Study Number: N49-98-06-028
Study Dates: 6 May 1997 - 10 March 1998

Title of Study: A Multicenter, Double-Blind, Placebo-Controlled Comparison of the Analgesic Activity of celecoxib 100 mg, celecoxib 200 mg, Propoxyphene Napsylate 100 mg with Acetaminophen 650 mg, and Placebo with Remedication Allowable in Post-Orthopedic Surgical Patients.

Investigator and Location: 12 investigators in the United States, 11 of whom enrolled at least one patient.

Objectives:
The primary objective of this study was to compare the analgesic activity of two different doses of celecoxib versus placebo for the first eight hours after the first dose of study medication in post-orthopedic surgical patients who had moderate to severe pain.
The secondary objectives of this study were to:

1. Compare the analgesic activity of two different doses of celecoxib versus placebo for the remainder of the first 24 hours after the first dose of study medication;
2. Compare the analgesic activity of Darvocet-N® 50 (2 tablets) versus placebo for the first 24 hours after the first dose of study medication;
3. Compare the analgesic activity of celecoxib (two different doses) and Darvocet-N® 50 (2 tablets) for the first 24 hours after the first dose of study medication;
4. Evaluate analgesic activity of celecoxib (two different doses) and Darvocet-N® 50 (2 tablets) for treatment Days 2 to 5; and
5. Evaluate the safety of celecoxib (two different doses) in post-orthopedic surgical patients with moderate to severe pain.

Study Description
This was a multicenter, multiple dose, double-blind, placebo-controlled, randomized, parallel group comparison of the safety and analgesic efficacy of celecoxib 100 mg BID PRN, celecoxib 200 mg BID PRN, propoxyphene napsylate 100 mg and acetaminophen 650 mg (two capsules, each containing one Darvocet-N® 50 tablet) QID PRN, or placebo QID PRN orally administered to patients with moderate to severe post-orthopedic surgical pain. Efficacy was assessed at Baseline, and at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18 and 24 hours postdose using self-rating scales. At each timepoint, levels of pain intensity (Categorical and Visual Analog Scale [VAS]) and pain relief, as well as whether or not the pain was reduced by 50% were evaluated. Time to onset of meaningful pain relief was evaluated using a stopwatch. Pain intensity (Categorical Scale) was assessed prior to any remedication on each of the treatment days as well as maximum pain and maximum pain relief every 24 hours following the first 24-hour period. Patients who withdrew or required rescue analgesics prior to the one hour assessments were replaced, and were not included in the efficacy analyses. Patients who required rescue analgesics were dropped from the study. The duration of study drug treatment was up to five days.

Schedule of Observations and Procedures

	Pretreatment Period (Up to 14 Days Prior to the First Dose of Study Medication)			Treatment Period					Final Assessment*
	Screening	Surgery	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	
Medical History	x								
Physical Examination	x								x
Vital Signs	x	x	x	x (a)	x (b)	x (b)	x (b)	x (b)	x
Clinical Lab Testing	x (c)		x (c)	x (c)					x
Pregnancy Test	x (d)		x (e)						x (e)
Pain Assessments			x (f)	x (g)	x (h)	x (h)	x (h)	x (h)	x
APS Pain Measure (i)				x	x	x	x	x	x
Study Drug			x (j)	x	x	x	x	x	
Global Evaluation									x (k)
Symptoms/ Meds			x	x	x	x	x	x	x
Diary Cards			x	x	x	x	x	x	x
Bleeding Time (SCIREX only)	x (c)		x (c)	x (c)					
12 Hour Urine Collection (SCIREX only)	x		x	x (l)					

*Day 5 or Early Termination.

a) Vital signs collected at 6, 12 and 24 hours after the first dose on Day 1.
b) Vital signs collected every 12 hours on each day. (Inpatients only)
c) Performed in the middle of the 12 hour urine collection. (SCIREX site only)
d) Female patients of childbearing potential must have a serum pregnancy test within 14 days prior to first dose of study medication (not collected on CRF).
e) Female patients of childbearing potential must have a negative urine pregnancy test just prior to first dose of study medication. Pregnancy test performed at Final Assessment on outpatients only.
f) Pain intensity only (Categorical and Visual Analog Scale).
g) Pain intensity, pain relief, pain at least half gone, Visual Analog Scale, Day 1 at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18 and 24 hours after the first dose of study medication and/or just prior to rescue medication.
h) Pain intensity only (Categorical Scale) will be assessed prior to every dose of study medication. Maximum pain and maximum pain relief will also be assessed every 24 hours and/or just prior to rescue medication.
i) APS pain measure will be completed 24 hours after first dose of study medication on each day and/or just prior to rescue analgesics.
j) First dose of study medication will be administered within 54 hours after the end of anesthesia.
k) A Patient's Overall Global Evaluation will be completed on Day 5 or Early Termination.
l) Performed 24 hours after the first dose of study medication. (SCIREX site only)

Eligibility:

1. Been of legal age of consent.
2. For women of childbearing potential, confirmed use of adequate contraception, not been lactating, and had a negative serum pregnancy test within 14 days prior to the first dose of study medication and a negative urine pregnancy test just before the first dose of study medication.
3. Been in satisfactory health as determined by the Investigator on the basis of medical history and physical examination.
4. Undergone orthopedic surgery for:
   a. a total or partial reconstruction procedure for the hip or
   b. a total or partial reconstruction procedure for the knee or
   c. a major orthopedic procedure requiring open manipulation of bone with periosteal elevation (without other concomitant or associated medical/surgical problems) such as shoulder reconstruction, total hip or knee replacement, open reduction and internal fixation of long bone fractures, laminectomy, and osteotomy for acquired or congenital malformations.
5. If the patient received a parenteral analgesic, including patient controlled analgesia (PCA), the patient must have tolerated at least one oral dose of an analgesic which proved to be efficacious for at least three hours prior to receiving the first dose of study medication within 54 hours after the end of anesthesia.
6. If the patient did not receive a parenteral analgesic including PCA, the patient was permitted administration of the first dose of study medication within 54 hours after the end of anesthesia.
7. Been expected to be hospitalized for at least 12 hours after the first dose of study medication.
8. Had a Baseline pain intensity (Categorical Scale) level of moderate to severe.
9. Provided written informed consent prior to undergoing any procedures for this study.

Exclusions:

1. Planned bilateral orthopedic surgical procedure.
2. A history of uncontrolled chronic disease which, in the opinion of the Investigator, would contraindicate study participation or confound interpretation of the results.
3. Any cognitive impairment that would preclude, in the Investigator's opinion, study participation or compliance with protocol mandated procedures.
4. A diagnosis of having or had treatment initiated for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to receiving the first dose of study medication.
5. Any laboratory abnormality which, in the opinion of the Investigator, would contraindicate study participation, including AST or ALT >1.5, creatinine >1.5, or BUN >1.5 times the upper limit of the reference range.
6. A history of known analgesic or narcotic abuse.
7. An unwillingness to abstain from alcohol from surgery, throughout the course of the study, and 24 hours after the last dose of study medication.
8. A known hypersensitivity to analgesics, NSAIDs, cyclooxygenase inhibitors, or sulfonamides.
9. Use of any investigational medication within 30 days prior to the first dose of study medication or during the course of the study.
10. Previous admission to this study.
11. Lactose intolerance requiring significant dietary modification or treatment with enzyme supplementation.
12. Has cancer and has been in remission and off any treatment for less than two years prior to study enrollment.

Treatments Administered:

- hard gelatin capsules containing either celecoxib 100 mg or 200 mg, each identical in size and color;
- hard gelatin placebo capsules each identical in size and appearance to the celecoxib capsules;
- hard gelatin capsules containing one Darvocet-N® 50 (propoxyphene napsylate 50 mg and acetaminophen 325 mg) tablet, each identical in size and appearance; and

- hard gelatin placebo capsules, identical in size and appearance to the capsules containing the Darvocet-N® 50 tablets.

Randomization was stratified by gender.

Blinding:

Each patient was assigned four bottles of study medication (Bottles A, B, C, and D). For patients randomized to an celecoxib group, Bottle A contained celecoxib (100 mg or 200 mg), Bottle B contained Darvocet-N® 50 placebo capsules, Bottle C contained celecoxib placebo capsules and Bottle D contained Darvocet-N® 50 placebo capsules. For patients randomized to receive Darvocet-N® 50, Bottle A contained celecoxib placebo capsules, Bottle B contained Darvocet-N® 50, Bottle C contained celecoxib placebo capsules, and Bottle D contained Darvocet-N® 50. For patients randomized to receive placebo, Bottles A and C contained celecoxib celecoxib placebo capsules and Bottles B and D contained Darvocet-N® 50 placebo capsules. Patients were instructed to take 3 capsules up to four times a day as needed: 1 capsule from Bottle A and 2 capsules from Bottle B for the first and second dose every 24 hour period and 1 capsule from Bottle C and 2 capsules from Bottle D for the third and fourth dose every 24 hour period. The first dose of medication was to be taken at least one hour before eating; subsequent doses could be taken with food.

