

Mean Pain Intensity Difference and Pain Relief (PRID, Categorical Scale)

Tables 17 and 18 present the mean PRID (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 in both the single dose and multiple dose analyses. These differences were statistically significant for celecoxib 200 mg BID PRN compared to placebo at the 6.0, 7.0 and 9.0 hour assessment times for the BOCF single dose and multiple dose analyses.

Tables 19 and 20 present the mean PRID (Categorical Scale) 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 200 mg BID PRN at the 4.0, 6.0 through 10.0 and 24.0 hour assessment times (LOCF single dose) and at 4.0 through 24 hours (LOCF multiple dose) compared to placebo. These differences were statistically significant for celecoxib 100 mg BID PRN at the 4.0 hour assessment time (LOCF single dose) compared to placebo.

Within the celecoxib treatment groups, the mean PRID (Categorical Scale) scores for the celecoxib 200 mg BID PRN group were numerically greater than for the celecoxib 100 mg BID PRN from 0.75 through 24 hours, except 4.0 hours (BOCF single dose) and 4.0, 5.0, 11.0 and 12.0 hours postdose (BOCF multiple dose). Except for the 9.0 hour assessment time (BOCF single dose) none of these differences were statistically significant.

In the LOCF analyses mean PRID (Categorical Scale) scores for celecoxib 200 mg BID PRN were numerically greater than for celecoxib 100 mg BID PRN at 0.75 through 24 hours for both single dose and multiple dose analyses. None of these differences were statistically significant (Tables 17-20).

The mean PRID (Categorical Scale) 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; 2.0 through 18 hour assessment times for the BOCF multiple dose analysis; and at 2.0 through 24 hour assessment times for the LOCF single dose and multiple dose analyses (Tables 17-20).

The mean PRID (Categorical Scale) scores for Darvocet-N[®] 50 (2 tablets) QID PRN for the BOCF single dose analysis were statistically significant at the 2.0 hour assessment time compared to celecoxib 200 mg BID PRN and at the 2.0, 3.0 and 5.0 hour assessment times compared to celecoxib 100 mg BID PRN (Table 17). The mean PRID (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, 5.0 and 8.0 through 11.0 hour assessment times compared to celecoxib 200 mg BID PRN and at the 2.0, 3.0, 5.0 through 11.0 and 18 hour assessment times compared to celecoxib 100 mg BID PRN (Table 18).

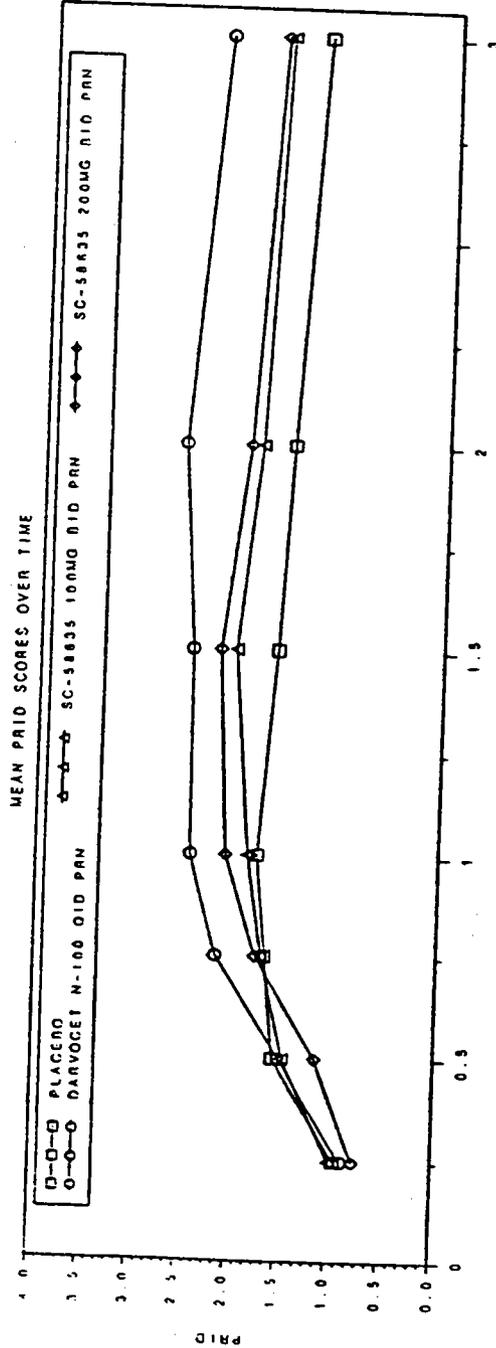
The mean PRID (Categorical Scale) scores for Darvocet-N[®] 50 (2 tablets) QID PRN for the LOCF (single dose and multiple dose) analyses were statistically significant at the 2.0 hour assessment time compared to celecoxib 200 mg BID PRN for both single dose and multiple dose analyses (Tables 17-18). The mean PRID (Categorical Scale) scores for Darvocet-N[®] 50 (2 tablets) QID PRN were statistically significant compared to celecoxib 100 mg BID PRN at the 2.0, 3.0, 5.0 and 6.0 hour assessment times for the LOCF single dose analysis and at the 2.0, 3.0, 5.0 through 9.0, 11.0, 18.0 and 24 hour assessment times for the LOCF multiple dose analysis (Tables 19-20).

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 17-20).

Overall, for the BOCF (single dose and multiple dose) and LOCF (single dose and multiple dose) analyses, celecoxib was numerically greater in mean PRID 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 2.0 through 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; and at the 2.0 through 24 hour assessment times for the LOCF single and multiple dose analyses, thus validating this pain model for the first 24 hours.

Table 17: Pain Intensity Difference and Pain Relief (PRID) (BOCF) – Single Dose Analysis
Page 1 of 3

TABLE 17
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID) CATEGORICAL SCALE, EXTRAPOLATED - BOCF, SINGLE DOSE)
MEANS (STANDARD DEVIATIONS). SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)

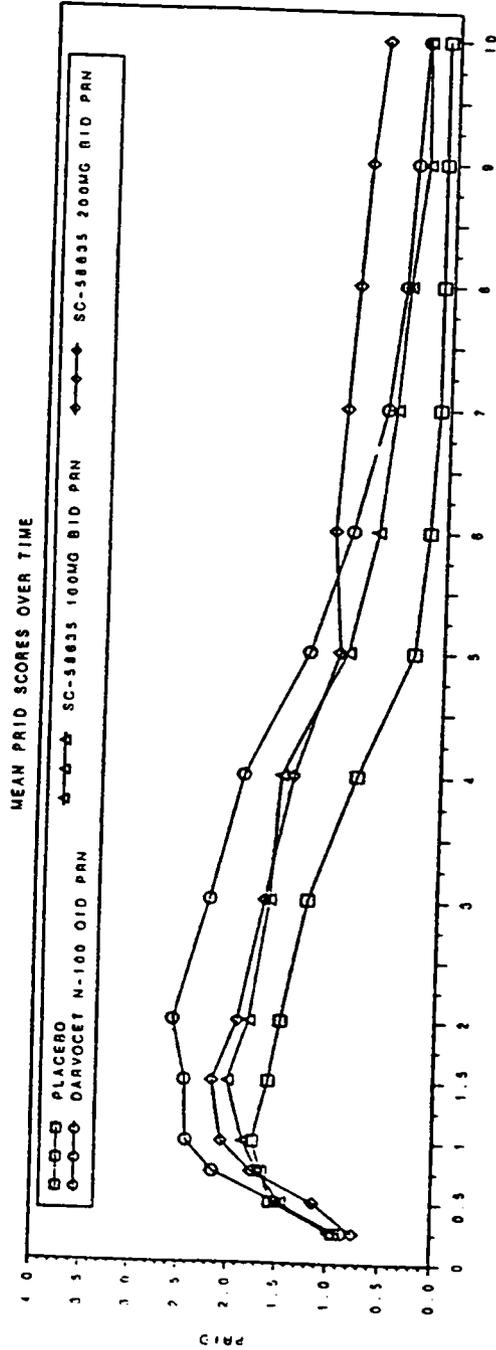


TREATMENT	ASSESSMENT TIME POINTS (IN HOURS)											
	0.25	0.50	0.75	1.00	1.50	2.00	3.00					
DARVOCECT N-100 OID PRN	0.87 (1.59) 81 (8)	1.50 (1.63) 81 (8)	2.15 (1.98) 81 (8)	2.43 (2.08) 81 (8)	2.45 (2.17) 81 (8)	2.58 (2.21) 81 (8)	2.23 (2.21) 81 (8)					
SC-58835 200MG BID PRN	0.78 (1.08) 81 (8)	1.14 (1.50) 81 (8)	1.78 (1.81) 81 (8)	2.07 (2.07) 81 (8)	2.17 (2.08) 81 (8)	2.92 (1.95) 81 (8)	3.07 (2.04) 81 (8)					
SC-58835 100MG BID PRN	0.88 (1.30) 81 (8)	1.48 (1.61) 81 (8)	1.70 (1.72) 81 (8)	1.95 (1.82) 81 (8)	2.01 (1.88) 81 (8)	2.81 (1.98) 81 (8)	3.62 (1.90) 81 (8)					
PLACEBO	0.93 (1.27) 81 (8)	1.56 (1.67) 81 (8)	1.88 (1.83) 81 (8)	1.75 (1.77) 81 (8)	1.60 (1.77) 81 (8)	1.49 (1.84) 81 (8)	3.25 (1.86) 81 (8)					
TREATMENT P-VALUE (b)	0.814	0.417	0.294	0.148	0.071	0.012	0.077					
TRT-BASELINE P-VALUE (c)	0.681	0.285	0.270	0.148	0.071	0.012	0.077					
TRT-CENTER P-VALUE (c)	0.901	0.800	0.873	0.873	0.468	0.850	0.979					
BASELINE P-VALUE (a)	0.901	0.800	0.873	0.873	0.468	0.850	0.979					
CENTER P-VALUE (a)	0.901	0.800	0.873	0.873	0.468	0.850	0.979					
SURGERY TYPE P-VALUE (d)	0.322	0.056	0.056	0.056	0.001	0.008	0.008					
RMS ERROR (b)	0.149	0.149	0.149	0.149	0.149	0.149	0.149					
	0.226	0.226	0.226	0.226	0.226	0.226	0.226					

Model: PRID = mu + T + P | O | S + error. (b) Model: PRID = mu + T + P | O | S + error. (c) Model: PRID = mu + T + P | O | S + error. (d) Model: PRID = mu + T + P | O | S + error.

