Single-Dose Analgesia Supplement: Study Summaries

The Single-Dose Analgesia Supplement contains the individual study summaries prepared by the sponsor for the single-dose analgesia studies. The report for study 20 was divided by the sponsor into two reports by based on the baseline pain severity, because of a treatment by baseline interaction (the 50 mg dose did much worse in the severe baseline pain group). Charts and tables prepared by the FDA from the recombined data set are also included in this supplement. Studies have been grouped by type, and the reports appear in the following order:

CONFIDENTIAL: SBA Summary for Bromfenac Protocol AHR-02-US

"Assessment of the Efficacy and Safety of Single Oral Doses of AHR-10282 in the Treatment of Pain"

IND DRUG:	Bromfenac	DOSES:	50, 25, 5 mg oral
REFERENCE DRUGS:	Aspirin Placebo	DOSE:	650 mg oral
TOTAL PTS ENROLLED:	202	DURATION OF DOSING:	Single dose, 6 hr
INVESTIGATORS:	Malcolm B. Zola, D.D.S., Glen Cove, NY, USA (site 201) Carl E. Schow, Jr., D.D.S., Galveston, TX, USA (site 203 to replace inactive site 202, Woodrow Kessler, M.D., Ph.D., Media, PA, USA)		

PURPOSE: This study was designed to evaluate the analgesic efficacy and safety of a single oral dose of bromfenac at 3 dose levels in comparison with aspirin and placebo in outpatients with moderate or severe pain following

METHOD: This was a single-dose, double-blind, randomized, parallel study with 5 treatment groups conducted by A. H. Robins at 2 centers. Patients took medication at the onset of moderate or severe pain following surgery (not restricted to

After rating the baseline pain intensity (verbal and 100-mm visual analog), both pain intensity and pain relief were assessed at 0.25, 0.5, 1, 1.5, and 2 hours and then hourly until 6 hours post-dose or until further analgesia was required. Six-point ordinal scales used to evaluate pain relief and pain intensity, as defined in the original protocol, were transformed to the standard 5-point pain relief and 4-point pain intensity scales for the analysis. Three- and 6-hour TOPARs, SPIDs, and SPRIDs were calculated, as well as 6-hour SPAIDs. Patients gave an overall (global) evaluation of the medication at the end of the study. The length of time the patient remained active in the study, the need for additional analgesic before the end of the 6-hour pain assessment period, and the incidence of study events were evaluated. Estimates of onset and duration of pain relief were computed. Results obtained from Dr. Zola (site 201) were also analyzed separately because the investigator's case report form copies from site 203 were inadvertently lost. The combined analysis included baseline pain intensity, investigator, treatment, and investigator-by-treatment interaction as sources of variation for the analysis of variance model. The analysis of the individual site used only baseline pain intensity and treatment as sources of variation.

RESULTS: Study medication was dispensed to 202 patients (100 each at two sites; additionally, 2 patients enrolled at site 202 were added to site 203 for analysis). No efficacy data were excluded from the combined analysis. The treatment groups and the number of patients analyzed per group were: bromfenac 50 mg, 41; bromfenac 25 mg, 40; bromfenac 5 mg, 40; aspirin 650 mg, 40; placebo, 41.

The following discussion is based on the pooled results; the results obtained from Dr. Zola's site were similar.

All doses of bromfenac were significantly ($p \leq 0.05$) superior to placebo for both the 3- and the 6-hour TOPAR, SPID and SPRID scores. TOPAR, SPID, and SPRID scores at 3 hours and at 6 hours for both 50 and 25 mg doses of bromfenac were significantly higher than those for aspirin ($p \leq 0.05$). The same results were obtained for 6-hour SPAID (not included in the Brief Study Summary tables). Results for aspirin were numerically better than those for placebo for the 3- and the 6-hour TOPARs, SPIDs, and SPRIDs.

The analgesic activity of bromfenac 50 and 25 mg was significantly superior to aspirin from hour 1.5 to hour 6 for pain relief, PID, and PRID. All three doses of bromfenac were superior to placebo from hour 1 to hour 6 for these variables.

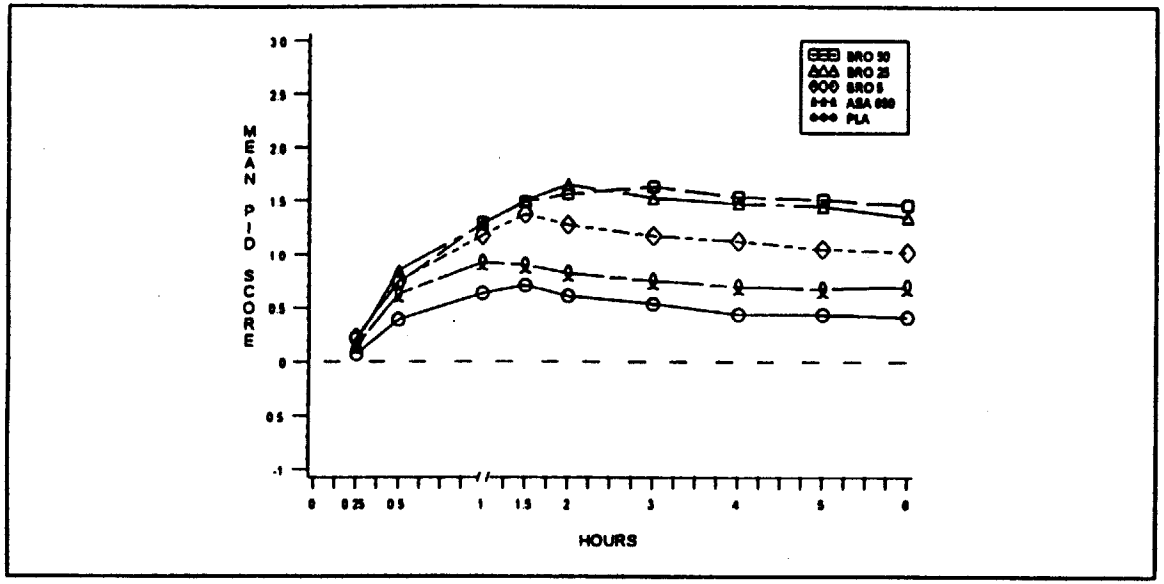
All doses of bromfenac had an earlier estimated onset of pain relief (on-PR) and a longer estimated duration of pain relief (dur-PR) than did either aspirin or placebo. Significantly fewer patients in the bromfenac groups remedicated than in the placebo group. For the 50- and the 25-mg groups, significantly fewer patients remedicated than in the aspirin group.

Nine (9) study events (1 on bromfenac 50 mg, 3 on bromfenac 25 mg, 2 on bromfenac 5 mg, 1 on aspirin, and 2 on placebo) among 7 patients were reported. One (1) study event in the bromfenac 5 mg group was described as a severe skin reaction to penicillin. No patient withdrew because of a study event.

CONCLUSIONS: Compared with placebo, significant analgesia was obtained with 50, 25, and 5 mg doses of bromfenac. A dose-response relationship was suggested: bromfenac 50 and 25 mg were superior to aspirin while bromfenac 5 mg was comparable to aspirin for providing analgesia. A longer duration of effect was seen for all bromfenac doses compared to aspirin and placebo. All study treatments were well tolerated in this study.

Figure 1, Table 1. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPID AND PEAK PID

Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 50 mg	41	3.71 A	8.30 A	1.73 A
Bromfenac 25 mg	40	3.75 A	8.11 AB	1.67 AB
Bromfenac 5 mg	40	3.16 AB	6.43 BC	1.45 BC
Aspirin 650 mg	40	2.18 BC	4.28 CD	1.17 CD
Placebo	41	1.56 C	2.91 D	0.98 D
Overall treatment p-value		0.0001	0.0001	0.0001
Root MSE		2.0082	4.4199	0.7889

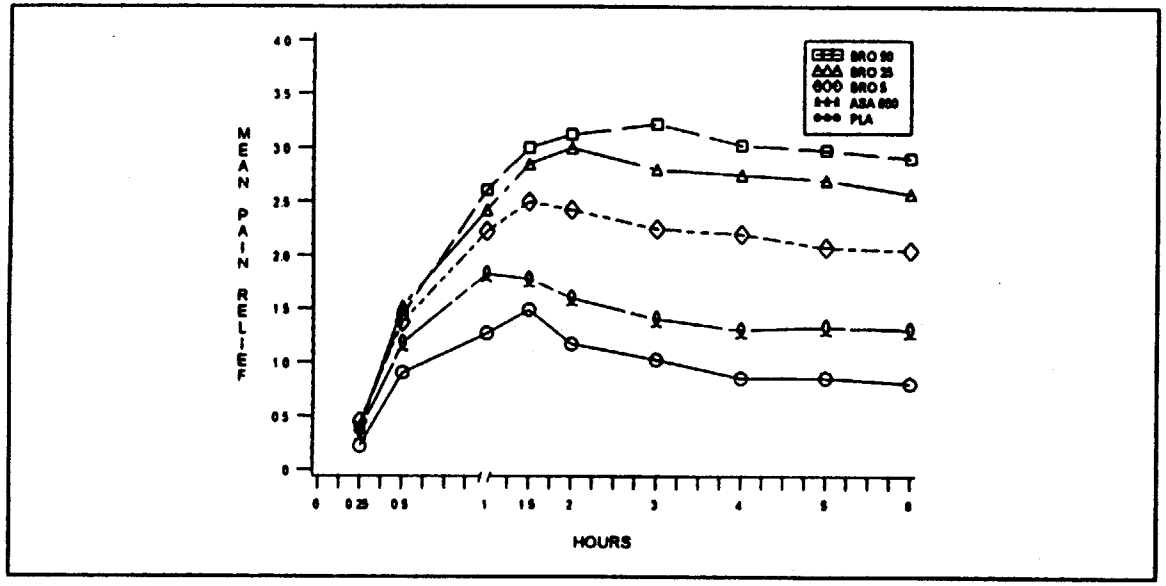
a. For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)																							
Treatment	1/4			1/2			1			1 1/2			2			3			4			5			6		
Bromfenac 50 mg	0.22	(0.42)		0.73	(0.63)		1.29	(0.64)		1.49	(0.78)		1.56	(0.78)		1.63	(0.80)		1.54	(0.90)		1.51	(0.95)		1.46	(0.98)	
	41 (a)			41			40	A (d)		39	A		36	A		36	A		36	A		34	A		33	A	
Bromfenac 25 mg	0.18	(0.59)		0.85	(0.92)		1.28	(0.96)		1.50	(1.01)		1.65	(0.92)		1.53	(0.99)		1.48	(1.04)		1.45	(1.04)		1.35	(1.00)	
	40			40			39	A		38	A		34	AB		32	AB		30	AB		29	AB		28	AB	
Bromfenac 5 mg	0.23	(0.58)		0.75	(0.84)		1.18	(0.96)		1.38	(0.84)		1.28	(0.96)		1.18	(0.98)		1.13	(1.02)		1.05	(1.01)		1.03	(0.97)	
	40			40			40	A		37	AB		32	BC		27	BC		25	BC		24	BC		22	BC	
Aspirin 650 mg	0.15	(0.58)		0.63	(0.74)		0.93	(0.92)		0.90	(0.90)		0.83	(0.96)		0.75	(0.90)		0.70	(0.94)		0.68	(1.00)		0.70	(0.97)	
	40			40			38	AB		36	BC		29	CD		23	CD		17	CD		17	CD		16	CD	
Placebo	0.07	(0.52)		0.39	(0.80)		0.63	(1.04)		0.71	(1.10)		0.61	(0.95)		0.54	(0.84)		0.44	(0.81)		0.44	(0.81)		0.41	(0.77)	
	41			41			39	B		32	C		21	D		14	D		12	D		11	D		11	D	
p-value Trt (b)	0.630			0.091			0.002			<0.001			<0.001			<0.001			<0.001			<0.001			<0.001		
p-value Trt*Investigator (b)	0.449			0.511			0.659			0.829			0.844			0.591			0.496			0.580			0.389		
p-value Trt*Baseline (c)	0.318			0.881			0.225			0.174			0.074			0.132			0.055			0.053			0.024		
Root MSE (b)	0.526			0.750			0.851			0.878			0.853			0.855			0.890			0.920			0.904		

(a) Sample sizes, not extrapolated
(b) Model: PID = u + T(i) + I(j) + TI(ij) + B(I)(jk) + error
(c) Model: PID = u + T(i) + I(j) + TI(ij) + B(I)(jk) + TB(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 2, Table 2. Pain Relief (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL TOPAR AND PEAK RELIEF

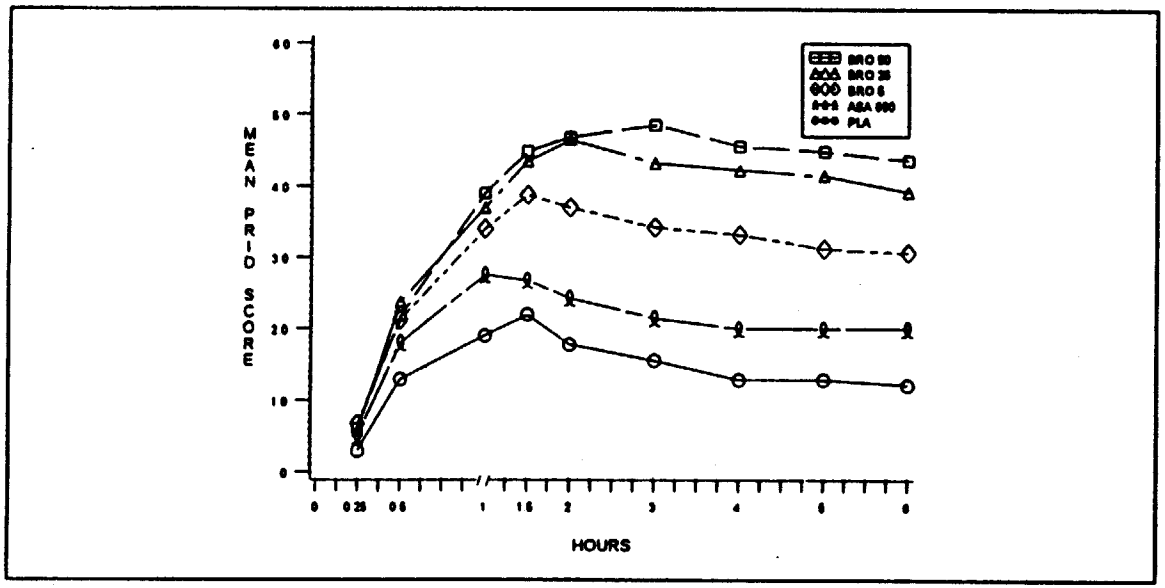
Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak Pain Relief
Bromfenac 50 mg	41	7.39 A	16.45 A	3.37 A
Bromfenac 25 mg	40	6.96 AB	15.10 AB	3.08 AB
Bromfenac 5 mg	40	5.93 BC	12.36 BC	2.65 BC
Aspirin 650 mg	40	4.23 CD	8.20 CD	2.20 CD
Placebo	41	3.16 D	5.78 D	1.66 D
Overall treatment p-value		0.0001	0.0001	0.0001
Root MSE		3.6914	8.3634	1.5533

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)															
Treatment	1/4		1/2		1		1 1/2		2		3		4		5		6	
Bromfenac 50 mg	0.39 (0.70) 41		1.44 (1.21) 41		2.61 (1.26) 40 A(d)		3.00 (1.41) 39 A		3.12 (1.44) 36 A		3.22 (1.44) 36 A		3.02 (1.59) 36 A		2.98 (1.70) 34 A		2.90 (1.74) 33 A	
Bromfenac 25 mg	0.40 (0.74) 40		1.53 (1.32) 40		2.43 (1.52) 39 AB		2.85 (1.56) 38 A		3.00 (1.59) 34 AB		2.80 (1.71) 32 AB		2.75 (1.78) 30 AB		2.70 (1.83) 29 AB		2.58 (1.78) 28 AB	
Bromfenac 5 mg	0.45 (0.93) 40		1.38 (1.35) 40		2.23 (1.53) 40 AB		2.50 (1.62) 37 AB		2.43 (1.81) 32 BC		2.25 (1.86) 27 B		2.20 (1.91) 25 B		2.08 (1.94) 24 BC		2.05 (1.92) 22 BC	
Aspirin 650 mg	0.35 (0.62) 40		1.18 (1.15) 40		1.83 (1.52) 38 BC		1.78 (1.66) 36 BC		1.60 (1.72) 29 CD		1.40 (1.72) 23 C		1.30 (1.70) 17 C		1.33 (1.76) 17 CD		1.30 (1.74) 16 CD	
Placebo	0.22 (0.47) 41		0.90 (1.16) 41		1.27 (1.43) 39 C		1.49 (1.70) 32 C		1.17 (1.66) 21 D		1.02 (1.57) 14 C		0.85 (1.49) 12 C		0.85 (1.49) 11 D		0.80 (1.45) 11 D	
p-value Trt (b)	0.660		0.167		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Investigator (b)	0.688		0.529		0.916		0.804		0.894		0.483		0.539		0.503		0.443	
p-value Trt*Baseline (c)	0.249		0.864		0.412		0.403		0.237		0.316		0.184		0.215		0.195	
Root MSE (b)	0.709		1.222		1.449		1.575		1.621		1.644		1.678		1.727		1.716	

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + I(j) + TI(ij) + B(I)(jk) + error
(c) Model: PR = u + T(i) + I(j) + TI(ij) + B(I)(jk) + TB(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 50 mg	41	11.10 A	24.76 A	5.10 A
Bromfenac 25 mg	40	10.71 AB	23.21 AB	4.75 AB
Bromfenac 5 mg	40	9.09 BC	18.79 BC	4.10 BC
Aspirin 650 mg	40	6.41 CD	12.48 CD	3.38 CD
Placebo	41	4.72 D	8.70 D	2.63 D
Overall treatment p-value		0.0001	0.0001	0.0001
Root MSE		5.6530	12.7212	2.3253

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)																	
Treatment	1/4		1/2		1		1 1/2		2		3		4		5		6	
Bromfenac 50 mg	0.61 41	(1.09)	2.17 41	(1.76)	3.90 40	(1.83) A (d)	4.49 39	(2.16) A	4.68 36	(2.18) A	4.85 36	(2.21) A	4.56 36	(2.45) A	4.49 34	(2.62) A	4.37 33	(2.69) A
Bromfenac 25 mg	0.58 40	(1.26)	2.38 40	(2.16)	3.70 39	(2.41) AB	4.35 38	(2.52) A	4.65 34	(2.46) AB	4.33 32	(2.65) AB	4.23 30	(2.78) AB	4.15 29	(2.83) AB	3.93 28	(2.74) AB
Bromfenac 5 mg	0.68 40	(1.46)	2.13 40	(2.13)	3.40 40	(2.42) AB	3.88 37	(2.42) AB	3.70 32	(2.74) BC	3.43 27	(2.82) BC	3.33 25	(2.90) BC	3.13 24	(2.94) BC	3.08 22	(2.89) BC
Aspirin 650 mg	0.50 40	(1.13)	1.80 40	(1.80)	2.75 38	(2.36) BC	2.68 36	(2.49) BC	2.43 29	(2.62) CD	2.15 23	(2.59) CD	2.00 17	(2.61) CD	2.00 17	(2.73) CD	2.00 16	(2.69) CD
Placebo	0.29 41	(0.93)	1.29 41	(1.87)	1.90 39	(2.39) C	2.20 32	(2.75) C	1.78 21	(2.55) D	1.56 14	(2.39) D	1.29 12	(2.27) D	1.29 11	(2.28) D	1.22 11	(2.21) D
p-value Trt (b)	0.620		0.111		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Investigator (b)	0.601		0.511		0.841		0.823		0.921		0.526		0.535		0.533		0.424	
p-value Trt*Baseline (c)	0.240		0.872		0.314		0.310		0.164		0.246		0.126		0.143		0.108	
Root MSE (b)	1.172		1.899		2.246		2.420		2.447		2.482		2.553		2.633		2.607	

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + I(j) + TI(ij) + B(I)(jk) + error
(c) Model: PRID = u + T(i) + I(j) + TI(ij) + B(I)(jk) + TB(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Table 4. Estimated Onset of Pain Relief (on-PR)

	PRID at 30 min			Estimated on-PR	
Treatment Group	Mean [a]	S.D.	n	Time (min)	95%-CI (min)
Bromfenac 50 mg	2.17	1.76	41	14	11 - 19
Bromfenac 25 mg	2.38	2.16	40	13	10 - 18
Bromfenac 5 mg	2.13	2.13	40	14	11 - 21
Aspirin 650 mg	1.80	1.80	40	17	13 - 25
Placebo	1.29	1.87	41	23	16 - 43

a Raw unadjusted mean of (unextrapolated) PRID scores.