Efficacy Assessment:

Patients remained in the study up to a maximum of five days and must have been hospitalized for at least 12 hours after the first dose of study medication. A trained site observer was present for all patient assessments during the patient's hospitalization. Patients continued to perform their pain assessments at home for up to five days or until they took rescue medication, and recorded their pain assessments in the patient diaries. A Nurse Observer telephoned the patients daily at home and ensured the patient had taken study medication, evaluated and recorded adverse events and recorded rescue medication. The nurse observer also ensured the patient's pain was adequately controlled, pain assessments were performed and the global evaluation completed, and answered the patient's questions or concerns.
Patients underwent the following assessments at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18 and 24 hours postdose and/or just prior to rescue medication:

1. Pain Intensity (none = 0, severe = 3)
2. Pain Relief (none = 0, complete = 4)
3. Pain at Least Half Gone
4. Pain Intensity (VAS)
7. Time to Meaningful Pain Relief (by one stopwatch)
8. Maximum Pain Intensity during the last 24 hours (none = 0, severe = 3)
9. Maximum Pain Relief during the last b24 hours (none = 0, complete = 4)
10. Patient's Global Evaluation (poor = 1, excellent = 5)

In addition, the American Pain Society (APS) Pain Measure (19) was completed by each patient 24 hours after the first dose of study medication on each of the treatment days

and/or just prior to rescue medication. The APS Pain Measure consisted of five questions (for questions 2-5, scored 0-10, a lower score was better):

1. Have you experienced any pain in the past 24 hours? (yes or no)
2. How much pain are you having right now? (0-10)
3. Indicate the worst pain you have had in the past 24 hours. (0-10)
4. Indicate the average level of pain you have had in the past 24 hours. (0-10)
5. Indicate how pain has interfered with you in:
   a. general activity (0-10)
   b. mood (0-10)
   c. walking ability (0-10)
   d. relations with other people (0-10)
   e. sleep (0-10)
   f. enjoyment of life (0-10)

Interim Efficacy Analysis

An interim analysis was performed on this study when approximately half of the patients had been enrolled. An interim analysis plan was issued before the interim data set closed. An independent Data Monitoring Committee conducted the interim efficacy analysis and made the recommendation to continue the trial as planned. The recommendation was communicated to the Head of Programming and Statistics and the Executive Director, Clinical Research, at Searle without unblinding Searle personnel. The results of the interim analysis were not disseminated to non-committee members. The efficacy measurements included in the interim analysis were: time-specific PID (Categorical Scale), PR, and PRID.

RESULTS:

Disposition of Patients

A total of 255 patients were enrolled at 11 centers and were randomized to receive one of four treatments for up to five days: 68 patients received celecoxib 100 mg BID PRN, 62 patients received celecoxib 200 mg BID PRN, 65 patients received Darvocet-N® 50 (2 tablets) QID PRN, and 60 patients received placebo. Three patients completed the study and 252 patients withdrew prior to completing the study. The reasons for withdrawal from the study, displayed by treatment group, are shown in the table below. The large number of patients who dropped was, in part, related to the definition of a completed patient. A completed patient was defined as one who completed 5 days of the study. Therefore, patients who were discharged from the hospital prior to completion of the 5 days were classified as premature terminations from the study because of noncompliance.

Table 1: Reasons For Study Termination

	Placebo (N= 60)	Celecoxib 100mg BID PRN (N= 68)	Celecoxib 200mg BID PRN (N= 62)	Darvocet N 100 mg QID PRN (N= 65)
Completed Study	1 (2%)	1 (1%)	0 (0%)	1 (2%)
Withdrawn 59(98%)		67 (99%)	62 (100%)	64 (98%)
Reason For Withdrawal				
Lost To Follow- Up	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pre- Existing Violation	2 (3%)	3 (4%)	0 (0%)	0 (0%)
Protocol Non- Compliance	3 (5%)	16 (24%)	10 (16%)	19 (29%)
Treatment Failure / Rescue Medication	51 (85%)	47 (69%)	43 (69%)	44 (68%)
Adverse Events	3 (5%)	1 (1%)	9 (15%)	1 (2%)

Baseline demographic characteristics are presented in Tables 2 and 3.
The treatment groups were comparable ($p \geq 0.175$) for age, race, and gender. For all patients, the age range was 19 to 87 years ($p=0.175$). Across treatment groups, 50% to 55% of the patients were male ($p=0.930$) and 83% to 95% were Caucasian ($p=0.248$). All treatment groups were comparable ($p \geq 0.459$) with respect to height, weight, vital signs, and diastolic blood pressure at Baseline. Across treatment groups, the mean systolic blood pressure values ranged from 122.8 mmHg to 132.2 mmHg, and were statistically significantly different ($p=0.012$), although the differences were not clinically relevant.

Table 2: Baseline Demographic Characteristics

	Placebo (N= 60)	Celecoxib 100mg BID PRN (N= 68)	Celecoxib 200mg BID PRN (N= 62)	Darvocet N 100mg QID PRN (N= 65)	p- VALUE
AGE (Years)					0.175 (a)
N	60	68	62	65	
Mean	52.2	55.7	59.0	56.4	
Std Dev	16.52	16.35	16.10	15.73	
Median	49.5	57.5	62.0	57.0	
Range	23 - 87	19 - 82	21 - 86	27 - 84	
<30	5(8%)	7(10%)	2(3%)	4(6%)	
30- 39	12(20%)	3(4%)	5(8%)	6(9%)	
40- 49	13(22%)	10(15%)	12(19%)	13(20%)	
50- 59	9(15%)	16(24%)	9(15%)	14(22%)	
60- 69	9(15%)	18(26%)	14(23%)	11(17%)	
70- 79	10(17%)	12(18%)	15(24%)	13(20%)	
>= 80	2(3%)	2(3%)	5(8%)	4(6%)	
Race/ Ethnic Origin					0.248 (b)
Asian	0(0%)	0(0%)	0(0%)	0(0%)	
Black	7(12%)	3(4%)	1(2%)	5(8%)	
Caucasian	51(85%)	60(88%)	59(95%)	54(83%)	
Hispanic	2(3%)	3(4%)	2(3%)	3(5%)	
Other	0(0%)	2(3%)	0(0%)	3(5%)	
Total	60(100%)	68(100%)	62(100%)	65(100%)	
Gender					0.930 (b)
Female	30(50%)	31(46%)	28(45%)	29(45%)	
Male	30(50%)	37(54%)	34(55%)	36(55%)	
Total	60(100%)	68(100%)	62(100%)	65(100%)	

(a) Two- Way Analysis of Variance with treatment group and center as factors.
(b) Pearson Chi- Square.

Table 3
Additional Baseline Characteristics

	Placebo (N= 60)	Celecoxib 100mg BID PRN (N= 68)	Celecoxib 200mg BID PRN (N= 62)	Darvocet N 100mg QID PRN (N= 65)	p- VALUE (a)
HEIGHT (Cm)					0.818
N	60	67	61	65	
Mean	170.02	171.90	170.97	170.85	
Std Dev	11.723	11.076	9.823	11.844	
Median	168.85	172.20	170.20	170.20	
WEIGHT (Kg)					0.952
N	60	68	62	64	
Mean	83.68	83.99	83.69	85.44	
Std Dev	19.217	17.601	18.820	19.556	
Median	82.80	81.65	82.85	83.90	

(a) Two- Way Analysis of Variance with treatment group and center as factors.

Summary of Orthopedic Surgery and Baseline Pain Data

A summary of orthopedic surgery information and Baseline Pain Intensity (Categorical Variables) is presented in Table 7. The type of surgical procedure performed (total reconstruction of the hip or knee, partial reconstruction of the hip or knee, hip or knee replacement, or other) was comparable across treatment groups (p=0.548). The Baseline Pain Intensity (moderate or severe) was also comparable across treatment groups (p=0.297).

Table 4: Summary Of Orthopedic Surgery And Baseline Pain Data (Categorical Variables)

	Placebo (N= 60)	Celecoxib 100mg BID PRN (N= 68)	Celecoxib 200mg BID PRN (N= 62)	Darvocet N 100mg QID PRN (N= 65)	p- VALUE (a)
Surgical Procedure					0.548
Total Reconstruction Of The Hip	5 (8%)	4 (6%)	3 (5%)	5 (8%)	
Total Reconstruction Of The Knee	3 (5%)	9 (13%)	7 (11%)	5 (8%)	
Partial Reconstruction Of The Hip	1 (2%)	0 (0%)	0 (0%)	0 (0%)	
Partial Reconstruction Of The Knee	1 (2%)	3 (4%)	0 (0%)	1 (2%)	
Hip Replacement	4 (7%)	6 (9%)	6 (10%)	11 (17%)	
Knee Replacement	9 (15%)	10 (15%)	8 (13%)	13 (20%)	
Other	37 (62%)	36 (53%)	38 (61%)	30 (46%)	
Total	60 (100%)	68 (100%)	62 (100%)	65 (100%)	
Baseline Pain Intensity (Categorical Rating)					0.297
Moderate	41 (68%)	52 (76%)	39 (64%)	50 (77%)	
Severe	19 (32%)	16 (24%)	22 (36%)	15 (23%)	
Total	60 (100%)	68 (100%)	61 (100%)	65 (100%)	

(a) Cochran- Mantel- Haenszel (General Association) test stratified by center for pain intensity.
Note: For patients whose surgery indicated more than one surgical category, only the principal procedure is summarized.

A summary of orthopedic surgery and Baseline Pain Intensity (Continuous Variables) is presented in Table 8. All treatment groups were comparable with respect to duration of surgery, time from end of anesthesia until taking study medication and Baseline Pain Intensity (Visual Analog Scale [VAS]) ($p \geq 0.279$). Mean duration of surgery across treatment groups was 1:45 to 1:60 (hour:minutes). Mean time from end of anesthesia until taking study medication was 30:03 to 33:54 (hour:minutes). Mean Baseline Pain Intensity (VAS) across treatment groups was 57.4 mm to 61.0 mm (0 to 100 mm scale).