Table 17: Pain Intensity Difference and Pain Relief (PRID) (BOCF) – Single Dose Analysis
Page 2 of 3

PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID) (BOCF) – SINGLE DOSE (CONTINUED)
MEANS (STANDARD DEVIATIONS). SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)



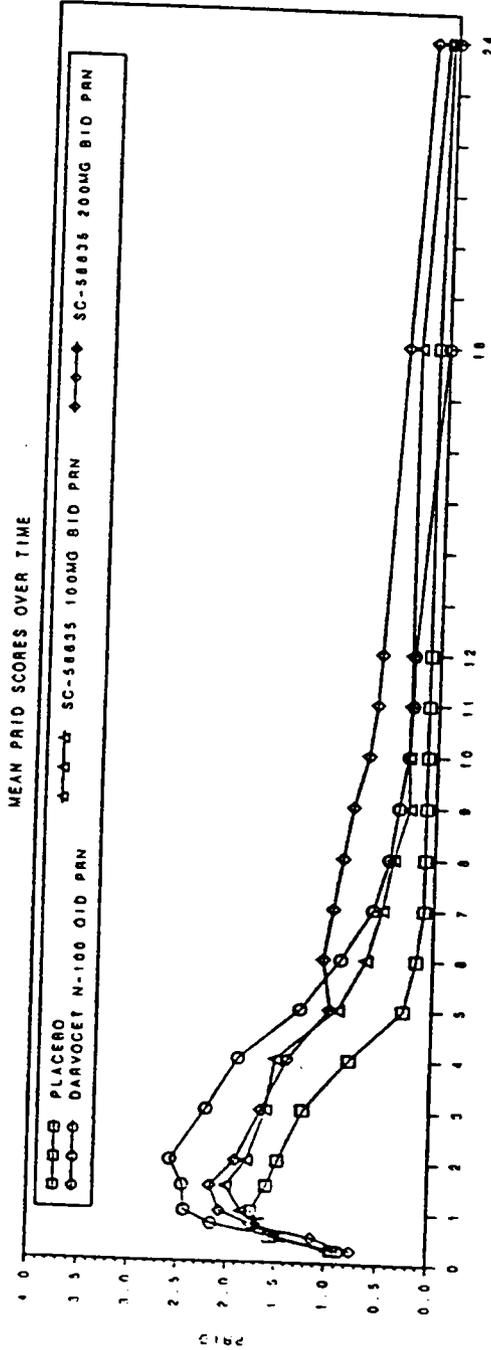
TREATMENT	4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCKET N-100 QID PRN	1.91 (2.18) 38(6) A(e)	1.29 (2.11) 20 (2.08)	1.00 (1.92) 12(7) A(b)	0.80 (1.82) 10 (1.83)	0.45 (1.53) 6(5) A(b)	0.37 (1.33) 4 (1.23)	0.29 (1.23) 4 (1.23)
SC-58635 200MG BID PRN	2.41 (2.08) 12(5) A(b)	1.00 (2.01) 12(5) A(b)	1.07 (2.13) 12(5) A(b)	0.88 (2.04) 10 (1.88)	0.80 (1.88) 8(5) A(b)	0.81 (1.88) 8(5) A(b)	0.87 (1.88) 7(5) A(b)
SC-58635 100MG BID PRN	1.93 (1.85) 12(5) A(b)	1.08 (1.77) 12(5) A(b)	0.88 (1.88) 12(5) A(b)	0.51 (1.40) 8(5) A(b)	0.41 (1.41) 6(5) A(b)	0.27 (1.19) 4(5) A(b)	0.28 (1.18) 2(5) A(b)
PLACEBO	2.01 (1.53) 12(5) A(b)	0.28 (1.03) 3 (0.97)	0.17 (0.87) 3 (0.78)	0.10 (0.78) 1(0) A(b)	0.10 (0.78) 1(0) A(b)	0.10 (0.78) 1(0) A(b)	0.10 (0.78) 1(0) A(b)
TREATMENT P-VALUE (b)	0.013	0.007	0.029	0.029	0.072	0.058	0.158
TREATMENT P-VALUE (c)	0.139	0.049	0.012	0.012	0.014	0.039	0.158
GENDER P-VALUE (b)	0.949	0.243	0.873	0.873	0.873	0.873	0.873
BASELINE P-VALUE (b)	0.243	0.243	0.201	0.201	0.201	0.201	0.201
COMPARISON P-VALUE (a)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
COMPARISON P-VALUE (a)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
RMS ERROR (b)	1.851	1.607	1.563	1.563	1.417	1.353	1.353

(b) Means that are not significantly different from each other.
(c) Means that are not significantly different from each other.
(a) Based on mean (b) LSDs for treatments with the same center.
(a) Pairwise and significantly different from each other.

Table 17: Pain Intensity Difference and Pain Relief (PRID) (BOCF) – Single Dose Analysis
Page 3 of 3

FINAL P10.SAS Wednesday, 20th May 1998
SC-58835 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028 Page 3 of 3

TABLE 17
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID) CATEGORICAL SCALE, EXTRAPOLATED - BOCF, SINGLE DOSE (CONTINUED)
HEADS (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED (SD COMPARISONS) (VERTICALLY)



TREATMENT	11.00	12.00	18.00	24.00
DARVOCECT N-100 QID PRN	0.28 (1.21)	0.26 (1.21)	0.01 (0.08)	0.00 (0.00)
SC-58835 200MG BID PRN	0.01 (1.60)	0.37 (1.53)	0.40 (1.41)	0.20 (0.91)
SC-58835 100MG BID PRN	0.28 (1.18)	0.28 (1.18)	0.28 (1.18)	0.09 (0.73)
PLACEBO	0.10 (0.78)	0.10 (0.78)	0.10 (0.78)	0.05 (0.38)

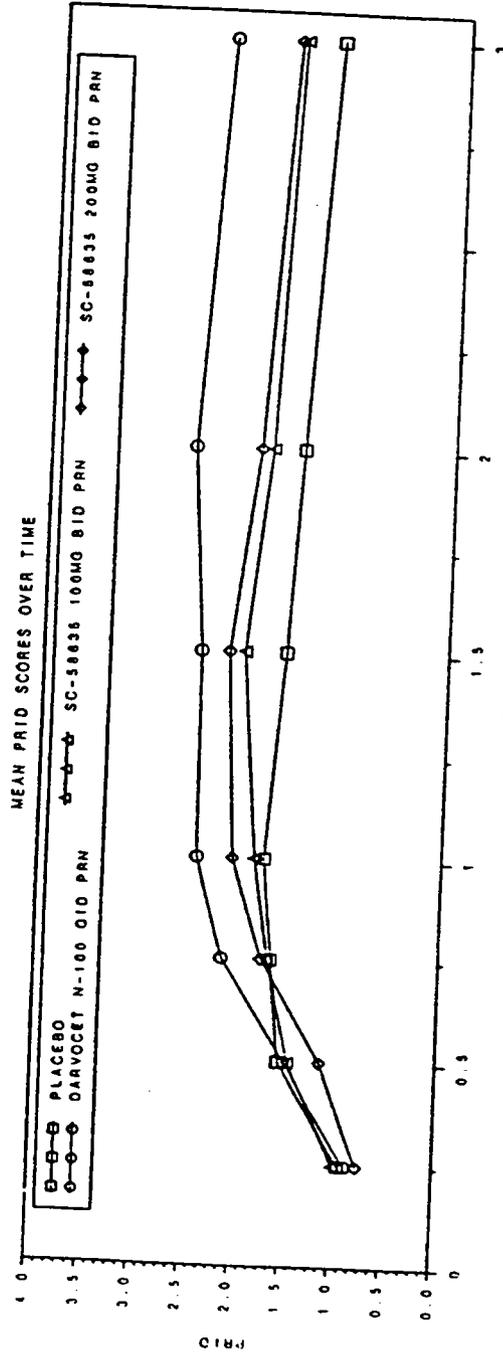
TREATMENT	P-VALUE (b)	P-VALUE (c)	P-VALUE (d)	P-VALUE (e)
PRID - BASELINE	0.272	0.239	0.272	0.272
PRID - CENTER	0.272	0.272	0.272	0.272
PRID - ERROR	0.272	0.272	0.272	0.272
PRID - TYPE	0.272	0.272	0.272	0.272
PRID - TYPE P-VALUE (a)	0.272	0.272	0.272	0.272
PRID - TYPE P-VALUE (b)	0.272	0.272	0.272	0.272
PRID - TYPE P-VALUE (c)	0.272	0.272	0.272	0.272
PRID - TYPE P-VALUE (d)	0.272	0.272	0.272	0.272
PRID - TYPE P-VALUE (e)	0.272	0.272	0.272	0.272

Model: PRID = mu + T + P110 + center + error. (b) Model: PRID = mu + T + P110 + center + error. (c) Model: PRID = mu + T + P110 + center + error. (d) Model: PRID = mu + T + P110 + center + error. (e) Model: PRID = mu + T + P110 + center + error.

Table 18: Pain Intensity Difference and Pain Relief (PRID) (BOCF)-Multiple Dose Analysis
Page 1 of 3

FINAL PID-SAS Wednesday, 20th May 1998
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N40-96-02-028 Page 1 of 3

TABLE 18
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID), CATEGORICAL SCALE, EXTRAPOLATED - BOCF, MULTIPLE DOSE
MEANS (STANDARD DEVIATIONS). SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)



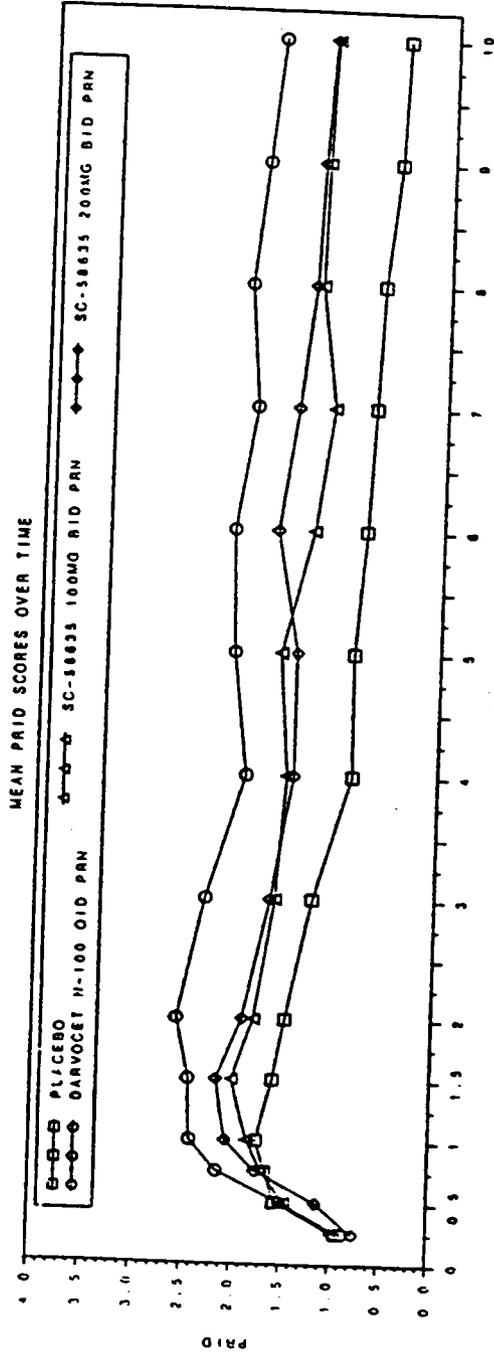
TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCKET N-100 QID PRN	0.87 (1.29)	1.30 (1.83)	2.19 (1.98)	2.43 (2.06)	2.45 (2.17)	2.58 (2.21)	2.32 (2.24)
SC-58635 200MG BID PRN	0.78 (1.08)	1.14 (1.50)	1.78 (1.81)	2.07 (2.07)	2.17 (2.08)	2.92 (1.95)	3.07 (2.04)
SC-58635 100MG BID PRN	0.88 (1.30)	1.48 (1.81)	1.70 (1.72)	1.85 (1.82)	2.01 (1.88)	1.81 (1.88)	1.82 (1.90)
PLACEBO	0.85 (1.27)	1.56 (1.87)	1.66 (1.65)	1.75 (1.77)	1.60 (1.77)	1.48 (1.84)	1.25 (1.86)

TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
TREATMENT (RE-VALUE) (b)	0.017	0.417	0.234	0.149	0.07	0.012	0.018
TREATMENT (C-VALUE) (c)	0.081	0.285	0.200	0.258	0.073	0.050	0.372
TREATMENT (D-VALUE) (d)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (E-VALUE) (e)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (F-VALUE) (f)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (G-VALUE) (g)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (H-VALUE) (h)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (I-VALUE) (i)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (J-VALUE) (j)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (K-VALUE) (k)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (L-VALUE) (l)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (M-VALUE) (m)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (N-VALUE) (n)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (O-VALUE) (o)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (P-VALUE) (p)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (Q-VALUE) (q)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (R-VALUE) (r)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (S-VALUE) (s)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (T-VALUE) (t)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (U-VALUE) (u)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (V-VALUE) (v)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (W-VALUE) (w)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (X-VALUE) (x)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (Y-VALUE) (y)	0.081	0.303	0.270	0.322	0.073	0.299	0.158
TREATMENT (Z-VALUE) (z)	0.081	0.303	0.270	0.322	0.073	0.299	0.158

Table 18: Pain Intensity Difference and Pain Relief (PRID) (BOCF)-Multiple Dose Analysis
Page 2 of 3

FINAL PID.SAS Wednesday, 20th May 1998
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-98-02-026 Page 2 of 3

TABLE 18
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID), CATEGORICAL SCALE, EXTRAPOLATED, BOCF, MULTIPLE DOSE) (CONTINUED)
MEANS (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED (SD COMPARISONS (VERTICALLY)



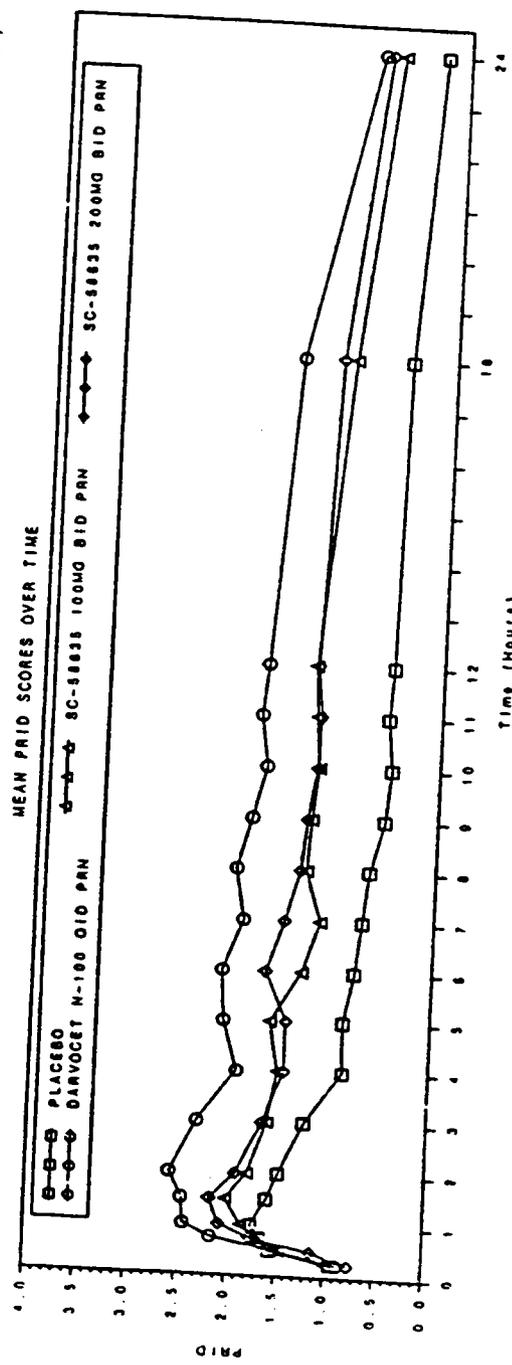
TREATMENT	4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCECT N-100 100 MG BID PRN	1.95 (2.18) 40 (b)	3.10 (2.25) 34 (b)	3.15 (2.27) 33 (2.11)	3.03 (2.11) 33 (2.11)	3.02 (2.18) 30 (2.18)	3.00 (2.18) 31 (2.18)	3.76 (1.96) 31 (1.96)
SC-58635 200MG BID PRN	2.47 (2.08) 26 (2.08)	2.47 (2.08) 26 (2.08)	2.30 (2.30) 26 (2.24)	2.02 (2.24) 26 (2.24)	1.38 (2.22) 20 (2.11)	1.33 (2.11) 20 (2.11)	1.24 (2.00) 25 (2.00)
SC-58635 100MG BID PRN	3.89 (1.85) 39 (1.87)	3.83 (1.87) 39 (1.87)	3.32 (1.87) 38 (1.81)	3.15 (1.81) 38 (1.81)	2.31 (1.93) 28 (1.93)	2.28 (2.00) 25 (2.00)	1.22 (1.91) 25 (1.91)
PLACEBO	0.87 (1.88) 25 (1.88)	0.86 (1.48) 24 (1.48)	0.76 (1.60) 19 (1.60)	0.73 (1.58) 19 (1.58)	0.68 (1.55) 13 (1.55)	0.54 (1.38) 10 (1.38)	0.49 (1.43) 10 (1.43)
TREATMENT P-VALUE (b)	0.003	0.004	0.002	0.002	0.001	< 0.001	0.000
INT. BASELINE P-VALUE (c)	0.003	0.004	0.002	0.002	0.001	< 0.001	0.000
CENTER P-VALUE (c)	0.003	0.004	0.002	0.002	0.001	< 0.001	0.000
SCHEMATA P-VALUE (b)	0.003	0.004	0.002	0.002	0.001	< 0.001	0.000
CENTER P-VALUE (b)	0.003	0.004	0.002	0.002	0.001	< 0.001	0.000
SURGERY TYPE P-VALUE (a)	0.003	0.004	0.002	0.002	0.001	< 0.001	0.000
RMS ERROR (b)	1.888	1.688	1.888	1.888	1.888	1.888	1.888

(a) Sample size is not extrapolated, interaction term + center + error. (b) Model: PRID = mu + T + P1(b) + effect term.
(c) Based on model (b) Scheffé's test; interaction term + center + error. (d) Model: PRID = mu + T + P1(b) + effect term.
Letters are not significantly different from each other.

Table 18: Pain Intensity Difference and Pain Relief (PRID) (BOCF) - Multiple Dose Analysis
Page 3 of 3

FINAL PID.SAS Wednesday, 20th May 1998
SC-58835 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-028 Page 3 of 3

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



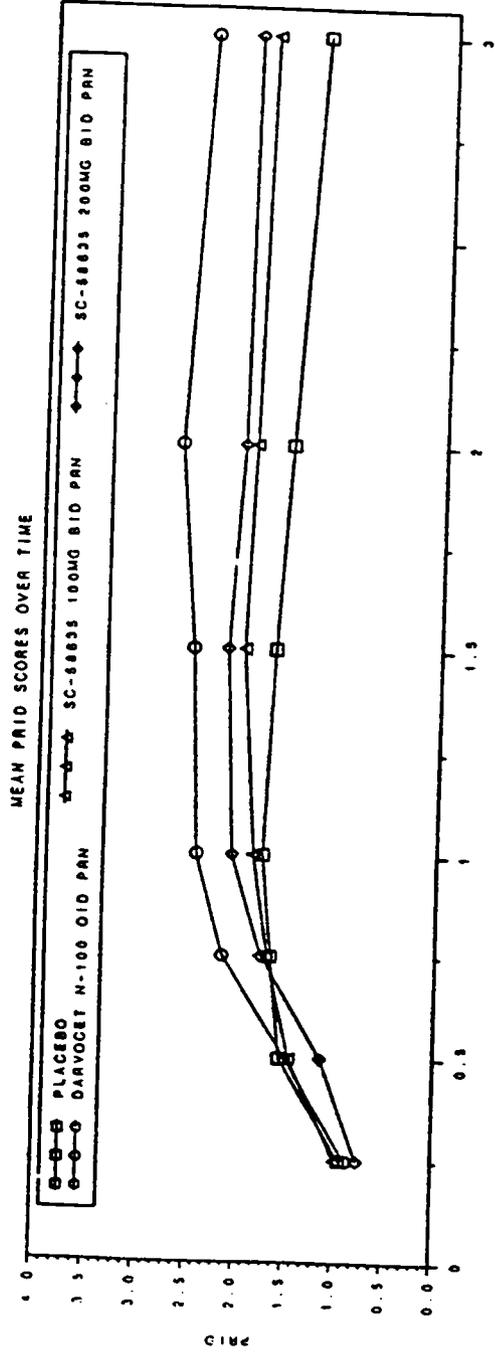
TREATMENT	ASSESSMENT TIME POINTS (IN HOURS)			
	11.00	12.00	18.00	24.00
DARVO CET N-100 QID PRN	1.82 (2.18)	1.78 (2.27)	1.96 (2.27)	0.87 (1.86)
SC-58835 200MG BID PRN	1.23 (2.05)	1.28 (2.12)	1.15 (2.20)	0.70 (1.88)
SC-58835 100MG BID PRN	1.27 (2.02)	1.30 (2.08)	1.02 (1.80)	0.87 (1.45)
PLACEBO	0.84 (1.48)	0.51 (1.58)	0.48 (1.55)	0.24 (0.83)
TREATMENT P-VALUE (a)	0.002	0.004	0.012	0.127
INT-BASELINE P-VALUE (c)	0.002	0.076	0.002	0.103
CENTER P-VALUE (e)	0.002	0.076	0.002	0.103
BASELINE P-VALUE (d)	0.002	0.076	0.002	0.103
CENTER P-VALUE (b)	0.002	0.076	0.002	0.103
SURGERY P-VALUE (f)	0.002	0.076	0.002	0.103
RMSE ERROR (b)	1.823	1.808	1.833	1.457

[a] Sample size is not extrapolated.
[c] Model: PRID = mu + pi[0] + interaction term + error. [b] Model: PRID = mu + pi[0] + center term + error.
[d] Based on model [b] (similarity of treatments with the same center). [e] Interaction term + error.
[f] Failure rate not significantly different from each other.