Figure 4. Estimated Duration of Analgesia
(Time-to-Remedication)

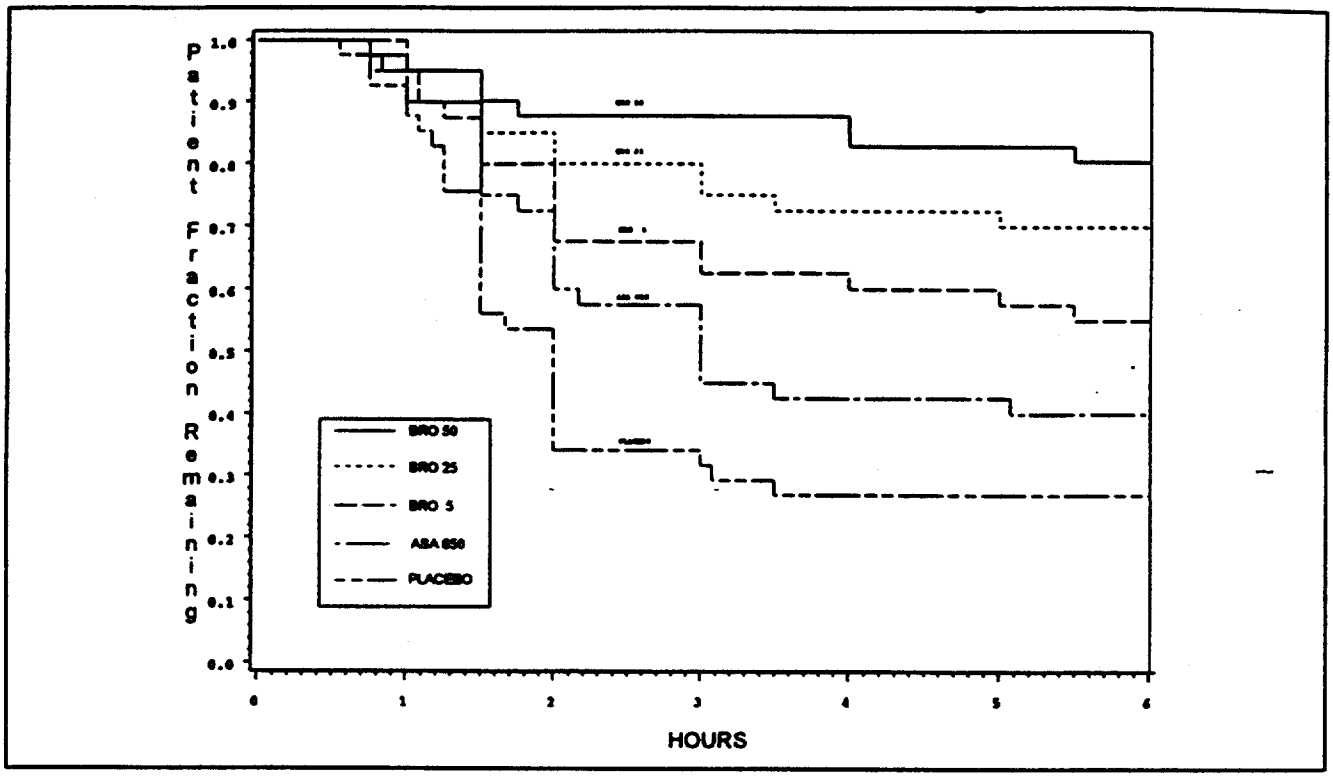


Table 5. Duration of Pain Relief (dur-PRs)

Treatment Group	n	Calculated Time to Remedication	
		Mean[a] h:min	95% CI[b] h:min
Bromfenac 50 mg	41	6:07 (A) [c]	(5:32, 6:43)
Bromfenac 25 mg	40	5:33 (AB)	(4:49, 6:17)
Bromfenac 5 mg	40	4:52 (BC)	(4:05, 5:38)
Aspirin 650 mg	40	4:03 (CD)	(3:16, 4:50)
Placebo	41	3:05 (D)	(2:19, 3:50)

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

CONFIDENTIAL: BROMFENAC AHR-02-US (ALL INVESTIGATORS)

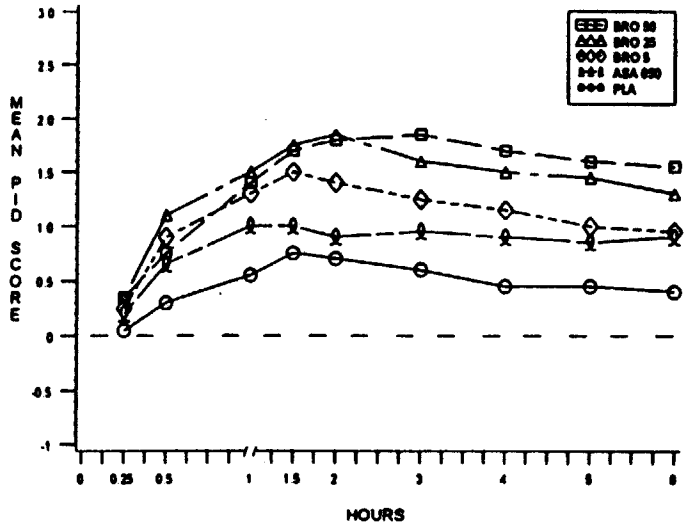
Table 6. Time-to-Remedication (Percentiles)

Treatment	----------Percentiles In Hours:minutes (95% C. I.)----------		
	25%	50% (Median)	75%
Bromfenac 50 mg	> 6 (4:00, > 6)	> 6 (NE)	> 6 (NE)
Bromfenac 25mg	3:15 (1:30, > 6)	> 6 (NE)	> 6 (NE)
Bromfenac 5 mg	2:00 (1:30, 5:00)	> 6 (3:00, > 6)	> 6 (NE)
Aspirin 650 mg	1:38 (1:30, 2:10)	3:00 (2:00, > 6)	> 6 (5:05, > 6)
Placebo	1:30 (1:05, 1:30)	2:00 (1:30, 2:00)	> 6 (2:00, > 6)

NE: Not estimable

Figure 5, Table 7. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPID AND PEAK PID

Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 50 mg	20	4.19 A	9.19 A	1.85 A
Bromfenac 25 mg	20	4.31 AB	8.71 AB	1.85 A
Bromfenac 5 mg	20	3.48 AB	6.73 B	1.55 AB
Aspirin 650 mg	20	2.44 BC	5.12 BC	1.35 AB
Placebo	20	1.60 C	3.00 C	1.05 B
Overall treatment p-value		0.0004	0.0002	0.0096
Root MSE		2.1394	4.6125	0.8136

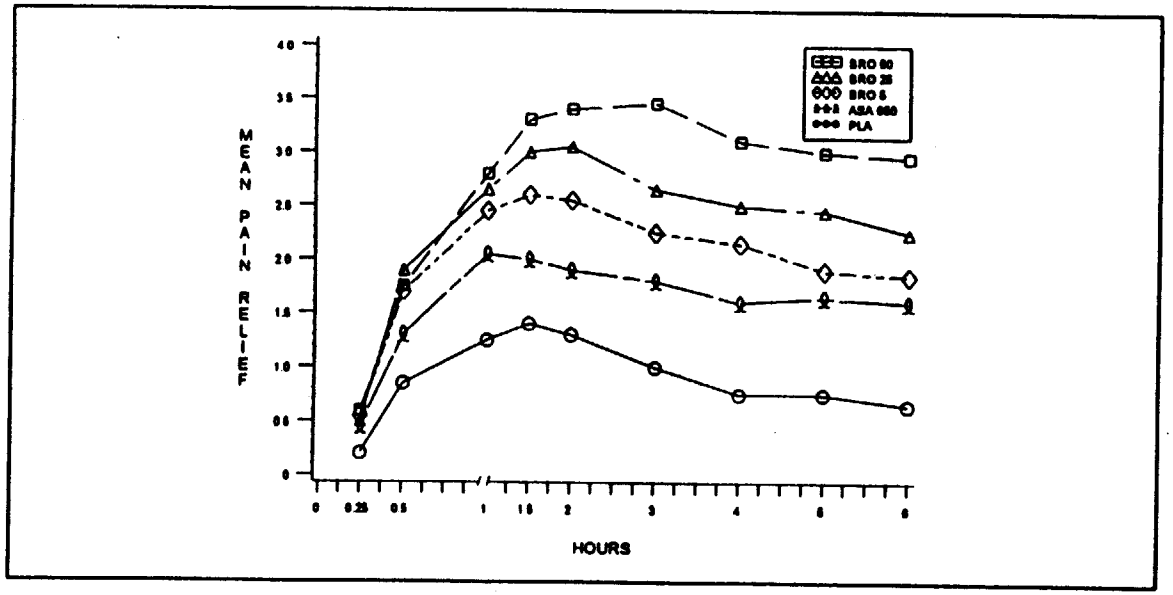
a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)																							
Treatment	1/4			1/2			1			1 1/2			2			3			4			5			6		
Bromfenac 50 mg	0.35	(0.49)	20 (a)	0.75	(0.72)	20	1.40	(0.75)	19 A (d)	1.70	(0.73)	18 A	1.80	(0.70)	18 A	1.85	(0.75)	18 A	1.70	(0.86)	18 A	1.60	(0.99)	16 A	1.55	(1.00)	16 A
Bromfenac 25 mg	0.35	(0.75)	20	1.10	(1.12)	20	1.50	(1.05)	19 A	1.75	(0.97)	18 AB	1.85	(0.99)	17 AB	1.60	(1.14)	16 AB	1.50	(1.24)	14 AB	1.45	(1.19)	13 AB	1.30	(1.13)	13 AB
Bromfenac 5 mg	0.25	(0.64)	20	0.90	(0.97)	20	1.30	(1.13)	20 A	1.50	(0.95)	18 AB	1.40	(1.05)	14 BC	1.25	(1.07)	13 B	1.15	(1.14)	12 B	1.00	(1.08)	11 BC	0.95	(1.00)	10 BC
Aspirin 650 mg	0.20	(0.70)	20	0.65	(0.93)	20	1.00	(1.03)	18 AB	1.00	(0.97)	16 BC	0.90	(1.07)	16 CD	0.95	(0.94)	13 BC	0.90	(1.02)	11 BC	0.85	(1.14)	11 BC	0.90	(1.07)	10 B
Placebo	0.05	(0.60)	20	0.30	(0.92)	20	0.55	(1.23)	18 B	0.75	(1.16)	11 C	0.70	(1.13)	9 D	0.60	(0.94)	7 C	0.45	(0.89)	6 C	0.45	(0.89)	5 C	0.40	(0.82)	5 C
p-value Trt (b)	0.510			0.117			0.016			0.001			<0.001			<0.001			<0.001			0.001			0.001		
p-value Trt*Baseline (c)	0.313			0.901			0.564			0.346			0.194			0.309			0.078			0.077			0.024		
Root MSE (b)	0.621			0.869			0.932			0.863			0.897			0.894			0.948			0.982			0.942		

(a) Sample sizes, not extrapolated
(b) Model: PID = u + T(i) + B(j) + error
(c) Model: PID = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 6, Table 8. Pain Relief (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL TOPAR AND PEAK RELIEF

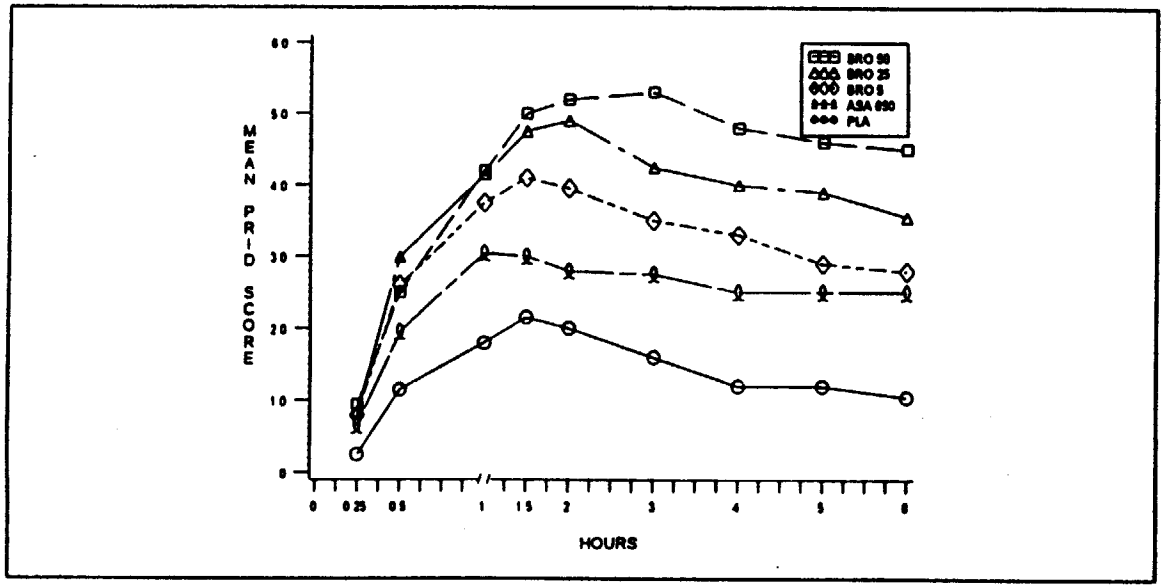
Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak Pain Relief
Bromfenac 50 mg	20	8.13 A	17.43 A	3.45 A
Bromfenac 25 mg	20	7.28 AB	14.68 AB	3.10 A
Bromfenac 5 mg	20	6.34 AB	12.44 B	2.70 A
Aspirin 650 mg	20	4.95 BC	9.90 BC	2.55 AB
Placebo	20	3.17 C	5.49 C	1.65 B
Overall treatment p-value		0.0009	0.0003	0.0071
Root MSE		3.8721	8.4994	1.5918

a. For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)																	
Treatment	1/4		1/2		1		1 1/2		2		3		4		5		6	
Bromfenac 50 mg	0.60 20 (a)	(0.88)	1.75 20	(1.33)	2.80 19	(1.36) A (d)	3.30 18	(1.34) A	3.40 18	(1.35) A	3.45 18	(1.36) A	3.10 18	(1.62) A	3.00 16	(1.78) A	2.95 16	(1.76) A
Bromfenac 25 mg	0.50 20	(0.89)	1.90 20	(1.55)	2.65 19	(1.50) A	3.00 18	(1.49) AB	3.05 17	(1.57) AB	2.65 16	(1.81) AB	2.50 14	(1.93) AB	2.45 13	(1.90) AB	2.25 13	(1.80) AB
Bromfenac 5 mg	0.55 20	(1.15)	1.70 20	(1.59)	2.45 20	(1.67) A	2.60 18	(1.73) AB	2.55 14	(1.85) AB	2.25 13	(1.92) B	2.15 12	(2.01) AB	1.90 11	(1.97) BC	1.85 10	(1.93) B
Aspirin 650 mg	0.45 20	(0.69)	1.30 20	(1.38)	2.05 18	(1.54) AB	2.00 16	(1.62) BC	1.90 16	(1.68) BC	1.80 13	(1.74) BC	1.60 11	(1.73) BC	1.65 11	(1.84) BC	1.60 10	(1.82) BC
Placebo	0.20 20	(0.41)	0.85 20	(1.23)	1.25 18	(1.55) B	1.40 11	(1.82) C	1.30 9	(1.75) C	1.00 7	(1.59) C	0.75 6	(1.41) C	0.75 5	(1.41) C	0.65 5	(1.31) C
p-value Trt (b)	0.584		0.154		0.013		0.002		<0.001		<0.001		<0.001		0.001		0.001	
p-value Trt*Baseline (c)	0.293		0.961		0.569		0.587		0.351		0.468		0.261		0.314		0.235	
Root MSE (b)	0.838		1.416		1.519		1.595		1.631		1.679		1.733		1.769		1.727	

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + B(j) + error
(c) Model: PR = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 7, Table 9. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 50 mg	20	12.33 A	26.63 A	5.30 A
Bromfenac 25 mg	20	11.59 AB	23.39 AB	4.95 A
Bromfenac 5 mg	20	9.81 AB	19.16 B	4.25 AB
Aspirin 650 mg	20	7.39 BC	15.02 BC	3.90 AB
Placebo	20	4.77 C	8.49 C	2.70 B
Overall treatment p-value		0.0006	0.0002	0.0074
Root MSE		5.9655	13.0391	2.3888

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)																							
Treatment	1/4			1/2			1			1 1/2			2			3			4			5			6		
Bromfenac 50 mg	0.95	20 (a)	(1.36)	2.50	20	(1.99)	4.20	19	(2.02) A (d)	5.00	18	(2.03) A	5.20	18	(2.02) A	5.30	18	(2.05) A	4.80	18	(2.44) A	4.60	16	(2.74) A	4.50	16	(2.72) A
Bromfenac 25 mg	0.85	20	(1.57)	3.00	20	(2.60)	4.15	19	(2.48) A	4.75	18	(2.38) AB	4.90	17	(2.49) A	4.25	16	(2.90) AB	4.00	14	(3.13) AB	3.90	13	(3.06) AB	3.55	13	(2.87) AB
Bromfenac 5 mg	0.80	20	(1.74)	2.60	20	(2.50)	3.75	20	(2.71) A	4.10	18	(2.63) AB	3.95	14	(2.86) AB	3.50	13	(2.95) B	3.30	12	(3.11) B	2.90	11	(3.02) BC	2.80	10	(2.91) B
Aspirin 650 mg	0.65	20	(1.31)	1.95	20	(2.21)	3.05	18	(2.48) AB	3.00	16	(2.51) BC	2.80	16	(2.69) BC	2.75	13	(2.63) BC	2.50	11	(2.70) BC	2.50	11	(2.93) BC	2.50	10	(2.86) BC
Placebo	0.25	20	(0.97)	1.15	20	(2.06)	1.80	18	(2.71) B	2.15	11	(2.94) C	2.00	9	(2.83) C	1.60	7	(2.50) C	1.20	6	(2.26) C	1.20	5	(2.28) C	1.05	5	(2.11) C
p-value Trt (b)	0.524			0.125			0.011			0.001			<0.001			<0.001			<0.001			0.001			0.001		
p-value Trt*Baseline (c)	0.269			0.941			0.550			0.504			0.285			0.413			0.176			0.207			0.121		
Root MSE (b)	1.393			2.221			2.400			2.429			2.498			2.550			2.661			2.734			2.653		

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + error
(c) Model: PRID = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Table 10. Estimated Onset of Pain Relief (on-PR)

	PRID at 30 min			Estimated on-PR	
Treatment Group	Mean [a]	S.D.	n	Time (min)	95%-CI (min)
Bromfenac 50 mg	2.50	1.99	20	12	9 - 19
Bromfenac 25 mg	3.00	2.60	20	10	7 - 17
Bromfenac 5 mg	2.60	2.50	20	12	8 - 21
Aspirin 650 mg	1.95	2.21	20	15	10 - 33
Placebo	1.15	2.06	20	26	14 - 161

a Raw unadjusted mean of (unextrapolated) PRID scores.

Figure 8. Estimated Duration of Analgesia
(Time-to-Remedication)

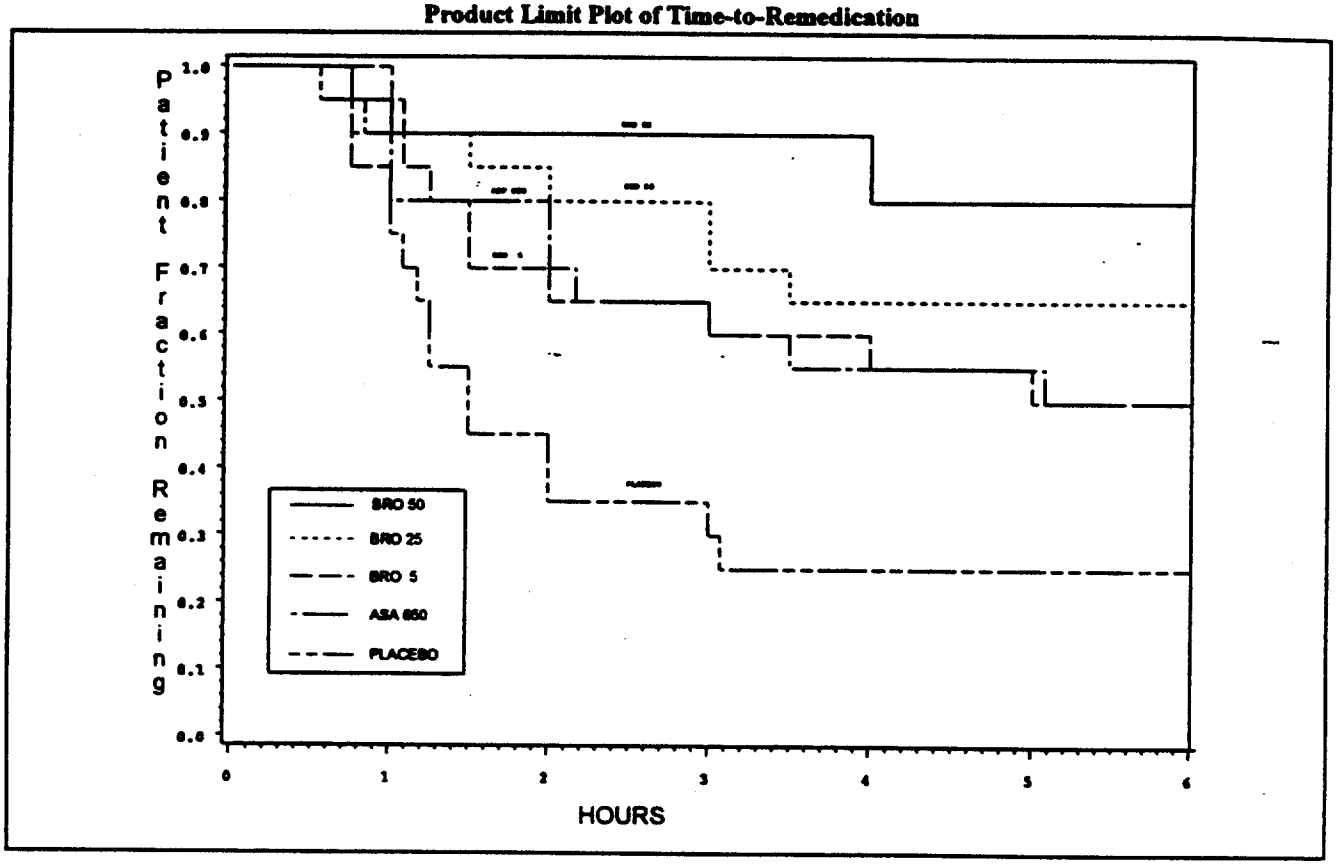


Table 11. Duration of Pain Relief (dur-PRs)

Treatment Group	n	Calculated Time to Remedication	
		Mean[a] h:min	95% CI[b] h:min
Bromfenac 50 mg	20	6:05 (A)[c]	(5:13, 6:58)
Bromfenac 25 mg	20	5:16 (AB)	(4:10, 6:22)
Bromfenac 5 mg	20	4:35 (ABC)	(3:23, 6:45)
Aspirin 650 mg	20	4:35 (BC)	(3:23, 6:45)
Placebo	20	2:50 (C)	(1:43, 3:58)

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

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Table 12. Time-to-Remedication (Percentiles)

Treatment	----------Percentiles In Hours:minutes (95% C. I.)----------		
	25%	50% (Median)	75%
Bromfenac 50 mg	> 6 (4:00, > 6)	> 6 (NE)	> 6 (NE)
Bromfenac 25 mg	3:00 (1:30, > 6)	> 6 (3:00, > 6)	> 6 (NE)
Bromfenac 5 mg	1:30 (1:05, 5:00)	6 (1:30, > 6)	> 6 (NE)
Aspirin 650 mg	2:00 (1:00, 5:05)	6:02 (2:00, > 6)	> 6 (NE)
Placebo	1:02 (0:45, 1:30)	1:30 (1:05, 3:05)	5:02 (1:30, > 6)

NE: Not estimable

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CONFIDENTIAL: SBA Summary for Bromfenac Protocol AHR-16-US

"A Double-blind Single-dose Evaluation of the Relative Analgesic Efficacy and Adverse Effect Liability of Bromfenac, Aspirin, Ibuprofen, and Placebo in the Treatment of Postoperative Pain Followin[illegible] Surgery"

IND DRUG: Bromfenac	DOSES: 25, 10, 5 mg oral
REFERENCE DRUGS: Aspirin (ASA) Ibuprofen (IBU) Placebo	DOSE: 650 mg oral 400 mg oral
TOTAL PTS ENROLLED: 288	DURATION OF DOSING: Single dose, 8 hr
INVESTIGATOR: James A. Forbes, M.S., Shrewsbury, PA, USA	

PURPOSE: The purpose of this study was to compare the efficacy and safety of single oral doses of bromfenac (25. 10 and 5 mg), aspirin (650 mg), ibuprofen (400 mg), and placebo in the treatment of moderate to severe pain resulting fron surgery.
METHOD: This was a single-dose, randomized, double-blind study of parallel design. The study medication was administered within 8 hours after [illegible] surgical procedures which resulted in moderate to severe pain. Pain intensity was assessed before dose, then both pain intensity and pain relief were assessed hourly for 8 hours after medication. Pain evaluations were not recorded after additional analgesics were taken or if the patient fell asleep after midnight. Mean pain relief, pain intensity difference (PID) and pain relief plus PID (PRID) were calculated from the hourly scores. TOPAR (3- and final), peak relief, SPID (3- and final), peak PID, and SPRID (3- and final) were derived from the mean hourly scores. Time from the end of surgery to dose (covariance), baseline pain intensity, and treatment were included as sources of variation in the analysis of variance model. Patients gave an overall pain relief rating at 8 hours or at the time of premature termination. The number of patients who remedicated within 8 hours was calculated.
RESULTS: A total of 288 patients was entered and stratified by severity of pain (moderate or severe). All 269 patients who took study medication and who returned any efficacy data were analyzed. The treatment groups and number of patients evaluated for efficacy per group were as follows: bromfenac 25 mg, 45; bromfenac 10 mg, 46; bromfenac 5 mg, 42; ASA, 46; IBU, 43; and placebo, 47.

All of the active treatments were significantly ($p \leq 0.05$) better than placebo as indicated by scores for 3-hour and 8-hour TOPAR and for 3-hour SPID. For pain relief, PID, and PRID data, only bromfenac 25 mg and IBU were significantly better than placebo for the entire 8-hour period; both were also superior to aspirin from hour 3 to hour 8 for pain relief, PID, and PRID as well as for TOPAR, SPID, and SPRID at hour 8. The 10 and 5 mg doses of bromfenac were comparable to aspirin. The 10 and 5 mg doses of bromfenac were similar to IBU at early efficacy assessments and for 3-hour TOPAR, SPID, and SPRID.

Bromfenac 25 mg had the fastest estimated onset of pain relief; bromfenac 10 mg and IBU had a similar onset of pain relief. Bromfenac 25 mg had the largest duration of pain relief; the duration of pain relief for bromfenac 10 and 5 mg was similar.

Significantly fewer patients from the bromfenac 25 mg and the IBU treatment groups required remedication compared to the ASA and placebo treatment groups. There were no significant differences in the number of patients remedicating between the bromfenac 25 mg dose and IBU.