Table 5: Summary Of Orthopedic Surgery And Baseline Pain Data (Continuous Variables)

	Placebo (N= 60)	Celecoxib 100mg BID PRN (N= 68)	Celecoxib 200mg BID PRN (N= 62)	Darvocet N 100mg QID PRN (N= 65)	p- VALUE (a)
Duration Of Surgery (Hh: Mm)					0.370
N	60	68	62	65	
Mean	1: 45	1: 48	1: 60	1: 50	
Std Dev	0: 49	0: 44	1: 06	1: 03	
Median	1: 40	1: 40	1: 51	1: 40	
Time (Hh: Mm) From End Of Anesthesia Until Taking Study Medication					0.279
N	60	68	60	65	
Mean	30: 03	30: 38	33: 54	33: 39	
Std Dev	14: 45	15: 37	14: 49	16: 02	
Median	27: 40	29: 54	40: 28	40: 20	
Baseline Pain Intensity Visual Analog Scale					0.437
N	60	68	61	64	
Mean	60.7	57.4	61.0	57.4	
Std Dev	18.57	17.55	18.54	17.63	
Median	64.0	56.0	57.0	57.0	

(a) Two- way Analysis of Variance with treatment group and center as factors.

Efficacy Analysis

Of the 246 patients in the ITT Cohort on Day 1, only 48 patients entered the Day 2 and this number was further reduced by day 5 of the study (see table). Therefor, the planned statistical tests for variables obtained on Day 2 through Day 5 were not carried out due to the small number of patients remaining in the study.

Disposition of Patients Throughout The Study

Table 6: Number Of Patients Entered This Study Day

	Placebo	Celecoxib 100mg	Celecoxib 200mg	Darvocet N-100
Day 1	59	66	58	61
Day 2	4	16	11	17
Day 3	3	8	5	10
Day 4	1	5	3	3
Day 5	1	3	3	1

Analysis of Primary Measures of Efficacy

Time-Specific Pain Intensity Difference (PID) (Categorical) – First 24 Hours

Tables 9 and 10 present the mean PID (Categorical Scale) scores for the first 24 hours for the BOCF single dose and multiple dose analyses, respectively. Mean scores for celecoxib 100 mg BID PRN and 200 mg BID PRN were numerically greater than placebo at 0.75 through 24 hours postdose in both the single dose and multiple dose analyses with the exception of celecoxib 100 mg BID PRN at the 1.0 hour post dose assessment. However, these differences were statistically significant for celecoxib 200 mg BID PRN compared to placebo at the 6.0 and 7.0 hour assessment times only, in the single dose analysis and at the 6.0 hour assessment time only, in the multiple dose analysis.

Tables 11 and 12 present the mean PID (Categorical Scale) scores for the LOCF single dose and multiple dose analyses, respectively. Mean scores for celecoxib 100 mg BID PRN and 200 mg BID PRN were numerically greater than placebo at 0.75 through 24 hours postdose in both the single dose and multiple dose analyses with the exception of celecoxib 100 mg BID PRN at the 1.0 hour post dose assessment. However, these differences were statistically significant for celecoxib 200 mg BID PRN compared to placebo at the 6.0 through 8.0 hour assessment times only, for the single dose analysis and at the 6.0 through 8.0, 10.0, and 12.0 through 24 hour assessment times only, for the multiple dose analysis.

Within the celecoxib treatment groups, the mean PID (Categorical Scale) scores for the celecoxib 200 mg BID PRN group were numerically greater than for the celecoxib 100 mg BID PRN group at the 1.0 through 24 hour assessment times for both the BOCF and LOCF analyses with the exception of 4.0 hours postdose (BOCF single dose) and 11.0 hours postdose (BOCF multiple dose). The numerical differences between the celecoxib treatment groups were statistically significant only at the 7.0 hour assessment time for the BOCF single dose analysis (Tables 9-12).

The mean PID (Categorical Scale) scores for Darvocet-N® 50 (2 tablets) QID PRN were statistically significant compared to placebo at the 1.0 though 6.0 hour assessment times for the BOCF single dose analysis; the 1.0 through 18.0 hour assessment times for the BOCF multiple dose analysis; and at the 1.0 through 24 hour assessment times for the LOCF single dose and multiple dose analyses (Tables 9-12).

The mean PID (Categorical Scale) scores for Darvocet-N® (2 tablets) QID PRN for the BOCF single dose analysis were statistically significant at the 2.0 though 4.0 hour assessment times compared to celecoxib 200 mg BID PRN and at the 1.0 and 2.0 though 5.0 hour assessment times compared to celecoxib 100 mg BID PRN (Table 9). The mean PID (Categorical Scale) scores for Darvocet-N® 50 (2 tablets) QID PRN for the BOCF multiple dose analysis were statistically significant at the 2.0, 3.0, 4.0, 8.0, 9.0 and 11.0 hour assessment times compared to celecoxib 200 mg BID PRN and at the 1.0 and 2.0 through 18 hour assessment times compared to celecoxib 100 mg BID PRN (Table 10).

The mean PID (Categorical Scale) scores for Darvocet-N® 50 (2 tablets) QID PRN were statistically significant at the 2.0 through 4.0 hour assessment times compared to celecoxib 200 mg BID PRN for the LOCF single dose and multiple dose analyses, and at the 1.0 through 24 hour assessment times compared to celecoxib 100 mg BID PRN for the LOCF single dose and multiple dose analyses (Tables 11 and 12).

There were statistically significant effects for center and surgery type as well as a treatment by center interaction at various timepoints. Further subgroup analyses were performed for the time-specific primary efficacy measures by center and surgery type. These analyses did not reveal any consistent pattern across timepoints (Tables 9-12).

Overall, for the BOCF (single dose and multiple dose) and LOCF (single dose and multiple dose) analyses, celecoxib was numerically greater in mean PID (Categorical Scale) scores compared to placebo. However, this superiority did not show any statistically significant consistency over the first 24 hours and did not show statistically significant superiority at all during the first 5 hours postdose. Darvocet-N® 50 (2 tablets) QID PRN was statistically significant superior compared to placebo at the 1.0 though 6.0 hour assessment times for the BOCF single dose analysis; at the 1.0 through 18.0 hour assessment times for the BOCF multiple dose analysis; and at the 1.0 through 24 hour assessment times for the LOCF single dose and multiple dose analyses, thus validating this pain model for the first 24 hours.

Table 9: Pain Intensity Difference (BOCF) – Single Dose Analysis

I FINAL PID.SAS Wednesday, 20th May 1998 Page 1 of 3

SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 9
PAIN INTENSITY DIFFERENCE (PID, CATEGORICAL SCALE, EXTRAPOLATED - BOCF, SINGLE DOSE)
MEANS (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEAN PID SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PID

Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCET N-100 QID PRN	0.23 (0.48) 81(a) A(c)	0.44 (0.67) 81 A	0.72 (0.78) 80 A	0.80 (0.80) 81 A	0.82 (0.80) 53 A	0.80 (0.80) 47 A	0.75 (0.80) 43 A
SC-58635 200MG BID PRN	0.22 (0.80) 58 A	0.22 (0.82) 57 A	0.48 (0.75) 57 A	0.60 (0.83) 58 AB	0.69 (0.80) 47 AB	0.83 (0.72) 38 B	0.50 (0.71) 33 B
SC-58635 100MG BID PRN	0.20 (0.33) 86 A	0.45 (0.88) 87 A	0.48 (0.71) 84 A	0.48 (0.78) 87 B	0.65 (0.74) 56 AB	0.52 (0.73) 46 B	0.48 (0.88) 36 B
PLACEBO	0.34 (0.84) 58 A	0.53 (0.70) 56 A	0.47 (0.70) 56 A	0.50 (0.74) 58 B	0.48 (0.74) 51 B	0.48 (0.75) 46 B	0.41 (0.80) 34 B
TREATMENT P-VALUE (b)	0.722	0.053	0.059	0.031	0.044	0.003	0.039
TRT-BASELINE P-VALUE (c)	0.068	0.188	0.134	0.282	0.118	0.708	0.232
TRT-CENTER P-VALUE (c)	0.040	0.048	0.032	0.881	0.588	0.716	0.251
GENDER P-VALUE (b)	0.807	0.813	0.847	0.371	0.212	0.346	0.288
BASELINE P-VALUE (b)	0.006	0.005	0.006	0.024	0.031	0.006	0.036
CENTER P-VALUE (b)	0.000	0.169	0.071	0.060	0.000	0.309	0.006
SURGERY TYPE P-VALUE (d)	0.000	0.854	0.739	0.939	0.324	0.974	0.978
RMS ERROR (b)	0.489	0.853	0.708	0.788	0.744	0.741	0.750

(a) Sample size is not extrapolated.
(b) Model: PID = mu + TI + PI(O)[] + interaction term + center + error. (d) Model: PID = mu + TI + PI(O)[] + center + error.
(c) Based on model (b) LSmeans. Treatments within the same center + error. (d) Model: PID = mu + TI + PI(O)[] + center + effect term + center * error.
letter are not significantly different from each other.