Table 19: Pain Intensity Difference and Pain Relief (PRID) (LOCF) – Single Dose Analysis
Page 1 of 3

I FINAL PID.SAS Wednesday, 20th May 1998
SC-58835 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-98-02-028 Page 1 of 3

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



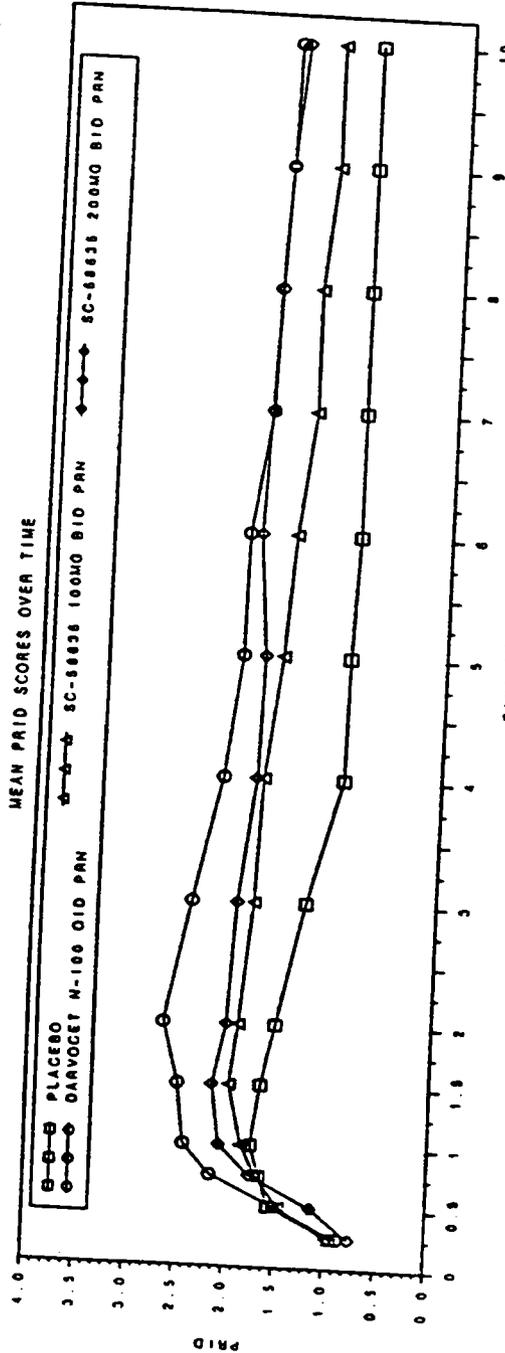
TREATMENT	0.75	1.00	1.25	1.50	1.75	2.00	2.25	2.50	2.75	3.00
DARVOCECT N-100 O10 PRN	0.87 (1.29) 618	1.10 (1.63) 618	1.15 (1.88) 618	1.43 (2.06) 618	1.50 (2.13) 618	1.66 (2.17) 618	1.72 (2.20) 618	1.88 (2.20) 618	1.97 (2.02) 618	2.02 (2.20) 618
SC-58835 200MG BID PRN	0.78 (1.00) 58	1.14 (1.50) 58	1.78 (1.81) 58	2.07 (2.07) 58	2.16 (2.13) 58	2.03 (1.96) 58	2.07 (2.02) 58	2.07 (2.02) 58	2.07 (2.02) 58	2.07 (2.02) 58
SC-58835 100MG BID PRN	0.98 (1.30) 66	1.48 (1.61) 66	1.70 (1.72) 66	1.85 (1.82) 66	1.99 (1.93) 66	1.91 (1.90) 66	1.91 (1.92) 66	1.91 (1.92) 66	1.91 (1.92) 66	1.91 (1.92) 66
PLACEBO	0.83 (1.27) 58	0.98 (1.67) 58	1.06 (1.65) 58	1.75 (1.77) 58	1.67 (1.74) 58	1.54 (1.64) 58				
TREATMENT P-VALUE (P)	0.014	0.412	0.149	0.070	0.070	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (C)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (T)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (B)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (A)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (D)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (E)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (F)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (G)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (H)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (I)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (J)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (K)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (L)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (M)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (N)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (O)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (P)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (Q)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (R)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (S)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (T)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (U)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (V)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (W)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (X)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (Y)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008
TREATMENT P-VALUE (Z)	0.081	0.285	0.258	0.513	0.513	0.007	0.008	0.008	0.008	0.008

Sample size is not extrapolated.
PRID = mean difference in PRID.
PRID = center + error. [a] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [b] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [c] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [d] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [e] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [f] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [g] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [h] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [i] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [j] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [k] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [l] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [m] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [n] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [o] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [p] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [q] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [r] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [s] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [t] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [u] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [v] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [w] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [x] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [y] Model: PRID = mu + T + P [1] [0] : center + error.
PRID = center + error. [z] Model: PRID = mu + T + P [1] [0] : center + error.

Table 19: Pain Intensity Difference and Pain Relief (PRID) (LOCF) – Single Dose Analysis
Page 2 of 3

FINAL PID.SAS Wednesday, 20th May 1998
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-96-02-026 Page 2 of 3

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



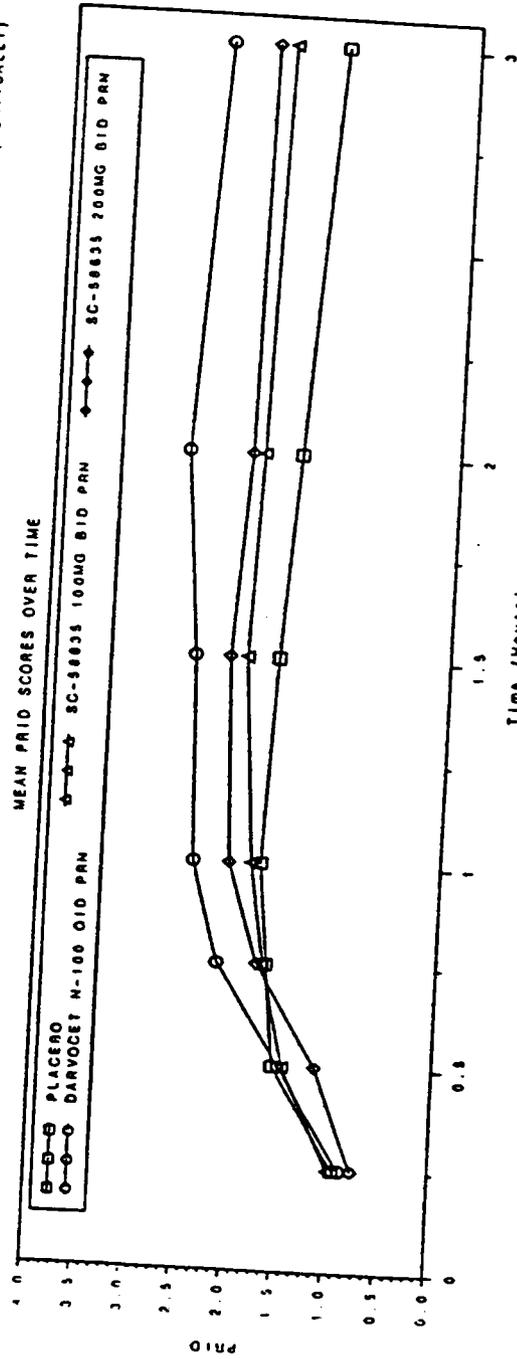
TREATMENT	4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCECT N-100 BID PRN	3.16 (2.16)	2.02 (2.07)	1.50 (2.08)	1.81 (1.88)	1.78 (1.88)	1.73 (1.88)	1.69 (1.88)
SC-58635 200MG BID PRN	2.03 (2.04)	1.78 (2.08)	1.68 (2.15)	1.83 (2.08)	1.78 (2.08)	1.72 (1.88)	1.62 (1.88)
SC-58635 100MG BID PRN	1.78 (1.88)	1.61 (1.82)	1.55 (1.87)	1.38 (1.70)	1.38 (1.70)	1.27 (1.87)	1.27 (1.87)
PLACEBO	2.06 (1.84)	3.00 (1.80)	3.00 (1.85)	3.00 (1.85)	3.00 (1.85)	3.00 (1.85)	3.00 (1.85)
TREATMENT (a) VALUE (b)	0.007	0.008	0.013	0.013	0.023	0.027	0.032
INT-CENTER VALUE (c)	0.327	0.393	0.449	0.481	0.499	0.508	0.516
SCORING P-VALUE (d)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONFIDENCE P-VALUE (e)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SURVEY P-VALUE (f)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SD (g)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SD ERROR (h)	1.848	1.757	1.712	1.712	1.717	1.728	1.739

(a) Sample size is not extrapolated.
(b) Mean PRID.
(c) Based on model (b).
(d) Fisher's protected LSD comparison.
(e) Based on model (b).
(f) Based on model (b).
(g) Standard deviation.
(h) Standard error.

Table 20: Pain Intensity Difference and Pain Relief (PRID) (LOCF)-Multiple Dose Analysis
Page 1 of 3

FINAL PID.SAS
Wednesday, 20th May 1998
SC-58833 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-98-02-028
Page 1 of 3

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



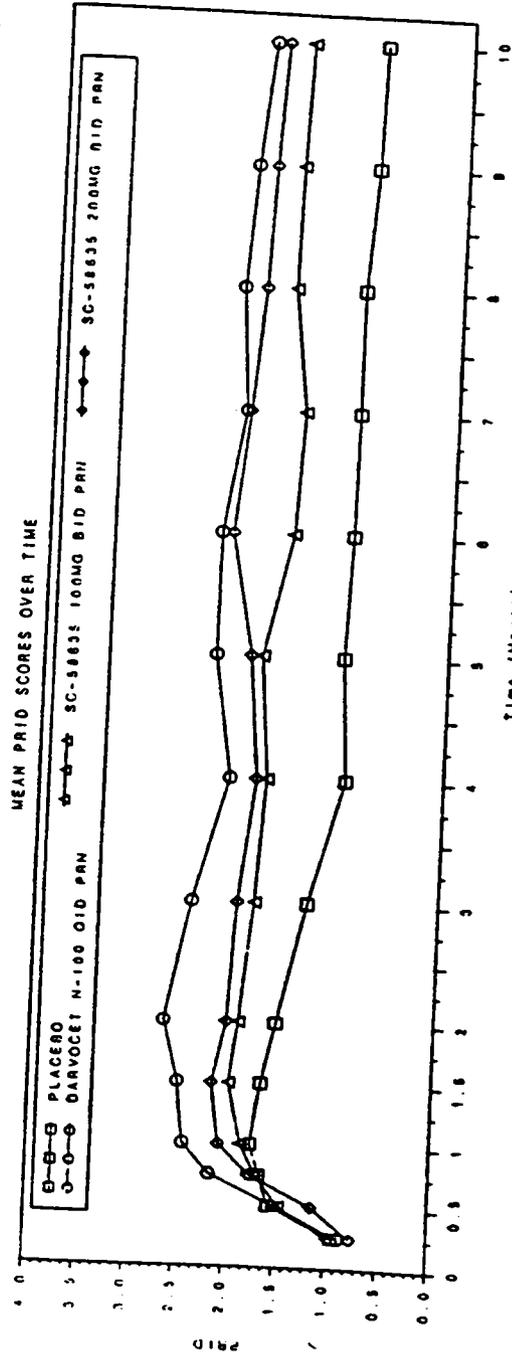
TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCE N-100 QID PRN	0.87 (1.28)	1.30 (1.63)	1.75 (1.98)	2.13 (2.06)	2.50 (2.13)	2.86 (2.17)	3.22 (2.20)
SC-58833 200MG BID PRN	0.76 (1.06)	1.14 (1.80)	1.76 (1.81)	2.07 (2.07)	2.16 (2.13)	2.03 (1.88)	1.97 (2.02)
SC-58833 100MG BID PRN	0.88 (1.30)	1.48 (1.81)	1.70 (1.72)	1.65 (1.82)	1.89 (1.82)	1.91 (1.88)	1.80 (1.82)
PLACEBO	0.83 (1.27)	1.06 (1.67)	1.06 (1.65)	1.78 (1.77)	1.67 (1.74)	1.54 (1.84)	1.28 (1.88)