Similar numbers and types of study events were reported for each of the treatment groups. All doses of bromfenac were well tolerated. There were no dropouts because of adverse experiences and no adverse experience was judged to be serious or unexpected.
CONCLUSIONS: Bromfenac (all doses), IBU, and ASA provided significantly better analgesia than did placebo. The analgesic activity of bromfenac 25 mg was superior to that of ASA 650 mg and equal to that of IBU 400 mg.

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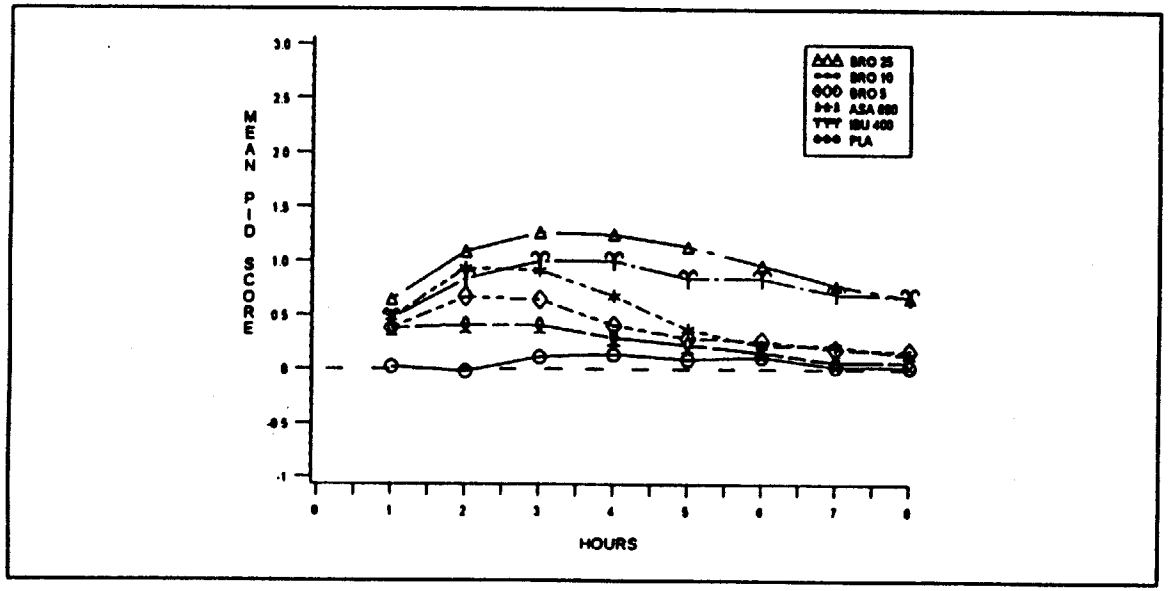
Figure 1, Table 1. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPID AND PEAK PID [a]

Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 25 mg	45	2.37A	7.46A	1.44A
Bromfenac 10 mg	46	1.87AB	3.87B	1.09AB
Bromfenac 5 mg	42	1.37AB	2.92B	0.83B
Aspirin 650 mg	46	0.98B	1.94BC	0.67B
Ibuprofen 400 mg	43	1.80AB	6.01A	1.28 AB
Placebo	45	0.06C	0.48C	0.13C
p-value		0.0001	0.0001	0.0001
Root MSE		1.9035	4.5638	0.9798

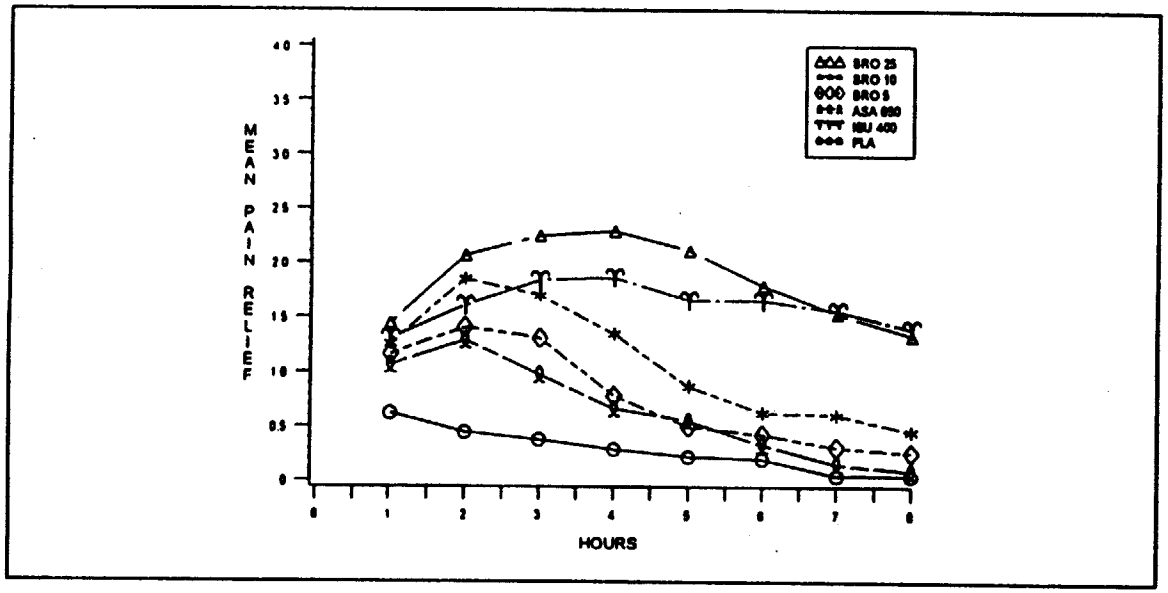
a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)							
Treatment	1	2	3	4	5	6	7	8
Bromfenac 25 mg	0.64 (0.86) 45 (a)	1.09 (1.06) 45 A (d)	1.27 (1.05) 33 A	1.24 (1.05) 32 A	1.13 (1.06) 26 A	0.97 (1.08) 23 A	0.78 (1.02) 17 A	0.67 (0.98) 14 A
Bromfenac 10 mg	0.48 (1.05) 46	0.93 (1.08) 44 A	0.91 (1.09) 34 AB	0.67 (0.87) 21 B	0.37 (0.68) 17 B	0.22 (0.59) 10 B	0.22 (0.59) 8 B	0.13 (0.50) 8 B
Bromfenac 5 mg	0.38 (0.82) 42	0.67 (0.95) 40 AB	0.64 (0.93) 25 BC	0.40 (0.86) 18 BC	0.29 (0.67) 8 B	0.26 (0.66) 5 B	0.19 (0.55) 3 B	0.17 (0.54) 2 B
Aspirin 650 mg	0.38 (0.83) 44	0.40 (0.99) 39 B	0.40 (0.78) 26 CD	0.29 (0.76) 15 BC	0.22 (0.67) 8 B	0.16 (0.52) 4 B	0.07 (0.33) 2 B	0.07 (0.33) 1 B
Ibuprofen 400 mg	0.47 (0.96) 43	0.84 (1.00) 40 A	1.00 (1.02) 33 A	1.00 (0.98) 27 A	0.84 (0.95) 21 A	0.84 (0.97) 19 A	0.70 (1.01) 20 A	0.67 (1.02) 17 A
Placebo	0.02 (0.84) 45	-0.02 (0.75) 41 C	0.11 (0.65) 15 D	0.13 (0.50) 6 C	0.09 (0.56) 3 B	0.11 (0.53) 2 B	0.02 (0.15) 1 B	0.02 (0.15) 1 B
p-value Trt (b)	0.054	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p-value Trt*Baseline (c)	0.350	0.819	0.273	0.450	0.891	0.867	0.384	0.492
Root MSE (b)	0.846	0.897	0.871	0.805	0.746	0.722	0.650	0.619

(a) Sample sizes, not extrapolated
(b) Model: PID = u + T(i) + B(j) + Surdose + error
(c) Model: PID = u + T(i) + B(j) +TB(ij) + Surdose + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS
Surdose = Time from end of surgery to dose.

Figure 2, Table 2. Pain Relief (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL TOPAR AND PEAK PAIN RELIEF[a]

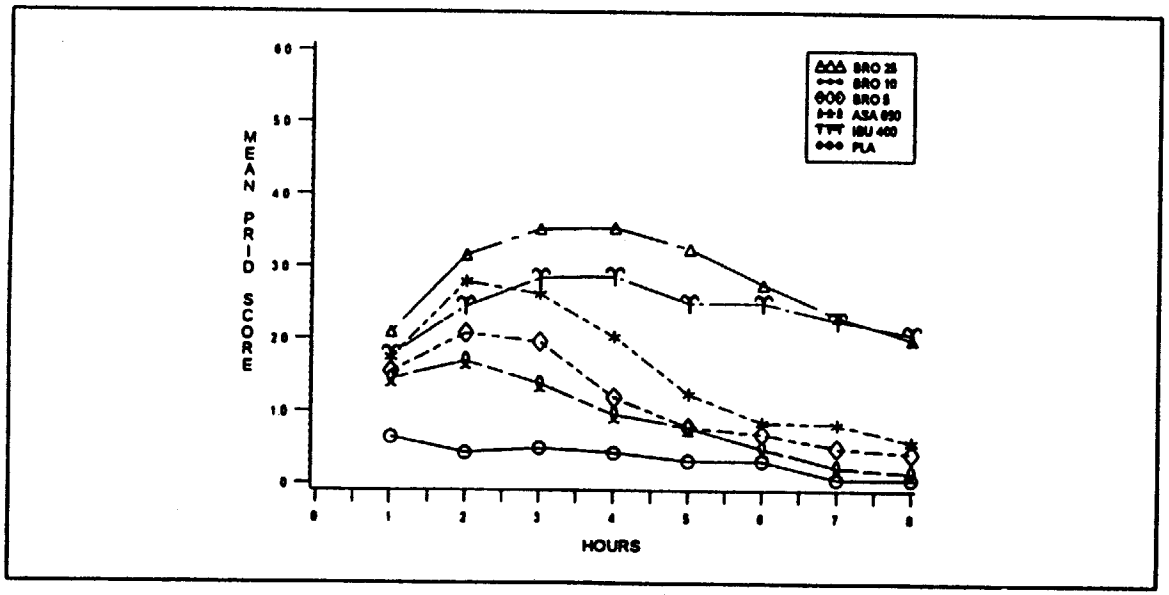
Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak PAIN RELIEF
Bromfenac 25 mg	45	4.63A	14.14A	2.71A
Bromfenac 10 mg	46	3.96AB	8.49B	2.26AB
Bromfenac 5 mg	42	3.23AB	6.04B	1.71BC
Aspirin 650 mg	46	2.84B	5.09BC	1.56C
Ibuprofen 400 mg	43	3.83AB	12.16A	2.44A
Placebo	45	1.26C	2.22C	0.82D
Prob > F		0.0001	0.0001	0.0001
Root MSE		2.7475	7.4844	1.3505

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)															
Treatment	1		2		3		4		5		6		7		8	
Bromfenac 25 mg	1.44 45 (a)	(1.14) A(d)	2.07 45	(1.47) A	2.24 33	(1.68) A	2.29 32	(1.69) A	2.11 26	(1.75) A	1.79 23	(1.75) A	1.53 17	(1.70) A	1.33 14	(1.67) A
Bromfenac 10 mg	1.26 46	(1.29) A	1.85 44	(1.46) AB	1.70 34	(1.58) AB	1.35 21	(1.54) B	0.87 17	(1.29) B	0.63 10	(1.25) B	0.61 8	(1.29) B	0.46 8	(1.07) B
Bromfenac 5 mg	1.17 42	(1.06) A	1.40 40 AB	(1.25) AB	1.31 25	(1.33) BC	0.79 18	(1.32) BC	0.50 8	(1.11) BC	0.43 5	(1.13) B	0.31 3	(0.92) B	0.26 2	(0.89) B
Aspirin 650 mg	1.07 44	(1.19) AB	1.29 39	(1.39) B	0.98 26	(1.42) C	0.67 15	(1.33) C	0.56 8	(1.25) BC	0.33 4	(0.98) B	0.16 2	(0.67) B	0.09 1	(0.60) B
Ibuprofen 400 mg	1.30 43	(1.30) A	1.60 40	(1.48) AB	1.84 33	(1.59) AB	1.86 27	(1.66) A	1.65 21	(1.69) A	1.65 19	(1.73) A	1.56 20	(1.69) A	1.40 17	(1.72) A
Placebo	0.62 45	(0.94) B	0.44 41	(0.78) C	0.38 15	(0.83) D	0.29 6	(0.82) C	0.22 3	(0.88) C	0.20 2	(0.84) B	0.04 1	(0.30) B	0.04 1	(0.30) B
p-value Trt (b)	0.045		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (c)	0.369		0.594		0.434		0.924		0.834		0.924		0.667		0.721	
Root MSE (b)	1.147		1.284		1.359		1.337		1.272		1.235		1.118		1.065	

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + B(j) + Surdose + error
(c) Model: PR = u + T(i) + B(j) +TB(ij) + Surdose + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS
Surdose = Time from end of surgery to dose.

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AN PEAK PRID [a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 25 mg	45	7.00A	21.60A	4.15A
Bromfenac 10 mg	46	5.83AB	12.36B	3.35AB
Bromfenac 5 mg	42	4.60AB	8.95B	2.50BC
Aspirin 650 mg	46	3.82B	7.03BC	2.20C
Ibuprofen 400 mg	43	5.63AB	18.17A	3.72A
Placebo	45	1.31C	2.70C	0.93D
Prob > F		0.0001	0.0001	0.0001
Root MSE		4.5183	11.814	2.2752

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)															
Treatment	1		2		3		4		5		6		7		8	
Bromfenac 25 mg	2.09 45 (a)	(1.88) A(d)	3.16 45	(2.43) A	3.51 33	(2.69) A	3.53 32	(2.68) A	3.24 26	(2.75) B	2.76 23	(2.78) A	2.31 17	(2.66) A	2.00 14	(2.59) A
Bromfenac 10 mg	1.74 46	(2.27) A	2.78 44	(2.44) A	2.61 34	(2.59) AB	2.02 21	(2.35) B	1.24 17	(1.92) B	0.85 10	(1.79) B	0.83 8	(1.83) B	0.59 8	(1.50) B
Bromfenac 5 mg	1.55 42	(1.78) A	2.07 40	(2.08) AB	1.95 25	(2.11) BC	1.19 18	(2.10) BC	0.79 8	(1.73) B	0.69 5	(1.76) B	0.50 3	(1.44) B	0.43 2	(1.38) B
Aspirin 650 mg	1.44 44	(1.93) A	1.69 39	(2.27) A	1.38 26	(2.15) C	0.96 15	(2.06) C	0.78 8	(1.88) B	0.49 4	(1.47) B	0.22 2	(0.97) B	0.16 1	(0.90) B
Ibuprofen 400 mg	1.77 43	(2.13) A	2.44 40	(2.25) AB	2.84 33	(2.53) AB	2.86 27	(2.54) A	2.49 21	(2.59) A	2.49 19	(2.66) A	2.26 20	(2.62) A	2.07 17	(2.68) A
Placebo	0.64 45	(1.68) B	0.42 41	(1.44) C	0.49 15	(1.42) D	0.42 6	(1.29) C	0.31 3	(1.40) B	0.31 2	(1.36) B	0.07 1	(0.45) B	0.07 1	(0.45) B
p-value Trt (b)	0.036		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (c)	0.353		0.675		0.379		0.868		0.898		0.961		0.695		0.677	
Root MSE (b)	1.909		2.082		2.164		2.094		1.976		1.921		1.717		1.639	

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + Surdose + error
(c) Model: PRID = PR = u + T(i) + B(j) +TB(ij) + Surdose + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS
Surdose = Time from end of surgery to dose.

Table 4. Estimated Onset of Pain Relief (on-PR)

Treatment Group	PRID at 30 min			Estimated on-PR	
	Mean[a]	SD	n	Time (min)	95%-CI (min)
Bromfenac 25 mg	2.09	1.88	45	29	23 - 39
Bromfenac 10 mg	1.74	2.27	46	35	25 - 56
Bromfenac 5 mg	1.55	1.78	42	39	29 - 60
Aspirin 650 mg	1.48	1.93	44	41	29 - 67
Ibuprofen 400 mg	1.77	2.13	43	34	25 - 54
Placebo	0.64	1.68	45	93	52 - 430
(a) Raw unadjusted mean of (unextrapolated) PRID scores.					

Figure 4. Estimated Duration of Analgesia
(Time-to-Remedication)

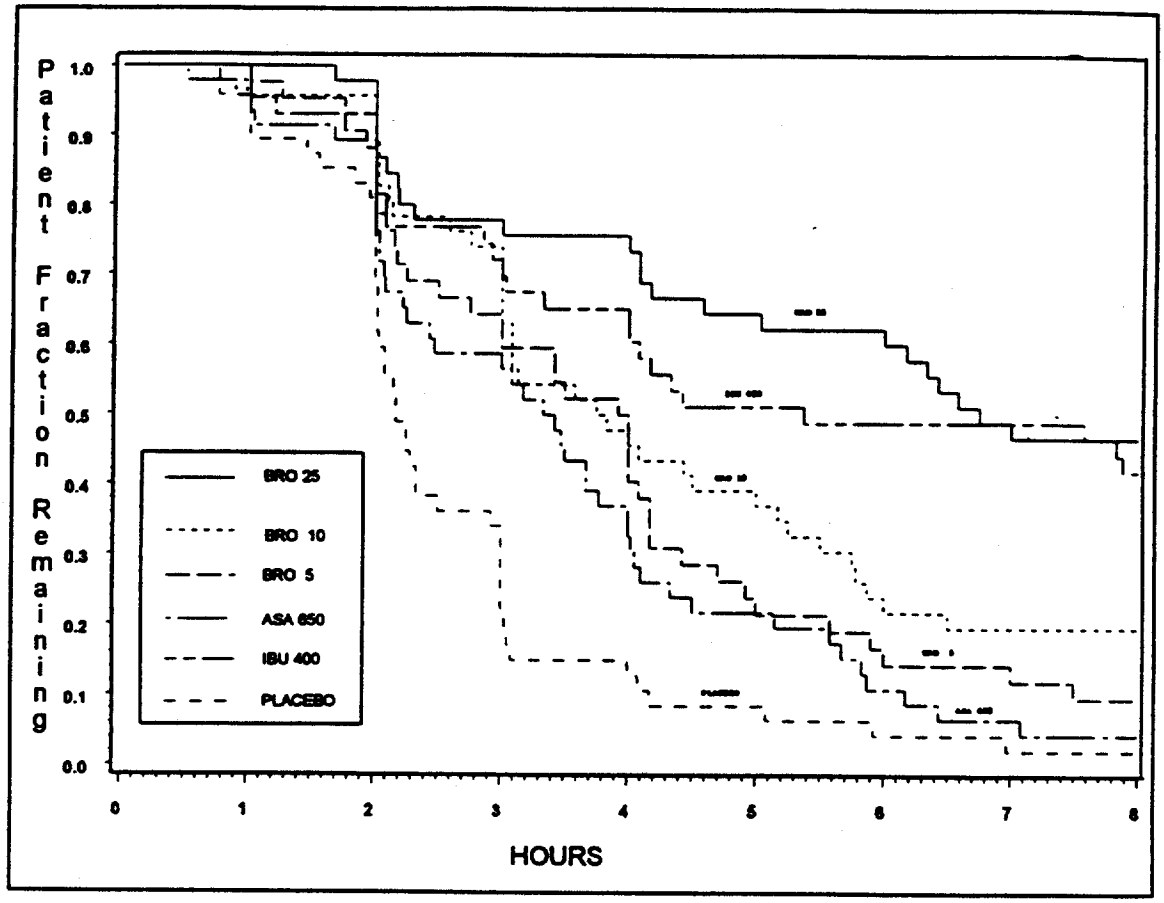


Table 5. Duration of Pain Relief (dur-PRs)

Treatment	n	Calculated Time to Remedication	
		Mean [a] h:min	95% CI [b] h:min
Bromfenac 25 mg	45	6:18 (A) [c]	5:27 - 7:09
Bromfenac 10 mg	46	4:35 (B)	3:50 - 5:20
Bromfenac 5 mg	42	4:02 (BC)	3:22 - 4:42
Aspirin 650 mg	44	3:33 (C)	2:59 - 4:07
Ibuprofen 400 mg	43	5:52 (A)	4:54 - 6:50
Placebo	45	2:40 (D)	2:14 - 3:06

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

Table 6. Time-to-Remedication (Percentiles)

Treatment	----------Percentiles In Hours:minutes (95% C. I.)----------		
	25%	50% (Median)	75%
Bromfenac 25	4:00 (2:05, 6:00)	6:45 (5:02, >8hr)	>8hr (NE)
Bromfenac 10	2:45 (2:01, 3:05)	3:47 (3:00, 5:10)	5:52 (5:00, >8hr)
Bromfenac 5	2:09 (2:00, 3:00)	3:58 (2:45, 4:10)	4:55 (4:05, 6:00)
Aspirin 650	2:02 (2:00, 2:26)	3:23 (2:15, 4:00)	4:20 (3:46, 5:50)
Ibuprofen 400	2:51 (2:00, 4:10)	7:35(4:00, >8hr)	>8hr (NE)
Placebo	2:00 (1:33, 2:02)	2:10 (2:01, 2:30)	3:00 (2:20, 4:00)

NE: Not estimable.

CONFIDENTIAL: SBA Summary for Bromfenac Protocol AHR-22-US

A Double-blind Single-dose Evaluation of the Relative Analgesic Efficacy and Adverse Effect Liability of Bromfenac, Ibuprofen, Aspirin, and Placebo in the Treatment of Postoperative Pain Following Surgery

IND DRUG:	Bromfenac	DOSES:	100, 50, 25, 10 mg oral
REFERENCE DRUGS:	Ibuprofen (IBU) Aspirin (ASA) Placebo	DOSE:	400 mg oral 650 mg oral
TOTAL PTS ENROLLED: 316		DURATION OF DOSING:	Single dose, 8 hr observation

INVESTIGATOR: James A. Forbes, M.S., Shrewsbury, PA, USA

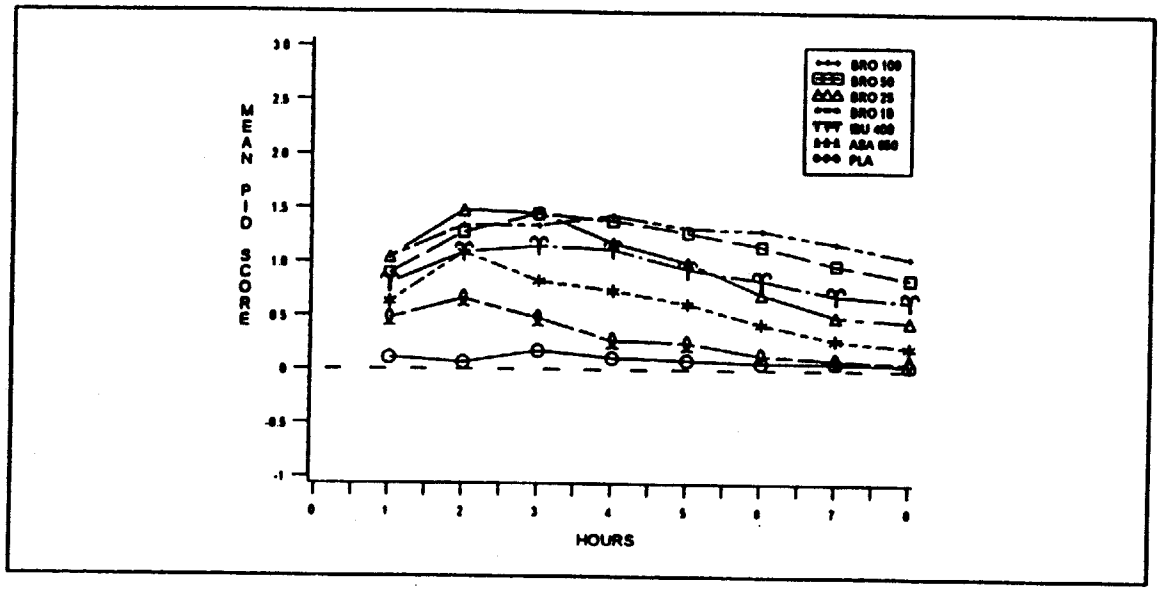
PURPOSE: The purpose of this study was to compare the efficacy and safety of single oral doses of bromfenac (100, 50, 25, and 10 mg), ibuprofen (400 mg), aspirin (650 mg), and placebo in the treatment of moderate to severe pain resulting from surgery.
METHOD: This was a single-dose, double-blind, randomized, parallel study with 7 treatments. Study medication was administered within 8 hours after surgery to patients with moderate or severe pain. Pain intensity was assessed before dose, then both pain intensity and pain relief were assessed hourly for 8 hours after medication. The following measurements of efficacy were derived from the patients' ratings: hourly pain relief score, total pain relief score (TOPAR), peak pain relief score, hourly pain intensity difference scores (PID), sum of the pain intensity difference scores (SPID), peak PID score, hourly pain relief plus PID scores (PRID), sum of the PRID scores (SPRID), peak PRID score, total hours of pain half-gone, and patient's global assessment. Estimates of the onset of pain relief (on-PR) and duration of pain relief (dur-PR) were also computed.
RESULTS: Three hundred sixteen (316) patients ingested study medication in the following treatment groups: bromfenac 100 mg, 44; bromfenac 50 mg, 47; bromfenac 25 mg, 44; bromfenac 10 mg, 46; IBU, 45; ASA, 44; and placebo, 46. All 316 patients who ingested study medication had data available for safety and efficacy analysis.