1 FINAL PID.SAS Wednesday, 20th May 1998 Page 2 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

TABLE 9
PAIN INTENSITY DIFFERENCE (PID), CATEGORICAL SCALE, EXTRAPOLATED - BOCF, SINGLE DOSE) (CONTINUED)

MEAN PID SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PID
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCET N-100 QID PRN	0.81 (0.88) 30(a) A(a)	0.42 (0.78) 20 A	0.31 (0.71) 13 A	0.21 (0.63) 9 AB	0.18 (0.61) 8 A	0.15 (0.54) 5 A	0.13 (0.53) 4 A
SC-58635 200MG BID PRN	0.41 (0.77) 27 B	0.34 (0.74) 14 AB	0.38 (0.77) 12 A	0.34 (0.71) 10 A	0.31 (0.71) 9 A	0.28 (0.64) 8 A	0.21 (0.55) 7 A
SC-58635 100MG BID PRN	0.42 (0.87) 16 B	0.27 (0.57) 8 B	0.21 (0.58) 12 AB	0.18 (0.45) 9 B	0.14 (0.47) 6 A	0.07 (0.40) 4 A	0.09 (0.36) 2 A
PLACEBO	0.22 (0.75) 24 B	0.12 (0.42) 5 B	0.05 (0.29) 3 B	0.03 (0.26) 1 B	0.03 (0.26) 1 A	0.03 (0.28) 1 A	0.03 (0.28) 1 A
TREATMENT P-VALUE (b)	0.018	0.025	0.022	0.033	0.082	0.073	0.270
TRT*BASELINE P-VALUE (c)	0.080	0.399	0.406	0.156	0.188	0.113	0.740
TRT*CENTER P-VALUE (c)	0.330	0.037	0.006	0.001	0.001	0.113	0.306
BASELINE P-VALUE (d)	0.770	0.684	0.744	0.524	0.777	0.186	0.185
CENTER P-VALUE (b)	0.007	0.781	0.860	0.474	0.464	0.686	0.688
SURGERY TYPE P-VALUE (d)	< 0.001	< 0.001	< 0.001	< 0.001	0.004	0.013	0.025
MSE ERROR (b)	0.986	0.532	0.875	0.795	0.859	0.933	0.988
	0.725	0.583	0.573	0.512	0.520	0.467	0.439

(a) Sample size is not extrapolated.
(b) Model: mu + Ti + P1(0) + interaction term + center + error. (c) Model: PID = mu + Ti + P1(0) + center + error.
(d) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other

Table 9: Pain Intensity Difference (BOCF) – Single Dose Analysis
Page 3 of 3

Table 10: Pain Intensity Difference (BOCF) – Multiple Dose Analysis
Page 1 of 3

1 FINAL PID.SAS Wednesday, 20th May 1998 Page 1 of 3

SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 10
PAIN INTENSITY DIFFERENCE (PID, CATEGORICAL SCALE, EXTRAPOLATED - BOCF, MULTIPLE DOSE)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY).

MEAN PID SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PID

Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCET N-100 QID PRN	0.23 (0.48) 81(81) A(a)	0.44 (0.67) 81 A	0.72 (0.76) 80 A	0.80 (0.80) 81 A	0.82 (0.80) 53 A	0.89 (0.89) 47 A	0.78 (0.91) 44 A
SC-58635 200MG BID PRN	0.22 (0.50) 58 A	0.22 (0.62) 57 A	0.48 (0.75) 57 A	0.66 (0.83) 58 AB	0.69 (0.80) 47 AB	0.63 (0.72) 39 B	0.50 (0.71) 33 B
SC-58635 100MG BID PRN	0.26 (0.53) 66 A	0.45 (0.68) 64 A	0.46 (0.71) 67 A	0.46 (0.78) 67 B	0.63 (0.74) 58 AB	0.52 (0.73) 46 B	0.46 (0.68) 38 B
PLACEBO	0.34 (0.54) 58 A	0.53 (0.70) 58 A	0.47 (0.70) 58 A	0.50 (0.74) 58 B	0.48 (0.74) 51 B	0.46 (0.75) 46 B	0.41 (0.80) 31 B
TREATMENT P-VALUE (b)	0.722	0.053	0.058	0.031	0.044	0.003	0.014
TRT*BASELINE P-VALUE (c)	0.066	0.168	0.134	0.202	0.518	0.708	0.247
INIT-CENTER P-VALUE (c)	0.440	0.848	0.832	0.691	0.516	0.216	0.150
GENDER P-VALUE (b)	0.667	0.813	0.847	0.371	0.232	0.340	0.371
BASELINE P-VALUE (b)	0.005	0.003	0.005	0.024	0.021	0.340	0.358
CENTER P-VALUE (b)	0.006	0.869	0.071	0.060	< 0.001	0.109	0.005
SURGERY TYPE P-VALUE (d)	0.000	0.854	0.730	0.939	< 0.001	0.926	0.913
RMS ERROR (b)	0.490	0.653	0.708	0.768	0.744	0.741	0.752

(a) Sample size is not extrapolated.
(c) Model: PID = mu + TI + PI(0)) + interaction term + center * error (b) Model: PID = mu + TI + PI(0)) + center * error (d) Model: PID = mu + TI + PI(0)) + effect term + center * error
(a) Letters are not significantly different from each other.

Table 10: Pain Intensity Difference (BOCF) – Multiple Dose Analysis
Page 2 of 3

I FINAL PID.SAS Wednesday, 20th May 1998 Page 2 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-98-02-028

TABLE 10
PAIN INTENSITY DIFFERENCE (PID, CATEGORICAL SCALE, EXTRAPOLATED - BOCF, MULTIPLE DOSE) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEAN PID SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

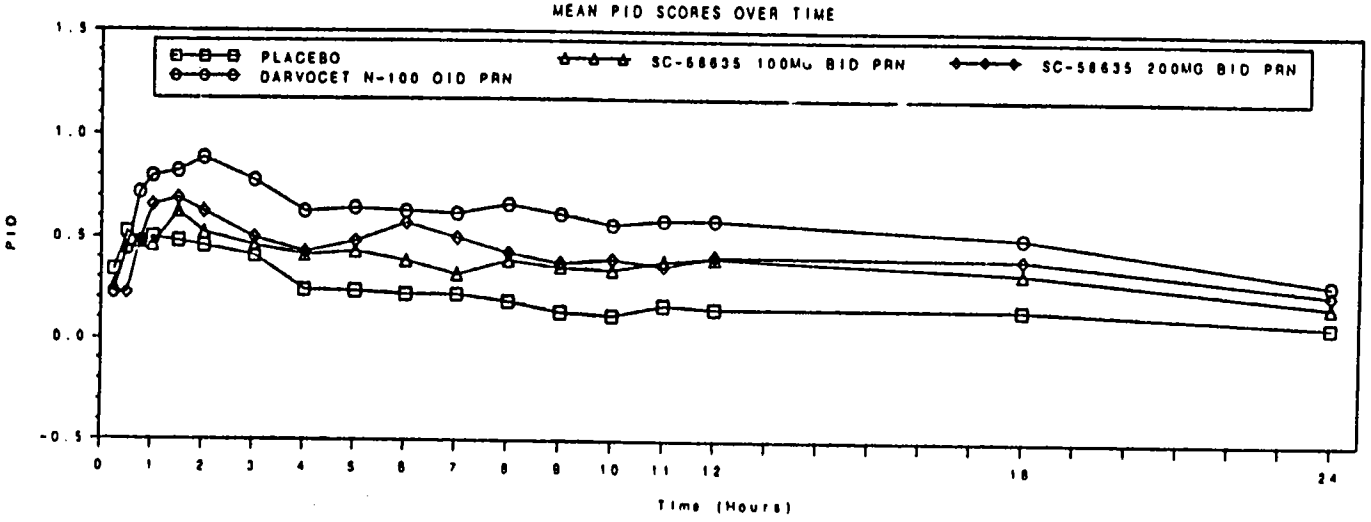
PID
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCET N-100 QID PRN	0.63 (0.87) 40[a] A[a]	0.65 (0.87) 38 A	0.63 (0.85) 34 A	0.62 (0.83) 33 A	0.67 (0.84) 33 A	0.62 (0.85) 30 A	0.57 (0.75) 31 A
SC-58635 200MG BID PRN	0.43 (0.77) 28 B	0.48 (0.80) 26 AB	0.57 (0.88) 23 AB	0.50 (0.82) 20 AB	0.43 (0.84) 18 B	0.38 (0.75) 20 B	0.40 (0.75) 17 AB
SC-58635 100MG BID PRN	0.42 (0.87) 33 B	0.43 (0.83) 33 B	0.39 (0.89) 33 BC	0.32 (0.87) 28 B	0.39 (0.88) 28 B	0.36 (0.89) 28 B	0.34 (0.86) 25 B
PLACEBO	0.24 (0.76) 25 B	0.24 (0.60) 24 B	0.22 (0.56) 17 C	0.22 (0.53) 15 B	0.18 (0.51) 13 B	0.14 (0.47) 11 B	0.12 (0.49) 10 B
TREATMENT P-VALUE (b)	0.017		0.008	0.005	0.001	< 0.001	
TRT*BASELINE P-VALUE (c)	0.021		0.594	0.857	0.702	0.830	0.971	0.002
TRT*CENTER P-VALUE (c)	0.025		0.042	0.008	0.004	0.024	0.201	0.066
GENDER P-VALUE (d)	0.188		0.610	0.710	0.006	0.955	0.070	0.368
BASELINE P-VALUE (b)	0.270		0.960	0.883	0.705	0.997	0.917	0.277
CENTER P-VALUE (b)	< 0.001		< 0.001	< 0.001	0.002	0.001	< 0.001	0.813
SURGERY TYPE P-VALUE (d)	0.503		0.411	0.420	0.486	0.790	0.613	0.001
RMS ERROR (b)	0.724		0.670	0.722	0.698	0.685	0.860	0.860
								0.631