TREATMENT	0.25	0.50	0.75	1.00	1.50	2.00	3.00
INT-COMPARISON P-VALUE (a)	0.017	0.017	0.017	0.017	0.017	0.017	0.017
INT-COMPARISON P-VALUE (c)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR P-VALUE (a)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR P-VALUE (c)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (a)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (c)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (b)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (d)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (e)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (f)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (g)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (h)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (i)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (j)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (k)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (l)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (m)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (n)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (o)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (p)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (q)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (r)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (s)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (t)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (u)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (v)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (w)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (x)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (y)	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GEN-ERR TYPE P-VALUE (z)	0.001	0.001	0.001	0.001	0.001	0.001	0.001

Table 20: Pain Intensity Difference and Pain Relief (PRID) (LOCF)-Multiple Dose Analysis
Page 2 of 3

FINAL PID.SAS Wednesday, 20th May 1998
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N19-96-02-028 Page 2 of 3

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

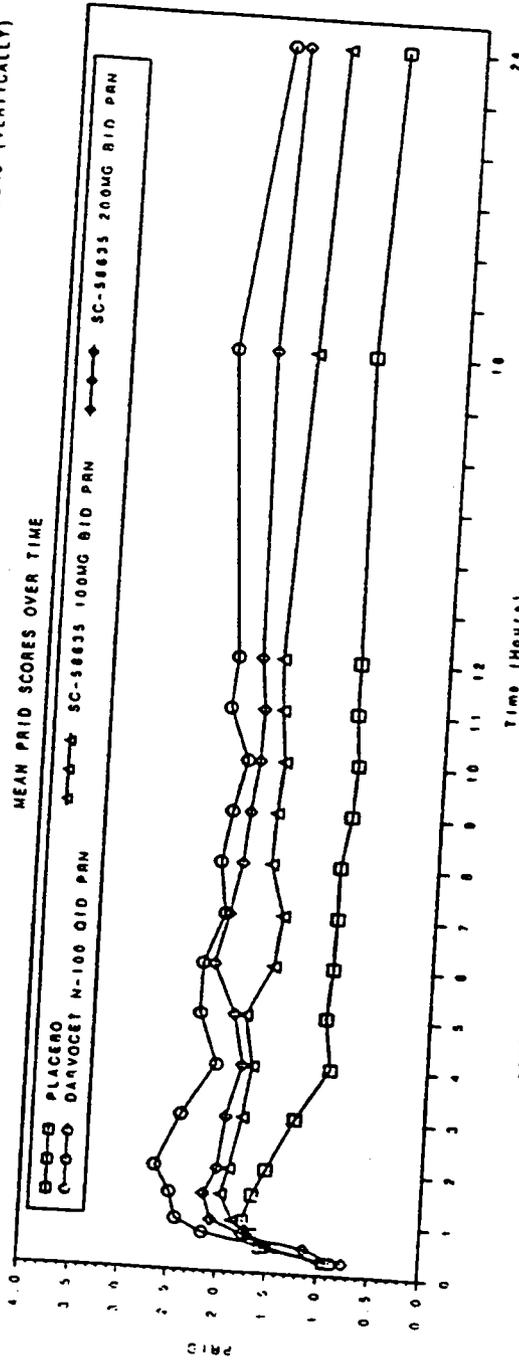


TREATMENT	4.00	3.00	6.00	7.00	8.00	9.00	10.00
DARVO CET N-100 QID PRN	2.09 (2.10) 40(6) A(6)	3.27 (2.16) 36(7) A(6)	3.27 (2.21) 35(8) A(7)	3.08 (2.07) 33(5) A(7)	3.15 (2.13) 30(6) A(7)	3.06 (2.13) 31(6) A(7)	3.04 (1.95) 31(6) A(7)
SC-58635 200MG BID PRN	2.83 (2.04) 28(5) A(6)	3.03 (2.05) 26(6) A(6)	3.18 (2.22) 25(6) A(6)	2.03 (2.17) 20(5) A(6)	1.93 (2.17) 19(5) A(6)	2.08 (2.08) 20(5) A(6)	1.81 (1.98) 17(5) A(6)
SC-58635 100MG BID PRN	3.73 (1.86) 37(2) A(6)	3.02 (1.87) 38(2) A(6)	3.58 (2.03) 35(2) A(6)	2.50 (1.91) 28(4) A(6)	2.84 (2.02) 28(4) A(6)	1.61 (2.00) 28(4) A(6)	2.57 (2.01) 25(7) A(6)
PLACEBO	0.86 (1.64) 25(6) C(6)	1.02 (1.55) 24(2) C(6)	1.08 (1.69) 19(6) C(6)	0.97 (1.69) 15(7) C(6)	0.97 (1.68) 15(7) C(6)	1.08 (1.58) 10(5) C(6)	0.85 (1.63) 10(5) C(6)
TREATMENT VALUE (a)	0.00	0.00	0.00	0.00	0.00	0.00	0.00
INT-BASELINE VALUE (b)	0.358	0.712	0.481	0.481	0.481	0.308	0.000
INT-CENTER VALUE (c)	0.358	0.712	0.481	0.481	0.481	0.308	0.000
INT-EDGE VALUE (d)	0.358	0.712	0.481	0.481	0.481	0.308	0.000
CONTRAST VALUE (e)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (f)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (g)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (h)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (i)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (j)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (k)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (l)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (m)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (n)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (o)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (p)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (q)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (r)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (s)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (t)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (u)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (v)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (w)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (x)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (y)	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CONTRAST VALUE (z)	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Table 20: Pain Intensity Difference and Pain Relief (PRID) (LOCF)-Multiple Dose Analysis
Page 3 of 3

FINAL PID.SAS
Wednesday, 20th May 1998
SC-58635 POST-ORTHOPEDIC SURGERY ANALGESIA STUDY
N49-98-02-026
Page 3 of 3

TABLE 20
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID) CATEGORICAL SCALE, EXTRAPOLATED - LOCF, MULTIPLE DOSES (CONTINUED)
MEANS (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED (SD COMPARISONS (VERTICALLY))



TREATMENT	11.00	12.00	18.00	24.00
DARVOGET N-100 BID PRN	2.14 (2.10)	2.09 (2.22)	2.28 (2.28)	1.89 (2.14)
SC-58635 200MG BID PRN	1.90 (2.04)	1.85 (2.09)	1.98 (2.10)	1.74 (1.91)
SC-58635 100MG BID PRN	2.01 (2.11)	1.94 (2.14)	1.98 (2.01)	1.54 (1.87)
PLACEBO	0.88 (1.00)	0.98 (1.73)	0.91 (1.00)	0.76 (1.44)

TREATMENT	PR-VALUE (P)	SC-VALUE (S)	LSMEAN (LS)	LS-VALUE (LS)				
SC-58635 200MG BID PRN	0.002	0.004	0.001	0.001	0.002	0.002	0.002	0.002
SC-58635 100MG BID PRN	0.002	0.004	0.001	0.001	0.001	0.001	0.001	0.001
PLACEBO	0.002	0.004	0.001	0.001	0.001	0.001	0.001	0.001

Sample size is not applicable
Data are not significantly different from each other
Interaction term center * error [a] Model: PRID = mu + T + P + [S] + center * error
[a] Model: PRID = mu + T + P + [S] + center * error

Time to Meaningful Pain Relief (see table below)

Forty three (64%) patients in the celecoxib 100 mg BID PRN group and 39 (67%) patients in the celecoxib 200 mg BID PRN group experienced meaningful pain relief compared with 35 (59%) patients in the placebo QID PRN group who experienced meaningful pain relief.

The median times to onset of meaningful pain relief in the celecoxib 100 mg BID PRN group (56 minutes) and the celecoxib 200 mg BID PRN group (43 minutes) were slightly shorter than in the placebo QID PRN group (70 minutes). This difference was not statistically significant.

Forty one patients (66%) in the Darvocet-N[®] 50 (2 tablets) QID PRN group experienced meaningful pain relief. The median time to onset of meaningful pain relief in the Darvocet-N[®] 50 (2 tablets) QID PRN group was 51 minutes. This was not statistically significantly different from the placebo QID PRN group or either of the celecoxib treatment groups.

Overall, the median time to onset of meaningful pain relief in both celecoxib treatment groups was slightly numerically less than in the placebo QID PRN group and was similar to, or slightly numerically shorter than, in the Darvocet-N[®] 50 (2 tablets) QID PRN group.

Time to Meaningful Pain Relief

Treatment	N	Patients Who Achieved Meaningful Pain Relief N (%)	Median Time In	95%- CI IN
			H : MIN (b, c)	H : MIN (d)
Darvocet N- 100 QID PRN	62	41 (66%)	00: 51 (A)	00:45 To 01:30
Celecoxib 200mg BID PRN	58	39 (67%)	00: 43 (A)	00:35 To 03:00
Celecoxib 100mg BID PRN	67	43 (64%)	00: 56 (A)	00:30 To 02:20
Placebo	59	35 (59%)	01: 10 (A)	00:46 To >24:00

(a) For patients who took rescue medication/ remediation before reaching meaningful pain relief, the time to meaningful pain relief is assigned an event time of 24.1 + 0.005/ (time rescue medication/ remediation taken - time study drug taken).

(b) Kaplan- Meier estimate (see Miller, Survival Analysis, page 75).

(c) Logrank test applied as in Fisher's Protected LSD.

Treatments with the same letter are not significantly different from each other.

(d) Method of & Lee, Cancer Treat Rep, 1982.

Time to Rescue/ Remediation (see table below)

Sixty five (97%) patients in the celecoxib 100 mg BID PRN group and 54 (93%) patients in the celecoxib 200 mg BID PRN group took rescue medication or remediation during the 24 hours following initial administration of study drug. Fifty-eight (98%) placebo patients took rescue medication or remediation during the same period.

The median times to rescue medication or remediation in the celecoxib 100 mg BID PRN group (4 hours 01 minutes) and the celecoxib 200 mg BID PRN group (3 hours 52

minutes) were numerically greater than in the placebo QID PRN group (3 hours 33 minutes). The difference was statistically significant when the celecoxib 100 mg BID PRN group was compared to placebo.

Sixty one (98%) patients in the Darvocet-N[®] 50 (2 tablets) QID PRN group took rescue medication or remediation during the 24 hours following initial administration of study drug. The median time to rescue medication or remediation in the Darvocet-N[®] 50 (2 tablets) QID PRN group (4 hours 05 minutes) was statistically significantly greater compared to the placebo QID PRN group. There were no statistically significant differences in the median times to rescue medication or remediation when the Darvocet-N[®] 50 (2 tablets) QID PRN group was compared to either celecoxib treatment group.