All doses of bromfenac and ibuprofen were significantly ($p \leq 0.05$) superior to aspirin and placebo for the 3-hour and final TOPAR, SPID, and SPRID. Bromfenac 100 mg was significantly superior to IBU for TOPAR and SPRID at 3 hours, for TOPAR, SPID, and SPRID at 8 hours, and for peak analgesic efficacy scores. Additionally, bromfenac 100 mg was superior to IBU for most hourly efficacy assessments, especially for the latter timepoints (5 to 8 hours). Bromfenac 50 mg and 25 mg were similar to IBU for most primary efficacy variables, peak analgesic efficacy scores, and hourly efficacy assessments. ASA was significantly superior to placebo for 3-hr and final TOPAR, SPID, and SPRID.

The on-PR was faster for bromfenac 100, 50, and 25 mg (less than or equal to 21 minutes) than for the other treatment groups. Based on 95% confidence limits, all bromfenac groups and ibuprofen had significantly faster on-PRs than placebo (83 minutes); on-PRs for bromfenac 100 and 25 mg were also significantly faster than for aspirin. The on-PR for bromfenac 10 mg and ibuprofen 400 mg were similar (approximately 25 minutes). The dur-PR was significantly longer for bromfenac 100, 50, and 25 mg and ibuprofen than for aspirin or placebo; the value for aspirin was significantly longer than that for placebo. Bromfenac 50 and 25 mg and ibuprofen had similar dur-PR values (approximately 6.5 hours). Bromfenac 100 mg was superior to IBU with respect to the percentage of patients remedicating by hour 8.

A total of 126 patients reported 1 or more treatment-emergent study events (TESE); 17 on bromfenac 100 mg, 13 on bromfenac 50 mg, 22 on bromfenac 25 mg, 26 on bromfenac 10 mg, 15 on IBU, 17 on ASA, and 16 on placebo. TESE were most commonly reported for the digestive and nervous systems. There were no serious or unexpected adverse effects and no patient withdrew because of an adverse effect.
CONCLUSIONS: Bromfenac was an effective analgesic for the relief of moderate to severe pain following oral surgery. The analgesic activity of all bromfenac doses was superior to that of ASA and placebo and bromfenac 100 mg was superior to IBU for almost all primary efficacy variables. All study treatments were well tolerated in this study.

Figure 1, Table 1. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) (Intent-to-Treat Patients)



3-HOUR AND FINAL SPID AND PEAK PID[a]

Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 100 mg	44	3.06AB	9.48A	1.80A
Bromfenac 50 mg	47	2.89A	8.83A	1.60AB
Bromfenac 25 mg	44	3.25AB	7.59AB	1.66AB
Bromfenac 10 mg	46	2.13C	4.72C	1.46B
Ibuprofen 400 mg	45	2.46BC	6.94BC	1.47B
Aspirin 650 mg	44	1.38D	2.40D	0.91C
Placebo	46	0.26E	0.70E	0.41D
p-value		<0.0001	<0.0001	<0.0001
Root MSE of Ranks		75.65	74.82	73.2356

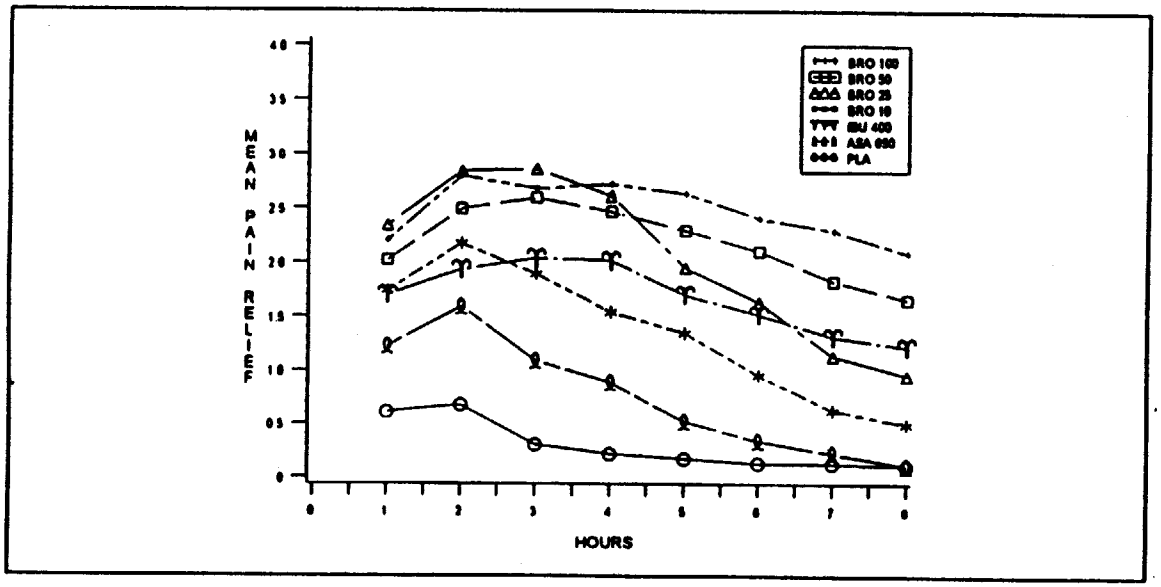
a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)															
Treatment	1		2		3		4		5		6		7		8	
Bromfenac 100 mg	1.05 44 (a)	(0.89) A (d)	1.34 44	(0.86) AB	1.34 38	(0.86) AB	1.43 38	(0.93) A	1.32 36	(0.98) A	1.30 31	(0.98) A	1.18 25	(1.04) A	1.05 21	(1.08) A
Bromfenac 50 mg	0.89 47	(0.94) A	1.28 47	(1.02) AB	1.45 40	(0.90) A	1.38 38	(0.95) A	1.28 35	(1.02) A	1.15 29	(1.04) A	0.98 23	(0.97) A	0.85 17	(0.96) AB
Bromfenac 25 mg	1.05 44	(0.68) A	1.48 44	(0.70) A	1.45 43	(0.85) AB	1.18 41	(0.84) A	1.00 36	(0.84) AB	0.70 28	(0.82) BC	0.50 22	(0.88) BC	0.45 12	(0.85) CD
Bromfenac 10 mg	0.63 46	(0.71) BC	1.09 45	(0.86) B	0.83 38	(0.85) C	0.74 32	(1.04) B	0.62 21	(1.02) C	0.43 17	(0.84) CD	0.28 15	(0.78) CD	0.22 10	(0.66) DE
Ibuprofen 400 mg	0.80 44	(0.92) AB	1.09 44	(0.95) B	1.15 40	(0.98) B	1.12 34	(1.02) A	0.93 25	(1.12) BC	0.84 21	(1.07) B	0.70 15	(1.05) B	0.64 11	(1.03) BC
ASA 650 mg	0.48 44	(0.93) C	0.66 43	(1.06) C	0.48 31	(0.88) D	0.27 24	(0.79) C	0.25 13	(0.75) D	0.14 9	(0.55) DE	0.09 5	(0.47) D	0.07 3	(0.33) E
Placebo	0.11 46	(0.77) D	0.07 42	(0.77) D	0.17 21	(0.64) E	0.11 9	(0.57) C	0.09 4	(0.35) D	0.07 2	(0.33) E	0.07 2	(0.33) D	0.04 2	(0.21) E
p-value Trt (b)	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (c)	0.014		0.318		0.426		0.728		0.359		0.127		0.354		0.744	
p-value Trt*Site (c)	0.927		0.964		0.864		0.676		0.719		0.926		0.942		0.975	
Root MSE of Ranks (b)	75.899		73.664		73.027		73.709		73.057		69.284		68.48		67.399	

(a) Sample sizes, not extrapolated
(b) Model: PID = u + T(i) + B(j) + TB(ij) + S(k) + TS(ik) + error
(c) Model: PID = u + T(i) + B(j) + TB(ij)+ S(k) + TS(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 2, Table 2. Pain Relief (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL TOPAR AND PEAK RELIEF[a]

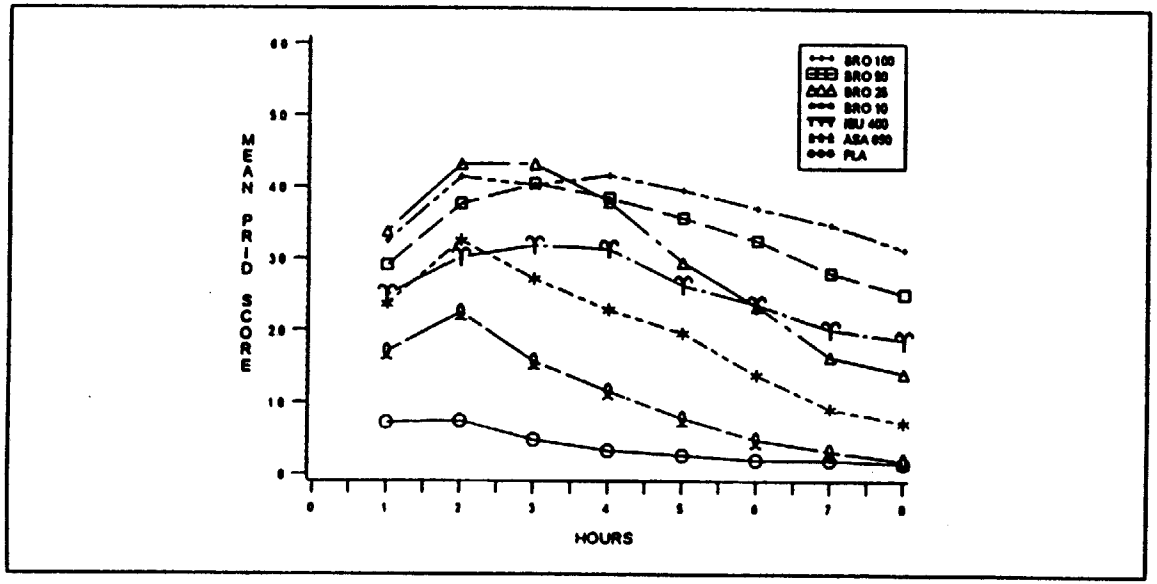
Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak PAIN RELIEF
Bromfenac 100 mg	44	6.34A	18.80A	3.36A
Bromfenac 50 mg	47	5.81A	16.64AB	2.89AB
Bromfenac 25 mg	44	6.61A	15.86AB	3.20AB
Bromfenac 10 mg	46	4.86B	10.53C	2.67B
Ibuprofen 400 mg	45	4.65B	12.83BC	2.56B
Aspirin 650 mg	44	3.36C	5.94D	1.89C
Placebo	46	1.43D	2.29E	0.89D
p-value		<0.0001	<0.0001	<0.0001
Root MSE of Ranks		77.25	74.42	76.0174

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)															
Treatment	1		2		3		4		5		6		7		8	
Bromfenac 100 mg	2.20	(1.02)	2.80	(1.17)	2.68	(1.29)	2.73	(1.39)	2.64	(1.45)	2.41	(1.57)	2.30	(1.61)	2.09	(1.68)
	44 (a)	A (d)	42	A	38	A	38	A	36	A	30	A	24	A	20	A
Bromfenac 50 mg	2.02	(1.24)	2.49	(1.37)	2.60	(1.48)	2.47	(1.56)	2.30	(1.69)	2.11	(1.75)	1.83	(1.71)	1.66	(1.72)
	47	AB	46	AB	38	AB	38	AB	32	AB	26	AB	22	AB	17	AB
Bromfenac 25 mg	2.34	(1.12)	2.84	(1.08)	2.86	(1.23)	2.61	(1.24)	1.95	(1.55)	1.64	(1.57)	1.14	(1.61)	0.95	(1.55)
	44	AB	44	A	41	A	40	AB	32	BC	26	B	19	CD	10	CD
Bromfenac 10 mg	1.74	(1.06)	2.17	(1.16)	1.89	(1.37)	1.54	(1.63)	1.35	(1.70)	0.96	(1.50)	0.63	(1.32)	0.50	(1.21)
	46	B	43	BC	35	C	28	C	18	C	14	C	11	DE	8	DE
Ibuprofen 400 mg	1.70	(1.15)	1.93	(1.23)	2.04	(1.38)	2.01	(1.58)	1.70	(1.65)	1.52	(1.68)	1.31	(1.63)	1.22	(1.61)
	44	B	43	C	36	CD	33	B	24	BC	17	B	13	BC	11	BC
ASA 650 mg	1.23	(1.26)	1.59	(1.50)	1.09	(1.38)	0.89	(1.40)	0.52	(1.19)	0.34	(1.03)	0.23	(0.89)	0.11	(0.62)
	44	C	43	C	23	D	18	D	12	D	8	D	3	E	3	E
Placebo	0.61	(0.93)	0.67	(1.01)	0.30	(0.87)	0.22	(0.84)	0.17	(0.68)	0.13	(0.62)	0.13	(0.62)	0.11	(0.53)
	46	D	39	D	14	E	6	E	3	D	2	D	2	E	2	E
p-value Trt (b)	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (c)	0.051		0.254		0.358		0.222		0.196		0.331		0.834		0.945	
p-value Trt*Site (c)	0.415		0.688		0.932		0.816		0.671		0.755		0.692		0.957	
Root MSE of Ranks (b)	79.354		77.803		74.088		73.121		73.136		71.417		68.371		66.466	

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + B(j) + S(k) + TB(ij) + error
(c) Model: PR = u + T(i) + B(j) + S(k) + TB(ij) + TS(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID[a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 100 mg	44	9.40A	28.27A	5.16A
Bromfenac 50 mg	47	8.70A	25.47AB	4.49AB
Bromfenac 25 mg	44	9.86A	23.45AB	4.86AB
Bromfenac 10 mg	46	6.99B	15.25C	4.13B
Ibuprofen 400 mg	45	7.12B	19.78BC	3.98B
Aspirin 650 mg	44	4.74C	8.34D	2.77C
Placebo	46	1.70D	2.99E	1.30D
p-value		<0.0001	<0.0001	<0.0001
Root MSE of Ranks		77.80	75.25	77.8712

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)															
Treatment	1		2		3		4		5		6		7		8	
Bromfenac 100 mg	3.25 44 (a)	(1.79) A (d)	4.14 42	(1.92) A	4.02 38	(2.05) AB	4.16 38	(2.24) A	3.95 36	(2.35) E	3.70 30	(2.45) A	3.48 24	(2.58) A	3.14 20	(2.69) A
Bromfenac 50 mg	2.91 47	(2.09) A	3.77 46	(2.30) AB	4.04 38	(2.31) A	3.85 38	(2.44) AB	3.57 32	(2.64) AB	3.26 26	(2.74) AB	2.81 22	(2.62) A	2.51 17	(2.63) AB
Bromfenac 25 mg	3.39 44	(1.73) A	4.32 44	(1.64) A	4.32 41	(1.97) A	3.80 40	(2.00) AB	2.95 32	(2.28) BC	2.34 26	(2.33) C	1.64 19	(2.45) BC	1.41 10	(2.38) CD
Bromfenac 10 mg	2.37 46	(1.66) BC	3.26 43	(1.88) BC	2.72 35	(2.10) C	2.28 28	(2.56) C	1.96 18	(2.66) D	1.38 14	(2.25) D	0.91 11	(2.04) CD	0.72 8	(1.81) DE
Ibuprofen 400 mg	2.50 44	(1.95) AB	3.02 43	(2.07) CD	3.19 36	(2.25) BC	3.13 33	(2.53) B	2.63 24	(2.70) CD	2.36 17	(2.70) BC	2.01 13	(2.63) B	1.87 11	(2.59) BC
ASA 650 mg	1.70 44	(2.09) C	2.25 43	(2.49) D	1.57 23	(2.13) D	1.16 18	(2.08) D	0.77 12	(1.87) E	0.48 8	(1.56) E	0.32 3	(1.34) D	0.18 3	(0.95) E
Placebo	0.72 46	(1.60) D	0.74 39	(1.68) E	0.48 14	(1.44) E	0.33 6	(1.38) D	0.26 3	(1.02) E	0.20 2	(0.93) E	0.20 2	(0.93) D	0.15 2	(0.73) E
p-value Trt (b)	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (c)	0.019		0.337		0.451		0.496		0.360		0.175		0.621		0.949	
p-value Trt*Site (c)	0.692		0.793		0.898		0.795		0.681		0.832		0.749		0.974	
Root MSE of Ranks (b)	80.367		78.97		76.072		75.315		75.035		71.58		69.967		68.146	

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + S(k) + TB(ij) + error
(c) Model: PRID = u + T(i) + B(j) + S(k) + TB(ij) + TS(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Table 4. Estimated Onset of Pain Relief (on-PR)

	PRID at 60 minutes			Estimated on-PR	
Treatment	Mean[a]	SD	n	Time (min)	95%-CI in min
Bromfenac 100 mg	3.25	1.79	44	18	16 - 22
Bromfenac 50 mg	2.91	2.09	47	21	17 - 26
Bromfenac 25 mg	3.39	1.73	44	18	15 - 21
Bromfenac 10 mg	2.37	1.66	46	25	21 - 32
Ibuprofen 400 mg	2.55	1.95	45	24	19 - 31
Aspirin 650 mg	1.70	2.09	44	35	26 - 56
Placebo	0.72	1.60	46	83	50 - 245

a Raw unadjusted mean of (unextrapolated) PRID scores.

Figure 4. Estimated Duration of Analgesia
(Time-to-Remedication)

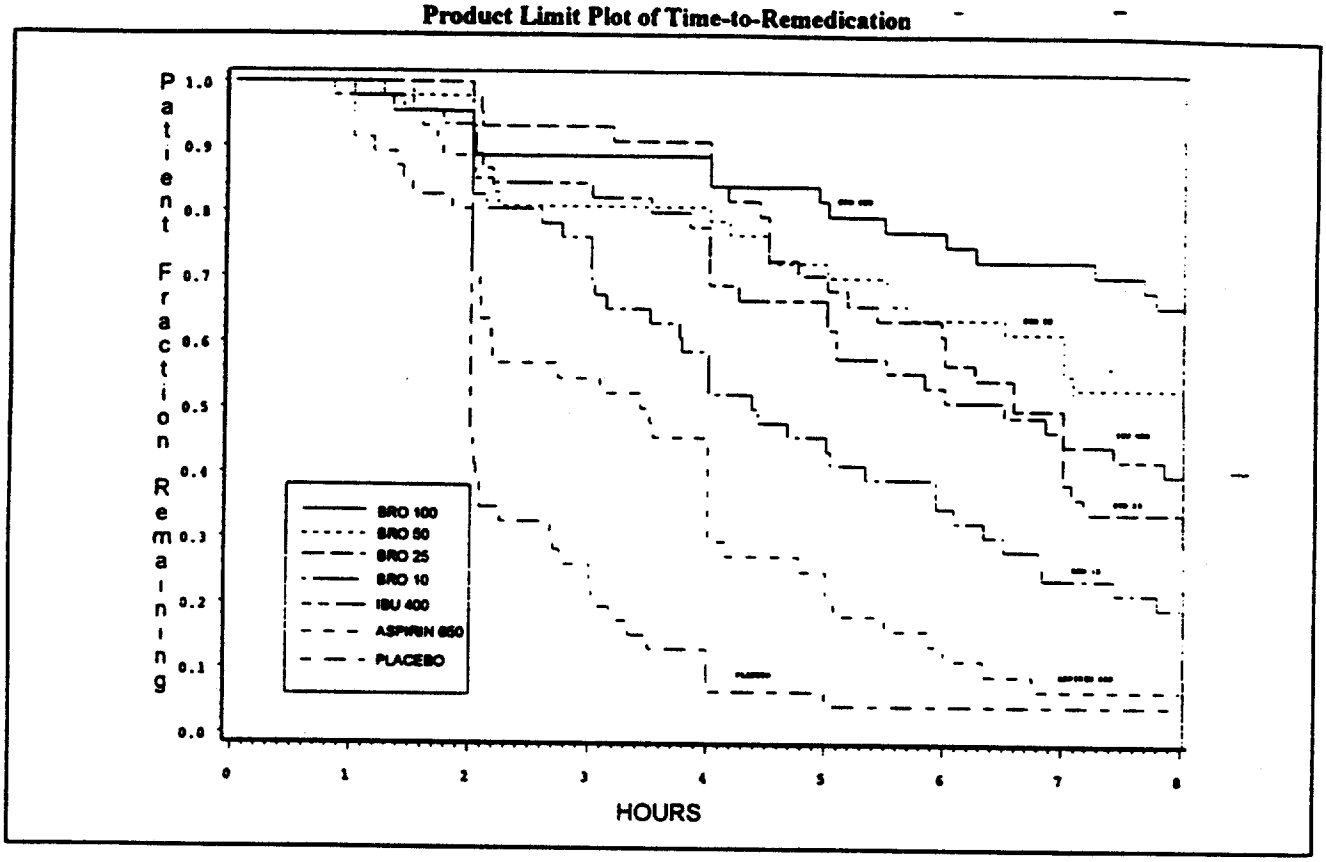


Table 5. Duration of Pain Relief (dur-PRs)

Treatment Group	n	Calculated Time to Remedication	
		Mean [a] h:min	95% CI [b] h:min
Bromfenac 100 mg	44	7:27 (A)[c]	6:42 to 8:12
Bromfenac 50 mg	47	6:44 (AB)	5:56 to 7:32
Bromfenac 25 mg	44	6:29 (B)	5:49 to 7:08
Bromfenac 10 mg	46	4:59 (C)	4:14 to 5:44
Ibuprofen 400 mg	45	6:11 (B)	5:23 to 6:59
Aspirin 650 mg	44	3:41 (D)	3:04 to 4:17
Placebo	46	2:34 (E)	2:05 to 3:02

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

Table 6. Time-to-Remedication (Percentiles)

Treatment	----------Percentiles In Hours:minutes (95% C. I.)----------		
	25%	50% (Median)	75%
Bromfenac 100 mg	6:08 (4:00,>8hr)	>8hr (NE)	>8hr (NE)
Bromfenac 50 mg	4:30 (2:01,7:00)	4:00 (6:30,>8hr)	>8hr (NE)
Bromfenac 25 mg	4:30 (4:00,6:00)	6:47 (5:25,7:10)	>8hr (7:00,>8hr)
Bromfenac 10 mg	3:00 (2:00,3:45)	4:24 (3:30,5:56)	6:50 (5:56,>8hr)
Ibuprofen 400 mg	4:00 (2:10,5:05)	6:30 (5:00,>8hr)	>8hr (NE)
Aspirin 650 mg	2:00 (2:00,2:10)	3:28 (2:05,4:00)	4:53 (4:00,5:52)
Placebo	2:00 (1:25,2:00)	2:00 (2:00,2:05)	3:00 (2:05,3:30)

NE: Not estimable

CONFIDENTIAL: SBA Summary for Bromfenac Protocol 792-A-301-US

A single-dose (placebo-controlled) and multiple-dose comparison of bromfenac sodium (AHR-10282B) 50 and 25 mg, and naproxen sodium 550/275 mg in patients with pain following surgery.