(a) Sample size is not extrapolated.
(c) Model: mu + T[i] + P[(i)] + interaction term + center + error (b) Model: PID = mu + T[i] + P[(i)] + center + error
(d) Based on model (b) Lsmeans Treatments with the same letter are not significantly different from each other

SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 10
PAIN INTENSITY DIFFERENCE (PID, CATEGORICAL SCALE, EXTRAPOLATED - BOCF, MULTIPLE DOSE) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)



ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	11.00	12.00	18.00	24.00
DARVOCET N-100 OID PRN	0.59 (0.79) 28[a] A[c]	0.59 (0.90) 29 A	0.51 (0.80) 21 A	0.29 (0.64) 14 A
SC-58635 200MG BID PRN	0.38 (0.74) 17 B	0.41 (0.75) 16 AB	0.40 (0.79) 12 AB	0.24 (0.60) 11 A
SC-58635 100MG BID PRN	0.39 (0.67) 23 B	0.40 (0.70) 20 B	0.34 (0.64) 15 B	0.18 (0.44) 14 A
PLACEBO	0.17 (0.50) 8 B	0.15 (0.55) 7 B	0.13 (0.55) 4 B	0.08 (0.34) 4 A

TREATMENT p-VALUE (b)	0.005	0.007	0.018	0.138
TRT*BASELINE p-VALUE [c]	0.641	0.779	0.587	0.676
TRT*CENTER p-VALUE (c)	0.091	0.105	0.088	0.310
GENDER p-VALUE (d)	0.251	0.401	0.858	0.669
BASELINE p-VALUE (b)	0.883	0.571	0.578	0.439
CENTER p-VALUE (b)	< 0.001	< 0.001	< 0.001	0.003
SURGERY TYPE p-VALUE (d)	0.818	0.462	0.161	0.004
RMS ERROR (b)	0.642	0.700	0.636	0.501

(a) Sample size is not extrapolated.
(b) Model: PID = mu + TI + PI(0)] + center + error.
(c) Model: PID = mu + TI + PI(0)] + interaction term + center + error
(d) Model: PID = mu + TI + PI(0)] + effect term + center + error.
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

Table 11: Pain Intensity Difference (LOCF) – Single Dose Analysis

1 FINAL PID.SAS Wednesday, 20th May 1998 Page 1 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-95-02-028

TABLE 11
PAIN INTENSITY DIFFERENCE (PID, CATEGORICAL SCALE, EXTRAPOLATED - LOCF, SINGLE DOSE)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEAN PID SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PID
1.5
1.0
0.5
0.0
-0.5
0
0.5
1
1.5
2
3
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCET N-100 QID PRN	0.23 (0.48) 81(a) A(c)	0.44 (0.67) 81 A	0.72 (0.76) 80 A	0.80 (0.80) 81 A	0.84 (0.87) 53 A	0.82 (0.91) 47 A	0.83 (0.93) 43 A
SC-58635 200MG BID PRN	0.22 (0.50) 58 A	0.22 (0.82) 57 AB	0.48 (0.78) 57 A	0.68 (0.83) 58 AB	0.88 (0.87) 47 AB	0.83 (0.82) 36 B	0.55 (0.80) 33 B
SC-58635 100MG BID PRN	0.28 (0.53) 88 A	0.45 (0.88) 87 A	0.48 (0.71) 87 A	0.48 (0.78) 87 B	0.57 (0.82) 58 B	0.49 (0.82) 46 B	0.43 (0.80) 38 B
PLACEBO	0.34 (0.54) 58 A	0.53 (0.70) 58 A	0.47 (0.70) 58 A	0.50 (0.74) 58 B	0.50 (0.74) 51 B	0.44 (0.78) 46 B	0.38 (0.88) 34 B
TREATMENT P-VALUE (b)	0.228		0.058	0.031	0.039	< 0.001	0.002
TRT*BASELINE P-VALUE (c)	0.086	0.188	0.134	0.282	0.738	0.845	0.806
TRT*CENTER P-VALUE (c)	0.849	0.840	0.832	0.661	0.216	0.427	0.345
GENDER P-VALUE (d)	0.000	0.813	0.847	0.371	0.287	0.464	0.188
BASELINE P-VALUE (b)	0.006	0.005	0.006	0.024	0.012	0.006	0.001
CENTER P-VALUE (b)	0.000	0.169	0.071	0.060	< 0.001	< 0.001	< 0.001
SURGERY TYPE P-VALUE (d)	0.000	0.854	0.739	0.939	0.287	0.701	0.005
RMS ERROR (b)	0.488	0.853	0.708	0.768	0.772	0.738	0.810

(a) Sample size is not extrapolated.
(b) Model: PID = mu + TI + PI(0)| + interaction term + center + error.
(c) Based on model (b) LSmeans, Treatments with the same letter are not significantly different from each other.
(d) Model: PID = mu + TI + PI(0)| + center + error + effect term +

1 FINAL PID SAS Wednesday, 20th May 1998 Page 2 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 11
PAIN INTENSITY DIFFERENCE (PID, CATEGORICAL SCALE, EXTRAPOLATED - LOCF, SINGLE DOSE) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEAN PID SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PID
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCET N-100 QID PRN	0.21 (0.81) 36[a] A[c]	0.63 (0.89) 20 A	0.61 (0.91) 13 A	0.53 (0.88) 9 A	0.52 (0.88) 8 A	0.48 (0.84) 5 A	0.48 (0.84) 4 A
SC-58635 200MG BID PRN	0.50 (0.88) 27 AB	0.50 (0.88) 14 AB	0.53 (0.88) 12 AB	0.52 (0.88) 10 AB	0.52 (0.88) 9 AB	0.47 (0.84) 6 AB	0.41 (0.80) 7 AB
SC-58635 100MG BID PRN	0.40 (0.78) 36 AB	0.33 (0.75) 18 BC	0.31 (0.77) 12 BC	0.25 (0.71) 8 BC	0.24 (0.72) 6 BC	0.18 (0.70) 4 B	0.18 (0.70) 2 B
PLACEBO	0.10 (0.65) 24 B	0.10 (0.82) 5 B	0.15 (0.78) 3 C	0.15 (0.78) 1 C	0.15 (0.78) 1 C	0.15 (0.78) 1 B	0.15 (0.78) 1 B
TREATMENT P-VALUE (b)	< 0.001		0.004	0.010	0.018	0.018	0.023
TRT*CENTER P-VALUE [c][e]	0.385		0.438	0.518	0.538	0.542	0.654
CENTER P-VALUE [e]	0.144		0.442	0.182	0.127	0.100	0.360
BASELINE P-VALUE [e]	0.123		0.006	0.506	0.491	0.540	0.360
CENTER*TYPE P-VALUE [b]	< 0.001		< 0.001	0.001	< 0.001	< 0.001	0.183
SURGERY TYPE P-VALUE (d)	< 0.001		< 0.001	0.006	0.012	< 0.001	< 0.001
RMS ERROR (b)	0.224		0.117	0.089	0.056	0.039	0.039
	0.788		0.765	0.782	0.771	0.755	0.745

(a) Sample PID is not originalized.
(c) Model: PID = mu + Ti + Si + Interaction term + center + error. (b) Model: PID = mu + Ti + Pi[Si] + center + error.
(e) Based on model (b) LSmeans(Oli) + Interaction term + center + error. (d) Model: PID = mu + Ti + Pi[Si] + center + error.
Testing are not significantly different from each other.

1 FINAL PID.SAS Wednesday, 20th May 1998 Page 3 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 11
PAIN INTENSITY DIFFERENCE (PID, CATEGORICAL SCALE, EXTRAPOLATED - LOCF, SINGLE DOSE) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEAN PID SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PID
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 11.00	12.00	10.00	24.00
DARVOCET N-100 QID PRN	$0_{5}^{.48}$ (0.84) A(b)	$0_{3}^{.40}$ (0.84) A	$0_{0}^{.46}$ (0.82) A	$0_{0}^{.45}$ (0.82) A
SC-58635 200MG BID PRN	$0_{6}^{.40}$ (0.78) AB	$0_{8}^{.38}$ (0.77) AB	$0_{4}^{.38}$ (0.77) AB	$0_{2}^{.38}$ (0.77) AB
SC-58635 100MG BID PRN	$0_{2}^{.18}$ (0.70) B	$0_{2}^{.18}$ (0.70) B	$0_{4}^{.18}$ (0.70) B	$0_{1}^{.19}$ (0.70) B
PLACEBO	$0_{1}^{.15}$ (0.78) B	$0_{1}^{.15}$ (0.78) B	$0_{1}^{.15}$ (0.78) B	$0_{1}^{.14}$ (0.75) B
TREATMENT P-VALUE (b)	0.028	0.028	0.043	0.038
INIT.BASELINE P-VALUE (c)	0.885	0.638	0.664	0.619
CENTER P-VALUE (d)	0.480	0.494	0.518	0.514
GENDER P-VALUE (b)	0.188	0.185	0.226	0.207
BASELINE P-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001
SURGERY TYPE P-VALUE (b)	0.048	0.052	0.064	0.049
RMS ERROR (b)	0.136	0.105	0.068	0.048
	0.745	0.740	0.734	0.725

(a) Sample PID, 18 not extrapolated.
(c) Based on model: PID = mu + PID(0) + Interaction term + center + error. (b) Model: PID = mu + FI + PID(0) + center + error
Tests, are not significantly different from each other. (d) Model: PID = mu + FI + PID(0) + center + error term.

