CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-998/S-010

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #: 20-998 / S-010

Drug Name

Established Name: Celecoxib

Proprietary Name: Celebrex(TM)

Dosage Form: Capsule **Route/Admin:** Oral

Sponsor: G.D. Searle & Co.

Proposed Indication: For the management of acute pain and primary dysmenorrhea

Date Submission: 12/18/2000

Documents Reviewed: Volume 1 through Volume 44.
Additionally submission in 07/03/01

Medical Reviewer: Schiffenbauer, Joel M.D.

1 Background and Introduction

Sponsor submitted a Supplemental NDA for Celebrex. The submission seeks approval for the following indications:

1. The management of acute pain in adults
2. For the treatment of primary dysmenorrhea

This application consists of 17 studies:

1. Post-oral surgery: 5 studies (4 of which have previously been reviewed as part of NDA 20,998)
2. Post-surgical pain: 9 studies (3 of which have previously been reviewed as part of NDA 20,998)
3. Musculo-skeletal pain: 1 study
4. Primary dysmenorrhea: 2 studies

Seven studies had been reviewed in the original NDA 20,998. Among the ten new studies in this supplement submission, only six of them were considered as pivotal (4 of Post-Surgical Pain studies and 2 Primary Dysmenorrhea studies). This review will focus only on these six studies.

Following table summarizes the new studies submitted in this supplement as pivotal.

Summary of studies for newly submitted and pivotal

Pain Management Studies	Study	Short Description (Celecoxib Dose)
Post –Surgical Pain Studies	N49-99-06-082	Single Dose Analgesic Efficacy After Orthopedic Surgery (200 mg)
	N49-99-06-083	Single Dose Analgesic Efficacy After General Surgery (200 mg)
	N49-99-06-085	Single and Multiple Dose Analgesic Efficacy After Orthopedic Surgery (200 mg/ 200 mg TID PRN)
	N49-99-06-086	Single and Multiple Dose Analgesic Efficacy After Orthopedic Surgery (200 mg/ 200 mg TID PRN)
Primary Dysmenorrhea	N-49-00-06-129	Analgesic Efficacy in Primary Dysmenorrhea (400 mg/200 mg BID PRN)
	N-49-00-06-130	Analgesic Efficacy in Primary Dysmenorrhea (400 mg/200 mg BID PRN)

2 Post-Surgical Pain Studies

These 4 post-surgical studies (082, 083, 085, 086) have very similar protocols except the surgery type and extended multiple dose period (for study 085, 086). This chapter will not specify the study number for the protocol synopsis and efficacy analysis plans for commonly applied facts.

2.1 Protocol Synopsis

Design

These were multicenter, single dose (082, 083), single and multiple dose (085, 086), double-blind, randomized, placebo-controlled parallel group studies designed to assess the analgesic efficacy and safety of orally administered Celecoxib 200 mg or hydrocodone 10 mg/acetaminophen 1000 mg compared to placebo in patients with moderate to severe pain after orthopedic surgery (083: general surgery). For each study, the duration of the single dose treatment period was up to 8 hours after administration of study medication. Pain was assessed by each patient at Baseline (0 hour), and at 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 hours from baseline. At each timepoint, levels of Pain Intensity (Categorical and Visual Analog Scales [VAS]), Pain Relief, as well as whether or not the pain had been reduced by 50%, were evaluated. Time to Onset of Perceptible Pain Relief and Time to Onset of Meaningful Pain Relief were evaluated using two stopwatches. A Patient's Global Evaluation was also recorded by the patient at the end of the Treatment Period. If the patient received rescue medication, pain assessments were conducted just before the use of rescue medication and no further pain assessments were conducted for that patient. If the patient required rescue medication during the study, the patient was dropped from the study and no further pain assessments were conducted after rescue.

For study 085 and 086, there was extended multiple dose assessment period (MDAP) up to 5 days after this 8-hour single dose assessment period (SDAP). During the MDAP, any patient who had been randomized to placebo during the SDAP and who was continued into the MDAP, was blindly pre-assigned to receive either Celecoxib 200 mg TID PRN or hydrocodone 10 mg/acetaminophen 1000 mg TID PRN; no patients received placebo during this period.

Objectives

1. Compare the analgesic activity of Celecoxib 200 mg versus placebo in patients with moderate to severe pain following orthopedic (general for 083) surgery; and
2. Evaluate the safety of Celecoxib 200 mg

Endpoints

Primary measures of efficacy – SDAP

1. Time-Specific Pain Intensity Difference (PID) on a Categorical Scale, derived by subtracting the Pain Intensity scores at the timepoints up to 8 hours after the first dose of study medication from the Baseline Pain Intensity scores.
2. Time-Specific Pain Relief (PR) measured at the timepoints up to 8 hours after the first dose of study medication.
3. Time-Specific Sum of PID on a Categorical Scale and PR (PRID) at the timepoints up to 8 hours after the first dose of study medication.
4. Time to Rescue Medication.
5. Time to Onset of Perceptible Pain Relief[1]

Secondary measures of efficacy – SDAP

1. Time-Specific Pain Intensity Difference (VAS) derived by subtracting the Pain Intensity scores at the timepoints after the first dose of study medication from the Baseline Pain Intensity score.
2. Peak Pain Intensity Difference (PPID), the highest PID score achieved at any timepoint during the first 8 hours of assessment.
3. Peak Pain Relief (PPR), the highest PR score achieved at any timepoint during the first 8 hours of assessment.
4. Summed Pain Intensity Difference (Categorical and VAS) SPID(4), SPID(6), SPID(8), for the sum of the PID scores through the first 4, 6, and 8 hours.
5. Total Pain Relief, TOTPAR(4), TOTPAR(6), TOTPAR(8), for the sum of the PR scores through the first 4, 6, and 8 hours, respectively.
6. Summed PRID scores, SPRID(4), SPRID(6), SPRID(8), for the sum of the PRID scores through the first 4, 6, and 8 hours, respectively.
7. Time First Experienced 50% Pain Relief.
8. Proportion of Patients Experiencing at Least 50% Pain Relief.
9. Time to Onset of Meaningful Pain Relief.
10. Patients' Global Evaluation. (082, 083)

Other measures of efficacy – SDAP

1. Time to Onset of Analgesia[1]
2. Summed Pain Intensity Difference (Categorical and VAS), SPID(3), for sum of the PID scores through the first 3 hours.
3. Total Pain Relief, TOTPAR(3), for the sum of the PR scores through the first 3 hours
4. Summed PRID scores, SPRID(3), for the sum of PRID scores through the first 3 hours

[1] We consider 'Time to Onset of Analgesia' in the category of 'Other measures of efficacy' to be more important than 'Time to Onset of Perceptible Pain Relief' in 'Primary measures of efficacy'. For 'Time to Onset of Analgesia', the definition of event time is the time to perceptible pain relief only if patients experienced both perceptible pain relief and meaningful pain relief. If the patient experience only perceptible pain relief, the event time will be censored at 8. In this review, 'Time to Onset of Analgesia' will replace the 'Time to Onset of Perceptible Pain Relief' in the summary of primary efficacy analysis results.

Measures of efficacy - MDAP (Study 085 and 086)

1. The Number of Patients (proportion) Who Dropped Out Due to Treatment Failure/Rescue Medication on Each of the Study Days
2. Number of Doses of Study Medication Taken on Each of the Study Days.
3. Duration Between Two Consecutive Doses.
4. Maximum Pain Intensity in the Past 24 Hours.
5. Maximum Pain Relief in the Past 24 Hours.
6. APS Pain Measure.
7. Patient's Global Evaluation
8. Pain Intensity Before Each Dose of Study Medication for each day.

Statistical analysis methods of Efficacy

The ITT Cohort included all patients who took the dose of study medication, excluding those who dropped out prior to one hour postdose and those who had two consecutive pain assessments interpolated by the same two values within the first two hours. All statistical analyses for efficacy were performed on the data from this group of patients.

Comments: ITT cohort should include all the patients who took the study medication, even a patient drop out in an hour. However in these post surgical studies, a little of the randomized patients were excluded from ITT Cohort (082:4 patients, 083:2 patients, 085:0, 086:0), see next section.

Isolated missing data were imputed on a patient-by-patient basis by linear interpolation between observed pain scale values. Allowable time windows were ±5 minutes in the first 45-minute period, and ±10 minutes for the remaining assessments in the 8-hour period. Values for observations outside those windows were imputed on a patient-by-patient basis by linear interpolation of the observation preceding it and the observation following it. If there were two consecutive scheduled assessments interpolated in the first two hours, the patient was excluded from the analysis for the efficacy variables.

For patients who took rescue medication after one hour but prior to 8 hours postdose, or who withdrew from the study before the Hour 8 observation, all missing pain intensity and PR values after the last recorded value were extrapolated separately by two different conventions, the Last Observation Carried Forward (LOCF) and the Baseline Observation Carried Forward (BOCF) convention (as originally planned).

Time-Specific PID (Categorical and VAS), Time-Specific PR, and Time-Specific PRID, were analyzed using ANOVA with treatment, center, and patients' pain intensity at Baseline (0 hour) as factors. For Time-Specific PR, the analysis was also performed without patients' pain intensity at Baseline (0 hour) included as a factor. The Baseline Pain Intensity (0-hour) was treated as a categorical variable. A p-value was provided for the treatment effect with treatment, center, and Baseline (0 hour) being the factors in the ANOVA model. Fisher's protected LSD multiple comparison procedure was applied to the least square treatment means.

Time to Onset of Analgesia and the Time to Rescue Medication were analyzed using survival analysis methods. The median time to event for each drug treatment 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 _____ The log-rank test was used to determine the statistical significance of drug differences in the time to event. These log-rank tests were done in the same fashion as Fisher's protected LSD. This means an

overall log-rank test on the time to event was performed. If the overall test was significant, pairwise comparisons were made between treatment groups using pairwise log-rank tests.

For Time to Onset of Analgesia, patients who did not take rescue medication and did not experience onset of analgesia in the study were considered censored at 8 hours. Patients who dropped out before Hour 8 because of reasons other than rescue medication were censored at the dropout time. Patients who took rescue medication before experiencing onset of analgesia were assigned a time according to the following formula:

$$8.1 + (0.005) / (\text{time to rescue analgesics})$$

For Time to Rescue Medication, patients who did not receive rescue medication were considered censored at 8 hours. Patients who dropped out and did not receive rescue medication were censored at the time of dropout. Patients who took rescue medication was taken from the start time that rescue medication was taken.

2.2 Sponsor's statistical analyses and results

Disposition of subjects

Single Dose Assessment Period

For study 082, 204 patients were enrolled at six centers and were randomized to receive a single dose of one of three treatments: 70 patients received Celecoxib 200 mg, 67 patients received hydrocodone 10 mg/acetaminophen 100 mg; and 67 patients received placebo. Two Celecoxib 200-mg patients and two placebo patients dropped prior to 1 hour postdose; therefore, the ITT Cohort consisted of 200 patients. Forty-three patients completed the study and 161 patients withdrew prior to completing the study.

For study 083, 198 patients were enrolled at seven centers and were randomized to receive a single dose of one of three treatments: 65 patients received Celecoxib 200 mg, 66 patients received hydrocodone 10 mg/acetaminophen 100 mg; and 67 patients received placebo. Two hydrocodone 10 mg/acetaminophen 100-mg patients dropped prior to 1 hour postdose; therefore, the ITT Cohort consisted of 196 patients. Thirty-one patients completed the study and 167 patients withdrew prior to completing the study.

For study 085, 198 patients were enrolled at 12 centers and were randomized to receive a single dose of one of three treatments: 67 patients received Celecoxib 200 mg, 62 patients received hydrocodone 10 mg/acetaminophen 100 mg; and 69 patients received placebo. The ITT cohort constituted all the randomized patients. Ninety-six patients completed the single dose period and 102 patients withdrew prior to completing the study.

For study 086, 220 patients were enrolled at 13 centers and were randomized to receive a single dose of one of three treatments: 74 patients received Celecoxib 200 mg, 74 patients received hydrocodone 10 mg/acetaminophen 100 mg; and 72 patients received placebo. The ITT cohort constituted all the randomized patients. A total of 98 patients completed the single dose period and 122 patients withdrew prior to completing the study.

Disposition of Patients for SDAP

Study Number	Item	Placebo	SC-58635 200mg SD	Hydrocodone 10mg / Acetaminophen 100 mg SD
082	All Randomized	67	70	67
	Intent-To-Treat	65	68	67
	Completed study	8 (12%)	18 (26%)	17 (25%)
	Withdrawn	59 (88%)	52 (74%)	50 (75%)
083	All Randomized	67	65	66
	Intent-To-Treat	67	65	64
	Completed study	4 (6%)	16 (25%)	11 (17%)
	Withdrawn	63 (94%)	49 (75%)	55 (83%)
085	All Randomized	69	67	62
	Intent-To-Treat	69	67	62
	Completed study	27 (39%)	37 (55%)	32 (52%)
	Withdrawn	42 (61%)	30 (45%)	30 (48%)
086	All Randomized	72	74	74
	Intent-To-Treat	72	74	74
	Completed study	24 (33%)	41 (55%)	33 (45%)
	Withdrawn	48 (67%)	33 (45%)	41 (55%)

The reasons for withdrawal are summarized in Table 1, Table 4, Table 7, and Table 10 of appendix for each study.

Multiple Dose Assessment Period

For study 085, one hundred seventy six patients entered the MDAP. One hundred forty five patients completed the entire MDAP and 31 patients withdrew during the MDAP. For study 086, one hundred ninety patients entered the MDAP. One hundred forty seven patients completed the entire MDAP and 43 patients withdrew during the MDAP.