Time to Rescue Medication

Treatment	N	Patients Who Took Rescue/ Remediation N (%) H : MIN (c)	Median Time In H : MIN (a, b)	95%- CI IN H : MIN (c)
Darvocet N- 100 QID PRN	62	61(98%)	04: 05 (A)	04: 00 To 04: 15
Celecoxib 200mg BID PRN	58	54(93%)	03: 52 (AB)	02: 40 To 04: 05
Celecoxib 100mg BID PRN	67	65(97%)	04: 01 (A)	02: 25 To 04: 05
Placebo	59	58(98%)	03: 33 (B)	02: 58 To 04: 00

(a) Kaplan- Meier estimate (see Miller, Survival Analysis, page 75).

(b) Logrank test applied as in Fisher's Protected LSD.

Treatments with the same letter are not significantly different from each other.

(c) Method of Simon & Lee, Cancer Treat Rep, 1982.

Analysis of Secondary Efficacy Measures (as defined in the protocol)

Mean Pain Intensity Difference Scores Over Time - Visual Analog Scale

The mean PID (VAS) scores for the first 24 hours generally paralleled those of the categorical scale scores. Mean scores were statistically significant greater for celecoxib 200 mg BID PRN compared to placebo at 7.0, 8.0 and 12.0 hour assessment times for the BOCF multiple dose analysis and for the celecoxib 100 mg BID PRN compared to placebo at 12.0 hour assessment time for the BOCF multiple dose analysis.

Mean scores were statistically significant greater for celecoxib 200 mg BID PRN compared to placebo at the 6.0 through 24 hour assessment times for the LOCF multiple dose analysis and for celecoxib 100 mg BID PRN compared to placebo at the 8.0, 9.0, 10.0 and 12.0 hour assessment times for the LOCF multiple dose analysis.

None of the numerical differences between the celecoxib treatment groups were statistically significant at any assessment time.

The mean PID (VAS) scores for Darvocet-N[®] 50 (2 tablets) QID PRN were statistically significant compared to placebo at the 1.5 through 3.0, and 5.0 hour assessment times for the BOCF single dose analysis; at the 1.5 through 3.0 and 5.0 through 12.0 hour assessment times for the BOCF multiple dose analysis; at the 1.5 through 6.0 hour assessment times for the LOCF single dose analysis; and at 1.5 through 24 hour assessment times for the LOCF multiple dose analysis.

The mean PID (VAS) scores for Darvocet-N[®] 50 (2 tablets) QID PRN for the BOCF single dose analysis were statistically significant at the 1.5 and 2.0 hour assessment times compared to celecoxib 200 mg BID PRN and at the 2.0 hour assessment time compared to celecoxib 100 mg BID PRN (Table 24). The mean PID (VAS) scores for Darvocet-N[®] 50 (2 tablets) QID PRN for the BOCF multiple dose analysis were statistically significant at the 1.5 through 3.0 assessment times compared to celecoxib 200 mg BID PRN and at the 2.0, and 6.0 through 8.0 hour assessment times compared to celecoxib 100 mg BID PRN.

The mean PID (VAS) scores for Darvocet-N[®] 50 (2 tablets) QID PRN for LOCF (single dose and multiple dose) analysis were statistically significant at the 1.5 through 4.0 hour assessment times compared to celecoxib 200 mg BID PRN. The mean PID (VAS) scores for Darvocet-N[®] 50 (2 tablets) QID PRN were statistically significant compared to the celecoxib 100 mg BID PRN at the 1.5 through 3.0 and 5.0 hour assessment times for the LOCF single dose analysis and at 1.5 through 3.0, 5.0 through 7.0 and 18.0 hour assessment times for the LOCF multiple dose analysis.

Again, celecoxib demonstrated no statistically significant superiority over the placebo during the first 5 hours postdose and scattered and inconsistent statistically significant superiority over the placebo later on. Celecoxib was significantly inferior to Darvocet-N[®] 50 (2 tablets) during the first couple of hours postdose. Darvocet-N[®] 50 (2 tablets) was statistically significant better than placebo, thus validating this pain model.

Peak Pain Intensity Difference (PPID), Peak Pain Relief (PPR) and Patient Global Evaluation

There was little difference seen in the mean PPID ("my maximum pain during the last 24 hours") (Categorical Scale) scores or mean PPID (VAS) scores for all four treatment groups. The mean PPID (Categorical Scale) scores for both celecoxib treatment groups were numerically slightly less than the placebo QID PRN group. None of the differences were statistically significant.

The mean PPR ("my maximum pain relief during the last 24 hours") scores for the celecoxib 100 mg and 200 mg BID PRN and Darvocet-N 50 (2 tablets) QID PRN groups were numerically greater than the mean PPR score for the placebo QID PRN group. These differences were not statistically significant.

The mean Patient Global Evaluation scores for the celecoxib 100 mg and celecoxib 200 mg BID PRN groups were numerically but not statistically significant greater than the mean Patient Global Evaluation score for the placebo QID PRN group. The mean Patient Global Evaluation score for the celecoxib 200 mg BID PRN group was numerically statistically significant slightly greater than the mean Patient Global Evaluation score for the celecoxib 100 mg BID PRN group.

The mean Patient Global Evaluation score for the Darvocet-N[®] 50 (2 tablets) QID PRN group was statistically significant greater than the mean Patient Global Evaluation scores for the placebo QID PRN group and for both celecoxib treatment groups.

Sum of Pain Intensity Difference (SPID) (Categorical Scale) (4, 6, 8, 12, and 24 Hours)
Mean SPID (Categorical Scale) scores for the celecoxib 100 mg BID PRN and 200 mg BID PRN groups were numerically greater than placebo at all assessment times (4, 6, 8, 12, and 24 hours) for both the BOCF single dose and multiple dose analyses. However, there were no statistically significant differences between the celecoxib treatment groups and the placebo QID PRN group at any assessment time for either analysis.

Mean SPID (Categorical Scale) scores for the celecoxib 100 mg BID PRN and 200 mg BID PRN groups were numerically greater than placebo at all assessment times (4, 6, 8, 12, and 24 hours) in both the LOCF single dose and multiple dose analyses. However, these differences were statistically significant for the LOCF multiple dose analysis for the celecoxib 200 mg BID PRN group compared to placebo only at the 24 hour assessment.

Within the celecoxib treatment groups, the mean SPID (Categorical Scale) scores for the celecoxib 200 mg BID PRN group were numerically greater than the mean SPID (Categorical Scale) scores for the celecoxib 100 mg BID PRN group at all assessment times (4, 6, 8, 12, and 24 hours) for both the BOCF (single dose and multiple dose) and the LOCF (single dose and multiple dose) analyses. None of these differences were statistically significant at any assessment time.

The mean SPID (Categorical Scale) scores for the Darvocet-N[®] 50 (2 tablets) QID PRN group were statistically significant better compared to placebo at the 4, 6, 8, and 12 hour assessment times for the BOCF single dose analysis, and at all assessment times (4, 6, 8, 12, and 24 hours) for the BOCF multiple dose analysis and for the LOCF single dose and multiple dose analyses (Tables 29-32).

The mean SPID (Categorical Scale) scores for the Darvocet-N[®] 50 (2 tablets) QID PRN group were statistically significant better compared to the celecoxib 200 mg BID PRN group at the 4 and 6 hour assessments, and at the 4, 6, 8, and 12 hour assessments compared to the celecoxib 100 mg BID PRN group for the BOCF single dose analysis. The mean SPID (Categorical Scale) scores for the Darvocet-N[®] 50 (2 tablets) QID PRN group were statistically significant better compared to both celecoxib treatment groups at all assessments (4, 6, 8, 12, and 24 hours) for the BOCF multiple dose analysis.

Overall, SPID (Categorical Scale) scores were consistent with the previous results, demonstrating statistically significant superiority of Darvocet-N[®] 50 (2 tablets) but not celecoxib over the placebo.

Sum of Pain Intensity Difference (SPID) (VAS) (4, 6, 8, 12, and 24 Hours)

SPID (VAS) scores were comparable with the SPID (Categorical Scale) scores, demonstrating statistically significant superiority of Darvocet-N[®] 50 (2 tablets) but not celecoxib over the placebo.

Total Pain Relief (TOTPAR) (4, 6, 8, 12, and 24 Hours)

Mean TOTPAR scores for the celecoxib 100 mg BID PRN and 200 mg BID PRN groups were numerically greater than placebo at all assessment times for the first 24 hours (4, 6, 8, 12, and 24 hours) for both the BOCF single dose and multiple dose analyses. However, these differences were statistically significant only for the celecoxib 200 mg BID PRN group compared to placebo at the 8 and 12 hour assessments for the BOCF single dose analysis.

Mean TOTPAR scores for the celecoxib 100 mg BID PRN and 200 mg BID PRN groups were numerically greater than placebo at all assessment times (4, 6, 8, 12, and 24 hours) in both the LOCF single dose and multiple dose analyses. These differences were statistically significant for the celecoxib 200 mg BID PRN group compared to placebo at the 8, 12, and 24 hour assessments for the LOCF single dose analysis, and at the 6, 8, 12, and 24 hour assessments for the LOCF multiple dose analysis.

Within the celecoxib treatment groups, the mean TOTPAR scores for the celecoxib 200 mg BID PRN group were numerically greater than the mean TOTPAR scores for the celecoxib 100 mg BID PRN group at some assessment times, however, none of these differences were statistically significant at any assessment time.

The mean TOTPAR scores for the Darvocet-N[®] 50 (2 tablets) QID PRN group were statistically significant compared to placebo at the 4, 6, 8, and 12 hour assessment times for the BOCF single dose analysis, and at all assessment times (4, 6, 8, 12, and 24 hours) for the BOCF multiple dose analysis and for the LOCF single dose and multiple dose analyses.

The mean TOTPAR score for the Darvocet-N[®] 50 (2 tablets) QID PRN group was statistically significant compared to the celecoxib 100 mg BID PRN group at the 6 hour assessment for the BOCF single dose analysis. The mean TOTPAR scores for the Darvocet-N[®] 50 (2 tablets) QID PRN group were statistically significant compared to the celecoxib 100 mg BID PRN group at the 6, 8, 12, and 24 hours assessments for the BOCF multiple dose analysis. The mean TOTPAR scores for the Darvocet-N[®] 50 (2 tablets) QID PRN group for the LOCF single dose and multiple dose analyses were not statistically significant at any assessment time (4, 6, 8, 12, and 24 hours) compared to either celecoxib treatment group.

Overall, for both the BOCF (single dose) and the LOCF (single dose and multiple dose), celecoxib 200 mg (but not 100 mg) demonstrated statistically significant superiority over the placebo at some of the assessment times. Darvocet-N[®] 50 (2 tablets) was consistently superior over the placebo.