Table 12: Pain Intensity Difference (LOCF) – Multiple Dose Analysis
Page 1 of 3

1 FINAL PID.SAS Wednesday, 20th May 1998 Page 1 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

PAIN INTENSITY DIFFERENCE (PID, CATEGORICAL SCALE, EXTRAPOLATED - LOCF, MULTIPLE DOSE)
TABLE 12
MEANS (STANDARD DEVIATIONS). SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEAN PID SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PID
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCET N-100 QID PRN	0.23 (0.48) 81	0.44 (0.87) 81 A(a)	0.72 (0.76) 80 A	0.80 (0.80) 81 A	0.84 (0.87) 53 A	0.92 (0.91) 47 A	0.83 (0.83) 44 A
SC-58635 200MG BID PRN	0.22 (0.50) 58 A	0.22 (0.62) 57 A	0.48 (0.75) 57 A	0.66 (0.83) 58 A	0.66 (0.87) 47 AB	0.63 (0.82) 38 B	0.55 (0.80) 33 B
SC-58635 100MG BID PRN	0.26 (0.53) 88 A	0.45 (0.88) 87 A	0.48 (0.71) 84 A	0.46 (0.78) 87 B	0.57 (0.82) 58 B	0.49 (0.82) 48 B	0.45 (0.80) 38 B
PLACEBO	0.34 (0.54) 58 A	0.53 (0.70) 58 A	0.47 (0.70) 58 A	0.50 (0.74) 58 B	0.50 (0.74) 51 B	0.44 (0.79) 46 B	0.38 (0.81) 34 B
TREATMENT P-VALUE (b)	0.282	0.053	0.038	0.031	0.033	< 0.001	0.002
TRT*BASELINE P-VALUE (c)	0.046	0.188	0.134	0.622	0.784	0.845	0.602
TRT*CENTER P-VALUE (c)	0.046	0.848	0.832	0.847	0.816	0.427	0.346
GENDER P-VALUE (d)	0.857	0.813	0.847	0.371	0.257	0.164	0.168
BASELINE P-VALUE (b)	0.006	0.003	0.005	0.024	0.012	0.005	0.001
CENTER P-VALUE (b)	0.006	0.166	0.071	0.080	< 0.001	< 0.001	< 0.001
SURGERY TYPE P-VALUE (d)	0.990	0.654	0.739	0.939	0.991	0.718	0.505
RMS ERROR (b)	0.489	0.653	0.708	0.768	0.772	0.789	0.810

(a) Sample size is not constant/pooled.
(b) Model: PID = mu + TI + PI(TI) + interaction term + center + error (c) Model: PID = mu + TI + PI(TI) + center + error term
(d) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

1 FINAL PID.SAS
Wednesday, 20th May 1998
Page 2 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028
TABLE 12
PAIN INTENSITY DIFFERENCE (PID, CATEGORICAL SCALE, EXTRAPOLATED - LOCF, MULTIPLE DOSE) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
MEAN PID SCORES OVER TIME
PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN
PID
Time (Hours)
TREATMENT
ASSESSMENT TIME POINTS (IN HOURS)
4.00
5.00
6.00
7.00
8.00
9.00
10.00
DARVOCET N-100 QID PRN
SC-58635 200MG BID PRN
SC-58635 100MG BID PRN
PLACEBO
TREATMENT P-VALUE (b)
INT*BASELINE P-VALUE (c)
INT*CENTER P-VALUE (d)
GENDER P-VALUE (b)
BASELINE P-VALUE (b)
CENTER P-VALUE (b)
SURGERY TYPE P-VALUE (d)
AGE (CENTERED) P-VALUE (b)
(a) Sample size is not appropriate
(b) Model: PID = mu + TI + PI(G) + center + error (d) Model: PID = mu + TI + PI(G) + center + error + surgery type
(c) Based on model (b) LSmeans(d) TI*center interaction term
(e) Entries are not significantly different from each other

Table 12: Pain Intensity Difference (LOCF) – Multiple Dose Analysis
Page 3 of 3

I FINAL PID.SAS Wednesday, 20th May, 1998 Page 3 of 3

SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 12
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
PAIN INTENSITY DIFFERENCE (PID, CATEGORICAL SCALE, EXTRAPOLATED - LOCF, MULTIPLE DOSE) (CONTINUED)

MEAN PID SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PID
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 11.00	12.00	18.00	24.00
DARVOCET N-100 QID PRN	0.85 (0.80) 28(a) A(c)	0.85 (1.00) 28 A	0.70 (0.95) 21 A	0.55 (0.90) 14 A
SC-58635 200MG BID PRN	0.48 (0.88) 17 AB	0.53 (0.84) 18 AB	0.57 (0.91) 12 AB	0.48 (0.82) 11 AB
SC-58635 100MG BID PRN	0.34 (0.86) 23 B	0.38 (0.86) 20 BC	0.31 (0.84) 15 BC	0.21 (0.76) 14 BC
PLACEBO	0.17 (0.81) 8 C	0.15 (0.85) 7 C	0.17 (0.85) 4 C	0.12 (0.74) 4 C
TREATMENT P-VALUE (b)	0.003	0.004	< 0.001	0.002
TRT.*BASELINE P-VALUE (c)	0.738	0.503	0.551	0.389
TRT.*CENTER P-VALUE (d)	0.449	0.561	0.383	0.235
GENDER P-VALUE (b)	0.072	0.001	0.464	0.143
RACE P-VALUE (b)	< 0.001	0.002	< 0.001	< 0.001
BASELINE P-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001
CENTER P-VALUE (b)	< 0.001	< 0.001	< 0.001	0.004
SURGERY TYPE P-VALUE (d)	0.381	0.343	0.234	0.037
RMS ERROR (b)	0.788	0.850	0.810	0.763

(a) Sample size - not extrapolated
(b) Model: PID = mu + TI + PI(01) + Interaction term + center + error (b) Model: PID = mu + TI + PI(01) + center + error
(c) Based on model (b) LSmeans(01), treatments with the same letter are not statistically different from each other
(d) Model: PID = mu + TI + PI(01) + center + error + effect term

Mean Pain Relief Scores Over Time

Tables 13 and 14 present the mean PR scores for the first 24 hours for the BOCF single dose and multiple dose analyses, respectively. Mean scores for celecoxib 100 mg BID PRN and 200 mg BID PRN were numerically greater than placebo at 0.75 through 24 hours postdose in both the single dose and multiple dose analyses. However, these differences were statistically significant only at the 4.0 hour (BOCF single dose) and 5.0 (BOCF multiple dose) for celecoxib 100 mg BID PRN and only at 6.0 hours (BOCF single dose) and 9.0 hours (BOCF multiple dose) for celecoxib 200 mg BID PRN compared to placebo.

Tables 15 and 16 present the mean PR scores for the first 24 hours for the LOCF single dose and multiple dose analyses, respectively. Mean scores for celecoxib 100 mg BID PRN and 200 mg BID PRN were numerically greater than placebo at 0.75 through 24 hours postdose in both the single dose and multiple dose analyses. These differences were statistically significant for celecoxib 100 mg BID PRN at 4.0 and 5.0 hours (LOCF single dose) and at 4.0, 5.0, 9.0 through 12.0 and 24 hours (LOCF multiple dose) compared to placebo. These differences were statistically significant for celecoxib 200 mg BID PRN at 4.0, 6.0, 7.0, and 24 hours (LOCF single dose) and 4.0 through 12.0 and 24 hours (LOCF multiple dose) compared to placebo.

Within the celecoxib treatment groups, the mean PR scores for the celecoxib 200 mg BID PRN group were numerically greater than for the celecoxib 100 mg BID PRN group at 0.75 through 3.0, and 6.0 through 24 hours (BOCF single dose) and 0.75 through 3.0, 6.0 through 9.0 and 24 hours postdose (BOCF multiple dose). In the LOCF analyses mean PR scores for celecoxib 200 mg BID PRN were numerically greater than for celecoxib 100 mg BID PRN at 0.75 through 1.5, 3.0 and 5.0 through 24 hours (LOCF single dose) and at 0.75 through 1.5, 3.0 and 6.0 through 24 hours (LOCF multiple dose). None of these differences between the celecoxib treatment groups were statistically significant (Tables 13-16).

The mean PR scores for Darvocet-N® 50 (2 tablets) QID PRN were statistically significant compared to placebo at the 2.0 through 6.0 assessment times for the BOCF single dose analysis; the 2.0 through 18.0 hour assessment times for the BOCF multiple dose analysis; the 2.0 through 7.0 and 24 hour assessments for the LOCF single dose analysis; and at the 2.0 through 24 hour assessment times for the LOCF multiple dose analysis (Tables 13-16).

The mean PR scores for Darvocet-N® 50 (2 tablets) QID PRN for the BOCF single dose analysis were statistically significant at the 5.0 hour assessment time compared to celecoxib 200 mg BID PRN and at the 2.0 and 5.0 hour assessment times compared to celecoxib 100 mg BID PRN (Table 13). The mean PR scores for Darvocet-N® 50 (2 tablets) QID PRN for the BOCF multiple dose analysis were statistically significant at the 5.0, 10.0, 11.0, and 18.0 hour assessment times compared to celecoxib 200 mg BID PRN

and at the 2.0, 3.0, and 6.0 through 11.0 and 18 hour assessment times compared to celecoxib 100 mg BID PRN (Table 14).

