarthritis or rheumatoid arthritis. Total celecoxib plasma concentrations ranged from 0 to 4000 ng/mL and unbound concentrations ranged from 0 to 22.56 ng/ml. As shown in the figure, the fraction of unbound drug remained rather constant (mean 2.55% unbound). Therefore, within the projected plasma concentration range for the clinical doses, total celecoxib plasma concentrations were considered an adequate measure for determination of celecoxib pharmacokinetics.



Conclusion:

Celecoxib is highly plasma protein bound (~97%). The fraction of unbound drug remained essentially constant (mean 2.55% unbound) at total plasma celecoxib concentrations up to 4000 ng/mL.

SINGLE DOSE PHARMACOKINETICS

Dose Escalation Study In Healthy Adult Volunteers (Study 001)

The objective of this exploratory study was to determine the safety, tolerability and pharmacokinetics of single, oral escalating doses of celecoxib administered to healthy male subjects. A total of 80 subjects participated and completed the fasting portion of the study. Six of the eight subjects who received the 200 and 400 mg doses under fasting conditions also received a single dose following a high fat breakfast. The detailed study design is given in Appendix 1 (p. 65).

Plasma data: The mean pharmacokinetic parameters for the doses ranging from 5 to 1200 mg are listed below. Under fasting conditions, C_{max} was achieved within 2 hours for all of the doses tested. The sponsor considered that AUC_{0-96} was dose proportional through the 600 mg dose and less than proportional at the 900-mg and 1200-mg doses. The plasma terminal half-life, $T_{1/2}$, ranged from 7 to 11 hours for the doses of 50-900 mg.

Food delayed peak plasma levels but increased the overall absorption of celecoxib ($AUC \uparrow 22\%$ for the 200 mg dose and $\uparrow 58\%$ for the 400 mg dose), suggesting a possible food effect.

Table: Mean (\pm SD) Parameter Values

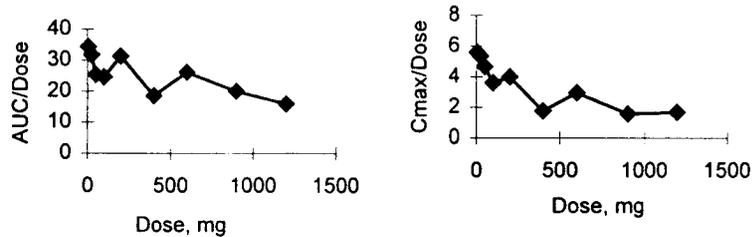
SC-58635 Dose	AUC(0-96) ng*hr/ml	Cmax ng/ml	Tmax hr	T1/2 hr
5 mg (n=4)	171.98 (40.85)	27.98 (9.71)	1.63 (1.11)	4.51 (0.78)
25 mg (n=4)	792.66 (249.30)	133.25 (45.18)	1.25 (0.50)	10.34 (3.84)
50 mg (n=4)	1271.48 (307.92)	233.25 (45.07)	2.00 (1.15)	7.69 (2.66)
100 mg (n=4)	2465.42 (690.41)	362.00 (155.98)	1.38 (0.75)	8.53 (2.89)
200 mg (n=4)	6271.63 (2846.27)	797.00 (498.78)	1.75 (1.50)	7.57 (5.47)
200 mg*(n=4)	7830.30 (4265.31)	875.50 (749.49)	6.25 (4.03)	9.51 (5.64)
400 mg (n=4)	7417.91 (904.52)	706.75 (104.08)	2.25 (1.50)	7.46 (2.38)
400 mg*(n=2)	11884.16 (3158.40)	1355.00 (7.07)	6.00 (2.83)	4.22 (2.31)
600 mg (n=4)	15725.65 (6689.83)	1771.00 (625.05)	1.50 (1.00)	9.56 (3.72)
900 mg (n=20)	18028.26 (7517.36)	1419.25 (683.38)	1.90 (0.91)	10.92 (5.15)
1200 mg (n=4)	19135.97 (4654.86)	2022.50 (751.99)	2.00 (0.82)	16.39 (17.28)

*Fed conditions

Reviewer's comments:

1. This study used a Phase 1 formulation which is different from the to-be-marketed formulation.
2. The sponsor considers that AUC was dose proportional up to 600 mg and less than proportional at 900 mg and above. This information is included in their proposed labeling.

As shown in the figures below, plots of dose adjusted AUC and Cmax versus dose indicate that there is a downward trend even for doses up to 600 mg for both AUC and Cmax, but the deviation from proportionality is greater for Cmax. The less than proportional increase in AUC is likely to be a result of less absorption due to the low solubility of the drug.



3. The long terminal half-life observed at the 1200 mg dose might be a complication of the absorption process since this is a low solubility drug.
4. The individual PK parameter values are not provided.

MULTIPLE DOSE PHARMACOKINETICS

a. Multiple-Dose Tolerability and PK Study In Healthy Subjects (Study 004)

This study was designed to determine the safety, tolerability and pharmacokinetics of SC-58635 after multiple dose administration in healthy subjects (17-44 yrs). Doses of 40 mg, 200 mg and 400 mg or placebo were administered under fasting conditions as single doses, followed 48 hours later by BID dosing for 7 days. A total of 36 subjects completed the study with 24 subjects on active treatments. The detailed study design is given in Appendix 1 (p. 68).