IND DRUG:	Bromfenac	DOSES:	50, 25 mg oral
REFERENCE DRUGS:	Naproxen sodium Placebo	DOSE:	550/275 mg oral
TOTAL PTS ENROLLED:216		DURATION OF DOSING:	Single dose, 8 hr Multiple dose, up to 7 days
INVESTIGATOR: James Forbes, M.S., Shrewsbury, PA, United States			

PURPOSE: The purpose of this study was to compare the efficacy and safety of single doses of bromfenac, naproxen sodium and placebo and to compare the efficacy and safety of multiple doses of only the active treatments in patients with moderate to severe post- surgery pain.

METHOD: This double-blind outpatient study was designed to compare the efficacy and safety of single doses of bromfenac, naproxen sodium and placebo in patients with moderate to severe pain after surgery followed by a comparison of the efficacy and safety of multiple doses of the active treatments. All patients received an initial single dose of one of four treatments, bromfenac 50 mg, bromfenac 25 mg, naproxen sodium 550 mg and placebo. Patients had the option of continuing in the multiple-dose phase in which they received one of the three active treatment regimens, bromfenac 50 mg, 25 mg or naproxen sodium 275 mg (a 550 mg loading dose was ingested by placebo-treated patients reassigned to the naproxen sodium group). In the single-dose phase, patients recorded their pain intensity, pain relief, and pain half-gone for up to 8 hours after the first dose; global assessments were also recorded. In the multiple-dose phase, patients recorded pain intensity at 0 and 2 hours for the first dose of each day, global bedtime assessments and sleep quality assessments.

RESULTS: A total of 216 patients, 99 men and 117 women ages 16 to 54, took the first dose of study medication for moderate or severe pain following surgery as follows: bromfenac 50 mg (n=35), bromfenac 25 mg (n=36), naproxen sodium (n=38) and placebo (n=107). Because of an administrative error in generating the randomization code, the patients were not equally distributed among 4 treatment groups for the first dose (35 to 38 patients in each active treatment group and 107 patients in the placebo group). This error did not have any apparent effect on the outcome of the study. One hundred ninety-nine (199) patients entered the multiple-dose phase and took study medication as follows: bromfenac 50 mg (n=68), bromfenac 25 mg (n=68) and naproxen sodium (n=63).

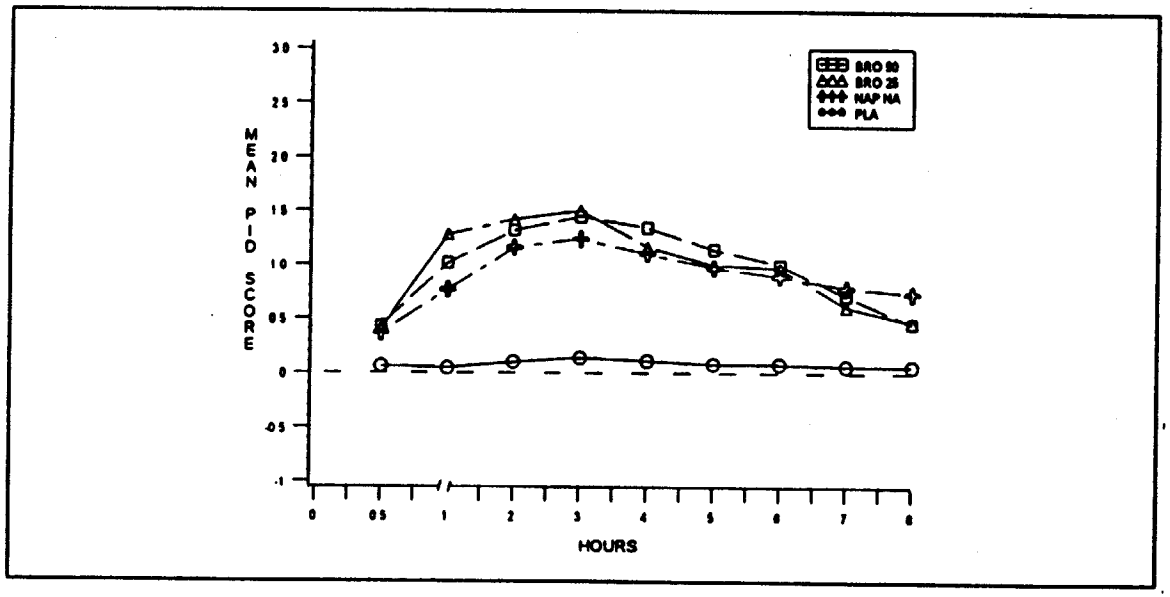
In the single-dose phase, both doses of bromfenac and naproxen sodium were significantly superior to placebo for all primary efficacy variables (3-hour and final TOPAR, SPID, and SPRID and peak pain relief, PID, and PRID) and for all hourly assessments from 0.5 hours through 8 hours. Both bromfenac doses were superior to naproxen sodium in several 3-hour sums and peak responses. Global assessments in the single-dose phase for patients taking bromfenac 50 mg or 25 mg or naproxen sodium were superior to those for placebo-treated patients; bromfenac 25 mg was also superior to naproxen sodium. In the multiple-dose phase, the global bedtime assessment scores and the 2-hour PID scores were higher for both bromfenac regimens than for naproxen sodium; the differences were statistically significant in 17 of 20 comparisons for days 2-6.

In the single-dose phase, one or more TESE were reported during the study by 3 (8.6%) patients who received bromfenac 50 mg, 3 (8.3%) patients who received bromfenac 25 mg, 2 (5.3%) patients who received naproxen sodium, and 5 (4.7%) patients who received placebo. In the multiple-dose phase, one or more TESE were reported by 14 (20.6%) patients who received bromfenac 50 mg, 13 (19.1%) patients who received bromfenac 25 mg and 16 (25.4%) patients who received naproxen sodium.

Two (2) placebo-treated patients in the single-dose phase discontinued treatment due to adverse study events. In the multiple-dose phase, 1 patient taking bromfenac 50 mg, 2 patients taking bromfenac 25 mg and 4 patients taking naproxen sodium withdrew from the study due to study events. Three (3) patients withdrew from the study due to study events which were considered to be serious. One (1) patient taking bromfenac 25 mg withdrew from the study due to pruritus, rash and swelling of the hands and feet, 1 patient taking naproxen sodium discontinued treatment due to a rash, and 1 patient taking placebo withdrew from the study for dizziness and syncope.

CONCLUSIONS: These results of this study indicate that single oral doses of 50 mg and 25 mg of bromfenac are at least as effective as the usual therapeutic dose of naproxen sodium in relieving pain after oral surgery and sometimes significantly superior, namely in the first 3 hours after the dose. All active treatments were significantly superior to placebo. In this study, multiple doses of bromfenac 50 mg and 25 mg were also superior to naproxen sodium on most days.

Figure 1, Table 1. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted) (Intent-to-Treat Patients)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)



3-HOUR AND FINAL SPID AND PEAK PID [a]

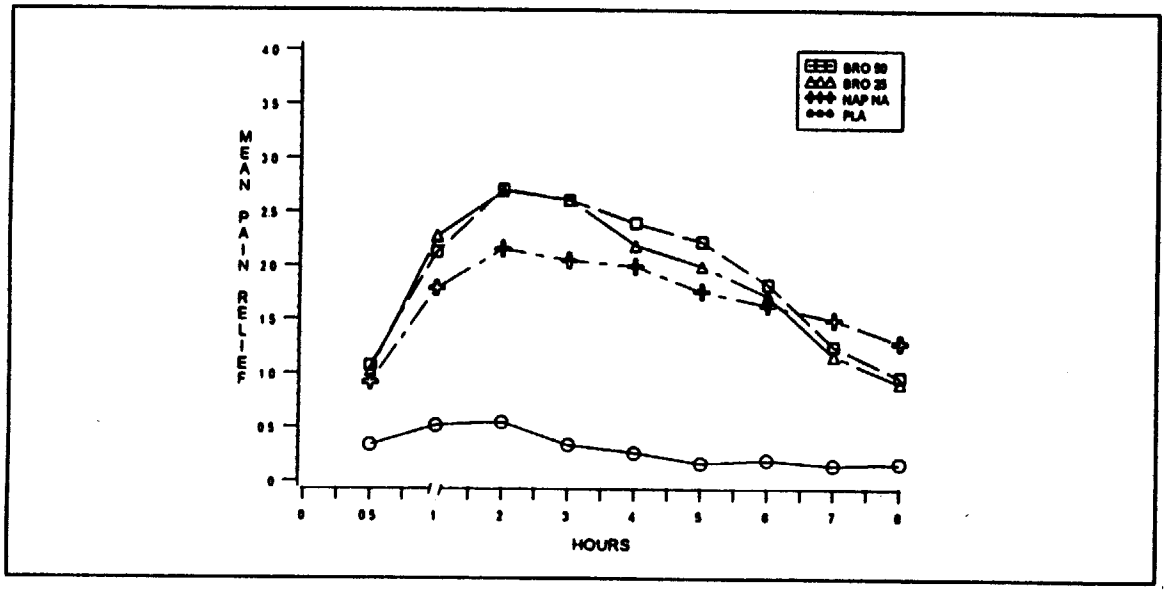
Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 50 mg	35	3.01 AB	8.16 A	1.74 A
Bromfenac 25 mg	36	3.33 A	8.07 A	1.64 AB
Naproxen Na 550 mg	38	2.53 B	7.28 A	1.45 B
Placebo	106	0.24 C	0.70 B	0.38 C
Overall treatment p-value		0.0001	0.0001	0.0001
Root MSE		1.5988	4.2188	0.6858

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)								
	1/2	1	2	3	4	5	6	7	8
Bromfenac 50 mg	0.44 (0.69) A (d) 34 (a)	1.01 (0.86) A 34	1.31 (0.96) A 34	1.44 (1.05) A 30	1.34 (1.14) A 24	1.14 (1.09) A 22	1.00 (1.00) A 18	0.71 (0.86) A 14	0.46 (0.82) A 10
Bromfenac 25 mg	0.42 (0.73) A 36	1.28 (0.85) A 36	1.42 (0.77) A 36	1.50 (0.77) A 36	1.17 (0.94) A 29	1.00 (1.01) A 21	0.97 (0.94) A 20	0.61 (0.90) A 17	0.47 (0.84) A 11
Naproxen Na 550 mg	0.37 (0.71) A 38	0.76 (0.82) B 38	1.16 (0.92) A 36	1.24 (0.91) A 32	1.11 (0.92) A 27	0.97 (0.94) A 24	0.89 (0.92) A 20	0.79 (0.91) A 13	0.74 (0.92) A 11
Placebo	0.07 (0.56) B 106	0.05 (0.65) C 106	0.10 (0.68) B 83	0.14 (0.49) B 37	0.11 (0.42) B 16	0.08 (0.31) B 9	0.08 (0.34) B 6	0.07 (0.29) B 5	0.07 (0.32) B 4
p-value Trt (b)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p-value Trt*Baseline (c)	0.629	0.618	0.151	0.001	0.009	0.016	0.010	0.169	0.444
Root MSE (b)	0.597	0.688	0.734	0.709	0.757	0.748	0.717	0.663	0.651

(a) Sample sizes, not extrapolated
(b) Model: PID = u + T(i) + B(j) + error
(c) Model: PID = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 2, Table 2. Pain Relief (Extrapolated, Unadjusted) **(Intent-to-Treat Patients)**
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)



3-HOUR AND FINAL TOPAR AND PEAK RELIEF [a]

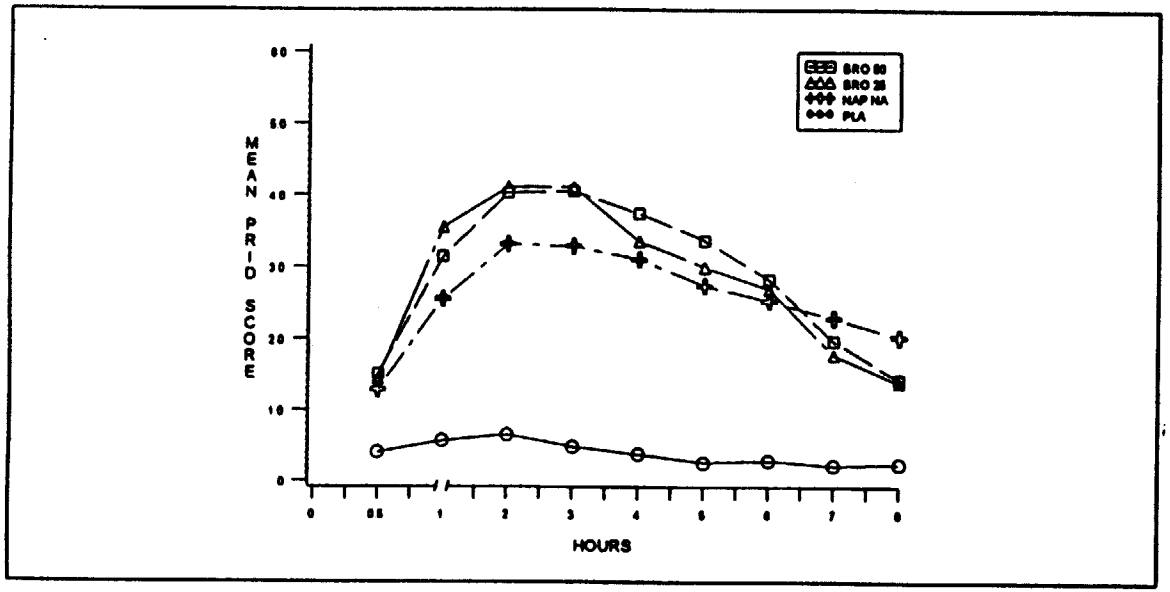
Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak PAIN RELIEF
Bromfenac 50 mg	35	6.16 A	15.66 A	3.20 A
Bromfenac 25 mg	36	6.22 A	15.07 A	3.03 A
Naproxen Na 550 mg	38	4.99 B	13.55 A	2.47 B
Placebo	106	1.28 C	2.31 B	0.88 C
Overall treatment p-value		0.0001	0.0001	0.0001
Root MSE		2.3267	7.1547	1.0986

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)															
	1/2		1		2		3		4		5		6		7		8	
Bromfenac 50 mg	1.08 34 (a)	(1.07) A (d)	2.13 34	(1.24) AB	2.71 34	(1.15) A	2.61 27	(1.56) AB	2.40 24	(1.74) A	2.23 20	(1.72) A	1.83 17	(1.71) A	1.26 10	(1.63) A	0.97 9	(1.48) A
Bromfenac 25 mg	1.03 36	(0.94) A	2.28 36	(1.26) A	2.69 36	(1.06) A	2.61 32	(1.29) A	2.19 26	(1.55) A	2.00 20	(1.66) A	1.72 18	(1.58) A	1.17 12	(1.52) A	0.92 9	(1.46) A
Naproxen Na 550 mg	0.92 38	(1.00) A	1.79 38	(1.12) B	2.16 35	(1.28) B	2.05 28	(1.47) B	2.00 25	(1.49) A	1.76 22	(1.58) A	1.63 17	(1.68) A	1.50 13	(1.67) A	1.29 9	(1.71) A
Placebo	0.34 106	(0.58) B	0.52 105	(0.72) C	0.55 74	(0.83) C	0.34 20	(0.88) C	0.26 14	(0.81) B	0.17 8	(0.65) B	0.20 6	(0.77) B	0.15 4	(0.66) B	0.17 4	(0.72) B
p-value Trt (b)	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (c)	0.767		0.928		0.812		0.562		0.597		0.260		0.069		0.240		0.176	
Root MSE (b)	0.820		0.995		1.018		1.200		1.263		1.258		1.286		1.219		1.193	

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + B(j) + error
(c) Model: PR = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) (Intent-to-Treat Patients) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)



3-HOUR AND FINAL SPRID AND PEAK PRID [a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 50 mg	35	9.17 A	23.83 A	4.94 A
Bromfenac 25 mg	36	9.56 A	23.14 A	4.67 AB
Naproxen Na 550 mg	38	7.52 B	20.84 A	3.92 B
Placebo	106	1.52 C	3.01 B	1.25 C
Overall treatment p-value		0.0001	0.0001	0.0001
Root MSE		3.7736	11.1258	1.7222

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)															
	1/2		1		2		3		4		5		6		7		8	
Bromfenac 50 mg	1.51 34 (a)	(1.67) A (d)	3.14 34	(2.03) AB	4.03 34	(2.04) A	4.06 27	(2.52) A	3.74 24	(2.81) A	3.37 20	(2.72) A	2.83 17	(2.64) A	1.97 10	(2.42) A	1.43 9	(2.24) A
Bromfenac 25 mg	1.44 36	(1.56) A	3.56 36	(2.02) A	4.11 36	(1.72) A	4.11 32	(1.95) A	3.36 26	(2.39) A	3.00 20	(2.59) A	2.69 18	(2.34) A	1.78 12	(2.34) A	1.39 9	(2.26) A
Naproxen Na 550 mg	1.29 38	(1.59) A	2.55 38	(1.78) B	3.32 35	(2.05) B	3.29 28	(2.20) A	3.11 25	(2.32) A	2.74 22	(2.40) A	2.53 17	(2.54) A	2.29 13	(2.52) A	2.03 9	(2.56) A
Placebo	0.41 106	(1.03) B	0.57 105	(1.25) C	0.65 74	(1.40) C	0.48 20	(1.32) B	0.38 14	(1.20) B	0.25 8	(0.96) B	0.28 6	(1.11) B	0.22 4	(0.94) B	0.24 4	(1.03) B
p-value Trt (b)	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (c)	0.724		0.887		0.614		0.179		0.307		0.173		0.070		0.302		0.296	
Root MSE (b)	1.318		1.598		1.669		1.835		1.974		1.946		1.945		1.839		1.806	

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + error
(c) Model: PRID = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Table 4. Estimated Onset of Pain Relief (on-PR)

	PRID at 30 min			Estimated on-PR	
Treatment Group	Mean [a]	S.D.	n	Time (min)	95%-CI (min)
Bromfenac 50 mg	1.53	1.69	34	20	14 - 32
Bromfenac 25 mg	1.44	1.56	36	21	15 - 33
Naproxen Na 550 mg	1.29	1.59	38	23	17 - 39
Placebo	0.41	1.03	106	74	50 - 145

a Raw unadjusted mean of (unextrapolated) PRID scores.

Figure 4. Estimated Duration of Analgesia
(Time-to-Remedication)

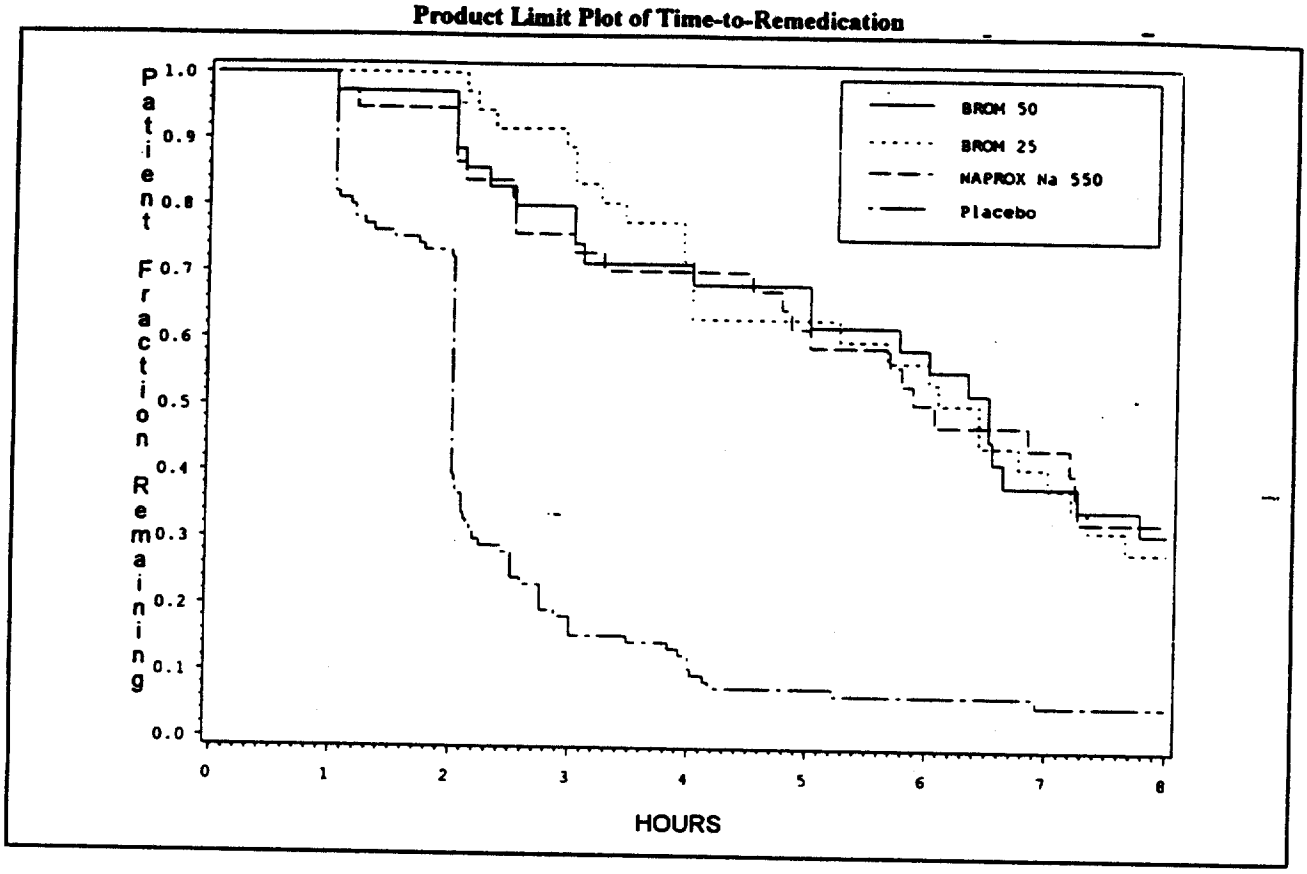


Table 5. Duration of Pain Relief (dur-PRs)

Treatment Group	n	Calculated Time to Remedication	
		Mean [a] h:min	95% CI [b] h:min
Bromfenac 50 mg	35	5:56 A[c]	5:01-6:52
Bromfenac 25 mg	36	6:01 A	5:12-6:50
Naproxen Na 550 mg	38	5:52 A	4:56-6:47
Placebo	106	2:27 B	2:07-2:49

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

Table 6. Time-to-Remedication (Percentiles)

Treatment	----------Percentiles In Hours:minutes (95% C. I.)----------		
	25%	50% (Median)	75%
Bromfenac 50 mg	3:00 (2:05,6:00)	6:30 (5:00,7:46)	>8h (6:32,>8h)
Bromfenac 25 mg	3:55 (3:00,5:39)	6:25 (4:00,7:20)	>8h (6:45,>8h)
Naproxen-Na 550 mg	3:00 (2:05,5:40)	6:03 (4:45,7:15)	>8h (7:11,>8h)
Placebo	1:30 (1:00,2:00)	2:00 (NE)	2:30 (2:05,3:00)

NE: Not estimable.

CONFIDENTIAL: SBA for Bromfenac Protocol 792-A-311-US

A double-blind, placebo-controlled, single-dose pharmacokinetic/pharmacodynamic evaluation of bromfenac in fasted and fed surgery patients.

IND DRUG:	Bromfenac	Doses: 200, 100, 50, 25, 5 mg oral
REFERENCE DRUGS:	Placebo	
TOTAL PTS ENROLLED: 208		DURATION OF DOSING: Single dose, 8 hr

INVESTIGATOR: Stephen A. Cooper, DMD, PhD, Philadelphia, PA, United States

Elliot V. Hersch, DMD, PhD, Philadelphia, PA, United States

Donald C. Reynolds, DDS, Washington DC, United States

PURPOSE: The primary objective of Section I was to study the relationship between the analgesic effect and plasma/effect site concentrations of bromfenac. A secondary objective was to examine the analgesic activity of bromfenac at 5 dose levels.