In the LOCF analyses the mean PR scores for Darvocet-N® 50 (2 tablets) QID PRN for the LOCF multiple dose analysis were only statistically significant at the 6.0 and 18.0 hour assessment times compared to celecoxib 100 mg BID PRN.

There were statistically significant effects for center and surgery type as well as a treatment by center interaction at various timepoints. Further subgroup analyses were performed for the time-specific primary efficacy measures by center and surgery type. These analyses did not reveal any consistent pattern across timepoints (Tables 13-16).

Overall, for the BOCF (single dose and multiple dose) and LOCF (single dose and multiple dose) analyses, celecoxib was numerically greater in mean PR scores compared to placebo. However, this superiority did not show any statistically significant consistency over the first 24 hours and did not show statistically significant superiority at all during the first 3 hours postdose. Darvocet-N® 50 (2 tablets) QID PRN was statistically significant superior compared to placebo at the 2.0 though 6.0 hour assessment times for the BOCF single dose analysis; at the 2.0 through 18.0 hour assessment times for the BOCF multiple dose analysis; at the 2.0 through 7.0 and 24 hour assessments for the LOCF single dose analysis; and at the 2.0 through 24 hour assessment times for the LOCF multiple dose analysis, thus validating this pain model for the first 24 hours.

Table 13: Pain Relief (BOCF) – Single Dose Analysis
Page 1 of 3

1 FINAL PID SAS Wednesday, 20th May 1998 Page 2 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 13
PAIN RELIEF (PR, EXTRAPOLATED - BOCF, SINGLE DOSE) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEAN PR SCORES OVER TIME

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCET N-100 QID PRN	1.30 (1.40) 39(a) A(b)	0.87 (1.40) 20 A	0.60 (1.26) 13 A	0.39 (1.05) 9 A	0.27 (0.94) 6 A	0.23 (0.84) 5 A	0.16 (0.73) 4 A
SC-58635 200MG BID PRN	1.00 (1.38) 27 A	0.68 (1.33) 14 A	0.69 (1.38) 12 A	0.64 (1.37) 10 A	0.59 (1.30) 8 A	0.55 (1.28) 8 A	0.47 (1.13) 7 A
SC-58635 100MG BID PRN	1.12 (1.35) 30 A	0.86 (1.24) 18 A	0.48 (1.12) 12 AB	0.36 (0.98) 9 A	0.28 (0.95) 6 A	0.19 (0.80) 4 A	0.19 (0.80) 2 A
PLACEBO	0.58 (0.88) 24 B	0.17 (0.65) 5 B	0.12 (0.59) 3 B	0.07 (0.52) 1 A	0.07 (0.52) 1 A	0.07 (0.52) 1 A	0.07 (0.52) 1 A
TREATMENT P-VALUE (b)	0.013	0.004	0.032	0.081	0.082	0.050	0.123
TRT-CENTER P-VALUE (c)	0.100	0.149	0.033	0.011	< 0.001	0.028	0.298
GENDER P-VALUE (d)	0.711	0.834	0.862	0.940	0.874	0.638	0.358
CENTER P-VALUE (d)	0.001	0.001	< 0.001	< 0.001	0.002	0.004	0.039
SURGERY TYPE P-VALUE (d)	0.103	0.103	0.374	0.258	0.385	0.264	0.193
RMS ERROR (b)	1.250	1.083	1.028	0.955	0.931	0.861	0.807

(a) Sample size is not extrapolated.
(c) Model: PR = mu + i + interaction term + center + error.
(d) Based on model (b) LSmeans. Letters are not significantly different from each other

(b) Model: PR = mu + TT + center + error.
(d) Model: PR = mu + TT + effect term + center + error.

Table 13: Pain Relief (BOCF) – Single Dose Analysis
Page 3 of 3

Table 14: Pain Relief (BOCF) – Multiple Dose Analysis
Page 1 of 3

I FINAL PID.SAS Wednesday, 20th May 1998 Page 1 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 14
PAIN RELIEF (PR, EXTRAPOLATED - BOCF, MULTIPLE DOSE)
SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEANS, (STANDARD DEVIATIONS), MEAN PR SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PR
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCET N-100 QID PRN	0.88 (0.83) 81(b) A(c)	1.06 (1.10) 81 A	1.44 (1.28) 80 A	1.83 (1.37) 81 A	1.83 (1.41) 53 A	1.69 (1.48) 47 A	1.54 (1.43) 44 A
SC-58635 200MG BID PRN	0.83 (0.78) 81 A	0.81 (1.01) 81 A	1.28 (1.18) 57 A	1.41 (1.35) 58 A	1.48 (1.38) 46 A	1.30 (1.30) 36 AB	1.17 (1.38) 33 AB
SC-58635 100MG BID PRN	0.72 (0.80) 80 A	1.01 (1.04) 81 A	1.22 (1.14) 84 A	1.39 (1.14) 87 A	1.39 (1.25) 58 A	1.28 (1.35) 48 B	1.16 (1.31) 38 B
PLACEBO	0.59 (0.87) 56 A	1.03 (1.07) 56 A	1.19 (1.07) 58 A	1.25 (1.15) 58 A	1.12 (1.16) 51 A	1.03 (1.19) 48 B	0.83 (1.23) 34 B
TREATMENT P-VALUE (b)	0.238	0.820	0.510	0.330	0.107	0.028	0.022
TRT*CENTER P-VALUE (c)	0.418	0.709	0.299	0.384	0.112	0.388	0.324
GENDER P-VALUE (d)	0.846	0.819	0.687	0.346	0.755	0.225	0.834
CENTER P-VALUE (b)	0.210	0.508	0.107	0.294	0.002	0.020	0.016
SURGERY TYPE P-VALUE (d)	0.210	0.631	0.534	0.294	0.416	0.830	0.220
RMS ERROR (b)	0.884	1.056	1.161	1.248	1.258	1.299	1.311

(a) Sample size is not extrapolated.
(b) Model PR = mu + interaction term + center + error
(c) Based on model (b), LSmeans of treatments with the same letter are not significantly different from each other.
(d) Model: PR = mu + TT + center + error, - error

Table 14: Pain Relief (BOCF) – Multiple Dose Analysis
Page 2 of 3

1 FINAL PID.SAS Wednesday, 20th May 1998 Page 2 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 14
PAIN RELIEF (PR) EXTRAPOLATED - BOCF, MULTIPLE DOSE (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEAN PR SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PR
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCET N-100 QID PRN	1.32 (1.30) 40[B] A[B]	1.45 (1.47) 36 A	1.50 (1.52) 34 A	1.31 (1.40) 33 A	1.35 (1.44) 33 A	1.27 (1.44) 30 A	1.19 (1.34) 31 A
SC-58635 200MG BID PRN	1.03 (1.30) 28 AB	0.88 (1.40) 26 BC	1.12 (1.49) 25 AB	1.02 (1.49) 26 AB	0.95 (1.48) 19 AB	0.95 (1.43) 20 AB	0.85 (1.34) 17 B
SC-58635 100MG BID PRN	1.12 (1.35) 31 AB	1.10 (1.32) 30 AB	0.94 (1.33) 33 B	0.83 (1.25) 28 B	0.82 (1.34) 28 B	0.93 (1.39) 28 BC	0.88 (1.32) 25 B
PLACEBO	0.83 (1.04) 25 B	0.65 (1.00) 24 C	0.57 (1.08) 17 B	0.51 (1.07) 15 B	0.49 (1.09) 13 B	0.41 (0.88) 11 C	0.37 (1.02) 10 B
TREATMENT P-VALUE (b)	0.023	0.003	< 0.001	0.003	0.002	0.002	< 0.002
TRT*CENTER P-VALUE (c)	0.128	0.077	0.047	0.007	0.066	0.153	0.002
GENDER P-VALUE (d)	0.862	0.370	0.477	0.624	0.251	0.648	0.940
CENTER P-VALUE (e)	< 0.001	< 0.001	< 0.001	0.001	< 0.001	< 0.001	< 0.001
SURGERY TYPE P-VALUE (e)	0.985	0.097	0.092	0.214	0.193	0.426	0.007
RMS ERROR (b)	1.253	1.240	1.309	1.261	1.278	1.236	1.160

(a) Sample size is not extrapolated.
Model on mu = TI + interaction term + center + error.
(b) Based on model (b) LSmeans, treatments within the same letter are not significantly different from each other.
(b) Model: PR = mu + TI + center + error.
(b) Model: PR = mu + TI + effect term + center + error.

Table 14: Pain Relief (BOCF) – Multiple Dose Analysis
Page 3 of 3

I FINAL PID.SAS Wednesday, 20th May 1998 Page 3 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 14
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
PAIN RELIEF (PR, EXTRAPOLATED - BOCF, MULTIPLE DOSE) (CONTINUED)

MEAN PR SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PR
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 11.00	12.00	18.00	24.00
DARVOCET N-100 QID PRN	1.24 (1.42) 28[e] A[d]	1.10 (1.48) 29 A	1.05 (1.51) 21 A	0.58 (1.25) 14 A
SC-58635 200MG BID PRN	0.87 (1.39) 15 B	0.80 (1.41) 15 AB	0.75 (1.43) 8 B	0.55 (1.14) 11 A
SC-58635 100MG BID PRN	0.88 (1.38) 23 B	0.80 (1.40) 20 AB	0.80 (1.28) 15 B	0.49 (1.04) 14 A
PLACEBO	0.37 (1.02) 8 B	0.30 (1.05) 10 B	0.30 (1.02) 8 B	0.15 (0.61) 4 A
TREATMENT P-VALUE (b)	0.002	0.004	0.008	0.117
TRT*CENTER P-VALUE [c]	0.002	0.004	0.002	0.216
GENDER P-VALUE [d]	0.882	0.885	0.984	0.835
CENTER P-VALUE [b]	< 0.001	< 0.001	< 0.001	< 0.001
SURGERY TYPE P-VALUE (d)	0.185	0.204	0.133	0.003
RMS ERROR (b)	1.257	1.281	1.234	0.881

[a] Sample size is not extrapolated.
[c] Model: PR = mu + trt*center + center + error
[e] Based on model [b] LSmeans; treatments with the same
letter are not significantly different from each other.