Plasma data: Steady state plasma levels, as observed through trough plasma concentrations, were achieved within five days of BID dosing. The mean pharmacokinetic parameters following single and multiple dosing are tabulated below.

Mean (\pm SD) Parameter Values

Dose	AUC ^(a) ng*hr/ml	Cmax ng/ml	Tmax hr	T1/2 hr	CL/F L/hr/70 kg	V _d /F L/70 kg
Single Dose Phase						
40 mg (n=8)	1217 (\pm 328)	197 (\pm 86)	1.50 (\pm 0.46)	4.18 (\pm 1.95)	34.3 (\pm 9.6)	194 (\pm 81.5)
200 mg (n=7)	5986 (\pm 4032)	646 (\pm 341)	1.64 (\pm 0.69)	8.01 (\pm 2.33)	40.1 (\pm 14.4)	483 (\pm 260)
400 mg (n=8)	13341 (\pm 3010)	1433 (\pm 523)	2.13 (\pm 0.79)	8.87 (\pm 3.57)	31.4 (\pm 6.9)	408 (\pm 208)
Multiple Dose Phase						
40 mg (n=8)	937 (\pm 288)	183 (\pm 52)	1.94 (\pm 0.90)	3.94 (\pm 1.55)	45.1 (\pm 14.4)	239 (\pm 98)

200 mg (n=8)	6726 (±3858)	1115 (±425)	1.75 (±0.71)	7.09 (±2.33)	33.9 (±10.8)	346 (±176)
400 mg (n=8)	11634 (±3745)	1833 (±478)	1.63 (±0.99)	9.57 (±4.16)	38.2 (±13.8)	557 (±407)

(a) $AUC_{0-\infty}$ for single-dose phase and AUC_{0-12} for multiple-dose phase

The single dose pharmacokinetics were generally predictive of those during multiple dosing (i.e., linear PK) as demonstrated by mean ratios of steady-state $AUC_{(0-12)}$ to single-dose $AUC_{(0-\infty)}$ of 79.3%, 118.7% and 84.8% for 40 mg BID, 200 mg BID and 400 mg BID doses, respectively. The terminal half-life was between 7 and 10 hours for the 200 mg and 400 mg doses. The accumulation ratios and %fluctuation as calculated from this study are presented below.

Table: Linearity, % Fluctuation and Accumulation Ratios

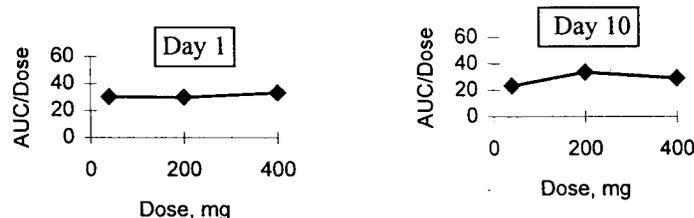
Dose	$AUC_{0-12(\text{Day } 10)} / AUC_{\text{inf}(\text{Day } 1)}$ (%)	% Fluctuation	Accumulation Ratio ¹	Accumulation Ratio ²
40 mg	79.3 (68.7-91.5)	205.6 (83.4)	1.03 (0.84-1.26)	1.88 (1.53-2.32)
200 mg	118.7 (102.9-137.0)	162.7 (67.1)	1.88 (1.53-2.32)	1.77 (1.37-2.29)
400 mg	84.8 (74.1 - 97.0)	114.1 (68.9)	1.42 (1.16-1.73)	1.19 (1.03-1.37)

$\% \text{ Fluctuation} = (C_{\text{max}} - C_{\text{min}}) / (AUC_{0-12} / 12) \times 100$ (Given as mean \pm SD)

Accumulation Ratio¹ = $AUC_{0-12(\text{Day } 10)} / AUC_{0-12(\text{Day } 1)}$ (Both mean and 90% CI are given)

Accumulation Ratio² = $C_{\text{max } 0-12(\text{Day } 10)} / C_{\text{max } 0-12(\text{Day } 1)}$ (Both mean and 90% CI are given)

As shown in the figures below, the AUCs on both Day 1 (single dose) and Day 10 (steady state) appeared dose proportional across the dose groups. The apparent volume of distribution at terminal phase (V_z/F) was much greater than total body water (42 L/70 kg), suggesting extensive distribution of celecoxib in humans.



Reviewer's comments:

1. Tables of individual PK parameter values should be provided.
2. Values for CL/F and V_z/F in the individual report (Vol. 1.85, pp. 43, 47) differ from those in the summary (Vol. 1.81, p. 166). The sponsor should clarify.

b. Multiple-Dose Study In Older Subjects (Healthy Volunteers and OA Patients) (Study 003)

This study was conducted to investigate the safety, tolerability and pharmacokinetics in an older population (age: 40-58 yrs). Ten out of 36 subjects were osteoarthritis patients. A single dose of 40, 200, 400 or placebo was given to subjects under fast conditions followed 48 hours later by BID dosing for 14 days. The detailed study design is given on page 69. Note that smoking and caffeine consumption were allowed in this study.