Sum of PID (Categorical Scale) and Pain Relief (SPRID) (4, 6, 8, 12, and 24 Hours)

Mean SPRID scores for the celecoxib 100 mg BID PRN and 200 mg BID PRN groups were numerically greater than placebo at all assessment times for the first 24 hours (4, 6, 8, 12, and 24 hours) for both the BOCF single dose and multiple dose analyses. However, these differences were statistically significant for only the BOCF single dose analysis for the celecoxib 200 mg BID PRN group compared to placebo at the 8 and 12 hour assessments.

Mean SPRID scores for the celecoxib 100 mg BID PRN and 200 mg BID PRN groups were numerically greater than placebo at all assessment times for the first 24 hours (4, 6, 8, 12, and 24 hours) in both the LOCF single dose and multiple dose analyses. These differences were statistically significant at the 8, 12, and 24 hour assessments for the celecoxib 200 mg BID PRN group compared to placebo for the LOCF single dose analysis, and at the 6, 8, 12, and 24 hour assessments for the celecoxib mg BID PRN group compared to placebo for the LOCF multiple dose analysis.

Within the celecoxib treatment groups, the mean SPRID scores for the celecoxib 200 mg BID PRN group were numerically greater than the mean SPRID scores for the celecoxib 100 mg BID PRN group at some assessment times, however, none of these differences were statistically significant at any assessment time.

The mean SPRID scores for the Darvocet-N[®] 50 (2 tablets) QID PRN group were statistically significant better compared to placebo at the 4, 6, 8, and 12 hour assessments for the BOCF single dose analysis, and at all assessment times (4, 6, 8, 12, and 24 hours) for the BOCF multiple dose analysis and for the LOCF (single dose and multiple dose) analyses.

The mean SPRID scores for the Darvocet-N[®] 50 (2 tablets) QID PRN group were statistically significant compared to the celecoxib 100 mg BID PRN group at the 4, 6, and 8 hour assessments for the BOCF single dose analysis. The mean SPRID scores for the Darvocet-N[®] 50 (2 tablets) QID PRN group were statistically significant better compared to the celecoxib 100 mg BID PRN group at all assessments (4, 6, 8, 12, and 24 hours), and at the 4, 6, 8, and 12 hour assessments compared to the celecoxib 200 mg BID PRN group for the BOCF multiple dose analysis.

The mean SPRID scores for the Darvocet-N[®] 50 (2 tablets) QID PRN group were statistically significant compared to the celecoxib 100 mg BID PRN group at the 4, 6, 8, and 12 hour assessments for the LOCF single dose analysis, and at all assessments (4, 6, 8, 12, and 24 hours) compared to the celecoxib 100 mg BID PRN group for the LOCF multiple dose analysis.

Overall, for both the BOCF (single dose) and the LOCF (single dose and multiple dose), celecoxib 200 mg (but not 100 mg) demonstrated statistically significant superiority over the placebo at some of the assessment times. Darvocet-N[®] 50 (2 tablets) was consistently superior over the placebo.

Time First Experienced at Least 50% Pain Relief

Thirty seven (55%) patients in the celecoxib 100 mg BID PRN group and 33 (57%) patients in the celecoxib 200 mg BID PRN group experienced at least 50% pain relief compared to 35 (59%) patients in the placebo QID PRN group.

The differences in median time to 50% pain relief in the celecoxib 100 mg (1 hour 46 minutes), celecoxib 200 mg BID PRN groups (2 hours), Darvocet-N[®] 50 (2 tablets) QID PRN group (51 minutes), and the placebo QID PRN group (1 hour 40 minutes) were not statistically significant.

Proportion of Patients Experiencing at Least 50% Pain Relief (0.25-24 Hours)

The proportion of patients who experienced at least 50% pain relief in the celecoxib 100 mg and 200 mg BID PRN groups was consistently numerically greater than the proportion of patients who experienced at least 50% pain relief in the placebo QID PRN group at the 3 through 24 hour assessments. However, these differences were statistically different only when the celecoxib 200 mg BID PRN group was compared to placebo at the 8 through 10 hour and the 24 hour assessments. There were no statistically significant differences between the celecoxib 100 mg BID PRN group and placebo at any time point.

The proportion of patients who experienced at least 50% pain relief in the Darvocet-N[®] 50 (2 tablets) QID PRN group was statistically significantly greater compared to placebo at the 2 through 6 hour, and the 8 through 24 hour assessments. The proportion of patients in the Darvocet-N[®] 50 (2 tablets) QID PRN group who experienced at least 50% pain relief was statistically significantly greater compared to the celecoxib 100 mg BID PRN group at the 2, 5, 6, and 11 through 18 hour assessments and at the 2 hour assessment compared to the celecoxib 200 mg BID PRN group.

Number and Proportion of Patients Needing 0, 1, 2, or 3 Remedications Within the First 24 Hours

(For patients in the celecoxib 100 mg and 200 mg BID PRN groups the second and third remedication doses were placebo).

Proportion of Patients Needing 0, 1, 2, or 3 Remedications Within the First 24 Hours

	Placebo (N= 59)	Celecoxib 100MG BID PRN (N= 67)	Celecoxib 200mg BID PRN (N= 58)	DARVOCET N- 100 QID PRN (N= 62)
Number Of Remedications During First 24 Hours				
0	35(59%)	31(46%)	37(64%)	25(40%)
1	14(24%)	11(16%)	7(12%)	10(16%)
2	5(8%)	13(19%)	8(14%)	9(15%)
3	5(8%)	12(18%)	6(10%)	18(29%)
TOTAL	59(100%)	67(100%)	58(100%)	62(100%)

NOTE: For the SC- 58635 100MG and SC- 58635 200MG treatment groups, second and third remedications (third and fourth doses) were placebo.

American Pain Society (APS) Pain Measure (Day 1)

(The ASP Pain Measurement was also used in the assessment of pain in the OA studies) Patients who required rescue medication prior to this time did not complete the APS Pain Measure prior to Amendment 4. After Amendment 4, patients were required to complete the APS Pain Measure if they received rescue medication. The pain questions were on a scale of 0-10, with lower scores meaning less pain.

The first question asked was "have you experienced any pain in the past 24 hours?". With the exception of one patient in the Darvocet-N[®] 50 (2 tablets) QID PRN group, all patients answered 'yes' to this question.

The mean scores for the question "how much pain are you having right now?" were 5.1 for the celecoxib 100 mg BID PRN group, 5.7 for the celecoxib 200 mg BID PRN group, and 6.0 for the placebo QID PRN group. The mean scores for the question "the worst pain you have had in the past 24 hours?" were 7.5 for the celecoxib 100 mg BID PRN group, 8.1 for the celecoxib 200 mg BID PRN group, and 7.9 for the placebo QID PRN group. The mean scores for the question "the average pain you have had in the past 24 hours?" were 4.6 for the celecoxib 100 mg BID PRN group, 5.4 for the celecoxib 200 mg BID PRN group, and 5.3 for the placebo QID PRN group. There were no statistically significant differences between the celecoxib groups and placebo or between the celecoxib groups themselves.

In the Darvocet-N[®] 50 (2 tablets) QID PRN group, the mean score for the question "how much pain are you having right now?" was 5.3, for the question "the worst pain you have had in the past 24 hours?" was 7.4, and for the question "the average pain you have had in the past 24 hours?" was 4.8. None of these mean pain scores were statistically different from the placebo QID PRN group or from either of the celecoxib treatment groups.

Looking at the results of the OA studies that also used the APS pain measures, reveals a similar failure in demonstrating efficacy of both celecoxib and active controls versus placebo within the first 24-48 hours. Only later during the studies, the APS tool became more successful.

Analyses of Exploratory Measures of Efficacy

Number of Doses and Time Between Two Consecutive Doses of Study Medication (Days 1-5)

At Day 1 in the celecoxib 100 mg BID PRN group, the mean time between doses was 6.0 hours for doses 1-2, 6.4 hours for doses 2-3, and 5.6 hours for doses 3-4, with a mean daily interval between doses of 6.6 hours. For the celecoxib 200 mg BID PRN group, the mean time between doses was 7.1 hours for doses 1-2, 6.4 hours for doses 2-3, and 4.9 hours for doses 3-4, with a mean daily interval between doses of 7.3 hours. For the placebo QID PRN group, the mean time between doses of study medication in the placebo QID PRN group was 4.3 hours for doses 1-2 and doses 2-3, and 4.9 hours for doses 3-4, with a mean daily interval between doses of 4.4 hours.

At Day 1 in the Darvocet-N[®] 50 (2 tablets) QID PRN group, the mean time between doses was 6.1 hours for doses 1-2, 6.0 hours for doses 2-3, and 7.8 hours for doses 3-4, with a mean daily interval between doses of 6.6 hours.

Because of the small number of patients in the treatment groups for time points from Day 2 through Day 5, the data from these assessments was not analyzed.

Safety Results

Extent of Exposure

A total of 255 patients were randomized into the study with all patients receiving at least one dose of study medication as follows: 60 patients received placebo, 68 patients received celecoxib 100 mg BID PRN, 62 patients received celecoxib 200 mg BID PRN, and 65 patients received Darvocet-N[®] 50 (2 tablets) QID PRN.

Adverse Events

Overall, 101 (40%) of the 255 patients receiving at least one dose of study drug reported one or more adverse events during the study (see table). Adverse events were reported by 23 (38%) of the patients receiving placebo; 25 (37%) of the patients receiving celecoxib 100 mg BID PRN; 25 (40%) of the patients receiving celecoxib 200 mg BID PRN; and 28 (43%) of the patients receiving Darvocet-N[®] 50 (2 tablets) QID PRN. The adverse events with the highest incidence (i.e., $\geq 5\%$ reported in any group including placebo) were nausea, headache, confusion, dyspepsia, fever, and vasodilation.

Incidence of Adverse Events In Patients With At Least One Dose Of Study Medication

Incidence Of Adverse Events Patients With At Least One Dose Of Study Medication

	PLACEBO (N= 60)	Celecoxib 100mg BID PRN (N= 68)	Celecoxib 200mg BID PRN (N= 62)	DARVOCET- N 100mg QID PRN (N= 65)
All Randomized Patients				
Patients With At Least One Adverse Event	23(38%)	25(37%)	25(40%)	28(43%)
Patients With No Adverse Events	37(62%)	43(63%)	37(60%)	37(57%)
Patients With No Adverse Event Information	0(0%)	0(0%)	0(0%)	0(0%)
All Patients With At Least One Dose	60(100%)	68(100%)	62(100%)	65(100%)

Note: If a patient had more than one adverse event within a body system, the patient is counted only once in the overall incidence.

Adverse Events Causing Withdrawal

A total of 14 (5%) patients withdrew from the study due to one or more adverse events: 3 (5%) placebo patients, 1 (1%) celecoxib 100 mg BID PRN patient, 9 (15%) celecoxib 200 mg BID PRN patients, and 1 (2%) Darvocet-N[®] 50 (2 tablets) QID PRN patient (see table). The 15% withdrawal rate in the celecoxib 200 BID PRN group is derived from only 9 patients and may reflect the relatively small sample size in this study.

Three patients withdrew from the study due to headache: 1 (2%) placebo patient, 1 (1%) celecoxib 100 mg BID PRN patient, and 1 (2%) celecoxib 200 mg BID PRN patient. Two celecoxib 200 mg BID PRN patients withdrew due to abdominal pain and two celecoxib 200 mg BID PRN patients withdrew due to confusion. Two patients withdrew from the study due to fever: 1 (2%) placebo patient and 1 (2%) Darvocet-N[®] 50 (2 tablets) QID PRN patient.