Disposition of Patients for MDAP

Study Num	MDAP	Celecoxib 200MG TID PRN			Hydrocodone 10mg/ Acetaminophen 100mg TID PRN		
	SDAP	Placebo[a]	Celecoxib	Total	Placebo[b]	Hyd/Ace	Total
085	Entered MDAP	29	62	91	28	57	85
	Completed study	24 (83%)	58 (94%)	82 (90%)	22 (79%)	41 (72%)	63 (74%)
	withdrawn	5 (17%)	4 (6%)	9 (10%)	6 (21%)	16 (26%)	22 (26%)
086	Entered MDAP	27	67	94	29	67	96
	Completed study	20 (74%)	55 (82%)	75 (80%)	22 (76%)	50 (75%)	72 (75%)
	withdrawn	7 (26%)	12 (18%)	19 (20%)	7 (24%)	17 (25%)	24 (25%)

a. Patients who were in Placebo treated group in SDAP and entered into Celecoxib treated group in MDAP.
b. Patients who were in Placebo treated group in SDAP and entered into Hydrocodone / Acetaminophen treated group in MDAP.

The reasons for withdrawal are summarized in Table 13 and 14 of appendix for each study.

Demographics and Baseline Characteristics

The by-treatment baseline demographic characteristics including age, race, gender, height, and weight for all randomized patients are presented in Table 2, 5, 8, and 11 of appendix. Type of surgical procedures and baseline pain data are also summarized by treatment group in Table 3, 6, 9, 12 of appendix. As shown in the tables, the treatment groups are well-randomized. However, in study 085 and 086 (Table 9 and 12), for type of surgical procedure, proportion of "other" is over 50% of the randomized subjects.

Sponsor's Statistical analysis Results and reviewer's comments

As specified in the protocol, sponsor considered five variables as primary efficacy endpoints. But in this review, as noted above, a primary efficacy variable of 'Time to Onset of Perceptive Pain Relief' was replaced by 'Time to Onset of Analgesia'. Following table presents the summary of primary analysis results using LOCF. For PID, PR, and PRID, hypothesis test results of pairwise comparison of Celecoxib and Placebo were presented, and for Duration and Onset of Analgesia, median time of the patients in Celecoxib treated group and statistical comparison to placebo treated group are presented.

Summary of Primary efficacy endpoint analyses; Celecoxib vs. Placebo, LOCF

	Time											
	0:15	0:30	0:45	1:00	1:30	2:00	3:00	4:00	5:00	6:00	7:00	8:00
N49-99-06-082 (N=68/65)[c]												
PID							*	*				
PR							*	*	*	*		
PRID							*	*	*			
Duration[a]							3:15 ( )					
Onset[b]			0:46 ( )									
N49-99-06-083 (N=65/67)[c]												
PID							*	*	*	*	*	*
PR							*	*	*	*	*	*
PRID							*	*	*	*	*	*
Duration[a]							3:18 (*)					
Onset[b]		0:38 ( )										
N49-99-06-085 (N=67/69)[c]												
PID						*	*	*	*	*	*	*
PR							*	*	*	*	*	*
PRID						*	*	*	*	*	*	*
Duration[a]												>8:00( )
Onset[b]			0:40 (*)									
N49-99-06-086 (N=74/72)[c]												
PID								*	*	*	*	*
PR								*	*		*	
PRID								*	*			
Duration[a]												>8:00(*)
Onset[b]		0:34 (*)										

*. Significantly different between Celecoxib and placebo treated groups
a. Median of Time to Rescue Medication for Celecoxib treated group
b. Median of Time to Onset of Analgesia for Celecoxib treated group
c. Sample Size (N=Celecoxib/Placebo)
Details are available in the appendix.

Study 082

Descriptive statistics and statistical analysis results of pairwise comparisons using Fisher's LSD method for PID, PR, and PRID are summarized in Table 15 through 17, and pain curves can be found from Figure 1 through 6 of appendix for both LOCF and BOCF. Product limit plots of Time to Rescue Medication and Time to Onset of Analgesia including median times and statistical analysis results are described in Figure 25 and 26 of appendix.

For the LOCF analyses of PID, PR, and PRID, no significant differences between Celecoxib and placebo treated groups are detected in first hour. In fact, as shown in Figure 1, 2 and 3 of appendix, there is no difference between Celecoxib and placebo treated groups during the first hour. The first time to show the significance is 3 hours after the baseline for all three variables. However, about half of the patients were already dropped out at 3 hours, and the dropout rates are different among treatment groups. So, the significant results with LOCF

from three hours are not reliable. On the other hand, Hydrocodone/ Acetaminophen treated group showed significant results earlier (at 2 hour) than Celecoxib treated group for PID and PRID as shown in Table 15, and 17 of appendix.
For the BOCF analyses, mean values of all three variables PID, PR, PRID show similar to the mean values using LOCF in first one hour, because most of the patients didn't dropout. After one hour, Celecoxib treated group still shows higher values than placebo treated group for all three variables. In statistical comparison, PID shows similar to the results of LOCF. However, PR shows significant results at 4 hour only, and PRID does not show significant results at any time during the 8 hours of study duration.
For Time to Rescue Medication, the median time for Celecoxib treated group is 3 hour 15 minutes. In statistical comparison to placebo treated group, Celecoxib treated group does not show the significant difference while Hydrocodone/ Acetaminophen treated group does. For Time to Onset of Analgesia, the median time for Celecoxib treated group is 46 minutes. In statistical comparison to placebo treated group, Celecoxib treated group does not show the significant difference while Hydrocodone/Acetaminophen treated group does.

Study 083

Descriptive statistics and statistical analysis results of pairwise comparisons using Fisher's LSD method for PID, PR, and PRID are summarized in Table 18 through 20, and pain curves can be found from Figure 7 through 12 of appendix for both LOCF and BOCF. Product limit plots of Time to Rescue Medication and Time to Onset of Analgesia including median times and statistical analysis results are described in Figure 27 and 28 of appendix.
For the LOCF analyses of PID, PR, and PRID, no significant differences between Celecoxib and placebo treated groups are detected in first hour. In fact, as shown in Figure 7, 8 and 9 of appendix, Celecoxib treated group is even worse than placebo treated groups during the first hour for all three PID, PR, PRID variables. The first time to show the significance is 3 hours after the baseline for all three variables. However, about half of the patients were already dropped out at 3 hours, and the dropout rates are different among treatment groups. So, as study 082, the significant results with LOCF from three hours are not reliable. On the other hand, Hydrocodone/Acetaminophen treated group showed significant results earlier than Celecoxib treated group for all three variables as shown in Table 18, 19 and 20 of appendix (PR:1.5 hr, PID/PRID: 2 hr).
For the BOCF analyses, mean values of all three variables PID, PR, PRID show similar to the mean values using LOCF in first one hour. After one hour, Celecoxib treated group shows higher values than placebo treated group for all three variables. In statistical comparison, the first time to show the significant difference from placebo shifted to 4 hour by using BOCF.
For Time to Rescue Medication, the median time for Celecoxib treated group is 3 hour 18 minutes, while the median of Hydrocodone/Acetaminophen treated group is 4 hour 39 minutes. In statistical comparison to placebo treated group, both Celecoxib and Hydrocodone/Acetaminophen treated group shows the significant difference. For Time to Onset of Analgesia, the median time for Celecoxib treated group is 38 minutes, while the median of Hydrocodone/Acetaminophen treated group is 23 minutes and placebo is 20 minutes. Though the median time of placebo treated group is earlier than two drug treated groups, after 30 minutes, Hydrocodone/Acetaminophen treated group has more fractions of onset patients as shown Figure 28 of appendix. On the other hand, Celecoxib treated group just catch up the placebo at one hour and stay at 60% with placebo treated group until the end of SDAP. There was no significant difference between any combination of treatment groups.

Study 085

Descriptive statistics and statistical analysis results of pairwise comparisons using Fisher's LSD method for PID, PR, and PRID are summarized in Table 21 through 23, and pain curves

can be found from Figure 13 through 18 of appendix for both LOCF and BOCF. Product limit plots of Time to Rescue Medication and Time to Onset of Analgesia including median times and statistical analysis results are described in Figure 29 and 30 of appendix.
For the LOCF analyses of PID, PR, and PRID, no significant differences between Celecoxib and placebo treated groups are detected in first hour. In fact, as shown in Figure 13, 14 and 15 of appendix, there is no difference between Celecoxib and placebo treated groups during the first thirty minutes for all three PID, PR, PRID variables. The first time to show the significance is 2 hours for PID and PRID, 3 hours for PR after the baseline. On the other hand, Hydrocodone/Acetaminophen treated group showed significant results from 1 hour after the baseline for all three variables.
For the BOCF analyses, mean values of all three variables PID, PR, PRID show similar to the mean values using LOCF in first one hour. After one hour, Celecoxib treated group shows higher values than placebo treated group for all three variables. In statistical comparison, the first times to show the significant difference from placebo are at 3 hours (same as using LOCF) for all three variables by using BOCF.
For Time to Rescue Medication, the median time for both Celecoxib and Hydrocodone/ Acetaminophen treated groups are bigger than 8 hours. In statistical comparison to placebo treated group, Celecoxib treated group does not show the significant difference while Hydrocodone/Acetaminophen treated group does. For Time to Onset of Analgesia, the median time for Celecoxib treated group is 40 minutes, while the median of Hydrocodone/ Acetaminophen treated group is 35 minutes. In statistical comparison to placebo treated group, both Celecoxib treated group and Hydrocodone/Acetaminophen treated group show significant differences.

Study 086

Descriptive statistics and statistical analysis results of pairwise comparisons using Fisher's LSD method for PID, PR, and PRID are summarized in Table 24 through 26, and pain curves can be found from Figure 19 through 24 of appendix for both LOCF and BOCF. Product limit plots of Time to Rescue Medication and Time to Onset of Analgesia including median times and statistical analysis results are described in Figure 31 and 32 of appendix.
For the LOCF analyses of PID, PR, and PRID, no significant differences between Celecoxib and placebo treated groups are detected in first one hour. In fact, as shown in Figure 19, 20 and 21 of appendix, there is no difference between Celecoxib and placebo treated groups for PID during the first hour, and for PR and PRID during the first 30 minutes. The first time to show the significance is 4 hours after the baseline for all PID, PR, and PRID. However, about half of the patients were already dropped out at 4 hours, and the dropout rates are different among treatment groups. So, the significant results with LOCF from three hours are not reliable.
For the BOCF analyses, mean values of all three variables PID, PR, PRID show similar to the mean values using LOCF in first one hour. After one hour, Celecoxib treated group shows higher values than placebo treated group for all three variables. In statistical comparison, the first times to show the significant difference from placebo are at 3 hours (same as using LOCF) for all three variables by using BOCF.
For Time to Rescue Medication, the median time for Celecoxib treated group is bigger than 8 hours. In statistical comparison to placebo treated group, Celecoxib treated group shows the significant difference. For Time to Onset of Analgesia, the median time for Celecoxib treated group is 34 minutes, while the median of Hydrocodone/Acetaminophen treated group is 26 minutes. In statistical comparison to placebo treated group, both Celecoxib treated group and Hydrocodone/ Acetaminophen treated group show significant difference.

MDAP

Efficacy results of Maximum Pain Intensity, Maximum Pain Relief, and Patients Global Evaluation for Multiple dose assessment periods are summarized in Table 27 through 30 and Figure 33 and 36 of appendix.

For study 085, Global evaluation on day 1 shows that 35% of Celecoxib treated patients answered of drug efficacy to be Poor or Fair, and 38% of the patients answered to be Excellent or Very good. At the end of the study (up to 5 days), 10% of the Celecoxib treated patients answered to be Poor or Fair, and 76% of the patients answered to be Excellent or very good. Global evaluation results for Celecoxib treated groups are not much different from the results for Hydrocodone/Acetaminophen treated groups. Maximum Pain Intensity, the line for Celecoxib treated group is under the line for Hydrocodone/ Acetaminophen as shown in Figure 21. For Maximum Pain Relief, two treatment groups show similar results.

For study 086, Global evaluation on day 1 shows that 36% of Celecoxib treated patients answered of drug efficacy to be Poor or Fair, and 40% of the patients answered to be Excellent or Very good. At the end of the study (up to 5 days), 20% of the Celecoxib treated patients answered to be Poor or Fair, and 59% of the patients answered to be Excellent or Very good. Global evaluation results for Celecoxib treated groups are not much different from the results for Hydrocodone/Acetaminophen treated groups. For Maximum Pain Intensity, the line for Celecoxib treated group is under the line for Hydrocodone/ Acetaminophen as shown in Figure 21. For Maximum Pain Relief, two treatment groups show similar results.

Conclusion of Post-Surgical Pain Studies

All four studies do not provide sufficient evidence of drug efficacy especially at first few hours of PID, PR, and PRID. Most of these time specific variable comparisons begin to show significant difference from 3 hours or after. For Time to Rescue Medication, the median times for Celecoxib treated group were 3 hour 15 minutes and 3 hour 18 minutes for study 082 and 083, respectively, and bigger than 8 hours for both 085, 086. For Time to onset of Analgesia, the median times for Celecoxib treated group were between 34 to 46 minutes.

3 Primary Dysmenorrhea

These 2 Primary Dysmenorrhea studies (129, 130) have very similar protocols. This chapter will not specify the study number for the protocol synopsis and efficacy analysis plans for commonly applied facts.

3.1 Protocol Synopsis

Design

These were randomized, double-blind, active and placebo-controlled three-way crossover, multiple-dose study designed to assess the analgesic efficacy and safety or orally administered Celecoxib, in the treatment of patients with moderate to severe menstrual cramping pain associated with primary dysmenorrhea.

Each patient was randomized into one of six treatment sequences as referenced in the following table. The sequences were based on the following two Latin Squares, where columns (S1-S6) represent sequences, rows (P1-P3) represent treatment periods. In this complete and balanced block design each treatment follows every other treatment twice.

Treatment Sequence Listed by Treatment Peroid

Period	Treatment Sequence					
	S1	S2	S3	S4	S5	S6
P1	Celecoxib	Placebo	Naproxen Na	Celecoxib	Placebo	Naproxen Na
P2	Naproxen Na	Celecoxib	Placebo	Placebo	Naproxen Na	Celecoxib
P3	Placebo	Naproxen Na	Celecoxib	Naproxen Na	Celecoxib	Placebo

Each patient received one of three treatment regimens during each of three menstrual cycles (treatment periods). The duration of treatment during each cycle was up to three days. The three treatment regimens were:

1. Celecoxib 400 mg (initial dose, Day 1) followed by a single dose of Celecoxib 200 mg no sooner than 12 hours after the first dose (up to a total daily dose of 600 mg on Day 1), then Celecoxib 200 mg Q12 hours PRN (up to a total daily dose of 400 mg on Days 2 and 3), and placebo matching Naproxen sodium capsules.
2. Naproxen sodium 550 mg (initial dose, Day 1) followed by a single dose of Naproxen sodium 550 mg no sooner than 12 hours after the first dose (up to a total daily dose of 1100 mg on Day 1), then Naproxen sodium 550 mg Q 12 hours PRN (up to a total daily dose of 1100 mg on Days 2 and 3), and placebo matching Celecoxib capsules.
3. Placebo matching Celecoxib capsules and placebo matching Naproxen sodium capsules.