[b] Model: PR = mu + TI + center + error
[d] Model: PR = mu + TI + effect term + center + error

Table 15: Pain Relief (LOCF) – Single Dose Analysis
Page 1 of 3

I FINAL PID.SAS Wednesday, 20th May 1998 Page 2 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 15
PAIN RELIEF (PR, EXTRAPOLATED - LOCF, SINGLE DOSE) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEAN PR SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCET N-100 QID PRN	1.48 (1.30) 38(B) A(C)	1.30 (1.33) 20 A	1.30 (1.33) 13 A	1.20 (1.27) 9 A	1.27 (1.28) 8 A	1.24 (1.24) 5 A	1.21 (1.22) 4 A
SC-58635 200MG BID PRN	1.33 (1.32) 27 A	1.20 (1.34) 14 AB	1.34 (1.37) 12 A	1.31 (1.37) 10 A	1.26 (1.32) 8 A	1.28 (1.29) 8 A	1.21 (1.21) 7 A
SC-58635 100MG BID PRN	1.38 (1.28) 36 A	1.20 (1.20) 18 A	1.22 (1.21) 12 AB	1.13 (1.14) 8 AB	1.14 (1.17) 6 A	1.07 (1.12) 4 A	1.07 (1.12) 2 A
PLACEBO	0.77 (1.05) 24 B	0.76 (1.04) 8 B	0.75 (1.03) 5 B	0.75 (1.03) 1 B	0.75 (1.03) 1 A	0.75 (1.03) 1 A	0.75 (1.03) 1 A
TREATMENT P-VALUE (b)	0.011	0.018	0.015	0.042	0.057	0.054	0.075
TRT-CENTER P-VALUE (c)	0.125	0.347	0.318	0.176	0.181	0.412	0.492
GENDER P-VALUE (d)	0.718	0.697	0.609	0.611	0.384	0.812	0.885
CENTER P-VALUE (d)	< 0.001	< 0.001	< 0.001	0.006	0.019	0.110	0.005
SURGERY TYPE P-VALUE (d)	0.850	0.344	0.470	0.228	0.273	0.231	0.200
RMS ERROR (b)	1.204	1.156	1.183	1.171	1.178	1.121	1.112

(a) Sample size is not extrapolated.
(b) Based on model: PR = mu + TI + interaction term + center + error
(c) Based on model: LSmeans. Treatments with the same letter are not significantly different from each other.
(d) Model: PR = mu + TI + center + effect term + center * error

Table 15: Pain Relief (LOCF) – Single Dose Analysis

1 FINAL PID.SAS Wednesday, 20th May 1998 Page 3 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 15
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
PAIN RELIEF (PR, EXTRAPOLATED - LOCF, SINGLE DOSE) (CONTINUED)

MEAN PR SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PR
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 11.00	12.00	18.00	24.00
DARVOCET N-100 QID PRN	1.21 (1.22) 3 (a) A (b)	1.21 (1.22) 3 A	1.21 (1.22) 0 A	1.21 (1.22) 0 A
SC-58635 200MG BID PRN	1.19 (1.20) 4 A	1.18 (1.18) 6 A	1.17 (1.24) 4 A	1.17 (1.17) 2 A
SC-58635 100MG BID PRN	1.07 (1.12) 2 A	1.07 (1.12) 4 A	1.07 (1.12) 4 A	1.07 (1.12) 1 AB
PLACEBO	0.75 (1.03) 1 A	0.75 (1.03) 1 A	0.75 (1.03) 1 A	0.71 (0.95) 1 B
TREATMENT P-VALUE (b)	0.078	0.087	0.087	0.045
TRT*CENTER P-VALUE (c)	0.570	0.834	0.565	0.581
GENDER P-VALUE (d)	0.835	0.893	0.894	0.792
CENTER P-VALUE (b)	0.007	0.008	0.014	0.005
SURGERY TYPE P-VALUE (d)	0.253	0.195	0.226	0.203
RMS ERROR (b)	1.110	1.107	1.125	1.084

(a) Sample size is not extrapolated.
(b) Model: PR = mu + trt + interaction term + center + error
(c) Based on model (b) LSmeans, treatments within the same center are not significantly different from each other
(d) Model: PR = mu + TI + center + error
(e) Model: PR = mu + TI + effect term*center + error

Table 16: Pain Relief (LOCF) – Multiple Dose Analysis
Page 1 of 3

I FINAL PID.SAS Wednesday, 20th May 1998 Page 1 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 16
PAIN RELIEF (PR, EXTRAPOLATED - LOCF, MULTIPLE DOSE)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

MEAN PR SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PR
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCET N-100 QID PRN	0.65 (0.83) 81(a) A(b)	1.06 (1.10) 81 A	1.44 (1.29) 80 A	1.63 (1.37) 81 A	1.66 (1.38) 53 A	1.74 (1.41) 47 A	1.59 (1.35) 44 A
SC-58635 200MG BID PRN	0.83 (0.75) 57 A	0.91 (1.01) 57 A	1.20 (1.18) 57 A	1.41 (1.35) 58 A	1.50 (1.37) 46 A	1.40 (1.24) 39 AB	1.41 (1.31) 33 AB
SC-58635 100MG BID PRN	0.72 (0.80) 86 A	1.01 (1.04) 87 A	1.22 (1.14) 84 A	1.39 (1.14) 87 A	1.42 (1.23) 56 A	1.42 (1.28) 46 AB	1.38 (1.24) 38 AB
PLACEBO	0.59 (0.87) 58 A	1.03 (1.07) 58 A	1.19 (1.07) 56 A	1.25 (1.15) 58 A	1.17 (1.15) 51 A	1.10 (1.17) 46 B	0.92 (1.22) 34 B
TREATMENT P-VALUE (b)	0.736	0.820	0.510	0.330	0.118	0.028	0.022
TRT*CENTER P-VALUE (c)	0.418	0.709	0.395	0.364	0.170	0.421	0.448
GENDER P-VALUE (d)	0.886	0.919	0.687	0.346	0.858	0.235	0.853
CENTER P-VALUE (d)	0.270	0.508	0.107	0.278	0.002	0.015	0.007
SURGERY TYPE P-VALUE (d)	0.018	0.631	0.334	0.744	0.486	0.934	0.263
RMS ERROR (b)	0.884	1.056	1.161	1.240	1.240	1.251	1.256

(a) Sample size is not extrapolated.
(b) Model: PR = mu + TI + interaction term + center + error.
(c) Based on model (b) LSmeans; treatments with the same letter are not significantly different from each other.
(d) Model: PR = mu + TI + effect term + center + error.

Table 16: Pain Relief (LOCF) – Multiple Dose Analysis
Page 2 of 3

Table 16: Pain Relief (LOCF) – Multiple Dose Analysis
Page 3 of 3

1 FINAL PID.SAS Wednesday, 20th May 1998 Page 3 of 3
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028

TABLE 16
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
PAIN RELIEF (PR, EXTRAPOLATED - LOCF, MULTIPLE DOSE) (CONTINUED)

MEAN PR SCORES OVER TIME

PLACEBO
DARVOCET N-100 QID PRN
SC-58635 100MG BID PRN
SC-58635 200MG BID PRN

PR
Time (Hours)

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 12.00	18.00	24.00
DARVOCET N-100 QID PRN	1.48 (1.38) 20(a) A(a)	1.44 (1.40) 20 A	1.38 (1.43) 21 A	1.34 (1.38) 14 A
SC-58635 200MG BID PRN	1.31 (1.33) 19 A	1.31 (1.36) 18 A	1.30 (1.42) 18 AB	1.20 (1.28) 11 A
SC-58635 100MG BID PRN	1.27 (1.37) 23 A	1.28 (1.38) 20 A	1.18 (1.30) 15 B	1.13 (1.23) 14 A
PLACEBO	0.71 (1.07) 8 B	0.73 (1.11) 8 B	0.74 (1.13) 4 B	0.64 (0.92) 4 B
TREATMENT P-VALUE (b)	0.004	0.010	0.002	0.005
TRT*CENTER P-VALUE (c)	0.131	0.277	0.137	0.053
GENDER P-VALUE (d)	0.670	0.437	0.733	0.509
SURGERY-TYPE P-VALUE (d)	< 0.001	< 0.001	< 0.001	< 0.001
RMS ERROR (b)	1.224	1.249	1.252	1.157

(a) Sample size is not extrapolated.
(c) Model: PR = mu + TI + interaction term + center + error.
(d) Based on model (b) LSmeans, significants with the same letter, are not significantly different from each other.
(b) Model: PR = mu + TI + center + error.
(d) Model: PR = mu + TI + effect term + center + error