The purpose of Section II was to determine the effect of various meals (liquid and soft food) on the bioavailability of bromfenac in surgery patients and to adopt a standard meal for use in Section III.

The purpose of Section III was to compare the PK/PD relationships between plasma concentrations and analgesic response to a single dose of bromfenac after a standard meal and to compare these results with those of Section I (fasted patients).

METHOD: **Section I.** This was a single-center (Univ. of Pennsylvania), single-dose, double-blind, placebo-controlled, randomized, parallel, pharmacokinetic and pharmacodynamic study relating drug plasma levels to the comparative analgesic activity of bromfenac (200, 100, 50, 25, and 5 mg).

Section II. The pilot phase of the extension was designed as an open-label, single-dose, randomized, food-controlled, pharmacokinetic study in patients receiving bromfenac 50 mg. Up to 3 specific diets were to be tested, however, the latter two were not necessary. No efficacy data were collected.

Section III. The third section of the study was designed as a single-center (Georgetown Univ.), double-blind (except preprandial bromfenac 25 mg group), randomized, parallel, single-dose, food-controlled, pharmacokinetic/pharmacodynamic analgesic study in patients following surgery. Patients were randomly assigned to receive 1 of 4 treatments: postprandial bromfenac 50 mg, preprandial bromfenac 25 mg, postprandial bromfenac 25 mg, and postprandial placebo. A preprandial bromfenac 25 mg group identical to that found in Section I is included in Section III to control for potential differences in patient population and study site.

The primary efficacy variables for Sections I and III were 3- and 8-hour total pain relief (TOPAR), summed pain intensity difference (SPID), summed pain relief and pain intensity difference (SPRID), and summed pain analog intensity differences (SPAID). Other variables were considered secondary for evaluation of efficacy (timed pain relief, PID, PRID, and PAID scores, global assessments, pain half-gone, on-PR and dur-PR).

RESULTS:

Efficacy: Section I. One hundred nineteen (119) patients were included in the valid-for-efficacy analysis. For all 8 primary variables bromfenac doses of 200, 100, 50, and 25 mg were significantly superior to placebo. Bromfenac 5 mg was significantly superior to placebo in three of eight primary variables (3-hour TOPAR, 3-hour SPRID, and 3-hour SPAID), and all peak measures. All doses of bromfenac were superior to placebo according to patient's global assessment.

Section III. All 80 patients were included in the valid-for-efficacy analysis. For all 8 primary variables bromfenac doses of 50 mg fed, 25 mg fasted, and 25 mg fed were significantly superior to placebo. All doses of bromfenac were also superior to placebo according to all four peak values, patient's global assessment, and pain half-gone. The difference between the response to 25 mg (fasted) in Sections I and III was large enough to preclude the use of the Section I group as control for Section III. The postprandial analgesic effect was significantly reduced (25 mg fasted versus 25 mg fed within Section III) but both bromfenac doses tested with food had well pronounced analgesic effects which were statistically and clinically superior to the response to placebo and comparable to the response to ibuprofen 400 mg observed in fasted historical controls at the same site.

Safety: Section I. One or more treatment-emergent study events were reported by 3 (14%) patients who received bromfenac 200 mg, 6 (30%) patients who received bromfenac 100 mg, 6 (30%) patients who received bromfenac 50 mg, 4 (20%) patients who received bromfenac 25 mg, 6 (24%) patients who received bromfenac 5 mg, and 5 (24%) patients who received placebo. The number of treatment-emergent study events (TESE) was not significantly different among the treatment groups for any (COSTART) body system or any specific event. Two patients were withdrawn from the study, both because of nausea and vomiting. No patients reported serious study events.

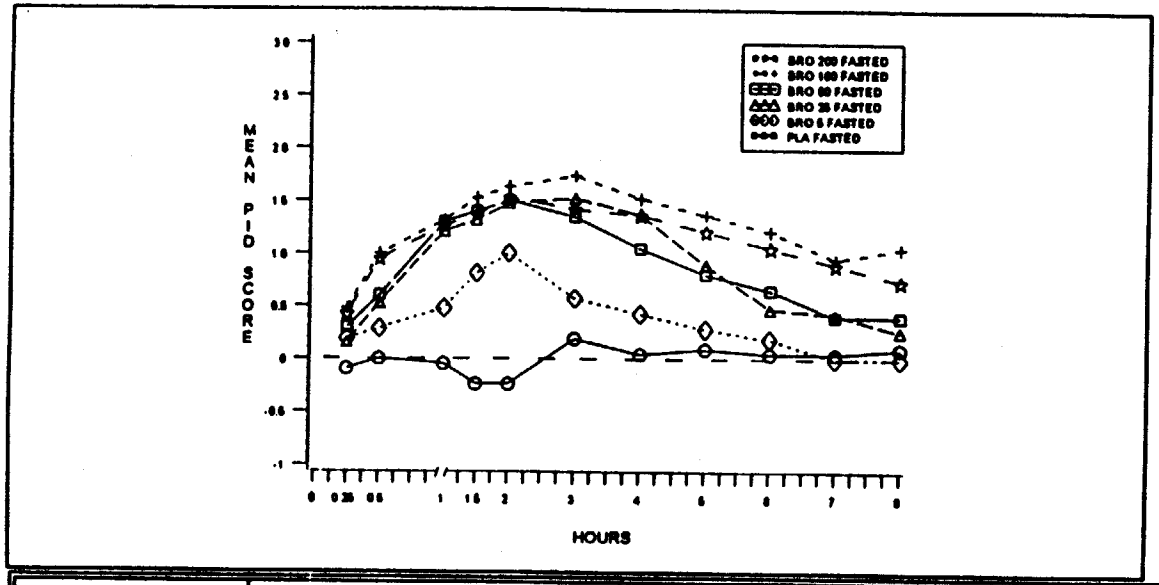
Section II. One or more TESE were reported by 5 (100%) patients who received bromfenac 50 mg (fed open-label). No patients reported serious study events.

Section III. One or more TESE were reported by 17 (85%) patients who received bromfenac 50 mg (fasted), 16 (76%) patients who received bromfenac 25 mg (fasted), 18 (90%) patients who received bromfenac 25 mg (fed), and 12 (63%) of patients who received placebo (fed). There were no statistically significant differences among the treatment groups in the number of TESE. No patients reported serious study events.

CONCLUSIONS: Bromfenac (5 to 100 mg) elicited dose-proportional analgesia in terms of the 8-hour summary scores Bromfenac was inconsistently superior to placebo in analgesic response at the lowest tested dose of 5 mg (threshold) and reached a maximum analgesic response at 100 mg. The plasma concentrations were also dose-proportional but the PK/PD relationship was not well defined. The analgesic response was significantly lower in the fed than the fasted patients but it was clinically and significantly superior to the placebo response; the reduction was not proportional to the decrease in plasma concentrations of bromfenac.

Figure 1, Table 1. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted) Section I
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Valid-for-Efficacy Patients)



3-HOUR AND FINAL SPID AND PEAK PID[a]

Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 200 mg, fasted	19	3.63A	9.24AB	1.89A
Bromfenac 100 mg, fasted	19	4.01A	10.45A	1.84A
Bromfenac 50 mg, fasted	20	3.45A	7.23AB	1.65A
Bromfenac 25 mg, fasted	19	3.37A	7.42B	1.68A
Bromfenac 5 mg, fasted	21	1.83B	3.02C	1.24B
Placebo, fasted	21	-0.25B	0.13C	0.43C
p-value		0.0001	0.0001	0.0001
Root MSE		1.8242	4.4754	0.6975

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

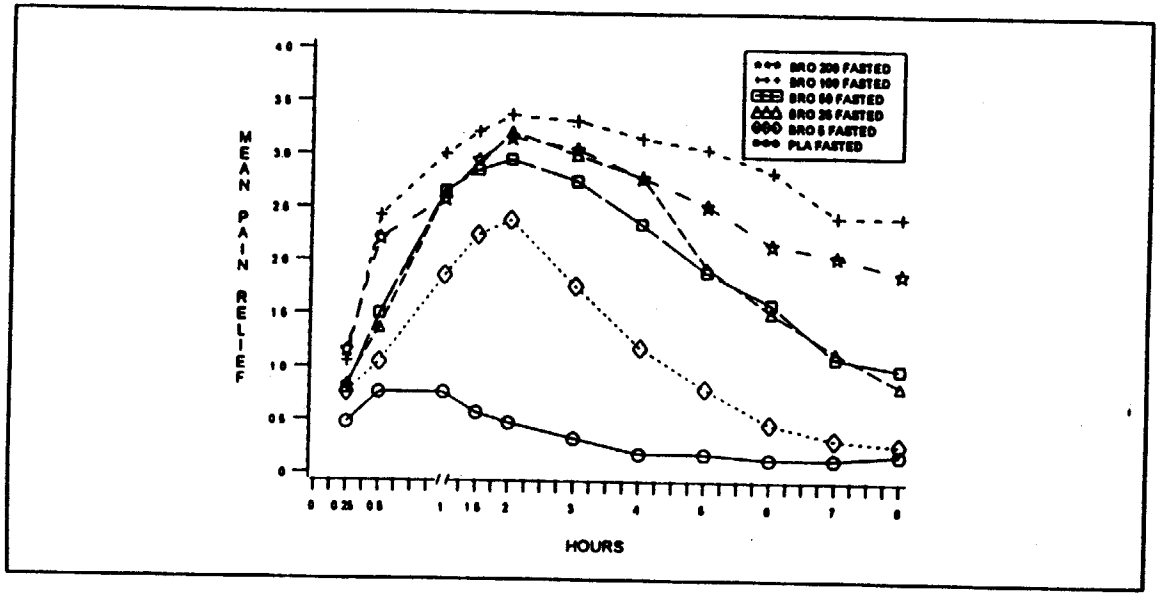
Treatment	Assessment Time Points (Hours)																	
	0.25		0.5		1		1.5		2		3		4		5		6		7		8	
Bromfenac 200 mg, fasted	0.42 (0.69) 19 (a)		0.95 (0.71) 19		1.26 (0.65) 19	A (c)	1.37 (0.68) 19	AB	1.53 (0.51) 19	A	1.42 (0.69) 18	A	1.37 (0.83) 17	A	1.21 (1.08) 17	AB	1.05 (0.97) 14	A	0.89 (0.88) 13	AB	0.74 (0.87) 12	AB
Bromfenac 100mg, fasted	0.47 (0.61) 19		1.00 (0.75) 19		1.32 (0.82) 19	A	1.53 (0.96) 19	A	1.63 (0.96) 19	A	1.74 (0.81) 17	A	1.53 (0.77) 17	A	1.37 (0.83) 17	A	1.21 (0.92) 17	A	0.95 (0.91) 15	A	1.05 (0.97) 14	A
Bromfenac 50 mg, fasted	0.30 (0.47) 20		0.60 (0.60) 20		1.30 (0.73) 20	A	1.40 (0.75) 20	A	1.50 (0.89) 20	A	1.35 (0.99) 17	A	1.05 (1.00) 17	A	0.80 (0.89) 13	ABC	0.65 (0.88) 12	B	0.40 (0.82) 9	C	0.40 (0.75) 6	BC
Bromfenac 25 mg, fasted	0.16 (0.69) 19		0.53 (0.77) 19		1.21 (0.71) 19	A	1.32 (0.75) 19	A	1.47 (0.84) 19	A	1.53 (0.84) 17	A	1.37 (0.83) 17	A	0.89 (0.88) 16	BC	0.47 (0.84) 11	B	0.42 (0.69) 8	BC	0.26 (0.56) 6	BC
Bromfenac 5 mg, fasted	0.19 (0.75) 21		0.29 (0.78) 21		0.48 (0.68) 21	B	0.81 (0.81) 21	B	1.00 (0.71) 21	B	0.57 (0.87) 17	B	0.43 (0.93) 14	B	0.29 (0.56) 8	CD	0.19 (0.40) 6	B	0.00 (0.32) 5	C	0.00 (0.00) 3	C
Placebo, fasted	-0.10 (0.54) 21		0.00 (0.77) 21		-0.05 (0.92) 21	B	-0.24 (0.94) 21	C	-0.24 (0.89) 21	C	0.19 (0.51) 4	B	0.05 (0.22) 2	B	0.10 (0.44) 2	D	0.05 (0.50) 2	B	0.05 (0.22) 1	C	0.10 (0.44) 1	C
p-value Trt (b)	0.168		0.102		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (b)	0.103		0.188		0.171		0.371		0.047		0.107		0.445		0.762		0.620		0.728		0.772	
Root MSE (b)	0.622		0.726		0.741		0.819		0.787		0.786		0.805		0.813		0.778		0.694		0.678	

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PID = u + T(i) + B(j) + TB(ij) + error

Figure 2, Table 2. Pain Relief (Extrapolated, Unadjusted) Section I
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Valid-for-Efficacy Patients)



3-HOUR AND FINAL TOPAR AND PEAK RELIEF[a]

Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak RELIEF
Bromfenac 200 mg, fasted	19	7.78A	19.78AB	3.53A
Bromfenac 100 mg, fasted	19	8.46A	22.80A	3.53A
Bromfenac 50 mg, fasted	20	7.10A	15.93B	3.20AB
Bromfenac 25 mg, fasted	19	7.39A	16.74B	3.42AB
Bromfenac 5 mg, fasted	21	5.30B	9.13C	2.76B
Placebo, fasted	21	1.60C	2.52C	1.10C
p-value		0.0001	0.0001	0.0001
Root MSE		2.7273	7.7941	1.0548

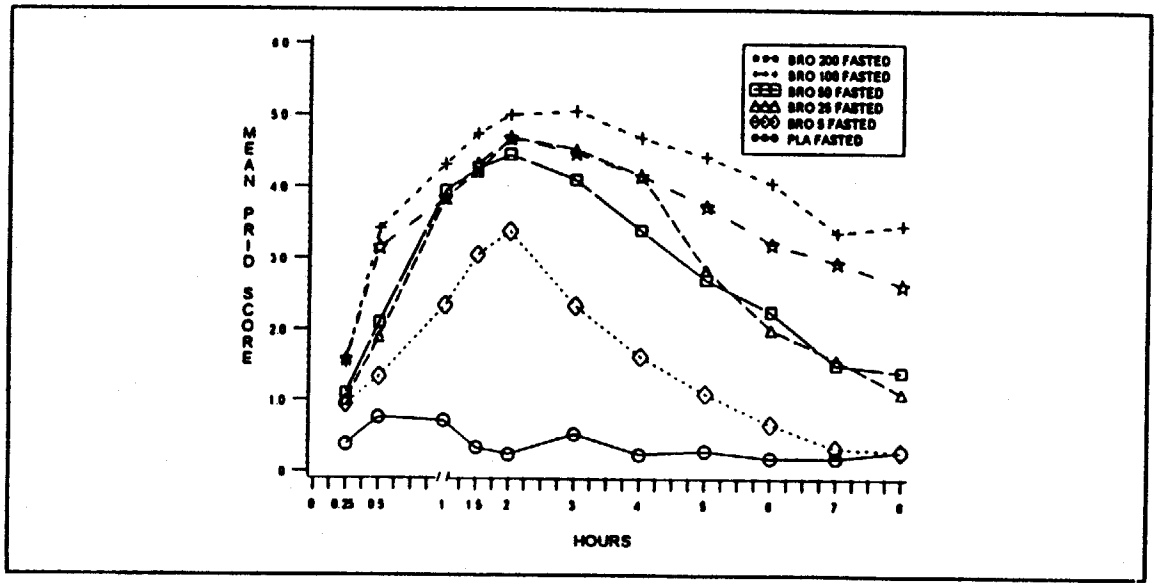
a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)																	
	0.25		0.5		1		1.5		2		3		4		5		6		7		8	
Bromfenac 200 mg, fasted	1.16	(1.17)	2.21	(1.27)	2.58	(1.22)	2.95	(1.22)	3.16	(0.90)	3.05	(1.18)	2.79	(1.40)	2.53	(1.65)	2.16	(1.68)	2.05	(1.65)	1.89	(1.66)
	19 (a)		19	A (c)	19	AB	19	AB	19	A	18	A	17	A	17	AB	14	AB	13	AB	12	AB
Bromfenac 100mg, fasted	1.05	(1.27)	2.42	(1.17)	3.00	(1.15)	3.21	(1.23)	3.37	(1.16)	3.32	(1.29)	3.16	(1.21)	3.05	(1.27)	2.84	(1.39)	2.42	(1.47)	2.42	(1.57)
	19		19	A	19	A	19	A	19	A	17	A	17	A	17	A	17	A	15	A	14	A
Bromfenac 50 mg, fasted	0.80	(0.89)	1.50	(1.00)	2.65	(1.23)	2.85	(1.27)	2.95	(1.32)	2.75	(1.48)	2.35	(1.53)	1.90	(1.59)	1.60	(1.73)	1.10	(1.59)	1.00	(1.56)
	20		20	AB	20	A	20	A	20	A	17	A	17	A	13	B	12	BCD	9	C	6	BC
Bromfenac 25 mg, fasted	0.84	(1.01)	1.37	(1.16)	2.63	(1.12)	2.89	(1.10)	3.21	(1.03)	3.00	(1.41)	2.79	(1.51)	1.95	(1.72)	1.53	(1.74)	1.16	(1.54)	0.84	(1.39)
	19		19	AB	19	A	19	AB	19	A	17	A	17	A	16	BC	11	BC	8	BC	6	BC
Bromfenac 5 mg, fasted	0.76	(1.04)	1.05	(0.97)	1.86	(1.01)	2.24	(1.34)	2.38	(1.28)	1.76	(1.58)	1.19	(1.69)	0.81	(1.36)	0.48	(0.81)	0.33	(0.73)	0.29	(0.72)
	21		21	B	21	B	21	B	21	B	17	B	14	B	8	CD	6	CD	5	C	3	C
Placebo, fasted	0.48	(0.81)	0.76	(1.00)	0.76	(1.18)	0.57	(1.16)	0.48	(1.03)	0.33	(0.97)	0.19	(0.68)	0.19	(0.68)	0.14	(0.65)	0.14	(0.65)	0.19	(0.87)
	21		21	B	21	C	21	C	21	C	14	B	12	B	12	D	12	D	11	C	11	C
p-value Trt (b)	0.471		0.011		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (b)	0.359		0.580		0.589		0.683		0.056		0.126		0.522		0.772		0.599		0.868		0.777	
Root MSE (b)	1.018		1.073		1.133		1.195		1.059		1.245		1.326		1.371		1.342		1.311		1.309	

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PR = u + T(i) + B(j) + TB(ij) + error

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Section I Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Valid-for-Efficacy Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID[a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 200 mg, fasted	19	11.41A	29.01AB	5.42A
Bromfenac 100 mg, fasted	19	12.47A	33.26A	5.37A
Bromfenac 50 mg, fasted	20	10.55A	23.15B	4.85A
Bromfenac 25 mg, fasted	19	10.76A	24.16B	5.11AB
Bromfenac 5 mg, fasted	21	7.13B	12.15C	4.00B
Placebo, fasted	21	1.35C	2.65C	1.52C
p-value		0.0001	0.0001	0.0001
Root MSE		4.4794	12.127	1.7136

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)										
	0.25	0.5	1	1.5	2	3	4	5	6	7	8
Bromfenac 200 mg, fasted	1.58 (1.74) 19 (a)	3.16 (1.89) 19 A (c)	3.84 (1.77) 19 A	4.32 (1.86) 19 AB	4.68 (1.34) 19 A	4.47 (1.81) 18 A	4.16 (2.17) 17 A	3.74 (2.66) 17 AB	3.21 (2.55) 14 AB	2.95 (2.48) 13 AB	2.63 (2.48) 12 AB
Bromfenac 100mg, fasted	1.53 (1.81) 19	3.42 (1.84) 19 A	4.32 (1.92) 19 A	4.74 (2.13) 19 A	5.00 (2.08) 19 A	5.05 (2.01) 17 A	4.68 (1.92) 17 A	4.42 (2.01) 17 A	4.05 (2.22) 17 A	3.37 (2.27) 15 A	3.47 (2.48) 14 A
Bromfenac 50 mg, fasted	1.10 (1.25) 20	2.10 (1.52) 20 AB	3.95 (1.88) 20 A	4.25 (1.94) 20 A	4.45 (2.14) 20 A	4.10 (2.40) 17 A	3.40 (2.48) 17 A	2.70 (2.41) 13 B	2.25 (2.57) 12 C	1.50 (2.37) 9 C	1.40 (2.28) 6 BC
Bromfenac 25 mg, fasted	1.00 (1.56) 19	1.89 (1.85) 19 AB	3.84 (1.74) 19 A	4.21 (1.78) 19 AB	4.68 (1.80) 19 A	4.53 (2.17) 17 A	4.16 (2.29) 17 A	2.84 (2.54) 16 BC	2.00 (2.49) 11 BC	1.58 (2.17) 8 BC	1.11 (1.91) 6 BC
Bromfenac 5 mg, fasted	0.95 (1.69) 21	1.33 (1.62) 21 B	2.33 (1.62) 21 B	3.05 (2.09) 21 B	3.38 (1.94) 21 B	2.33 (2.37) 17 B	1.62 (2.58) 14 B	1.10 (1.89) 8 CD	0.67 (1.15) 6 C	0.33 (0.91) 5 C	0.29 (0.72) 3 C
Placebo, fasted	0.38 (1.24) 21	0.76 (1.67) 21 B	0.71 (1.98) 21 B	0.33 (2.01) 21 C	0.24 (1.84) 21 C	0.52 (1.47) 4 B	0.24 (0.89) 2 B	0.29 (1.10) 2 D	0.19 (1.12) 2 C	0.19 (0.87) 1 C	0.29 (1.31) 1 C
p-value Trt (b)	0.270	0.020	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p-value Trt*Baseline (b)	0.210	0.349	0.381	0.539	0.047	0.134	0.527	0.838	0.660	0.855	0.806
Root MSE (b)	1.538	1.720	1.822	1.979	1.816	1.995	2.097	2.141	2.062	1.949	1.941

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PRID = u + T(i) + B(j) + TB(ij) +error

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Table 4. Estimated Onset of Pain Relief (on-PR)

	PRID at 30 minutes			Estimated on-PR	
Treatment group	Mean[a]	S.D.	n	Time in (min)	95% - CI in (min)
Bromfenac 200 mg, fasted	3.16	1.89	19	10	7-13
Bromfenac 100 mg, fasted	3.42	1.84	19	9	7-12
Bromfenac 50 mg, fasted	2.10	1.52	20	14	11-22
Bromfenac 25 mg, fasted	1.89	1.85	19	16	11-30
Bromfenac 5 mg, fasted	1.33	1.62	21	23	14-50
Placebo, fasted	0.76	1.67	21	39	20- (b)

(a) Raw unadjusted mean of (unextrapolated) PRID scores.
(b) Exceeded the total minutes of study.