Patients who satisfied the criteria for admission took one of each of the three treatment regimens in a randomized crossover fashion during the course of three menstrual cycles. The study could have been extended up to five consecutive cycles if the patient did not medicate for a maximum of two non-consecutive cycles because of a lack of moderate to severe menstrual cramping pain, illness, travel, or any other reason deemed acceptable by the investigator. If two consecutive menstrual cycles were missed, the patient was discontinued from the study.

Treatment period

The Single Dose Assessment Period (SDAP) was up to 12 hours in length. Evaluation of the response to initial treatment on Day 1 of each cycle was based on each patient's self-rating of the intensity of their menstrual cramping pain and the degree of relief during the treatment period. The patient evaluated the intensity of her menstrual cramping pain just prior to taking the first dose of study medication. The patient then evaluated her pain intensity and pain relief periodically for 12 hours following the administration of the first dose of study medication. Each patient was given two stopwatches to measure the time to onset of perceptible pain relief and time to onset of meaningful pain relief. At the time of dosing with the study medication, each patient had to start the stopwatches. The patient was instructed to stop the first stopwatch when she first experienced perceptible pain relief and to stop the second stopwatch when she first experienced meaningful pain relief. At the end of this 12-hour initial assessment period, she provided an overall impression (global evaluation) of the effectiveness of the study medication in relieving her menstrual cramping pain.

If the patient received rescue medication, pain assessments and global evaluation were conducted just prior to the use of rescue medication and throughout the remainder of the treatment period. The patient was not permitted to take any more study medication during that treatment period. Patients who withdrew or required rescue medication prior to the one-hour assessments were excluded from the efficacy analysis for that treatment period.

During the SDAP, pain was assessed by each patient at 0 hour, 15, 20 and 45 minutes, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hours after the first dose of study medication. At each time point, pain intensity (categorical) and pain relief was evaluated. Time to onset of perceptible pain relief and time to onset of meaningful pain relief was evaluated by using two stopwatches.

The Multiple Dose Assessment Period (MDAP) of the study began 12 hours after the first dose of study medication and continued up to three days. All the patients were remained in the same treatment group as SDAP of the cycle. On Day 1 (second dose if applicable), Days 2 and 3 of each cycle, patients assessed the intensity of their menstrual cramping pain immediately before taking any additional doses of study medication. In addition, at bedtime on Days 2 and 3 or when treatment was discontinued or prior to taking rescue medication, patients completed a questionnaire regarding the maximum intensity of their menstrual cramping pain for that day as well as a global evaluation of study medication.

Objectives

The primary objective of this study was to compare the analgesic efficacy of Celecoxib versus placebo in the treatment of patients with moderate to severe menstrual cramping pain associated with primary dysmenorrhea. The time to onset was also assessed in the primary dysmenorrhea setting.

Endpoints

Primary measures of efficacy

1. Summed PID, SPID(8), the sum of the PID scores through the first 8 hours (categorical scale).
2. Total pain relief, TOTPAR(8), the sum of the PR scores through the first 8 hours.

Secondary measures of efficacy

1. Time to onset of analgesia as measured by the two-stopwatch technique.
2. Time to rescue medication.
3. Time to perceptible pain relief.
4. Time to meaningful pain relief.
5. Time-specific pain intensity difference (PID), categorical scale, derived by subtracting the pain intensity scores at the time points up to 12 hours after the first dose of study medication from the Baseline pain intensity score.
6. Time specific pain relief (PR), measured at the time points up to 12 hours after the first dose of study medication.
7. (PRID), the sum of PID (categorical scale) and PR at the time points up to 12 hours after the first dose of study medication.
8. Peak PID (PPID), the highest PID score achieved at any time point during the first 12-hour assessment.
9. Summed PID, the sum of the PID scores through 12 hours, SPID(12).
10. Peak pain relief, the highest PR score achieved at any time point.
11. Total pain relief, the sum of the PR scores through 12 hours, TOTPAR(12).
12. Summed PRID, the sum of the PRID scores through 8 and 12 hours, SPRID(12), respectively.
13. Patient Global Evaluation of study medication.

Secondary measures of efficacy for the MDAP

1. Daily Maximum Pain Intensity.
2. The number of patients (percentage) who dropped out due to treatment failure/rescue medication on each of the study days.

3. Patient Global Evaluation.
4. Pain Intensity before each dose for that day.

Statistical analysis methods of Efficacy

All the analyses for efficacy were performed on patients who took at least one dose of study medication in three treatment periods, did not require rescue medication prior to one hour in any of the treatment periods and did not have two consecutive pain assessments interpolated by the same two values within the first two hours.

Comments: The primary efficacy analysis should include all the patients who took at least one study medication, and no other restrictions are allowed. Additional analyses of the patients with new criteria were submitted by agency's request, and will be results will be discussed later.

For the SDAP, isolated missing data (or data that were not within the time window of ±5 minutes before the first hour period, and ±10 minutes in the remaining observation period) were imputed on a patient-by-patient basis by linear interpolation of the observation preceding the missing value and the observation following the missing value. For patients who took rescue medication after one hour but prior to 12 hours or stopped pain assessment before 12 hours for other reasons, pain assessment was imputed by the last observation carried forward (LOCF) method. For daily maximum pain intensity and Patient's Global Evaluation of study medication, missing values were imputed by the LOCF method.

SPID(8), SPID(12), TOTPAR(8), TOTPAR(12), SPRID(8), SPRID(12), PID, PR, PRID, PPID, PPR and Patients' Global Evaluation of study medication were analyzed by ANOVA with fixed effect for treatment, period, sequence, and random effect for patient.

For time to onset of analgesia, time to rescue medication, time to perceptible pain relief, and time to meaningful pain relief, survival analysis was performed. The median time to the event for each treatment period was calculated using the Kaplan-Meier estimator with Miller's adjustment. Pairwise treatment groups were compared by Cox regression stratified by patient, if the overall test was significant. For time to perceptible pain relief, time to onset of analgesia and time to meaningful pain relief, patients who did not take rescue medication, did not experience perceptible pain relief and did not drop out before 12 hours were censored at 12 hours. Patients who dropped out before 12 hours for reason other than rescue medication were censored at the dropout time. Patients who took rescue medication during the 12 hours before experiencing perceptible pain relief were assigned an event time according to the following formula: 12.1 + 0.1/time to rescue medication (min). For time to rescue medication, patients who did not require rescue medication were censored at 12 hours. If a patient dropped out before 12 hours, the time to rescue was censored at the dropout time.

Determination of sample size

The sample size calculation was based on one efficacy variable, PID, and the primary comparison: Celecoxib 200 mg versus placebo to detect statistically significant differences in the early stage of the pain assessment curves. The estimate of standard deviation used for sample size calculations in the PID scores was 0.850 based on a previous dental pain study with approximately 5% increase in the standard deviation due to the complexity of the current study. A sample size of 120 patients per treatment group was required to detect a difference of at least 0.3 in the PID score with at least 80% power and an alpha level of 0.05 (two-sided test). Taking into account a 20% drop out rate, it was planned to enroll approximately 150 patients in this study.

Comments: Sponsor's sample size calculation results into 150 per each treatment group using mean difference of 0.3 and standard deviation of 0.85, and 20% dropout. If the mean difference of 0.4 and standard deviation of 0.8 was used, sample size will be 62 per treatment group. On the other hand, 120 subjects per treatment group with mean difference 0.4 and standard deviation 0.8 will give a statistical power of 97%. To cover this issue, additional analyses of cycle 1 (with 40 patients per treatment group) were requested by agency to the sponsor. Results will be discussed later.

1.2 Study Results

Disposition of subjects

There were a total of 149 patients who were randomized into study 129. Overall during the study, 136 patients received study medication in at least one treatment period and 122 patients received at least one dose of study medication in all three-treatment periods and were included in the efficacy analysis. Subsequent to receiving study medication during Cycle 1, 12 patients withdrew from the study. Subsequent to receiving study medication during Cycle 2, 2 patients withdrew from the study.

There were a total of 154 patients who were randomized into study 130. Overall during the study, 135 patients received study medication in at least one treatment period and 121 patients received at least one dose of study medication in all three-treatment periods and were included in the efficacy analysis. Subsequent to receiving study medication during Cycle 1, 13 patients withdrew from the study. Subsequent to receiving study medication during Cycle 2, 1 patients withdrew from the study.

Comments: The primary efficacy analysis should include all the patents that received at least one dose of study medication in at least one treatment period. So, the patients who terminated after receiving study medication should be included in the analysis. This issue will be discussed later.

Table 31 and 36 of Appendix presents the disposition of patients by treatment sequence and study cycle for both studies. Table 32 and 37 of appendix presents the reasons for study termination from SDAP by treatment with combined 3 cycles. Table 33 and 38 of appendix presents the reasons for study termination from MDAP by treatment with combined 3 cycles.

Patient Demographics and Baseline

Table 34 and 39 of appendix summarize baseline demographics (age, race/ethnic origin, height, and weight) by treatment sequence. For study 129, demographic data across treatment sequences were similar at baseline, except for the weight variable. The mean weight ranged from 62.65 kg to 74.47 kg ($p=0.037$). For study 130, there were significant differences between the treatment sequences with respect to age ($p=0.043$), weight ($p=0.028$). Since all patients in each treatment sequence received all the three study medications (crossover design), these differences were unlikely to have an effect on the outcome of the study.

Sponsor's statistical analysis results of efficacy and reviewer's comments

Analyses of the Primary Efficacy Measures specified in the protocol

The mean SPID(8) score in the Celecoxib treatment period was significantly greater than the mean SPID(8) score in the placebo treatment period for both studies. The mean TOTPAR(8) score in the Celecoxib treatment period was significantly greater than the mean TOTPAR(8)

score in the placebo treatment period for both studies. Following table summarizes the analyses of primary efficacy variables.

Study	Variable	LSMean (Std Dev)			P-value
		Placebo	Celecoxib 400mg/ 200mg q12hr prn	Naproxen Na 550mg q12hr prn	Celecoxib vs. Placebo
129	N	122	122	122	
	SPID(8)	5.96 (7.19)	10.06 (7.09)	11.48 (6.42)	< 0.001
	TOTPAR(8)	12.82 (10.23)	18.28 (10.21)	20.59 (9.18)	< 0.001
130	N	121	121	121	
	SPID(8)	6.41 (6.82)	9.60 (6.34)	11.71 (5.63)	< 0.001
	TOTPAR(8)	12.98 (10.20)	17.98 (9.49)	21.27 (7.80)	< 0.001

However, the mean scores in the Naproxen sodium treatment period are always greater than the mean scores in the Celecoxib treatment period for both variables for both studies. For SPID(8), the mean scores in the Naproxen sodium treatment period are significantly greater than the mean scores in the Celecoxib treatment period for both studies (study129: p=0.021, study130: p=004). This trend is shown in most of secondary efficacy variables.

Five secondary efficacy variables were reviewed which are considered as important in single dose acute pain study; PID, PR, PRID, Time to rescue medication, Time to onset of analgesia (as measured by the two stopwatch technique). Following table presents the summary of these five analyses results. For PID, PR, and PRID, hypothesis test results of pairwise comparison of Celecoxib and Placebo were presented, and for Duration and Onset of Analgesia, median time of the patients in Celecoxib treated group and statistical comparison to placebo treated group are presented.

Summary of five important efficacy endpoint analyses; Celecoxib vs. Placebo, LOCF

	Time															
	0:15	0:30	0:45	1:00	1:30	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	10:00	11:00	12:00
N49-98-02-129 (N=122/122)[c]																
PID					*	*	*	*	*	*	*	*	*	*	*	*
PR					*	*	*	*	*	*	*	*	*	*	*	*
PRID					*	*	*	*	*	*	*	*	*	*	*	*
Duration[a]																>12:00(*)
Onset[b]			0:52(*)													
N49-98-02-130 (N=121/121)[c]																
PID					*	*	*	*	*	*	*	*	*	*	*	*
PR				*	*	*	*	*	*	*	*	*	*	*	*	*
PRID				*	*	*	*	*	*	*	*	*	*	*	*	*
Duration[a]																>12:00(*)
Onset[b]			0:53(*)													

* = Significantly different between Celecoxib and placebo treatment periods
[a] Median of Time to Rescue Medication
[b] Median of Time to Onset of Analgesia
[c] Sample Size (N=Celecoxib/Placeb)

Study 129

Using LOCF, descriptive statistics and statistical analysis results of pairwise comparisons using Fisher's LSD method for PID, PR, and PRID are summarized in Table 41 through 43, and pain curves can be found from Figure 37 through 39 of appendix. Product limit plots of

Time to Rescue Medication and Time to Onset of Analgesia including median times and statistical analysis results are described in Figure 43 and 44 of appendix.
For the LOCF analysis of PID, PR, and PRID, the first time to show the significance is 1 hour and 30 minutes after the baseline for all three variables. In fact, as shown in Figure 37, 38 and 39 of appendix, there are little differences between Celecoxib and placebo treated groups during the first hour, and began to separate from 1 hour and 30 minutes. On the other hand, Naproxen treated group showed significant results earlier (at 30 minutes) than Celecoxib treated group for PID and PRID as shown in Table 41 and 43 of appendix. The analysis result of descriptive statistics and statistical comparison using BOCF method supports the LOCF method because the results are very similar.
For Time to Rescue Medication, the median time for Celecoxib treated group is over 12 hours. In statistical comparison to placebo treated group, Celecoxib treated group shows the significant difference. Naproxen treated group shows similar results with Celecoxib treated group. For Time to Onset of Analgesia, the median time for Celecoxib treated group is 52 minutes, while the median of Naproxen treated group is 45 minutes. In statistical comparison to placebo treated group, Celecoxib treated group does not show the significant difference while Naproxen treated group shows significant difference from both Celecoxib and placebo treated group.