The remaining adverse events causing withdrawal from the study (bowel disease, depression, dysphagia, nausea, urinary incontinence, and hypertonia) were reported by only one patient apiece.

Incidence Of Adverse Events Causing Withdrawal Patients With At Least One Dose Of Study Medication

Adverse Event	Placebo (N= 60)	Celecoxib 100mg bid PRN (N= 68)	Celecoxib 200mg bid PRN (N= 62)	Darvocet N-100mg qid PRN (N= 65)
Abdominal Pain	0 (0%)	0 (0%)	2 (3%)	0 (0%)
Confusion	0 (0%)	0 (0%)	2 (3%)	0 (0%)
Headache	1 (2%)	1 (1%)	1 (2%)	0 (0%)
Bowel Disease	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Depression	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Dysphagia	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Nausea	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Urinary Incontinence	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Fever	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Hypertonia	1 (2%)	0 (0%)	0 (0%)	1 (2%)

Note: A patient is counted once for each adverse event reported as causing withdrawal.

Serious Adverse Events

Serious adverse events causing prolonged hospitalization or rehospitalization, were reported by a total of six patients: three placebo patients, one celecoxib 100 mg BID PRN patient, one celecoxib 200 mg BID PRN patient, and one Darvocet-N[®] 50 (2 tablets) QID PRN patient (see table). All of these events were not considered to be related to study drug.

Incidence Of Serious Adverse Events Patients With At Least One Dose Of Study Medication

Serious Adverse Event	PLACEBO (N= 60)	Celecoxib 100mg bid PRN (N= 68)	Celecoxib 200mg bid PRN (N= 62)	DARVOCET N- 100 qid PRN (N= 65)
Ileus	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Back Pain	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Cellulitis	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Dysphagia	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Healing Impaired	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Pneumothorax	0 (0%)	1 (1%)	0 (0%)	0 (0%)

Note: A patient is counted once for each adverse event reported as serious.

Clinical Laboratory Evaluation

No clinically significant changes from baseline laboratory tests have been demonstrated.

Discussion and Overall Conclusions for Study # 028

The key issue in regard to this study is that the post major orthopedic surgery may not be an appropriate model for the study drug. Of the 246 patients on Day 1, only 48 patients entered the Day 2 and this number was further reduced by day 5 of the study. Therefore, 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. Moreover, this pain model was not validated by the active control Darvocet-N[®] 50 (2 tablets) QID PRN beyond the first 24 hours for the same reason, thus implying that the severity of pain involved in this model beyond 24 hours post surgery is too high for the medications tested. However, the withdrawal rate occurred equally in all treatment groups and the sponsor suggests that it was partially related to the limited length of hospital stay mandated by managed care practices.

For the first 24 hours, using BOCF analysis, the celecoxib showed no statistically significant superiority over the placebo at either dose in the PID multiple dose analysis and was superior to placebo only for the 200 mg dose, only at 6 and 7 hours, in the PID single dose analysis. In the PR multiple dose analysis, celecoxib was statistically significant superior to placebo only at 100 mg, at 5 hours and at 200 mg at 9 hours and in the single dose analysis, only at 100 mg at 4 hours and at 200 mg at 6 hours. In PRID multiple as well as single dose analyses, celecoxib was statistically significant superior to placebo only at 200 mg, at 6, 7 and at 9. (Using LOCF analysis demonstrated somewhat more favorable results for the celecoxib). With the single exception of PID (Categorical Scale) at 1.0 hour for the celecoxib 100 mg BID PRN treatment group, both doses of celecoxib, for all three primary efficacy variables (PR, PID [Categorical Scale] and PRID), were numerically greater than the placebo QID PRN group from 0.75 hours through 8.0 hours.

The summed variables SPRID(8), TOTPAR(8) and SPID(8) for the first eight hours were all numerically greater for the celecoxib treatment groups compared to placebo. These

differences were statistically significantly different favoring celecoxib 200 mg BID PRN compared to placebo for TOTPAR(8) and SPRID(8).

In contrary, the Darvocet validated the first 24 hours of the study by being statistically significant better than placebo at 1 through 7 hours in the PID single dose analysis, and at 1 through 18 hours for the PID multiple dose analysis, and at 2 through 6 hours in the PR and PRID single dose analyses and at 2 through 18 hours for the PR and PRID multiple dose analyses.

No major safety issues have been demonstrated.

CONCLUSIONS

It is concluded that, in this study:

Oral doses of celecoxib 100 mg BID PRN and celecoxib 200 mg BID PRN administered at a minimum interval of four hours were reasonably safe and tolerated;

Oral doses of celecoxib 100 mg BID PRN and celecoxib 200 mg BID PRN administered at a minimum interval of four hours, displayed numerically better analgesic activity than the placebo over a 24 hour dosing period in patients with moderate to severe post-orthopedic surgical pain. However, this analgesic activity did not show any consistent statistically significance.

Study Number: N49-95-02-005

This study is not considered to be pivotal by the sponsor

Study Dates: 20 August 1995 – October 12 1995

Title of Study: A single-blind, placebo-controlled, single dose comparison of the analgesic activity of celecoxib 100 mg, celecoxib 400 mg, aspirin (acetylsalicylic acid) caplets 650 mg and placebo in a postsurgical dental pain model.

Investigator and Location:

Objectives:

Primary Objective

The primary objectives of this study were to compare the analgesic activities of single doses of two dosing levels of celecoxib (100 mg and 400 mg) versus placebo in relieving moderate to severe postsurgical dental pain and, additionally, to assess the safety of single doses of celecoxib 100 mg and 400 mg in a dental pain model.

Secondary Objectives

Secondarily, the study was designed to compare the analgesic activity of aspirin 650 mg versus placebo in patients with moderate to severe pain in a postsurgical dental pain model and to assess the relationship between celecoxib plasma concentrations and pain intensity difference (PID) scores one hour posttreatment.

Study Description

This was a single-center, single-dose, randomized, placebo-controlled, single-blind, parallel group study. Patients experiencing moderate to severe pain following dental surgery received a single dose of one of the four following treatments: celecoxib 100 mg, celecoxib 400 mg, aspirin 650 mg or placebo.

Pain assessments were performed at 15, 30 and 45 minutes, 1 hour, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours postdosing or until a rescue analgesic was taken. Blood samples were collected one hour postdosing for celecoxib concentration determination and eight hours postdosing for clinical laboratory evaluations. Ice packs for pain relief were allowed after one hour postdosing, provided they were removed 15 minutes prior to successive pain assessments. Rescue analgesic medications were provided as needed, although patients were encouraged to delay the use of rescue medications until one hour postdosing.

Patients were discharged from the study facility eight hours postdosing and returned to the study site within five to nine days following surgery for a limited physical examination.

Table 1: Schedule of Observations and Procedures

	Pre-treatment	Base-line	Treatment											Post-treatment	
	-14 to 0 days	0 hr	15 min	30 min	45 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr	5-9 days
Medical History	X ^a														
Physical Examination-Vital Signs	X														X
Clinical Laboratory Testing	X													X	
Pregnancy Test ^d	X														
Pain Assessments ^b		X ^c													
Study Drug		X ^e	X	X	X	X	X	X	X	X	X	X	X	X	
Celecoxib Plasma Sampling						X ^f									

- (a) Female patients of childbearing potential will have a negative serum pregnancy test within 72 hours prior to receiving study drug.
- (b) Pain intensity, visual analog scale, pain relief, pain at least half gone.
- (c) Pain intensity only (categorical and visual analog scale).
- (d) At the end of the eight-hour observation period or immediately prior to taking rescue medication, the patient will complete a global evaluation.
- (e) Study drug will be administered immediately after baseline (0 hr) pain assessment.
- (e) One blood sample for SC-58635 plasma analysis will be collected one hour following study medication dosing for all patients (blood sample to be obtained after the patient's one hour posttreatment pain assessments).
- (f) Pretreatment medication taken within three days prior to dosing of study medication (versus 14 days) will be recorded. Concurrent medication will also be recorded during the study through eight hours following study medication dosing (or immediately prior to rescue medication) on surgery day.

Eligibility:

To qualify for study participation, candidates must have:

- male or female patient between the ages of 18 and 65 years, inclusive;
- females of childbearing potential must have been using adequate contraception, been non-lactating, and had a negative serum pregnancy test within 72 hours prior to receiving study medication;
- good health, as determined by medical history and physical examination;
- surgical extraction of one or more impacted third molar teeth requiring bone removal with moderate to severe postsurgical dental pain. If only one third molar was extracted, it must have been a mandibular third molar tooth requiring bone removal;
- written informed consent.

Exclusions:

- history of uncontrolled chronic disease, which in the opinion of the investigator, would contraindicate study participation;
- history of gastrointestinal (GI) ulcer or GI surgery within the past two months or current significant gastrointestinal complaints, as determined by the investigator;
- use of analgesics or other agents within six hours preceding surgery that could confound the analgesic responses (or longer if long-acting or sustained-release products).

Specifically excluded were tricyclic antidepressants, narcotic analgesics, antihistamines, tranquilizers, hypnotics, sedatives, NSAIDs, or corticosteroids. Presurgical medications such as xylocaine with epinephrine, Valium, brexital, fentanyl and Demerol (Demerol required a three hour washout) were exempt from this exclusion;

- chronic administration of antibiotic therapy and/or intraoperative or postoperative antibiotic medication requirement within eight hours of dosing. The following preoperative prophylactic antibiotic medications were allowed: amoxicillin, ampicillin, V-Cillin K, erythromycin (E.E.S.), or Keflex;
- history of chronic analgesic or tranquilizer use or known substance abuse within the last three months;
- unwillingness to abstain from alcohol for at least six hours prior to and eight hours following dosing;
- receipt of any other investigational medication within 30 days prior to dosing or during the course of this study;
- known hypersensitivity to analgesics, SC-58635, cyclooxygenase inhibitors, NSAIDs, lactose or sulfonamides;
- any laboratory abnormality, which in the opinion of the investigator, would contraindicate study participation;
- previous admission to this study.

Treatments Administered:

Capsules containing 100 mg celecoxib or matching and 325 mg aspirin caplets were provided by Searle. Aspirin was supplied as Genuine BAYER® commercially available caplets.

Each patient received a single dose of four capsules and/or caplets. Medication was placed in an opaque plastic dispensing cup by an independent third party and the patient was instructed to take the entire contents of the cup without inspection. The four regimens were administered with water as follows:

- 100 mg celecoxib: one 100 mg celecoxib capsule and three placebo capsules;
- 400 mg celecoxib: four 100 mg celecoxib capsules;
- 650 mg aspirin: two 325 mg Genuine BAYER caplets and two placebo capsules;
- placebo: four placebo capsules.

Efficacy Assessment:

1. Pain Intensity (none = 0, severe = 3)
2. Pain Relief (none = 0, complete = 4)
3. Pain at Least Half Gone
4. Patient's Global Evaluation (poor = 1, excellent = 5)
5. Time to Rescue Medication