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Figure 4. Estimated Duration of Analgesia
(Time-to-Remedication)

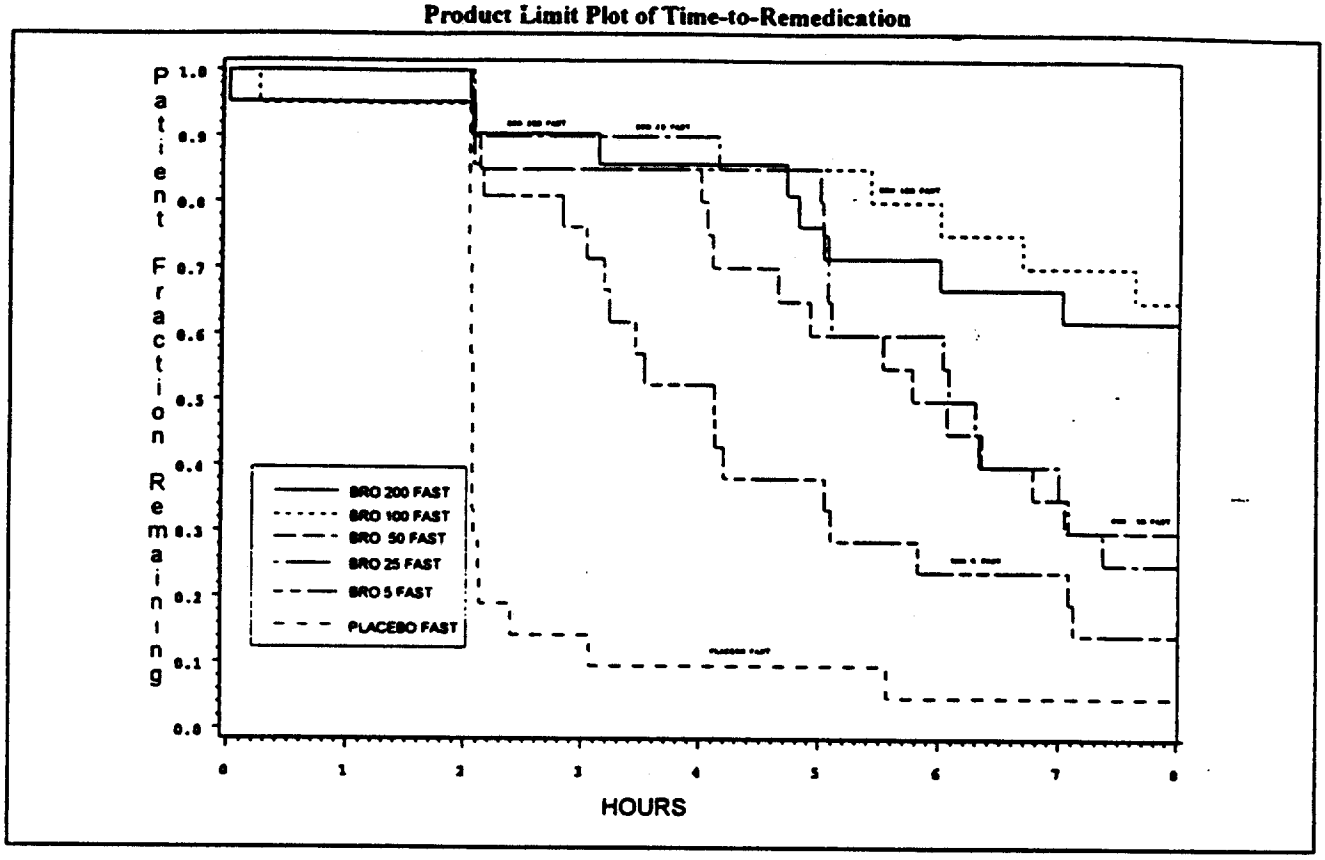


Table 5. Duration of Pain Relief (dur-PRs)

Treatment Group	n	Calculated time to remedication	
		Mean h:min [a]	95% CI h:min [b]
Bromfenac 200 mg, fasted	19	7:25 (AB) [c]	(6:21, 8:28)
Bromfenac 100 mg, fasted	19	7:53 (A)	(6:52, 8:54)
Bromfenac 50 mg, fasted	20	6:07 (BC)	(5:01, 7:13)
Bromfenac 25 mg fasted,	19	6:12 (C)	(5:13, 7:11)
Bromfenac 5 mg, fasted	21	4:38 (C)	(3:38, 5:38)
Placebo, fasted	21	2:37 (D)	(1:55, 3:20)

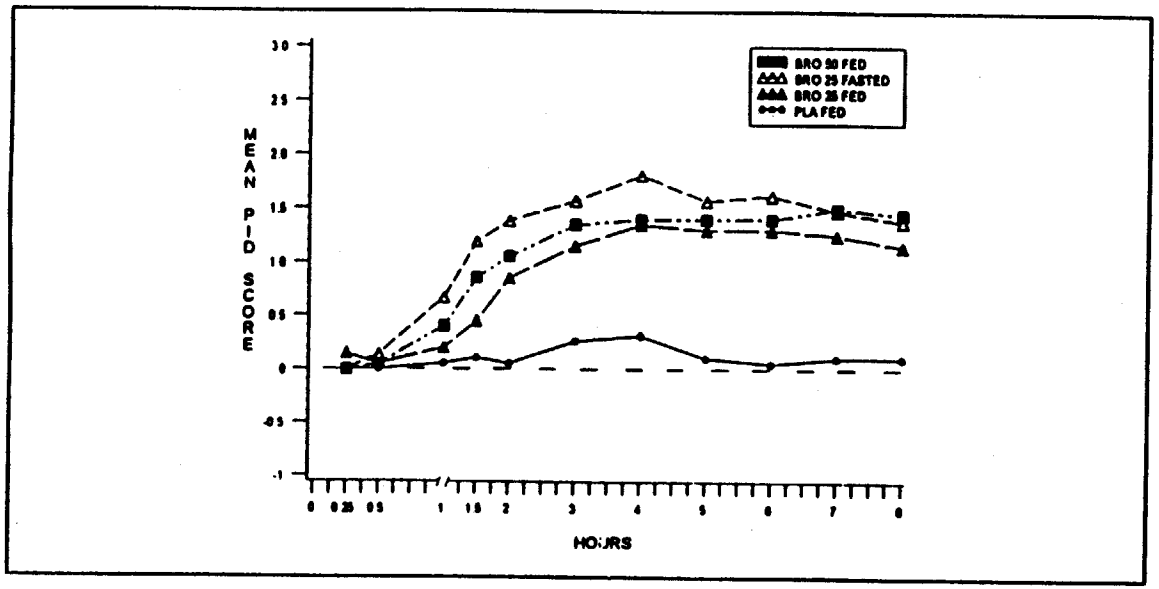
(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

Table 6. Time-to-Remedication (Percentiles)

Treatment	----------Percentiles in hours (95% CI)----------		
	25%	50% (Median)	75%
Bromfenac 200 mg, fasted	5:02 (4:43, >8hr)	>8hr (6:00, >8hr)	>8hr (NE)
Bromfenac 100 mg, fasted	7:38 (5:25, >8hr)	>8hr (NE)	>8hr (NE)
Bromfenac 50 mg, fasted	4:06 (2:07, 6:04)	6:04 (4:39,>8hr)	>8hr (6:21, >8hr)
Bromfenac 25 mg fasted,	5:01 (4:09, 6:05)	6:05 (5:04, 7:22)	>8hr (6:05, >8hr)
Bromfenac 5 mg, fasted	3:02 (2:04, 3:32)	4:07 (3:11, 5:06)	5:50 (4:08, >8hr)
Placebo, fasted	2:02 (2:02, 2:04)	2:04 (2:03, 2:05)	2:07 (2:04, 3:04)

NE: Not estimable.

Figure 5, Table 7. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted) Section III
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPID AND PEAK PID[a]

Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 50 mg., fed	20	2.11AB	9.21A	1.60AB
Bromfenac 25 mg, fasted	21	2.80A	10.76A	1.91A
Bromfenac 25 mg, fed	20	1.59B	7.94A	1.40B
Placebo, fed	19	0.25C	1.01B	0.42C
p-value		0.0001	0.0001	0.0001
Root MSE		1.6905	4.9615	0.7783

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

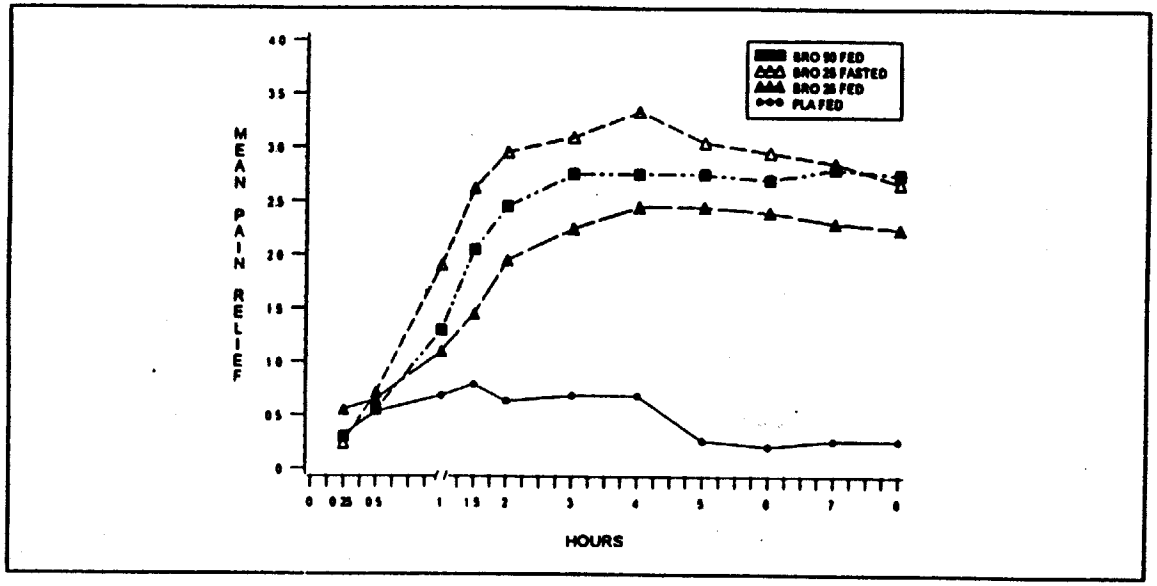
Treatment	Assessment Time Points (Hours)																			
	0.25		0.5		1		1.5		2		3		4		5		6		7		8	
Bromfenac 50 mg, fed	0.00 20 (a)	(0.46)	0.05 20	(0.51)	0.40 20	(0.75)	0.85 20 AB (c)	(0.81)	1.05 20 AB	(0.83)	1.35 18 A	(0.75)	1.40 17 A	(0.82)	1.40 17 A	(0.82)	1.40 17 A	(0.88)	1.50 16 A	(0.95)	1.45 16 A	(0.94)
Bromfenac 25 mg, fasted	0.00 21	(0.45)	0.14 21	(0.65)	0.67 21	(0.86)	1.19 21 A	(0.93)	1.38 21 A	(0.74)	1.57 21 A	(0.75)	1.81 21 A	(0.75)	1.57 21 A	(0.87)	1.62 20 A	(0.80)	1.48 19 A	(0.98)	1.38 19 A	(0.97)
Bromfenac 25 mg, fed	0.15 20	(0.49)	0.05 20	(0.60)	0.20 20	(0.83)	0.45 20 BC	(1.05)	0.85 20 B	(1.14)	1.15 15 A	(1.04)	1.35 14 A	(1.04)	1.30 14 A	(1.03)	1.30 14 A	(0.98)	1.25 14 A	(0.97)	1.15 14 A	(1.04)
Placebo, fed	0.00 19	(0.58)	0.00 19	(0.58)	0.05 19	(0.71)	0.11 19 C	(0.74)	0.05 19 C	(0.71)	0.26 10 B	(0.56)	0.32 6 B	(0.48)	0.11 6 B	(0.32)	0.05 3 B	(0.23)	0.11 2 B	(0.32)	0.11 2 B	(0.32)
p-value Trt (b)	0.683		0.886		0.082		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (b)	0.371		0.305		0.207		0.183		0.564		0.187		0.129		0.179		0.284		0.043		0.038	
Root MSE (b)	0.464		0.534		0.716		0.785		0.780		0.755		0.756		0.781		0.781		0.818		0.839	

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PID = u + T(i) + B(j) + TB(ij) + error

Figure 6, Table 8. Pain Relief (Extrapolated, Unadjusted) Section III
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL TOPAR AND PEAK RELIEF[a]

Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak RELIEF
Bromfenac 50 mg, fed	20	5.17AB	18.92AB	3.00AB
Bromfenac 25 mg, fasted	21	6.35A	21.42A	3.43A
Bromfenac 25 mg, fed	20	4.24B	16.09B	2.55B
Placebo, fed	19	1.83C	3.72C	1.11C
p-value		0.0001	0.0001	0.0001
Root MSE		2.6728	8.2234	1.2695

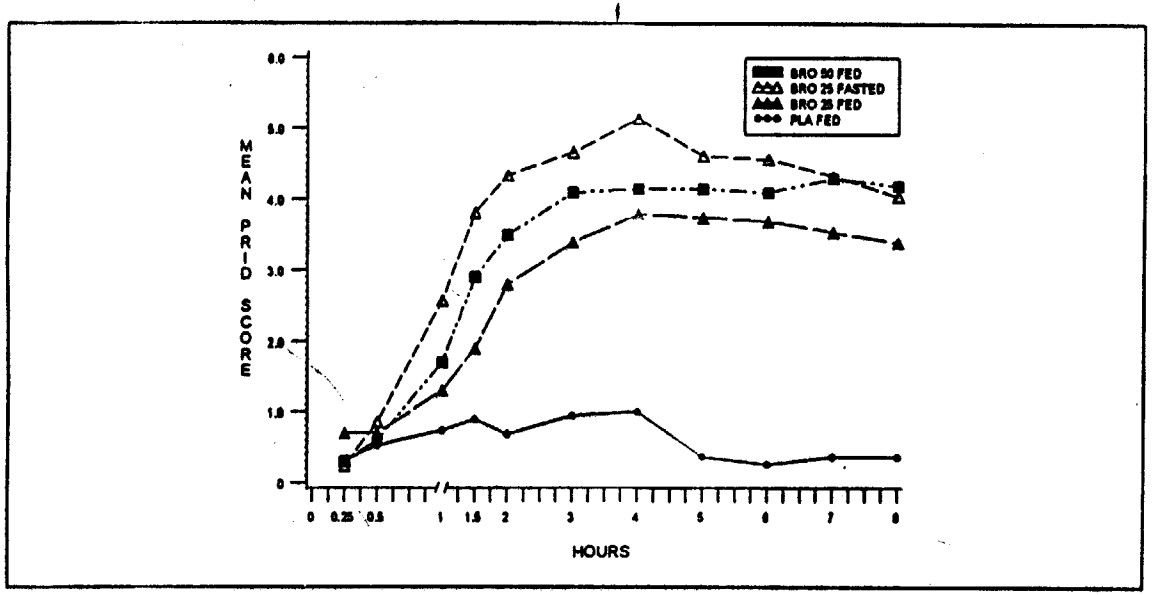
a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)											
	0.25	0.5	1	1.5	2	3	4	5	6	7	8
Bromfenac 50 mg, fed	0.30 (0.57) 20 (a)	0.55 (0.76) 20	1.30 (1.22) 20 AB (c)	2.05 (1.36) 20 AB	2.45 (1.19) 20 AB	2.75 (1.29) 18 AB	2.75 (1.33) 17 AB	2.75 (1.33) 17 A	2.70 (1.42) 17 A	2.80 (1.54) 16 A	2.75 (1.55) 16 A
Bromfenac 25 mg, fasted	0.24 (0.62) 21	0.71 (0.96) 21	1.90 (1.14) 21 A	2.62 (0.74) 21 A	2.95 (0.38) 21 A	3.10 (0.62) 21 A	3.33 (0.48) 21 A	3.05 (0.86) 21 A	2.95 (1.12) 20 A	2.86 (1.11) 19 A	2.67 (1.15) 19 A
Bromfenac 25 mg, fed	0.55 (1.10) 20	0.65 (1.04) 20	1.10 (1.25) 20 B	1.45 (1.47) 20 BC	1.95 (1.54) 20 B	2.25 (1.62) 15 B	2.45 (1.73) 14 B	2.45 (1.70) 14 A	2.40 (1.73) 14 A	2.30 (1.72) 14 A	2.25 (1.77) 14 A
Placebo, fed	0.32 (0.58) 19	0.53 (0.90) 19	0.68 (0.89) 19 B	0.79 (0.98) 19 C	0.63 (0.96) 19 C	0.68 (1.11) 10 C	0.68 (1.11) 6 C	0.26 (0.81) 6 B	0.21 (0.63) 3 B	0.26 (0.81) 2 B	0.26 (0.81) 2 B
p-value Trt (b)	0.634	0.860	0.012	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p-value Trt*Baseline (b)	0.784	0.130	0.378	0.302	0.445	0.320	0.344	0.506	0.304	0.223	0.175
Root MSE (b)	0.767	0.909	1.141	1.171	1.105	1.209	1.241	1.232	1.265	1.3201	1.339

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PR = u + T(i) + B(j) + TB(ij) + error

Figure 7, Table 9. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Section III Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) (Intent-to-Treat Patients)



3-HOUR AND FINAL SPRID AND PEAK PRID[a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 50 mg, fed	20	7.28AB	28.13AB	4.60AB
Bromfenac 25 mg, fasted	21	9.16A	32.18A	5.33A
Bromfenac 25 mg, fed	20	5.84B	24.04B	3.95B
Placebo, fed	19	2.08C	4.74C	1.47C
p-value		0.0001	0.0001	0.0001
Root MSE		4.2618	13.046	2.0123

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours) 0.25	0.5	1	1.5	2	3	4	5	6	7	
Bromfenac 50 mg, fed	0.30 (0.92) 20 (a)	0.60 (1.10) 20	1.70 (1.87) 20 AB (c)	2.90 (2.07) 20 AB	3.50 (1.91) 20 AB	4.10 (1.97) 18 AB	4.15 (2.08) 17 AB	4.15 (2.08) 17 A	4.10 (2.22) 17 A	4.30 (2.43) 16 A	4.20 (2.44) 16 A
Bromfenac 25 mg, fasted	0.24 (1.00) 21	0.86 (1.49) 21	2.57 (1.89) 21 A	3.81 (1.57) 21 A	4.33 (1.02) 21 A	4.67 (1.28) 21 A	5.14 (1.15) 21 A	4.62 (1.66) 21 A	4.57 (1.83) 20 A	4.33 (1.98) 19 A	4.05 (2.01) 19 A
Bromfenac 25 mg, fed	0.70 (1.53) 20	0.70 (1.53) 20	1.30 (1.98) 20 B	1.90 (2.43) 20 BC	2.80 (2.61) 20 B	3.40 (2.60) 15 B	3.80 (2.73) 14 B	3.75 (2.67) 14 A	3.70 (2.68) 14 A	3.55 (2.65) 14 A	3.40 (2.76) 14 A
Placebo, fed	0.32 (1.00) 19	0.53 (1.31) 19	0.74 (1.45) 19 B	0.89 (1.59) 19 C	0.68 (1.57) 19 C	0.95 (1.62) 10 C	1.00 (1.56) 6 C	0.37 (1.12) 6 B	0.26 (0.81) 3 B	0.37 (1.12) 2 B	0.37 (1.12) 2 B
p-value Trt (b)	0.595	0.842	0.020	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p-value Trt*Baseline (b)	0.662	0.131	0.282	0.267	0.602	0.297	0.326	0.455	0.350	0.160	0.126
Root MSE (b)	1.137	1.336	1.786	1.906	1.843	1.926	1.971	1.990	2.015	2.114	2.149

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PRID = u + T(i) + B(j) + TB(ij) + error

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Table 4. Estimated Onset of Pain Relief (on-PR)

	PRID at 30 minutes			Estimated on-PR	
Treatment group	Mean[a]	S.D.	n	Time in minutes	95% - CI in minutes
Bromfenac 50 mg fed	0.60	1.10	20	50	27-344
Bromfenac 25 mg fasted	0.86	1.49	21	35	20-169
Bromfenac 25 mg fed	0.70	1.53	20	43	21- (b)
Placebo fed	0.53	1.31	19	57	26- (b)

(a) Raw unadjusted means of (unextrapolated) PRID scores.
(b) Exceeded the total minutes of the study.

Figure 8. Estimated Duration of Analgesia
(Time-to-Remedication)

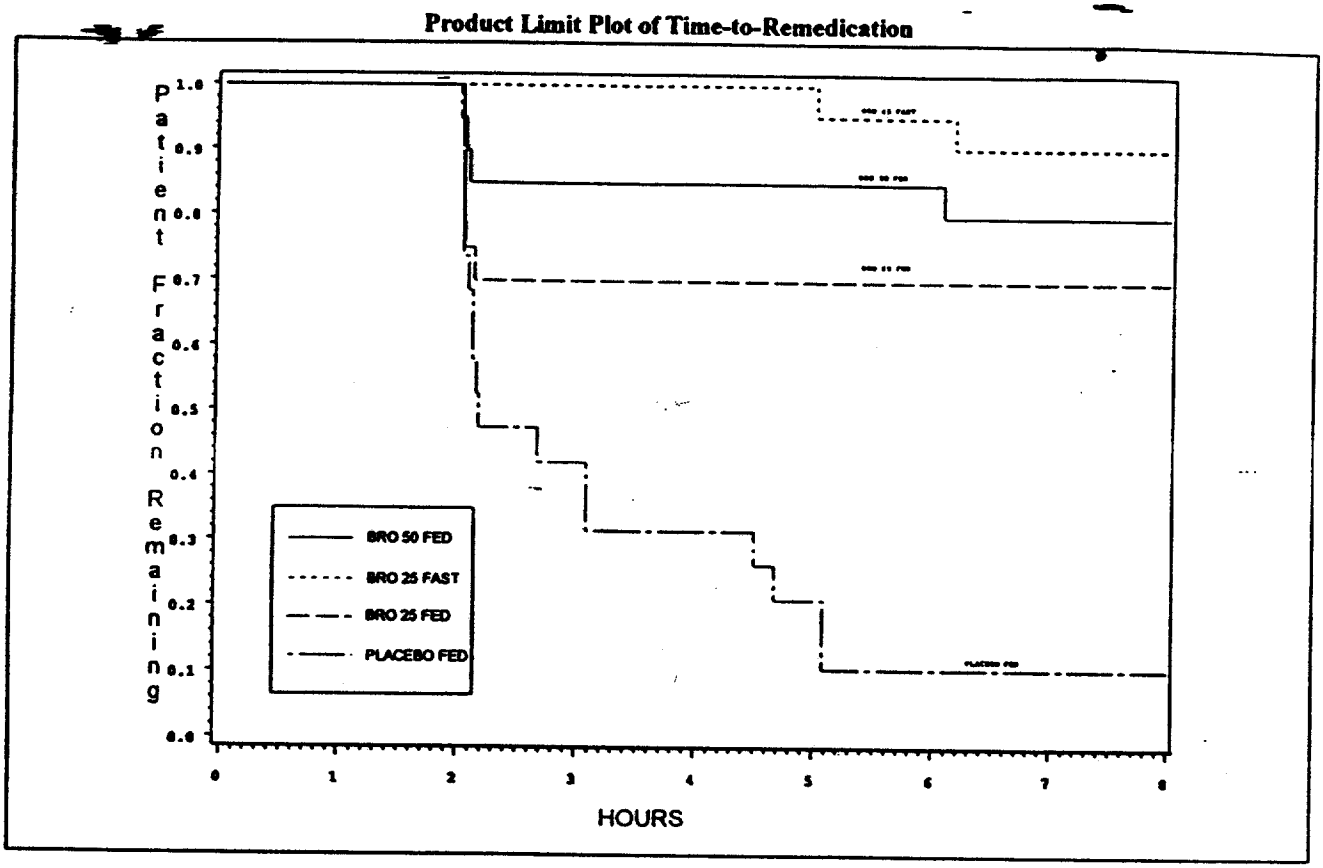


Table 5. Duration of Pain Relief (dur-PRs)

Treatment Group	n	Calculated time to remedication	
		Mean[a] h:min	95% CI[b] h:min
Bromfenac 50 mg, fed	20	7:49 (A)[c]	(5:01, 7:13)
Bromfenac 25 mg, fasted	21	8:40 (A)	(5:13, 7:11)
Bromfenac 25 mg, fed	20	6:55 (A)	(3:38, 5:38)
Placebo, fed	19	3:31 (B)	(1:55, 3:20)

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

Table 6. Time-to-Remedication (Percentiles)

Treatment	----------Percentiles in hours (95% CI)----------		
	25%	50% (Median)	75%
Bromfenac 50 mg, fed	>8hr (2:05, >8hr)	>8hr (NE)	>8hr (NE)
Bromfenac 25 mg, fasted	>8hr (NE)	>8hr (NE)	>8hr (NE)
Bromfenac 25 mg, fed	2:05 (2:02, >8hr)	>8hr (2:08, >8hr)	>8hr (NE)
Placebo, fed	2:02 (2:02, 2:10)	2:10 (2:05, 4:30)	4:40 (2:10, 5:05)

NE: Not estimable.