Study 130
Using LOCF, descriptive statistics and statistical analysis results of pairwise comparisons using Fisher's LSD method for PID, PR, and PRID are summarized in Table 44 through 46, and pain curves can be found from Figure 40 through 42 of appendix. Product limit plots of Time to Rescue Medication and Time to Onset of Analgesia including median times and statistical analysis results are described in Figure 45 and 46 of appendix.
For the LOCF analysis of PID, PR, and PRID, the first time to show the significance is 1 hour after the baseline for both PR and PRID, and 1.5 hour for PID. In fact, as shown in Figure 37, 38 and 39 of appendix, there are little differences between Celecoxib and placebo treated groups during the first forty five minutes, and began to separate from 1 hour slightly. On the other hand, Naproxen treated group showed significant results at 45 minutes from baseline for all three variables. The analysis result of descriptive statistics and statistical comparison using BOCF method supports the LOCF method because the results are very similar.
For Time to Rescue Medication, the median time for Celecoxib treated group is over 12 hours. In statistical comparison to placebo treated group, both Celecoxib and Naproxen treated group show the significant difference. For Time to Onset of Analgesia, the median time for Celecoxib treated group is 53 minutes, while the median of Naproxen treated group is 50 minutes. In statistical comparison to placebo treated group, Celecoxib treated group shows significant earlier than placebo treated group. On the other hand, Naproxen treated group shows significantly earlier than both Celecoxib and placebo treated group.

Efficacy results for MDAP
Efficacy results of Maximum Pain Intensity and Patient Global Evaluation of Study Medication for Multiple dose assessment periods are summarized in Figure 47 through 50 of appendix. For Maximum Pain Intensity, the three lines of Celecoxib, Naproxen, and placebo treated groups are very similar shown in Figure 47 and 49 of appendix. For Global evaluation, Naproxen shows the best results, and Celecoxib treated group is the next consistently as shown in Figure 48 and 50 of appendix.

Conclusion of the review of sponsor's analysis
For the three time specific variables, PID, PR, and PRID, both studies show significant separation between Celecoxib and placebo treated groups from 1 hour or 1 hour and 30

minutes to 12 hours (end of SDAP). This supports the efficacy of study medication. But there are two issues that need to be verified – Definition of ITT cohort and Overpower issue. These two issues are discussed in the reviewer's comments above. To resolve these issues, additional analyses were requested by agency, performed and submitted by sponsor. Results are explained and discussed in the following section.
For Time to Rescue Medication, the median time for Celecoxib treated group is over 12 hours for both studies. This supports the efficacy of study drug. For Time to Onset of Analgesia, the median time for Celecoxib treated group is 52-53 minutes.

Additional Analyses

Analyses efficacy variables based on Corrected ITT

As mentioned above, all the sponsor's efficacy analyses were performed on restricted ITT population, which excludes the patients who did not complete three cycles. But ITT should include all the patients who took at least one study medication, and no other restrictions are allowed. Sponsor submitted additional efficacy analysis results by the request of agency, which is based on the corrected ITT population - including all the patients who took at least one study medication. The efficacy variables requested to analyze were two primary variables (SPID(8) and TOTPAR(8)) and PID, PR, PRID, and time to rescue medication. For the patients who did not completed three cycles, following imputation method was used.

1. If only one observation (one cycle) is available: for each individual patient imputes this to other cycles.
2. If data is available from 2 cycles: for each individual patient if placebo is missing, impute results from Celecoxib for the placebo; if Celecoxib is missing impute data from placebo; if Naproxen is missing then impute data from placebo.

Corrected ITT population based analysis results were similar from the analysis results based on the sponsor's original (restricted) ITT population. The analyses of primary efficacy variables remained to be still significantly different between Celecoxib and placebo treatment periods for both SPID, and TOTPAR, and for both studies as shown in Table 47 of appendix. For the analyses of PID, PR, and PRID for specific times, the first time to show the significant difference remained same with original analysis results as shown in Table 48 of Appendix. Detail results of the analyses of PID, PR, and PRID are summarized in the Table 49 through 54 in appendix. This supports the efficacy reliability of analysis results of sponsor's restricted ITT cohort.

Analyses efficacy variables for the first cycle

Sponsor also submitted additional analyses using the observations in first cycle only by the request of agency. The reasons of requesting this analysis are to check the consistency of efficacy results over the cycles, and to check the sensitivity of sample size calculation. For the primary variables, it turned out to be still significantly different between Celecoxib and placebo treatment periods for both SPID, and TOTPAR, for both studies. For the analyses of PID, PR, and PRID, the first time to show the significant difference between treatment periods remained same (at 1.5 hour) for study 129. However for study 130, the first times to showing the significant differences are delayed (PID/PRID: 4 hour, PR: 3 hour). Figure 39 and 40 of Appendix shows the mean values of the efficacy variables with original data and cycle 1 only for PID and PR respectively. As shown in the graphs, during the first few hours, the difference between the treatments using cycle 1 is smaller than using 3 cycles due to placebo effect in cycle 1. Especially at 1 hour and 1.5 hour (when the 3 cycle analyses showed significant separations), there is no difference for both variables. However, both PID, and PR for Celecoxib treated group between 1 cycle and 3 cycle are almost same in first few hours. Overall, this supports 3 cycle analyses.

Conclusion of additional analyses

Two issues ITT cohort and over-power, has been resolved by additional analyses. These additional analysis results support sponsor's original analysis results.

4 Conclusion

Before this NDA supplement, sponsor submitted NDA for acute pain indication, and only dental pain model has succeeded. Agency requires at least two successes of pain models for acute pain indication. In this NDA supplement, sponsor submitted 6 additional pivotal studies (4 of Post-Surgical Pain studies and 2 of Primary Dysmenorrhea studies) to complete the requirement. For each study, this review mostly focuses on 5 efficacy variables (PID, PR, PRID, Time to Rescue Medication, Time to Onset of Analgesia), which are considered as the most important measurements for acute pain indication.

Post-Surgical Pain Studies

All 4 studies failed to show significant differences of PID, PR, and PRID between Celecoxib and placebo treated group in first one hour after taking dose. Most of these time specific variable comparisons begin to show significant difference from 3 hours or after. For Time to Rescue Medication, the median times for Celecoxib treated group were 3 hour 15 minutes and 3 hour 18 minutes for study 082 and 083, respectively, and bigger than 8 hours for both 085, 086. For Time to onset of Analgesia, the median times for Celecoxib treated group were between 34 to 46 minutes.

Primary Dysmenorrhea Studies

Study 129 showed significant differences of PID, PR, and PRID between Celecoxib and placebo treated group from 1 hour 30 minutes after taking dose. Study 130 showed a significant difference from 1.5 hour after taking dose for PID, and from 1 hour for PR, PRID. For Time to Rescue Medication, the median times for Celecoxib treated group were over 12 hours for both studies. For Time to onset of Analgesia, the median times for Celecoxib treated group were 52 and 53 minutes for study 129 and 130, respectively.

In conclusion, Post-Surgical Pain Studies shows too weak evidence of drug efficacy for acute pain indication especially during the first few hours of PID, PR, and PRID. On the other hand, Primary Dysmenorrhea studies showed some evidence of efficacy of study medication.

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HFD-550/ Schiffenbauer/Goldkind
HFD-725/Choi/S.Lin/Huque
HFD-725/Division File/Chron

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Post-Surgical Studies

Table 1. Reasons for study termination; N49-98-02-082

Reason for Withdrawal	Placebo	SC-58635	Hyd / Ace
Lost to follow-up	0 (0%)	0 (0%)	0 (0%)
Pre-existing violation	2 (3%)	1 (1%)	1 (1%)
Protocol non-compliance	0 (0%)	0 (0%)	1 (1%)
Treatment Failure	56 (84%)	49 (70%)	46 (69%)
Adverse Sign	1 (1%)	2 (3%)	2 (3%)
Withdrawn	59 (88%)	52 (74%)	50 (75%)
Completed Study	8 (12%)	18 (26%)	17 (25%)

Table 2: Patient Demographics; N49-98-02-082

		Placebo	SC-58635	Hyd / Ace
Age	N	67	70	67
	Mean	64.4	65.7	65.8
	Std dev	12.59	12.85	12.57
Race	Asian	0 (0%)	0 (0%)	0 (0%)
	Black	2 (3%)	5 (7%)	3 (4%)
	Caucasian	63 (94%)	59 (84%)	62 (93%)
	Hispanic	1 (1%)	2 (3%)	0 (0%)
	Other	1 (1%)	4 (6%)	2 (3%)
Gender	Female	33 (49%)	29 (41%)	31 (46%)
	Male	34 (51%)	41 (59%)	36 (54%)
Height	N	66	70	67
	Mean	171.30	170.96	170.17
	Std dev	9.868	8.808	11.218
Weight	N	67	70	67
	Mean	87.43	85.73	87.46
	Std dev	20.018	20.735	18.276

Table 3: Summary of orthopedic surgery and baseline pain data; N49-98-02-082

		Placebo	SC-58635	Hyd / Ace
Surgical Procedure	Hip replacement	23 (34%)	31 (44%)	25 (37%)
	Knee replacement or reconstruction	29 (43%)	28 (40%)	30 (45%)
	Shoulder reconstruction	7 (10%)	5 (7%)	6 (9%)
	Other	8 (12%)	6 (9%)	6 (9%)
Pain Intensity Visual Analog Scale	N	67	70	67
	Mean	58.0	59.8	58.1
	Std Dev	11.14	12.01	13.89

Table 4. Reasons for study termination; N49-98-02-083

Reason for Withdrawal	Placebo	SC-58635	Hyd / Ace
Lost to follow-up	0 (0%)	0 (0%)	0 (0%)
Pre-existing violation	0 (0%)	0 (0%)	0 (0%)
Protocol non-compliance	1 (1%)	0 (0%)	1 (2%)
Treatment Failure	61 (91%)	49 (75%)	51 (77%)
Adverse Sign	1 (1%)	0 (0%)	3 (5%)
Withdrawn	63 (94%)	49 (75%)	55 (83%)
Completed Study	4 (6%)	16 (25%)	11 (17%)

Table 5: Patient Demographics; N49-98-02-083

		Placebo	SC-58635	Hyd / Ace
Age	N	67	65	66
	Mean	41.6	43.0	44.6
	Std dev	7.82	12.21	11.03
Race	Asian	1 (1%)	0 (0%)	0 (0%)
	Black	1 (1%)	2 (3%)	2 (3%)
	Caucasian	61 (91%)	59 (91%)	60 (91%)
	Hispanic	3 (4%)	4 (6%)	2 (3%)
	Other	1 (1%)	0 (0%)	2 (3%)
Gender	Female	67 (100%)	65 (100%)	66 (100%)
	Male	0 (0%)	0 (0%)	0 (0%)
Height	N	67	65	66
	Mean	164.49	162.37	163.77
	Std dev	6.906	6.297	5.556
Weight	N	67	65	66
	Mean	76.41	74.00	72.03
	Std dev	15.940	17.417	16.327

Table 6: Summary of orthopedic surgery and baseline pain data; N49-98-02-083

		Placebo	SC-58635	Hyd / Ace
Surgical Procedure	Abdominal Hysterectomy	48 (72%)	39 (60%)	39 (59%)
	Vaginal Hysterectomy	19 (28%)	26 (40%)	27 (41%)
Pain Intensity Visual Analog Scale	N	67	65	66
	Mean	64.6	65.0	61.3
	Std Dev	13.18	13.24	12.19

Table 7. Reasons for study termination from SDAP; N49-98-02-085

Reason for Withdrawal	Placebo	SC-58635	Hyd / Ace
Lost to follow-up	0 (0%)	0 (0%)	0 (0%)
Pre-existing violation	0 (0%)	0 (0%)	0 (0%)
Protocol non-compliance	0 (0%)	0 (0%)	0 (0%)
Treatment Failure	42 (61%)	29 (43%)	29 (47%)
Adverse Sign	0 (0%)	1 (1%)	1 (2%)
Withdrawn	42 (61%)	30 (45%)	30 (48%)
Completed Study	27 (39%)	37 (55%)	32 (52%)

Table 8: Patient Demographics; N49-98-02-085

		Placebo	SC-58635	Hyd / Ace
Age	N	69	67	62
	Mean	40.7	46.0	40.7
	Std dev	13.17	13.64	12 81
Race	Asian	2 (3%)	0 (0%)	0 (0%)
	Black	18 (26%)	20 (30%)	11 (18%)
	Caucasian	43 (62%)	40 (60%)	46 (74%)
	Hispanic	6 (9%)	7 (10%)	3 (5%)
	Other	0 (0%)	0 (0%)	2 (3%)
Gender	Female	42 (61%)	39 (58%)	39 (63%)
	Male	27 (39%)	28 (42%)	23 (37%)
Height	N	69	65	62
	Mean	172.01	170.96	170.57
	Std dev	11.496	12.696	10.501
Weight	N	67	66	61
	Mean	81.19	81.14	78.30
	Std dev	20.063	21.125	16.607

Table 9: Summary of orthopedic surgery and baseline pain data; N49-98-02-085

		Placebo	SC-58635	Hyd / Ace
Surgical Procedure	Bunionectomy	18 (26%)	12 (18%)	7 (11%)
	Anterior Cruciate Ligament Repair	5 (7%)	1 (1%)	4 (6%)
	Fixation of Long Bone Fractures	0 (0%)	1 (1%)	0 (0%)
	Laminectomy	1 (1%)	1 (1%)	2 (3%)
	Osteotomy	1 (1%)	0 (0%)	0 (0%)
	Other Orthopedic Procedure	1 (1%)	2 (3%)	5 (8%)
	Other	43 (62%)	50 (75%)	44 (71%)
Pain Intensity Visual Analog Scale	N	69	67	62
	Mean	65.5	67.3	63.4
	Std Dev	14.96	17.17	13.59

Table 10. Reasons for study termination from SDAP; N49-98-02-086

Reason for Withdrawal	Placebo	SC-58635	Hyd / Ace
Lost to follow-up	0 (0%)	0 (0%)	0 (0%)
Pre-existing violation	0 (0%)	0 (0%)	0 (0%)
Protocol non-compliance	0 (0%)	0 (0%)	0 (0%)
Treatment Failure	48 (67%)	33 (45%)	41 (55%)
Adverse Sign	0 (0%)	0 (0%)	0 (0%)
Withdrawn	48 (67%)	33 (45%)	41 (55%)
Completed Study	24 (33%)	41 (55%)	33 (45%)

Table 11: Patient Demographics; N49-98-02-086

		Placebo	SC-58635	Hyd / Ace
Age	N	72	74	74
	Mean	49.8	48.7	46.5
	Std dev	17.28	16.13	16.64
Race	Asian	1 (1%)	1 (1%)	0 (0%)
	Black	6 (8%)	8 (11%)	10 (14%)
	Caucasian	62 (86%)	64 (86%)	60 (81%)
	Hispanic	3 (4%)	1 (1%)	2 (3%)
	Other	0 (0%)	0 (0%)	2 (3%)
Gender	Female	42 (58%)	45 (61%)	46 (62%)
	Male	30 (42%)	29 (39%)	28 (38%)
Height	N	72	74	73
	Mean	169.61	170.65	169.15
	Std dev	10.361	11.071	9.779
Weight	N	72	73	73
	Mean	83.54	83.57	80.72
	Std dev	22.454	20.334	18.691

Table 12: Summary of orthopedic surgery and baseline pain data; N49-98-02-086

		Placebo	SC-58635	Hyd / Ace
Surgical Procedure	Bunionectomy	10 (14%)	7 (9%)	12 (16%)
	Anterior Cruciate Ligament Repair	7 (10%)	6 (8%)	9 (12%)
	Fixation of Long Bone Fractures	0 (0%)	0 (0%)	0 (0%)
	Laminectomy	12 (17%)	10 (14%)	10 (14%)
	Osteotomy	2 (3%)	1 (1%)	0 (0%)
	Other Orthopedic Procedure	6 (8%)	7 (9%)	6 (8%)
	Other	35 (49%)	43 (58%)	37 (50%)
Pain Intensity Visual Analog Scale	N	72	74	74
	Mean	65.8	63.9	62.3
	Std Dev	18.01	15.47	13.74

Table 13: Reasons for Study Termination from MDAP by treatment; N49-00-06-085

MDAP	SC-58635 200MG TID PRN			Hydrocodone 10mg/ Acetaminophen 100mg TID PRN		
SDAP	Placebo	SC-58635	Total	Placebo	Hyd/Ace	Total
Reason for Withdrawal						
Lost to follow-up	1 (3%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Pre-existing violation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Protocol non-compliance	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (2%)	2 (2%)
Treatment Failure	4 (14%)	1 (2%)	5 (5%)	4 (14%)	14 (25%)	18 (21%)
Adverse Sign	0 (0%)	3 (5%)	3 (3%)	1 (4%)	1 (2%)	2 (2%)
Withdrawn	5 (17%)	4 (6%)	9 (10%)	6 (21%)	16 (28%)	22 (26%)
Completed Study	24 (83%)	58 (94%)	82 (90%)	22 (79%)	41 (72%)	63 (74%)

Table 14: Reasons for Study Termination from MDAP by treatment; N49-00-06-086

MDAP	SC-58635 200MG TID PRN			Hydrocodone 10mg/ Acetaminophen 100mg TID PRN		
SDAP	Placebo	SC-58635	Total	Placebo	Hyd/Ace	Total
Reason for Withdrawal						
Lost to follow-up	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pre-existing violation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Protocol non-compliance	0 (0%)	1 (1%)	1 (1%)	1 (3%)	0 (0%)	1 (1%)
Treatment Failure	6 (22%)	11 (16%)	17 (18%)	5 (17%)	13 (19%)	18 (19%)
Adverse Sign	1 (4%)	0 (0%)	1 (1%)	1 (3%)	4 (6%)	5 (5%)
Withdrawn	7 (24%)	12 (18%)	19 (20%)	7 (24%)	17 (25%)	24 (25%)
Completed Study	20 (74%)	55 (82%)	75 (80%)	22 (76%)	50 (75%)	72 (75%)

Table 15: Pain Intensity Difference (PID, Categorical Scale, Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-082

	Time	Description	Placebo	SC-58635	Hyd / Ace
	0.25	Mean (Std dev)	0.28 (0.48)	0.24 (0.49)	0.37 (0.60)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	0.37 (0.63)	0.38 (0.73)	0.58 (0.74)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	0.51 (0.64)	0.48 (0.82)	0.78 (0.78)
		LSD comparison	AB	B	A
	1.00	Mean (Std dev)	0.56 (0.89)	0.57 (0.89)	0.84 (0.79)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	0.41 (0.95)	0.57 (0.98)	0.81 (0.86)
L		LSD comparison	A	A	A
	2.00	Mean (Std dev)	0.35 (1.04)	0.58 (1.07)	0.84 (0.95)
O		LSD comparison	B	AB	A
	3.00	Mean (Std dev)	0.17 (0.94)	0.54 (1.06)	0.66 (0.93)
C		LSD comparison	B	A	A
	4.00	Mean (Std dev)	0.09 (0.93)	0.53 (1.07)	0.51 (0.86)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.03 (0.92)	0.44 (1.03)	0.43 (0.80)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.04 (0.92)	0.38 (1.01)	0.33 (0.77)
		LSD comparison	A	A	A
	7.00	Mean (Std dev)	0.00 (0.92)	0.34 (0.99)	0.28 (0.79)
		LSD comparison	A	A	A
	8.00	Mean (Std dev)	0.00 (0.92)	0.35 (1.00)	0.25 (0.79)
		LSD comparison	A	A	A
	0.25	Mean (Std dev)	0.28 (0.48)	0.24 (0.49)	0.37 (0.60)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	0.37 (0.63)	0.38 (0.73)	0.58 (0.74)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	0.51 (0.64)	0.48 (0.82)	0.78 (0.78)
		LSD comparison	AB	B	A
	1.00	Mean (Std dev)	0.56 (0.89)	0.57 (0.89)	0.84 (0.79)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	0.53 (0.95)	0.66 (0.98)	0.81 (0.86)
B		LSD comparison	A	A	A
	2.00	Mean (Std dev)	0.51 (1.04)	0.70 (1.07)	0.84 (0.95)
O		LSD comparison	B	AB	A
	3.00	Mean (Std dev)	0.37 (0.94)	0.65 (1.06)	0.66 (0.93)
C		LSD comparison	B	A	A
	4.00	Mean (Std dev)	0.32 (0.93)	0.59 (1.07)	0.51 (0.86)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.25 (0.92)	0.53 (1.03)	0.43 (0.80)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.25 (0.92)	0.49 (1.01)	0.33 (0.77)
		LSD comparison	A	A	A
	7.00	Mean (Std dev)	0.22 (0.92)	0.41 (0.99)	0.28 (0.79)
		LSD comparison	A	A	A
	8.00	Mean (Std dev)	0.20 (0.92)	0.41 (1.00)	0.25 (0.79)
		LSD comparison	A	A	A

Table 16: Pain Relief (PR, Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-082

	Time	Description	Placebo	SC-58635	Hyd / Ace
	0.25	Mean (Std dev)	0.78 (0.84)	0.71 (0.85)	0.91 (0.95)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.08 (1.08)	1.13 (1.21)	1.45 (1.16)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.35 (1.16)	1.37 (1.20)	1.75 (1.21)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.48 (1.34)	1.58 (1.30)	1.94 (1.31)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	1.37 (1.40)	1.66 (1.43)	1.86 (1.36)
L		LSD comparison	A	A	A
	2.00	Mean (Std dev)	1.36 (1.46)	1.62 (1.51)	1.97 (1.41)
O		LSD comparison	A	A	A
	3.00	Mean (Std dev)	1.09 (1.33)	1.62 (1.53)	1.79 (1.42)
C		LSD comparison	B	A	A
	4.00	Mean (Std dev)	0.94 (1.30)	1.53 (1.55)	1 58 (1.32)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.85 (1.28)	1.34 (1.47)	1.52 (1.30)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.82 (1.25)	1.31 (1.49)	1.33 (1.19)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	0.78 (1.24)	1.19 (1.43)	1.25 (1.17)
		LSD comparison	A	A	A
	8.00	Mean (Std dev)	0.78 (1.24)	1.25 (1.47)	1.24 (1.17)
		LSD comparison	A	A	A
	0.25	Mean (Std dev)	0.78 (0.86)	0.71 (0.85)	0.91 (0.95)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.08 (1.08)	1.13 (1.21)	1.45 (1.16)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.35 (1.16)	1.37 (1.20)	1.75 (1.21)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.48 (1.34)	1.56 (1.30)	1.94 (1.31)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	1.34 (1.42)	1.63 (1.45)	1.84 (1.37)
B		LSD comparison	A	A	A
	2.00	Mean (Std dev)	1.28 (1.51)	1.51 (1.57)	1.90 (1.48)
O		LSD comparison	A	A	A
	3.00	Mean (Std dev)	0.94 (1.37)	1.44 (1.62)	1.63 (1.54)
C		LSD comparison	B	AB	A
	4.00	Mean (Std dev)	0.74 (1.31)	1.26 (1.64)	1.30 (1.46)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.58 (1.27)	1.07 (1.54)	1.09 (1.44)
		LSD comparison	A	A	A
	6.00	Mean (Std dev)	0.52 (1.23)	1.04 (1.55)	0.76 (1.28)
		LSD comparison	A	A	A
	7.00	Mean (Std dev)	0.48 (1.21)	0.85 (1.46)	0.64 (1.23)
		LSD comparison	A	A	A
	8.00	Mean (Std dev)	0.40 (1.13)	0.87 (1.52)	0.60 (1.21)
		LSD comparison	A	A	A

Table 17: Pain Intensity Difference and Pain Relief (PRID, Categorical Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-082

	Time	Description	Placebo	SC-58635	Hyd / Ace
L O C F	0.25	Mean (Std dev)	1.06 (1.18)	0.94 (1.26)	1.28 (1.41)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.45 (1.61)	1.51 (1.86)	2.03 (1.79)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.86 (1.69)	1.82 (1.92)	2.52 (1.88)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	2.05 (2.12)	2.13 (2.11)	2.78 (1.99)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	1.77 (2.25)	2.24 (2.35)	2.66 (2.12)
		LSD comparison	A	A	A
	2.00	Mean (Std dev)	1.72 (2.42)	2.19 (2.52)	2.81 (2.27)
		LSD comparison	B	AB	A
	3.00	Mean (Std dev)	1.26 (2.20)	2.16 (2.52)	2.45 (2.24)
		LSD comparison	B	A	A
	4.00	Mean (Std dev)	1.03 (2.14)	2.06 (2.56)	2.09 (2.07)
		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.88 (2.10)	1.78 (2.43)	1.96 (2.00)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.86 (2.08)	1.69 (2.43)	1.66 (1.84)
		LSD comparison	A	A	A
	7.00	Mean (Std dev)	0.78 (2.07)	1.53 (2.34)	1.54 (1.85)
		LSD comparison	A	A	A
	8.00	Mean (Std dev)	0.78 (2.07)	0.60 (2.41)	1.49 (1.85)
		LSD comparison	A	A	A
B O C F	0.25	Mean (Std dev)	1.06 (1.18)	0.94 (1.26)	1.28 (1.41)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.45 (1.61)	1.51 (1.86)	2.03 (1.79)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.86 (1.69)	1.82 (1.92)	2.52 (1.88)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	2.05 (2.12)	2.13 (2.11	2.78 (1.99)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	1.87 (2.13)	2.29 (2.27)	2.68 (2.09)
		LSD comparison	A	A	A
	2.00	Mean (Std dev)	1.79 (2.30)	2.21 (2.43)	2.79 (2.25)
		LSD comparison	A	A	A
	3.00	Mean (Std dev)	1.31 (2.00)	2.09 (2.46)	2.30 (2.30)
		LSD comparison	B	AB	A
	4.00	Mean (Std dev)	1.06 (1.93)	1.85 (2.51)	1.81 (2.15)
		LSD comparison	A	A	A
	5.00	Mean (Std dev)	0.83 (1.88)	1.60 (2.33)	1.51 (2.09)
		LSD comparison	A	A	A
	6.00	Mean (Std dev)	0.77 (1.84)	1.53 (2.31)	1.04 (1.86)
		LSD comparison	A	A	A
	7.00	Mean (Std dev)	0.69 (1.82)	1.26 (2.19)	0.93 (1.80)
		LSD comparison	A	A	A
	8.00	Mean (Std dev)	0.60 (1.68)	1.28 (2.27)	0.87 (1.77)
		LSD comparison	A	A	A

Table 18: Pain Intensity Difference (PID, Categorical Scale, Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-083

	Time	Description	Placebo	SC-58635	Hyd / Ace
	0.25	Mean (Std dev)	0.42 (0.68)	0.33 (0.59)	0.21 (0.51)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	0.73 (0.73)	0.58 (0.77)	0.48 (0.71)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	0.84 (0.77)	0.65 (0.84)	0.74 (0.75)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	0.86 (0.85)	0.67 (0.92)	0.77 (0.78)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	0.67 (0.89)	0.70 (0.91)	0.78 (0.83)
L		LSD comparison	A	A	A
	2.00	Mean (Std dev)	0.53 (0.89)	0.75 (0.95)	0.86 (0.93)
O		LSD comparison	B	AB	A
	3.00	Mean (Std dev)	0.30 (0.82)	0.63 (1.02)	0.92 (0.92)
C		LSD comparison	B	A	A
	4.00	Mean (Std dev)	0.13 (0.76)	0.48 (0.87)	0.59 (0.92)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.04 (0.71)	0.48 (0.92)	0.48 (0.92)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	-0.09 (0.57)	0.42 (0.86)	0.30 (0.93)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	-0.10 (0.58)	0.40 (0.83)	0.17 (0.78)
		LSD comparison	B	A	A
	8.00	Mean (Std dev)	-0.12 (0.56)	0.35 (0.82)	0.15 (0.75)
		LSD comparison	B	A	A
	0.25	Mean (Std dev)	0.42 (0.68)	0.33 (0.59)	0.21 (0.51)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	0.73 (0.73)	0.58 (0.77)	0.48 (0.71)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	0.84 (0.77)	0.65 (0.84)	0.74 (0.75)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	0.86 (0.85)	0.67 (0.92)	0.77 (0.78)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	0.70 (0.85)	0.75 (0.85)	0.81 (0.78)
B		LSD comparison	A	A	A
	2.00	Mean (Std dev)	0.56 (0.82)	0.80 (0.87)	0.88 (0.89)
O		LSD comparison	A	A	A
	3.00	Mean (Std dev)	0.37 (0.67)	0.65 (0.96)	0.82 (0.84)
C		LSD comparison	B	AB	A
	4.00	Mean (Std dev)	0.22 (0.57)	0.49 (0.75)	0.59 (0.85)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.15 (0.50)	0.46 (0.81)	0.48 (0.82)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.06 (0.24)	0.40 (0.75)	0.32 (0.79)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	0.06 (0.24)	0.37 (0.70)	0.23 (0.55)
		LSD comparison	B	A	AB
	8.00	Mean (Std dev)	0.03 (0.17)	0.32 (0.69)	0.20 (0.50)
		LSD comparison	B	A	AB

Table 19: Pain Relief (PR, Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-083

	Time	Description	Placebo	SC-58635	Hyd / Ace
	0.25	Mean (Std dev)	0.97 (1.03)	0.81 (0.92)	0.76 (0.89)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.45 (1.17)	1.25 (1.08)	1.23 (1.03)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.63 (1.22)	1.43 (1.14)	1.61 (1.19)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.68 (1.25)	1.53 (1.23)	1.80 (1.19)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	1.41 (1.32)	1.46 (1.26)	1.95 (1.25)
L		LSD comparison	B	B	A
	2.00	Mean (Std dev)	1.25 (1.31)	1.49 (1.37)	1.09 (1.42)
O		LSD comparison	B	B	A
	3.00	Mean (Std dev)	0.94 (1.20)	1.43 (1.50)	1.93 (1.39)
C		LSD comparison	C	B	A
	4.00	Mean (Std dev)	0.67 (1.05)	1.24 (1.36)	1.60 (1.37)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.54 (0.94)	1.12 (1.36)	1.41 (1.33)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.33 (0.64)	1.03 (1.38)	1.11 (1.29)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	0.34 (0.66)	0.98 (1.32)	1.01 (1.17)
		LSD comparison	B	A	A
	8.00	Mean (Std dev)	0.33 (0.64)	0.94 (1.31)	1.00 (1.14)
		LSD comparison	B	A	A
	0.25	Mean (Std dev)	0.97 (1.03)	0.81 (0.92)	0.76 (0.89)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.45 (1.17)	1.25 (1.08)	1.23 (1.03)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.63 (1.22)	1.43 (1.14)	1.61 (1.19)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.68 (1.25)	1.53 (1.23)	1.80 (1.19)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	1.40 (1.33)	1.44 (1.27)	1.95 (1.25)
B		LSD comparison	B	B	A
	2.00	Mean (Std dev)	1.19 (1.33)	1.41 (1.43)	2.05 (1.47)
O		LSD comparison	B	B	A
	3.00	Mean (Std dev)	0.87 (1.21)	1.29 (1.58)	1.82 (1.49)
C		LSD comparison	B	B	A
	4.00	Mean (Std dev)	0.51 (1.05)	1.05 (1.44)	1.39 (1.49)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.37 (0.92)	0.91 (1.43)	1.12 (1.47)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.15 (0.53)	0.78 (1.44)	0.75 (1.36)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	0.16 (0.57)	0.74 (1.37)	0.62 (1.22)
		LSD comparison	B	A	A
	8.00	Mean (Std dev)	0.10 (0.46)	0.69 (1.36)	0.48 (1.11)
		LSD comparison	B	A	A

Table 20: Pain Intensity Difference and Pain Relief (PRID, Categorical Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-083

	Time	Description	Placebo	SC-58635	Hyd / Ace
L	0.25	Mean (Std dev)	1.39 (1.62)	1.14 (1.38)	0.98 (1.33)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	2.18 (1.81)	1.83 (1.68)	1.73 (1.65)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	2.46 (1.90)	2.07 (1.85)	2.38 (1.87)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	2.54 (2.00)	2.20 (2.03)	2.59 (1.87)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	2.08 (2.11)	2.16 (2.06)	2.75 (1.98)
		LSD comparison	A	A	A
O	2.00	Mean (Std dev)	1.77 (2.12)	2.24 (2.22)	2.98 (2.26)
		LSD comparison	B	B	A
C	3.00	Mean (Std dev)	1.24 (1.91)	2.06 (2.43)	2.74 (2.22)
		LSD comparison	B	A	A
F	4.00	Mean (Std dev)	0.81 (1.69)	1.72 (2.12)	2.21 (2.20)
		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.58 (1.52)	1.60 (2.19)	1.91 (2.18)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.24 (1.05)	1.45 (2.16)	1.42 (2.12)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	0.24 (1.09)	1.38 (2.05)	1.19 (1.84)
		LSD comparison	B	A	A
	8.00	Mean (Std dev)	0.21 (1.04)	1.29 (2.04)	1.16 (1.77)
		LSD comparison	B	A	A
B	0.25	Mean (Std dev)	1.39 (1.62)	1.14 (1.38)	0.98 (1.33)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	2.18 (1.81)	1.83 (1.68)	1.73 (1.65)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	2.46 (1.90)	2.07 (1.85)	2.38 (1.87)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	2.54 (2.00)	2.20 (2.03)	2.59 (1.87)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	2.10 (2.09)	2.19 (2.01)	2.78 (1.93)
		LSD comparison	A	A	A
O	2.00	Mean (Std dev)	1.74 (2.09)	2.21 (2.21)	2.95 (2.28)
		LSD comparison	B	B	A
C	3.00	Mean (Std dev)	1.24 (1.83)	1.94 (2.47)	2.66 (2.25)
		LSD comparison	B	AB	A
F	4.00	Mean (Std dev)	0.73 (1.58)	1.55 (2.13)	2.01 (2.28)
		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.52 (1.37)	1.37 (2.20)	1.61 (2.24)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.21 (0.75)	1.18 (2.16)	1.08 (2.10)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	0.22 (0.79)	1.11 (2.05)	0.86 (1.74)
		LSD comparison	B	A	A
	8.00	Mean (Std dev)	0.13 (0.63)	1.02 (2.03)	0.69 (1.60)
		LSD comparison	B	A	AB

Table 21: Pain Intensity Difference (PID, Categorical Scale, Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-085

	Time	Description	Placebo	SC-58635	Hyd / Ace
	0.25	Mean (Std dev)	0.22 (0.48)	0.11 (0.44)	0.17 (0.38)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	0.35 (0.66)	0.39 (0.61)	0.32 (0.50)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	0.44 (0.72)	0.54 (0.78)	0.63 (0.64)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	0.45 (0.72)	0.65 (0.83)	0.83 (0.68)
		LSD comparison	B	AB	A
	1.50	Mean (Std dev)	0.56 (0.82)	0.75 (0.82)	0.95 (0.79)
L		LSD comparison	B	AB	A
	2.00	Mean (Std dev)	0.53 (0.85)	0.84 (0.81)	1.02 (0.81)
O		LSD comparison	B	A	A
	3.00	Mean (Std dev)	0.44 (0.84)	0.91 (0.98)	1.02 (0.95)
C		LSD comparison	B	A	A
	4.00	Mean (Std dev)	0.30 (0.80)	0.84 (0.99)	1.00 (0.90)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.30 (0.83)	0.79 (1.03)	0.74 (0.90)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.29 (0.84)	0.79 (0.84)	0.71 (0.90)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	0.24 (0.81)	0.79 (0.81)	0.58 (0.93)
		LSD comparison	B	A	A
	8.00	Mean (Std dev)	0.19 (0.82)	0.75 (0.82)	0.47 (0.93)
		LSD comparison	B	A	A
	0.25	Mean (Std dev)	0.22 (0.48)	0.11 (0.44)	0.17 (0.38)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	0.35 (0.66)	0.38 (0.60)	0.32 (0.50)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	0.44 (0.72)	0.53 (0.78)	0.63 (0.64)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	0.45 (0.72)	0.64 (0.82)	0.83 (0.68)
		LSD comparison	B	AB	A
	1.50	Mean (Std dev)	0.60 (0.76)	0.73 (0.80)	0.97 (0.76)
B		LSD comparison	B	AB	A
	2.00	Mean (Std dev)	0.59 (0.76)	0.83 (0.77)	1.02 (0.79)
O		LSD comparison	B	AB	A
	3.00	Mean (Std dev)	0.52 (0.73)	0.91 (0.92)	0.98 (0.95)
C		LSD comparison	B	A	A
	4.00	Mean (Std dev)	0.34 (0.67)	0.84 (0.91)	0.95 (0.87)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.38 (0.66)	0.78 (0.97)	0.65 (0.84)
		LSD comparison	B	A	AB
	6.00	Mean (Std dev)	0.36 (0.66)	0.78 (0.92)	0.63 (0.82)
		LSD comparison	B	A	AB
	7.00	Mean (Std dev)	0.30 (0.62)	0.78 (0.95)	0.53 (0.80)
		LSD comparison	B	A	AB
	8.00	Mean (Std dev)	0.25 (0.63)	0.72 (0.93)	0.43 (0.74)
		LSD comparison	B	A	B

Table 22: Pain Relief (PR, Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-085

	Time	Description	Placebo	SC-58635	Hyd / Ace
	0.25	Mean (Std dev)	0.44 (0.74)	0.53 (0.91)	0.48 (0.77)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	0.79 (0.94)	0.82 (0.98)	0.78 (0.87)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	0.99 (1.06)	1.14 (1.15)	1.33 (1.00)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.10 (1.15)	1.36 (1.21)	1.65 (1.13)
		LSD comparison	B	AB	A
	1.50	Mean (Std dev)	1.35 (1.33)	1.49 (1.26)	2.00 (1.19)
L		LSD comparison	B	B	A
O	2.00	Mean (Std dev)	1.29 (1.35)	1.58 (1.31)	2.13 (1.19)
		LSD comparison	B	B	A
C	3.00	Mean (Std dev)	1.13 (1.27)	1.70 (1.45)	2.12 (1.40)
		LSD comparison	B	A	A
F	4.00	Mean (Std dev)	0.99 (1.18)	1.74 (1.46)	1.98 (1.37)
		LSD comparison	B	A	A
	5.00	Mean (Std dev)	1.01 (1.23)	1.66 (1.48)	1.87 (1.37)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.85 (1.06)	1.66 (1.44)	1.72 (1.42)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	0.82 (1.06)	1.66 (1.47)	1.57 (1.37)
		LSD comparison	B	A	A
	8.00	Mean (Std dev)	0.78 (1.04)	1.66 (1.48)	1.45 (1.35)
		LSD comparison	B	A	A
	0.25	Mean (Std dev)	0.44 (0.74)	0.53 (0.91)	0.48 (0.77)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	0.79 (0.94)	0.82 (0.98)	0.78 (0.87)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	0.99 (1.06)	1.14 (1.15)	1.33 (1.00)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.10 (1.15)	1.36 (1.21)	1.65 (1.13)
		LSD comparison	B	AB	A
	1.50	Mean (Std dev)	1.33 (1.34)	1.49 (1.26)	1.97 (1.23)
B		LSD comparison	B	B	A
O	2.00	Mean (Std dev)	1.25 (1.36)	1.52 (1.32)	2.08 (1.25)
		LSD comparison	B	B	A
C	3.00	Mean (Std dev)	1.05 (1.29)	1.59 (1.51)	2.02 (1.50)
		LSD comparison	B	A	A
F	4.00	Mean (Std dev)	0.85 (1.21)	1.58 (1.55)	1.84 (1.49)
		LSD comparison	B	A	A
	5.00	Mean (Std dev)	0.87 (1.27)	1.47 (1.57)	1.64 (1.53)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	0.68 (1.09)	1.44 (1.54)	1.42 (1.55)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	0.63 (1.07)	1.44 (1.57)	1.27 (1.48)
		LSD comparison	B	A	A
	8.00	Mean (Std dev)	0.57 (1.05)	1.39 (1.60)	1.10 (1.45)
		LSD comparison	B	A	A

Table 23: Pain Intensity Difference and Pain Relief (PRID, Categorical Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-085

	Time	Description	Placebo	SC-58635	Hyd / Ace
	0.25	Mean (Std dev)	0.66 (1.11)	0.65 (1.26)	0.65 (1.04)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.15 (1.50)	1.22 (1.42)	1.10 (1.26)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.43 (1.66)	1.70 (1.76)	1.97 (1.52)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.55 (1.76)	20.3 (1.92)	2.48 (1.71)
		LSD comparison	B	AB	A
	1.50	Mean (Std dev)	1.91 (2.05)	2.26 (1.98)	2.95 (1.85)
L		LSD comparison	B	AB	A
	2.00	Mean (Std dev)	1.82 (2.10)	2.44 (1.97)	3.15 (1.86)
O		LSD comparison	B	A	A
	3.00	Mean (Std dev)	1.57 (1.57)	2.64 (2.33)	3.13 (2.24)
C		LSD comparison	B	A	A
	4.00	Mean (Std dev)	1.28 (1.87)	2.60 (2.33)	2.98 (2.15)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	1.32 (1.93)	2.48 (2.38)	2.61 (2.14)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	1.13 (1.78)	2.48 (2.31)	2.43 (2.17)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	1.06 (1.72)	2.48 (2.37)	2.14 (2.16)
		LSD comparison	B	A	A
	8.00	Mean (Std dev)	0.97 (1.71)	2.43 (2.34)	1.92 (2.34)
		LSD comparison	B	A	A
	0.25	Mean (Std dev)	0.66 (1.11)	0.64 (1.25)	0.65 (1.04)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.15 (1.50)	1.20 (1.42)	1.10 (1.26)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.43 (1.66)	1.67 (1.76)	1.97 (1.52)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.55 (1.76)	2.00 (1.92)	2.48 (1.71)
		LSD comparison	B	AB	A
	1.50	Mean (Std dev)	1.94 (2.01)	2.23 (1.97)	2.93 (1.87)
B		LSD comparison	B	AB	A
	2.00	Mean (Std dev)	1.84 (2.03)	2.34 (1.99)	3.10 (1.92)
O		LSD comparison	B	AB	A
	3.00	Mean (Std dev)	1.57 (1.94)	2.50 (2.37)	3.00 (2.35)
C		LSD comparison	B	A	A
	4.00	Mean (Std dev)	1.20 (1.83)	2.40 (2.40)	2.79 (2.28)
F		LSD comparison	B	A	A
	5.00	Mean (Std dev)	1.25 (1.87)	2.25 (2.46)	2.29 (2.29)
		LSD comparison	B	A	A
	6.00	Mean (Std dev)	1.04 (1.69)	2.22 (2.40)	2.04 (2.31)
		LSD comparison	B	A	A
	7.00	Mean (Std dev)	0.93 (1.61)	2.22 (2.46)	1.79 (2.21)
		LSD comparison	B	A	A
	8.00	Mean (Std dev)	0.82 (1.59)	2.11 (2.45)	1.53 (2.12)
		LSD comparison	B	A	AB

Table 24: Pain Intensity Difference (PID, Categorical Scale, Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-086

	Time	Description	Placebo	SC-58635	Hyd / Ace
	0.25	Mean (Std dev)	0.30 (0.62)	0.22 (0.54)	0.17 (0.48)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	0.44 (0.66)	0.33 (0.69)	0.33 (0.67)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	0.43 (0.73)	0.54 (0.78)	0.54 (0.78)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	0.55 (0.73)	0.71 (0.79)	0.63 (0.80)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	0.61 (0.84)	0.76 (0.81)	0.81 (0.89)
L		LSD comparison	A	A	A
	2.00	Mean (Std dev)	0.60 (0.87)	0.78 (0.86)	0.80 (0.87)
O		LSD comparison	A	A	A
	3.00	Mean (Std dev)	0.58 (0.95)	0.76 (0.93)	0.73 (0.86)
C		LSD comparison	A	A	A
	4.00	Mean (Std dev)	0.42 (0.89)	0.85 (0.99)	0.63 (0.93)
F		LSD comparison	B	A	AB
	5.00	Mean (Std dev)	0.37 (0.89)	0.78 (1.01)	0.56 (0.92)
		LSD comparison	B	A	AB
	6.00	Mean (Std dev)	0.36 (0.87)	0.72 (1.00)	0.48 (0.86)
		LSD comparison	B	A	AB
	7.00	Mean (Std dev)	0.27 (0.78)	0.60 (0.96)	0.33 (0.81)
		LSD comparison	B	A	AB
	8.00	Mean (Std dev)	0.24 (0.81)	0.53 (0.96)	0.19 (0.72)
		LSD comparison	B	A	B
	0.25	Mean (Std dev)	0.30 (0.62)	0.22 (0.54)	0.17 (0.48)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	0.44 (0.66)	0.33 (0.69)	0.33 (0.67)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	0.43 (0.73)	0.54 (0.78)	0.54 (0.78)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	0.55 (0.73)	0.71 (0.79)	0.63 (0.80)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	0.59 (0.82)	0.76 (0.80)	0.81 (0.87)
B		LSD comparison	A	A	A
	2.00	Mean (Std dev)	0.61 (0.82)	0.77 (0.83)	0.82 (0.83)
O		LSD comparison	A	A	A
	3.00	Mean (Std dev)	0.65 (0.83)	0.78 (0.86)	0.76 (0.80)
C		LSD comparison	A	A	A
	4.00	Mean (Std dev)	0.49 (0.77)	0.88 (0.90)	0.69 (0.84)
F		LSD comparison	B	A	AB
	5.00	Mean (Std dev)	0.45 (0.73)	0.79 (0.93)	0.65 (0.79)
		LSD comparison	A	A	A
	6.00	Mean (Std dev)	0.41 (0.71)	0.73 (0.90)	0.57 (0.73)
		LSD comparison	A	A	A
	7.00	Mean (Std dev)	0.31 (0.60)	0.63 (0.85)	0.45 (0.63)
		LSD comparison	B	A	AB
	8.00	Mean (Std dev)	0.30 (0.62)	0.56 (0.85)	0.31 (0.55)
		LSD comparison	A	A	A

Table 25: Pain Relief (PR, Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-086

	Time	Description	Placebo	SC-58635	Hyd / Ace
	0.25	Mean (Std dev)	0.76 (0.97)	0.69 (0.78)	0.77 (0.94)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.01 (1.06)	1.17 (1.06)	1.11 (1.10)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.20 (1.14)	1.36 (1.10)	1.37 (1.16)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.36 (1.17)	1.66 (1.23)	1.42 (1.20)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	1.53 (1.31)	1.77 (1.32)	1.75 (1.40)
L		LSD comparison	A	A	A
	2.00	Mean (Std dev)	1.56 (1.38)	1.85 (1.34)	1.79 (1.36)
O		LSD comparison	A	A	A
	3.00	Mean (Std dev)	1.48 (1.44)	1.87 (1.44)	1.78 (1.39)
C		LSD comparison	A	A	A
	4.00	Mean (Std dev)	1.28 (1.44)	1.93 (1.48)	1.69 (1.40)
F		LSD comparison	B	A	AB
	5.00	Mean (Std dev)	1.22 (1.40)	1.88 (1.45)	1.63 (1.33)
		LSD comparison	B	A	AB
	6.00	Mean (Std dev)	1.27 (1.44)	1.81 (1.45)	1.55 (1.36)
		LSD comparison	A	A	A
	7.00	Mean (Std dev)	1.13 (1.30)	1.67 (1.40)	1.39 (1.25)
		LSD comparison	B	A	AB
	8.00	Mean (Std dev)	1.10 (1.30)	1.47 (1.38)	1.25 (1.20)
		LSD comparison	A	A	A
	0.25	Mean (Std dev)	0.76 (0.97)	0.69 (0.78)	0.77 (0.94)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.01 (1.06)	1.17 (1.06)	1.11 (1.10)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.20 (1.14)	1.36 (1.10)	1.37 (1.16)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.36 (1.17)	1.66 (1.23)	1.42 (1.20)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	1.50 (1.33)	1.76 (1.33)	1.71 (1.43)
B		LSD comparison	A	A	A
	2.00	Mean (Std dev)	1.50 (1.42)	1.81 (1.37)	1.72 (1.42)
O		LSD comparison	A	A	A
	3.00	Mean (Std dev)	1.36 (1.49)	1.81 (1.48)	1.69 (1.47)
C		LSD comparison	A	A	A
	4.00	Mean (Std dev)	1.14 (1.48)	1.86 (1.53)	1.56 (1.48)
F		LSD comparison	B	A	AB
	5.00	Mean (Std dev)	1.01 (1.43)	1.77 (1.53)	1.42 (1.45)
		LSD comparison	B	A	AB
	6.00	Mean (Std dev)	0.99 (1.46)	1.62 (1.55)	1.33 (1.46)
		LSD comparison	B	A	AB
	7.00	Mean (Std dev)	0.83 (1.29)	1.48 (1.49)	1.12 (1.36)
		LSD comparison	B	A	AB
	8.00	Mean (Std dev)	0.79 (1.28)	1.24 (1.46)	0.94 (1.29)
		LSD comparison	A	A	A

Table 26: Pain Intensity Difference and Pain Relief (PRID, Categorical Extrapolated) Means, (Std Dev), and Fisher's Protected LSD Comparisons; N49-98-02-086

	Time	Description	Placebo	SC-58635	Hyd / Ace
	0.25	Mean (Std dev)	1.06 (1.43)	0.93 (1.15)	0.96 (1.30)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.45 (1.62)	1.50 (1.59)	1.45 (1.65)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.63 (1.75)	1.90 (1.71)	1.91 (1.75)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.91 (1.80)	2.36 (1.89)	2.04 (1.84)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	2.14 (2.05)	2.53 (2.01)	2.56 (2.15)
L		LSD comparison	A	A	A
	2.00	Mean (Std dev)	2.15 (2.14)	2.64 (2.09)	2.60 (2.08)
O		LSD comparison	A	A	A
	3.00	Mean (Std dev)	2.06 (2.29)	2.63 (2.27)	2.52 (2.15)
C		LSD comparison	A	A	A
	4.00	Mean (Std dev)	1.71 (2.22)	2.78 (2.37)	2.32 (2.16)
F		LSD comparison	B	A	AB
	5.00	Mean (Std dev)	1.59 (2.18)	2.66 (2.35)	2.20 (2.07)
		LSD comparison	B	A	AB
	6.00	Mean (Std dev)	1.63 (2.22)	2.53 (2.35)	2.03 (2.05)
		LSD comparison	A	A	A
	7.00	Mean (Std dev)	1.40 (1.97)	2.27 (2.27)	1.72 (1.92)
		LSD comparison	A	A	A
	8.00	Mean (Std dev)	1.34 (1.98)	2.00 (2.24)	1.44 (1.77)
		LSD comparison	A	A	A
	0.25	Mean (Std dev)	1.06 (1.43)	0.93 (1.15)	0.96 (1.30)
		LSD comparison	A	A	A
	0.50	Mean (Std dev)	1.45 (1.62)	1.50 (1.59)	1.45 (1.65)
		LSD comparison	A	A	A
	0.75	Mean (Std dev)	1.63 (1.75)	1.90 (1.71)	1.91 (1.75)
		LSD comparison	A	A	A
	1.00	Mean (Std dev)	1.91 (1.80)	2.36 (1.89)	2.04 (1.84)
		LSD comparison	A	A	A
	1.50	Mean (Std dev)	2.09 (2.06)	2.51 (2.01)	2.52 (2.16)
B		LSD comparison	A	A	A
	2.00	Mean (Std dev)	2.11 (2.14)	2.58 (2.11)	2.54 (2.11)
O		LSD comparison	A	A	A
	3.00	Mean (Std dev)	2.00 (2.25)	2.59 (2.26)	2.45 (2.18)
C		LSD comparison	A	A	A
	4.00	Mean (Std dev)	1.63 (2.18)	2.74 (2.36)	2.25 (2.17)
F		LSD comparison	B	A	AB
	5.00	Mean (Std dev)	1.46 (2.11)	2.56 (2.37)	2.07 (2.09)
		LSD comparison	B	A	AB
	6.00	Mean (Std dev)	1.40 (2.13)	2.34 (2.38)	1.90 (2.06)
		LSD comparison	A	A	A
	7.00	Mean (Std dev)	1.14 (1.84)	2.10 (2.26)	1.58 (1.91)
		LSD comparison	B	A	AB
	8.00	Mean (Std dev)	1.09 (1.84)	1.79 (2.23)	1.26 (1.75)
		LSD comparison	A	A	A

Table 27: Maximum Pain Intensity, Maximum Pain Relief, and Patients Global Evaluation for Day 1 – MDAP: N49-98-02-085

MDAP	SC-58635 200MG TID PRN			Hydrocodone 10mg/ Acetaminophen 100mg TID PRN		
SDAP	Placebo	SC-58635	Total	Placebo	Hyd/Ace	Total
Maximum Pain Intensity						
None	0 (0%)	1 (2%)	1 (1%)	0 (0%)	1 (2%)	1 (1%)
Mild	0 (0%)	3 (5%)	3 (3%)	0 (0%)	3 (6%)	3 (4%)
Moderate	8 (29%)	28 (48%)	36 (42%)	14 (50%)	25 (46%)	39 (48%)
Severe	20 (71%)	26 (45%)	46 (53%)	14 (50%)	25 (46%)	39 (48%)
Total	28	58	86	28	54	82
Maximum Pain Relief						
None	3 (11%)	2 (4%)	5 (6%)	1 (4%)	2 (4%)	3 (4%)
A little	4 (14%)	9 (16%)	13 (15%)	4 (14%)	5 (9%)	9 (11%)
Some	9 (32%)	19 (33%)	28 (33%)	12 (43%)	14 (26%)	26 (32%)
A lot	12 (43%)	16 (28%)	28 (33%)	8 (29%)	21 (39%)	29 (35%)
Complete	0 (0%)	11 (19%)	11 (13%)	3 (11%)	12 (22%)	15 (18%)
Total	28	57	85	28	54	82
Patient Global evaluation						
Poor	8 (29%)	8 (14%)	16 (19%)	7 (25%)	3 (6%)	10 (12%)
Fair	5 (18%)	9 (16%)	14 (16%)	7 (25%)	10 (19%)	17 (21%)
Good	7 (25%)	16 (28%)	23 (27%)	7 (25%)	14 (26%)	21 (26%)
Very Good	6 (21%)	16 (28%)	22 (26%)	5 (18%)	21 (39%)	26 (32%)
Excellent	2 (7%)	9 (16%)	11 (13%)	2 (7%)	6 (11%)	8 (10%)
Total	28	58	86	28	54	82

Table 28: Maximum Pain Intensity, Maximum Pain Relief, and Patients Global Evaluation for Day 1 – MDAP: N49-98-02-086

MDAP	SC-58635 200MG TID PRN			Hydrocodone 10mg/ Acetaminophen 100mg TID PRN		
SDAP	Placebo	SC-58635	Total	Placebo	Hyd/Ace	Total
Maximum Pain Intensity						
None	1 (3%)	1 (2%)	2 (2%)	0 (0%)	1 (2%)	1 (1%)
Mild	4 (13%)	9 (15%)	13 (14%)	0 (0%)	5 (8%)	5 (6%)
Moderate	12 (39%)	30 (51%)	42 (47%)	16 (57%)	33 (56%)	49 (56%)
Severe	14 (45%)	19 (32%)	33 (37%)	12 (43%)	20 (34%)	32 (37%)
Total	31	59	90	28	59	87
Maximum Pain Relief						
None	4 (13%)	3 (5%)	7 (8%)	2 (7%)	2 (3%)	4 (5%)
A little	5 (17%)	9 (15%)	14 (16%)	2 (7%)	8 (14%)	10 (12%)
Some	9 (30%)	18 (31%)	27 (30%)	10 (36%)	11 (19%)	21 (24%)
A lot	7 (23%)	18 (31%)	25 (28%)	11 (39%)	28 (48%)	39 (45%)
Complete	5 (17%)	11 (19%)	16 (18%)	3 (11%)	9 (16%)	12 (14%)
Total	30	59	89	28	58	86
Patient Global evaluation						
Poor	6 (21%)	11 (19%)	17 (19%)	5 (18%)	10 (17%)	15 (17%)
Fair	7 (24%)	8 (14%)	15 (17%)	5 (18%)	6 (10%)	11 (13%)
Good	4 (14%)	17 (29%)	21 (24%)	12 (43%)	12 (21%)	24 (28%)
Very Good	8 (28%)	13 (22%)	21 (24%)	6 (21%)	17 (29%)	23 (27%)
Excellent	4 (14%)	10 (17%)	14 (16%)	0 (0%)	13 (22%)	13 (15%)
Total	29	59	88	28	58	86

Table 29: Patient Global Evaluation Day2 - Day5 - MDAP: N49-98-02-085

	MDAP	SC-58635 200MG TID PRN			Hydrocodone 10mg/ Acetaminophen 100mg TID PRN		
	SDAP	Placebo	SC-58635	Total	Placebo	Hyd/Ace	Total
Day 2							
Poor		0 (0%)	1 (2%)	1 (1%)	0 (0%)	2 (4%)	2 (3%)
Fair		5 (20%)	5 (9%)	10 (13%)	3 (13%)	5 (11%)	8 (11%)
Good		7 (28%)	15 (27%)	22 (28%)	8 (33%)	14 (30%)	22 (31%)
Very Good		8 (32%)	19 (35%)	27 (34%)	6 (25%)	17 (37%)	23 (33%)
Excellent		5 (20%)	15 (27%)	20 (25%)	7 (29%)	8 (17%)	15 (21%)
Total		25	55	80	24	46	70
Day 3							
Poor		0 (0%)	1 (2%)	1 (1%)	0 (0%)	2 (5%)	2 (3%)
Fair		2 (8%)	0 (0%)	2 (3%)	1 (5%)	2 (5%)	3 (5%)
Good		7 (27%)	15 (31%)	22 (30%)	5 (25%)	12 (32%)	17 (29%)
Very Good		9 (35%)	18 (38%)	27 (36%)	9 (45%)	14 (37%)	23 (40%)
Excellent		8 (31%)	14 (29%)	22 (30%)	5 (25%)	8 (21%)	13 (22%)
Total		26	48	74	20	38	58
Day 4							
Poor		0 (0%)	1 (2%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Fair		3 (13%)	0 (0%)	3 (4%)	1 (6%)	1 (3%)	2 (4%)
Good		4 (17%)	13 (28%)	17 (24%)	4 (22%)	10 (29%)	14 (27%)
Very Good		9 (38%)	16 (35%)	25 (36%)	7 (39%)	15 (44%)	22 (42%)
Excellent		8 (33%)	16 (35%)	24 (34%)	6 (33%)	8 (24%)	14 (27%)
Total		24	46	70	18	34	52
Day 5							
Poor		0 (0%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Fair		2 (11%)	0 (0%)	2 (3%)	1 (6%)	1 (3%)	2 (4%)
Good		4 (21%)	9 (22%)	13 (22%)	1 (6%)	9 (30%)	10 (21%)
Very Good		7 (37%)	15 (37%)	22 (37%)	9 (53%)	8 (27%)	17 (36%)
Excellent		6 (32%)	16 (39%)	22 (37%)	6 (35%)	12 (40%)	18 (38%)
Total		19	41	60	17	30	47
End of Study							
Poor		1 (4%)	3 (5%)	4 (5%)	0 (0%)	4 (7%)	4 (5%)
Fair		4 (14%)	1 (2%)	5 (6%)	5 (19%)	6 (11%)	11 (14%)
Good		1 (4%)	11 (19%)	12 (14%)	6 (23%)	11 (20%)	17 (21%)
Very Good		11 (39%)	22 (37%)	33 (38%)	9 (35%)	19 (35%)	28 (35%)
Excellent		11 (39%)	22 (37%)	33 (38%)	6 (23%)	14 (26%)	20 (25%)
Total		28	59	87	26	54	80

Table 30: Patient Global Evaluation Day2 - Day5 - MDAP: N49-98-02-086

	MDAP	SC-58635 200MG TID PRN			Hydrocodone 10mg/ Acetaminophen 100mg TID PRN		
	SDAP	Placebo	SC-58635	Total	Placebo	Hyd/Ace	Total
Day 2							
Poor		0 (0%)	5 (9%)	5 (7%)	0 (0%)	1 (2%)	1 (1%)
Fair		2 (11%)	9 (16%)	11 (14%)	3 (13%)	6 (10%)	9 (11%)
Good		4 (21%)	14 (25%)	18 (24%)	13 (57%)	14 (24%)	27 (33%)
Very Good		9 (47%)	19 (33%)	28 (37%)	5 (22%)	27 (46%)	32 (39%)
Excellent		4 (21%)	10 (18%)	14 (18%)	2 (9%)	11 (19%)	13 (16%)
Total		19	57	76	23	59	82
Day 3							
Poor		0 (0%)	2 (4%)	2 (3%)	0 (0%)	2 (4%)	2 (3%)
Fair		0 (0%)	5 (10%)	5 (7%)	0 (0%)	2 (4%)	2 (3%)
Good		6 (33%)	11 (22%)	17 (25%)	11 (50%)	14 (27%)	25 (34%)
Very Good		8 (44%)	19 (39%)	27 (40%)	8 (36%)	17 (33%)	25 (34%)
Excellent		4 (22%)	12 (24%)	16 (24%)	3 (14%)	16 (31%)	19 (26%)
Total		18	49	67	22	51	73
Day 4							
Poor		0 (0%)	2 (4%)	2 (3%)	0 (0%)	1 (2%)	1 (1%)
Fair		0 (0%)	4 (9%)	4 (6%)	0 (0%)	2 (4%)	2 (3%)
Good		3 (18%)	11 (24%)	14 (23%)	8 (42%)	11 (23%)	19 (28%)
Very Good		8 (47%)	14 (31%)	22 (35%)	6 (32%)	21 (44%)	27 (40%)
Excellent		6 (35%)	14 (31%)	20 (32%)	5 (26%)	13 (27%)	18 (27%)
Total		17	45	62	19	48	67
Day 5							
Poor		0 (0%)	2 (5%)	2 (3%)	0 (0%)	1 (2%)	1 (2%)
Fair		0 (0%)	4 (9%)	4 (7%)	0 (0%)	2 (4%)	2 (3%)
Good		2 (12%)	10 (23%)	12 (20%)	7 (37%)	7 (15%)	14 (22%)
Very Good		8 (47%)	15 (35%)	23 (38%)	6 (32%)	20 (43%)	26 (40%)
Excellent		7 (41%)	12 (28%)	19 (32%)	6 (32%)	16 (35%)	22 (34%)
Total		17	43	60	19	46	65
End of Study							
Poor		0 (0%)	7 (11%)	7 (9%)	2 (8%)	4 (7%)	6 (7%)
Fair		2 (10%)	7 (11%)	9 (11%)	2 (8%)	6 (10%)	8 (9%)
Good		4 (19%)	14 (23%)	18 (22%)	8 (31%)	7 (11%)	15 (17%)
Very Good		10 (48%)	16 (26%)	26 (32%)	7 (27%)	24 (39%)	31 (36%)
Excellent		5 (24%)	17 (28%)	22 (27%)	7 (27%)	20 (33%)	27 (31%)
Total		21	61	82	26	61	87

Primary Dysmenorrhea Studies

Table 31: Patient Disposition by Treatment Cycle and Treatment Sequence; N49-00-06-129

	Seq 1	Seq 2	Seq 3	Seq 4	Seq 5	Seq 6	Total
Total	25	25	25	23	25	26	149
Not Treated	3	1	4	3	2	0	13
Cycle 1							
Treated drug	A[a]	C	B	A	C	B	
Entered	22	24	21	20	23	26	136
Withdrawal prior to cycle 2	3	0	1	2	4	2	12
Reason for withdrawal							
Lost to follow-up	0	0	0	0	1	0	1
Protocol violation	0	0	0	1	0	0	1
Protocol noncompliance	0	0	0	0	3	1	4
Adverse sign	0	0	1	0	0	0	1
2 conseq non-dosing cycles	3	0	0	1	0	1	5
Cycle 2							
Treated drug	B	A	C	C	B	A	
Entered	19	24	20	18	19	24	124
Withdrawal prior to cycle 3	0	1	0	0	0	1	2
Reason for withdrawal							
2 conseq non-dosing cycles	0	1	0	0	0	1	2
Cycle 3							
Treated drug	C	B	A	B	A	C	
Entered	19	23	20	18	19	23	122
Withdrawal	0	0	0	0	0	0	0

a. A=Celecoxib 400 mg/200 mg Q12 hr PRN, B=Naproxen Na 550 mg Q12 hr PRN, C=Placebo

Table 32: Reasons for Study Termination from SDAP (first 12 hours of first day) by treatment (3 cycles combined); N49-00-06-129

Reason for Withdrawal	Placebo (N=127)	Celecoxib (N=129)	Naproxen Na (N=126)
Took rescue medication	58 (46%)	26 (20%)	22 (17%)
Lost to follow-up	0	0	0
Protocol violation	0	0	0
Protocol noncompliance	1 (1%)	0	2 (2%)
Adverse sign	0	0	0
Withdrawn	59 (46%)	26 (20%)	24 (19%)
Completed 12 hours (SDAP)	68 (54%)	103 (80%)	102 (81%)

Table 33: Reasons for Study Termination from MDAP by treatment (3 cycles combined); N49-00-06-129

Reason for Withdrawal	Placebo (N=67)	Celecoxib (N=103)	Naproxen Na (N=101)
Took rescue medication	7 (10%)	7 (7%)	10 (10%)
Lost to follow-up	0 (0%)	0 (0%)	0 (0%)
Protocol violation	0 (0%)	0 (0%)	0 (0%)
Protocol noncompliance	3 (4%)	3 (3%)	1 (1%)
Adverse sign	0 (0%)	0 (0%)	0 (0%)
Withdrawn	10 (15%)	10 (10%)	11 (11%)
Completed treatment cycle	57 (85%)	93 (%90)	90 (89%)

Table 34: Patient Demographics; N49-00-06-129

		Seq 1	Seq 2	Seq3	Seq 4	Seq 5	Seq 6	P-value
Age	N	25	25	25	23	25	26	0.345
	Mean	26.6	24.1	26.0	26.1	23.4	26.9	
	Std dev	6.23	6.08	7.84	6.73	5.15	8.01	
Race	Caucasian	24	23	23	22	25	26	0.620
	Black	0	0	0	0	0	0	
	Asian	0	1	1	0	0	0	
	Hispanic	0	0	1	1	0	0	
	Other	1	1	0	0	0	0	
Height	N	25	25	25	23	25	26	0.256
	Mean	168.31	163.73	166.12	165.37	167.13	165.05	
	Std dev	5.824	7.001	5.636	9.675	7.100	6.365	
Weight	N	25	25	25	23	25	26	0.037
	Mean	74.47	62.89	62.65	65.63	73.29	65.33	
	Std dev	18.644	13.369	12.217	19.892	20.743	12.902	

a. seq 1 = A B C, seq 2 = C A B, seq 3 = B C A, seq4 = A C B, seq 5 = C B A, seq 6 = B A C
where A = Celecoxib, B=Naproxen Na, C=Placebo

Table 35: Baseline Menstrual Cramping Pain by Treatment; N49-00-06-129

Baseline Pain Intensity	Placebo (N=127)	Celecoxib (N=129)	Naproxen Na (N=126)	P-value
Moderate	78 (61%)	80 (62%)	85 (67%)	0.546
Severe	49 (39%)	49 (38%)	41 (33%)	
Total	127	129	126	

Table 36: Patient Disposition by Treatment Cycle and Treatment Sequence; N49-00-06-130

	Seq 1	Seq 2	Seq 3	Seq 4	Seq 5	Seq 6	Total
Total	26	26	24	25	26	27	154
Not Treated	4	4	3	5	2	1	19
Cycle 1							
Treated drug	A[a]	C	B	A	C	B	
Entered	22	22	21	20	24	26	135
Withdrawal prior to cycle 2	0	6	1	3	1	2	13
Reason for withdrawal							
Lost to follow-up	0	2	0	0	0	2	4
Protocol violation	0	2	1	1	0	0	4
Protocol noncompliance	0	1	0	2	0	0	3
Adverse sign	0	0	0	0	0	0	0
2 conseq non-dosing cycles	0	1	0	0	1	0	2
Cycle 2							
Treated drug	B	A	C	C	B	A	
Entered	22	16	20	17	23	24	122
Withdrawal prior to cycle 3	0	0	1	0	0	0	1
Reason for withdrawal							
Protocol noncompliance	0	0	1	0	0	0	1
Cycle 3							
Treated drug	C	B	A	B	A	C	
Entered	22	16	19	17	23	24	121
Withdrawal	0	0	0	0	0	0	0

a. A=Celecoxib 400 mg/200 mg Q12 hr PRN, B=Naproxen Na 550 mg Q12 hr PRN, C=Placebo

Table 37: Reasons for Study Termination from SDAP (first 12 hours of first day) by treatment (3 cycles combined); N49-00-06-130

Reason for Withdrawal	Placebo (N=129)	Celecoxib (N=124)	Naproxen Na (N=125)
Took rescue medication	50 (39%)	30 (24%)	16 (13%)
Lost to follow-up	0	0	2 (2%)
Protocol violation	0	0	0
Protocol noncompliance	0	0	0
Adverse sign	0	0	0
Withdrawn	50 (39%)	30 (24%)	18 (14%)
Completed 12 hours (SDAP)	79 (61%)	94 (76%)	107 (86%)