CONFIDENTIAL: SBA Summary for Bromfenac Protocol AHR-05-UK

A Double-blind, Parallel, Single-dose Evaluation of the Safety and Efficacy of Bromfenac (25, 10, and 5 mg) Compared With Acetaminophen (1000 mg) and Placebo in the Treatment of Postoperative Orthopedic Pain

IND DRUG:	Bromfenac	DOSES:	25, 10, 5 mg oral	—
REFERENCE DRUGS:	Acetaminophen (APAP) Placebo	DOSE:	1000 mg oral	•
TOTAL PTS ENROLLED: 159		DURATION OF DOSING: Single dose, 6 hr		
INVESTIGATOR:	Henry McQuay, D.M., Abingdon, UK			

PURPOSE: The purpose of this study was to compare the analgesic efficacy and safety of bromfenac at 3 dose levels with those of APAP and placebo in hospitalized patients experiencing moderate to severe pain following orthopedic surgery.

METHOD: This was a single-dose, randomized, parallel, double-blind study with 5 treatment groups. The study medication was given within 72 hours following surgery. Patients evaluated their baseline (0 hour) pain intensity (4-word, 8-word, and 100-mm visual analog scales) and subsequent pain intensity and pain relief (5-word and 100-mm visual analog scales) at 0.5, 1, 1.5 and 2 hours and then hourly until 6 hours after medication or until additional analgesic was required. The derived efficacy variables that were analyzed included pain intensity difference (PID), hourly pain relief plus PID (PRID), the summed total pain relief (TOPAR), the summed total analog pain relief (TOTPAR), the summed pain intensity difference (SPID), the summed pain relief plus PID (SPRID), and the summed analog pain intensity difference (SPAID). At the end of 6 hours or when the patient left the study, both the patient and the investigator gave an overall (global) evaluation of the study medication. Baseline pain intensity and treatment were included as sources of variation in the analysis of variance model. Peak pain relief was calculated from both the ordinal and the 100-mm visual analog scales. The time the patients remained active in the study was also calculated. Safety was assessed by measuring vital signs, sedation, the patient's mood, and any reported adverse events.

RESULTS: A total of 159 patients was admitted to the study, 157 of whom were evaluated. One (1) patient did not receive study medication because the assigned bottle was mispackaged. One (1) patient vomited intact study medication capsules and did not undergo the scheduled assessments. The number of patients in each treatment group was as follows: bromfenac 25 mg, 31; bromfenac 10 mg, 32; bromfenac 5 mg, 31; APAP 1000 mg, 32; placebo, 31.

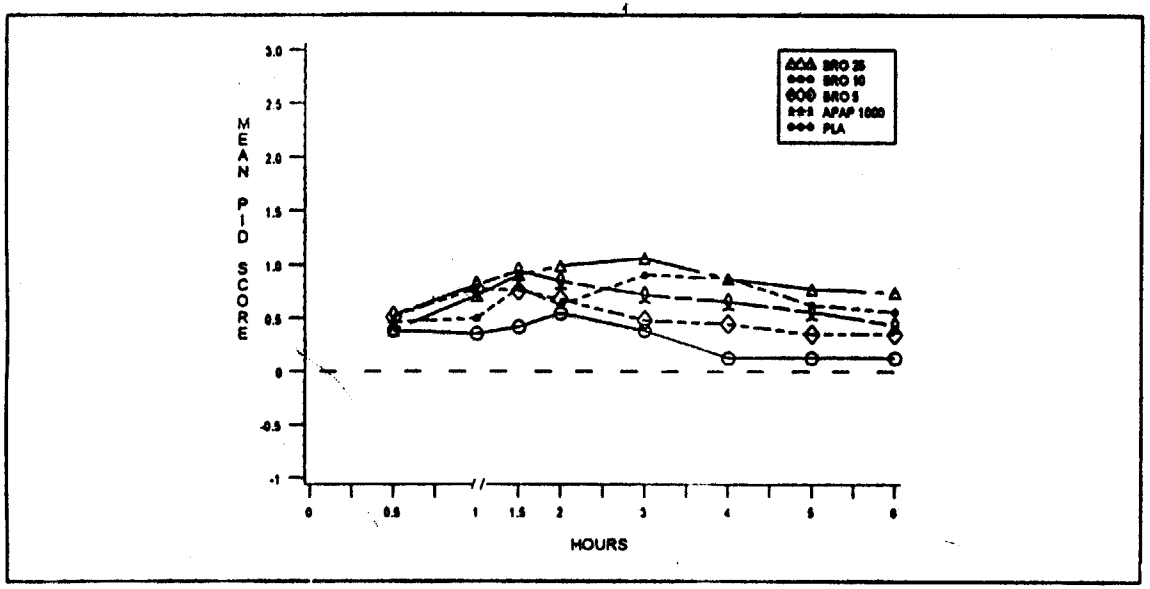
TOPAR scores at 3 and at 6 hours were significantly ($p \leq 0.05$) higher for the 25 and 10 mg doses of bromfenac and for APAP than for placebo. The mean value for bromfenac 5 mg was numerically larger than that for placebo for these variables, without reaching a statistically significant difference. While there was no significant difference for the 6-hour TOPAR among the bromfenac 25 and 10 mg treatments and APAP, a significant difference favored bromfenac 25 mg over bromfenac 5 mg. Bromfenac 25 and 10 mg and APAP were significantly better than placebo for pain relief and for PID at most hourly assessments, as well as for peak relief and for the 6-hour SPID and SPRID. SPRID scores at 3 hours were significantly higher for bromfenac 25 mg and for APAP than for placebo. APAP had the shortest estimated onset of relief, with the three bromfenac doses having similar times to onset of pain relief. Bromfenac 25 mg had the longest estimated duration of pain relief, followed by bromfenac 10 mg (both significantly longer than in the placebo group); the duration of pain relief for bromfenac 5 mg and APAP was similar. The bromfenac 25 mg, the bromfenac 10 mg, the bromfenac 5 mg, and the APAP treatment groups had a significantly lower percent of patients remedicating within 6 hours than did the placebo treatment group.

The safety profiles of all 5 treatments were similar. No serious or unexpected adverse effects or changes in vital signs were reported. No patient withdrew because of a drug-related adverse safety event.

CONCLUSIONS: Bromfenac at doses of 25 and 10 mg provided analgesia comparable to that of a 1000 mg dose of APAP. The analgesic effect of bromfenac appeared to improve as the dosage increased. The analgesic threshold dose for bromfenac was 5 mg. All 3 doses of bromfenac were well tolerated.

Figure 1, Table 1. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPID AND PEAK PID [a]

Treatment Group	n	3-hour SPID	Final SPID	PEAK PID
Bromfenac 25 mg	31	2.27	4.82 A	1.42 A
Bromfenac 10 mg	32	1.80	4.03 AB	1.28 B
Bromfenac 5 mg	31	1.77	3.00 BC	1.10 AB
APAP 1000 mg	32	2.13	3.93 AB	1.25 A
Placebo	31	1.19	1.70 C	0.81 B
p-value		0.0828	0.0050	0.0310
Root MSE		1.6580	3.3941	0.7970

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

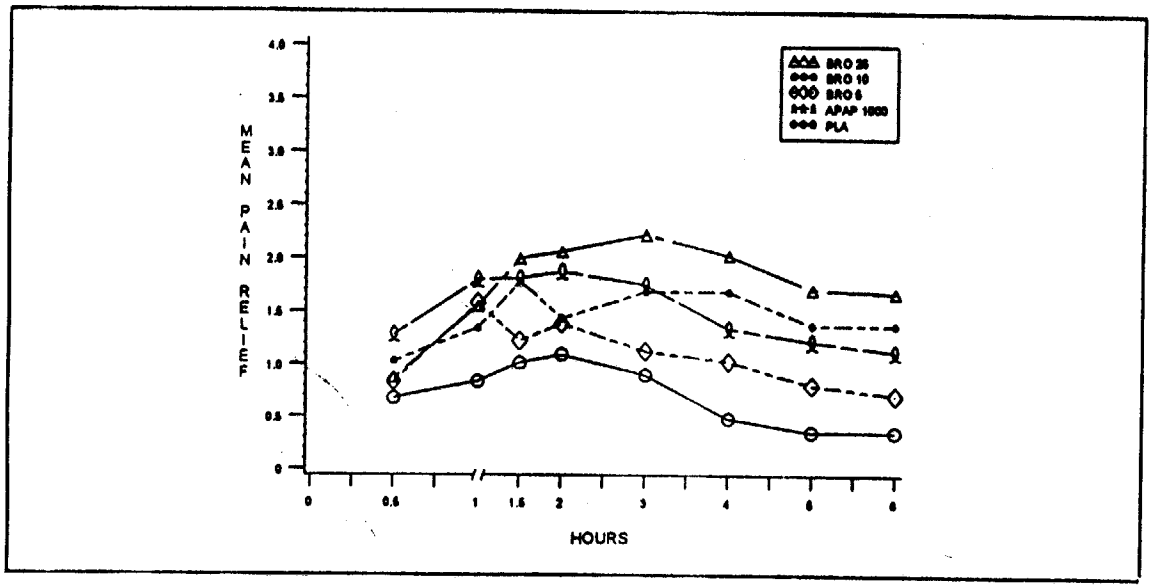
	Assessment Time Points (Hours)											
Treatment	1/2		1		1 1/2		2		3		4	
Bromfenac 25 mg	0.39	(0.62)	0.71	(0.64)	0.90	(0.83)	0.99	(0.90)	1.06	(0.77)	0.87	(0.88)
	31 (a)		30		29		26		26	A (d)	24	A
Bromfenac 10 mg	0.47	(0.62)	0.50	(0.92)	0.78	(0.83)	0.63	(0.91)	0.91	(0.93)	0.88	(0.94)
	32		32		28		27		25	A	22	A
Bromfenac 5 mg	0.52	(0.68)	0.77	(0.72)	0.76	(0.76)	0.68	(0.83)	0.48	(0.72)	0.45	(0.62)
	31		31		28		25		21	B	18	BC
Acetaminophen 1000 mg	0.53	(0.72)	0.81	(0.82)	0.94	(0.88)	0.84	(0.81)	0.72	(0.77)	0.66	(0.83)
	32		31		28		25		21	AB	17	AB
Placebo	0.39	(0.56)	0.35	(0.61)	0.42	(0.89)	0.55	(0.77)	0.39	(0.80)	0.13	(0.43)
	31		31		25		18		16	B	10	C
p-value Trt (b)	0.813		0.055		0.097		0.236		0.004		<0.001	
p-value Trt*Baseline (c)	0.088		0.513		0.896		0.303		0.761		0.748	
Root MSE (b)	0.624		0.728		0.828		0.845		0.803		0.769	

	Assessment Time Points (Hours)									
Treatment	5		6							
Bromfenac 25 mg	0.77	(0.92)	0.74	(0.86)						
	21	A	19	A						
Bromfenac 10 mg	0.63	(0.79)	0.56	(0.84)						
	18	AB	16	AB						
Bromfenac 5 mg	0.35	(0.55)	0.35	(0.61)						
	15	BC	11	B						
Acetaminophen 1000 mg	0.56	(0.84)	0.44	(0.84)						
	13	AB	13	ABC						
Placebo	0.13	(0.43)	0.13	(0.43)						
	4	C	4	C						
p-value Trt (b)	0.007		0.021							
p-value Trt*Baseline (c)	0.885		0.904							
Root MSE (b)	0.730		0.733							

(a) Sample sizes, not extrapolated
(b) Model: PID = u + T(i) + B(j) + error
(c) Model: PID = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 2, Table 2. Pain Relief (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL TOPAR AND PEAK PAIN RELIEF [a]

Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak Pain Relief
Bromfenac 25 mg	31	4.87A	10.56A	2.77 A
Bromfenac 10 mg	32	4.00A	8.59AB	2.47 A
Bromfenac 5 mg	31	3.43AB	6.19BC	2.23 AB
APAP 1000 mg	32	4.73A	8.73AB	2.50 A
Placebo	31	2.54B	4.01C	1.58 B
p-value		0.0119	0.0011	0.0080
Root MSE		2.9137	6.3866	1.3130

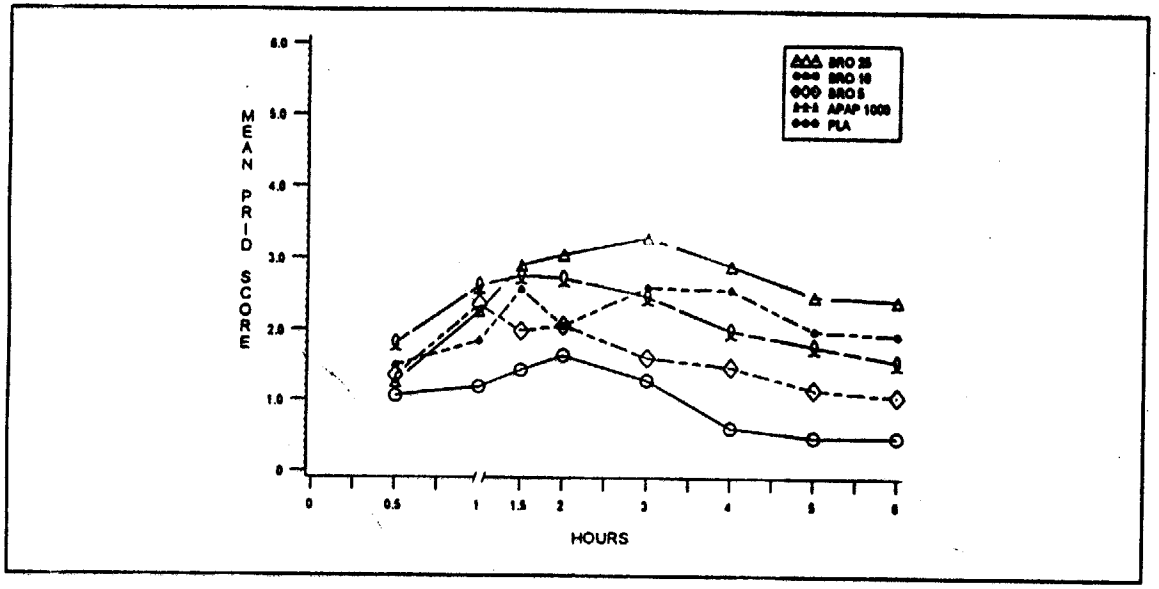
a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)											
Treatment	1/2		1		1 1/2		2		3		4		5		6	
Bromfenac 25 mg	0.87 (0.85) 31 (a)		1.55 (1.18) 30 A (d)		2.00 (1.37) 29 A		2.06 (1.41) 26		2.23 (1.48) 26 A		2.03 (1.52) 24 A		1.71 (1.60) 21 A		1.68 (1.66) 19 A	
Bromfenac 10 mg	1.03 (1.00) 32		1.34 (1.15) 32 AB		1.78 (1.34) 28 AB		1.44 (1.48) 27		1.69 (1.51) 25 AB		1.69 (1.67) 22 AB		1.38 (1.54) 18 AB		1.38 (1.64) 16 AB	
Bromfenac 5 mg	0.84 (0.73) 31		1.58 (1.12) 31 A		1.23 (1.18) 28 BC		1.39 (1.38) 25		1.13 (1.15) 21 BC		1.03 (1.33) 18 BC		0.81 (1.19) 15 BC		0.71 (1.24) 11 BC	
Acetaminophen 1000 mg	1.28 (1.05) 32		1.80 (1.28) 31 A		1.81 (1.47) 28 AB		1.88 (1.48) 25		1.75 (1.59) 21 AB		1.34 (1.66) 17 AB		1.22 (1.72) 13 AB		1.13 (1.62) 13 AB	
Placebo	0.68 (0.87) 31		0.84 (0.93) 31 B		1.02 (1.17) 25 C		1.10 (1.40) 18		0.90 (1.40) 16 C		0.48 (1.09) 10 C		0.35 (1.02) 4 C		0.35 (1.02) 4 C	
p-value Trt (b)	0.093		0.015		0.015		0.064		0.003		<0.001		0.003		0.003	
p-value Trt*Baseline (c)	0.561		0.424		0.763		0.841		0.990		0.853		0.662		0.774	
Root MSE (b)	0.910		1.143		1.314		1.419		1.427		1.443		1.404		1.427	

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + B(j) + error
(c) Model: PR = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPRID AND PEAK PRID[a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 25 mg	31	7.15A	15.39A	4.19 A
Bromfenac 10 mg	32	5.80AB	12.63AB	3.75 A
Bromfenac 5 mg	31	5.20AB	9.19BC	3.29 AB
APAP 1000 mg	32	6.86A	12.66AB	3.75 A
Placebo	31	3.73B	5.71C	2.35 B
p-value		0.0215	0.0015	0.0070
Root MSE		4.4663	9.6182	2.0310

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)													
Treatment	1/2		1		1 1/2		2		3		4		5		6	
Bromfenac 25 mg	1.26 31 (a)	(1.37)	2.26 30	(1.73) A (d)	2.90 29	(2.12) A	3.05 26	(2.21)	3.29 26	(2.19) A	2.90 24	(2.27) A	2.48 21	(2.46) A	2.42 19	(2.46) A
Bromfenac 10 mg	1.50 32	(1.52)	1.84 32	(1.95) AB	2.56 28	(2.06) A	2.06 27	(2.26)	2.59 25	(2.31) AB	2.56 22	(2.53) A	2.00 18	(2.26) AB	1.94 16	(2.44) AB
Bromfenac 5 mg	1.35 31	(1.33)	2.35 31	(1.72) A	1.98 28	(1.81) AB	2.06 25	(2.14)	1.61 21	(1.76) BC	1.48 18	(1.84) BC	1.16 15	(1.68) BC	1.06 11	(1.79) BC
Acetaminophen 1000 mg	1.81 32	(1.64)	2.61 31	(1.94) A	2.75 28	(2.27) A	2.72 25	(2.11)	2.47 21	(2.27) AB	2.00 17	(2.41) AB	1.78 13	(2.47) AB	1.56 13	(2.38) ABC
Placebo	1.06 31	(1.36)	1.19 31	(1.42) B	1.44 25	(1.99) B	1.65 18	(2.12)	1.29 16	(2.10) C	0.61 10	(1.48) C	0.48 4	(1.43) C	0.48 4	(1.43) C
p-value Trt (b)	0.292		0.016		0.030		0.086		0.002		<0.001		0.002		0.005	
p-value Baseline (c)	0.060		0.170		0.519		0.318		0.529		0.052		0.017		0.014	
p-value Trt*Baseline (c)	0.382		0.479		0.854		0.652		0.984		0.882		0.774		0.883	
Root MSE (b)	1.438		1.761		2.061		2.169		2.143		2.125		2.074		2.108	

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + error
(c) Model: PRID = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Table 4. Estimated Onset of Pain Relief (on-PR)

Treatment Group	PRID at 30 min			Estimated on-PR	
	Mean[a]	S.D.	n	Time (min)	95%-CI (min)
Bromfenac 25 mg	1.26	1.37	31	24	17 - 40
Bromfenac 10 mg	1.50	1.52	32	20	15 - 32
Bromfenac 5 mg	1.35	1.33	31	22	16 - 35
Acetaminophen 1000 mg	1.81	1.64	32	17	12 - 25
Placebo	1.06	1.36	31	28	19 - 53

a Raw unadjusted mean of (unextrapolated) PRID scores.

Figure 4. Estimated Duration of Analgesia
(Time-to-Remedication)

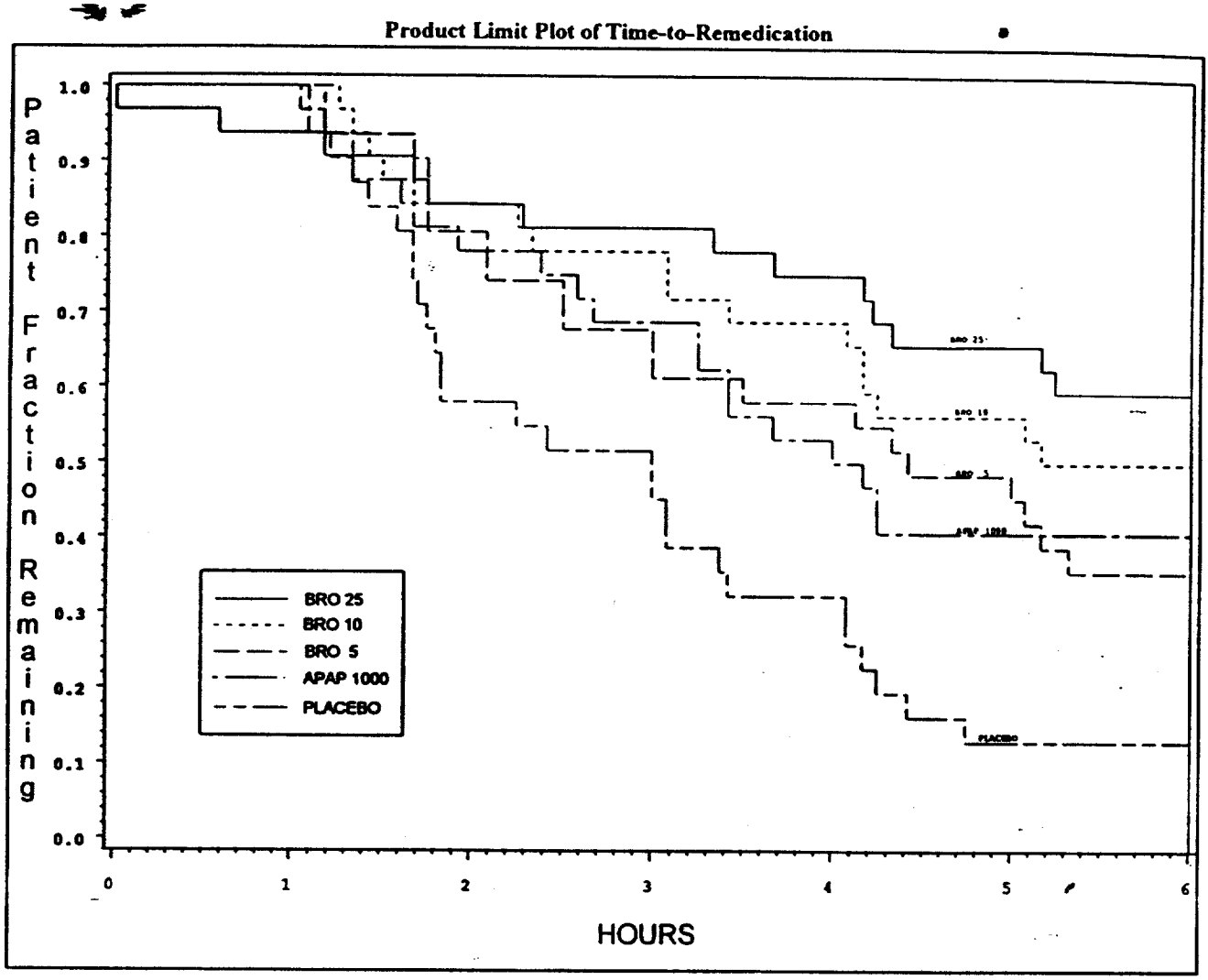


Table 5. Duration of Pain Relief (dur-PR)

		Calculated Time to Remedication	
Treatment Group	n	Mean [a] h:min	95% CI [b] h:min
Bromfenac 25 mg	31	5:30 A [c]	(4:46, >6h)
Bromfenac 10 mg	32	5:01 A	(4:14, 5:47)
Bromfenac 5 mg	31	4:33 A	(3:45, 5:21)
Acetaminophen 1000 mg	32	4:31 A	(3:42, 5:20)
Placebo	31	3:08 B	(2:29, 3:47)

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77)
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

Table 6. Time-to-Remedication (Percentiles)

Treatment	----------Percentiles In Hours:minutes (95% C. I.)----------		
	25%	50% (Median)	75%
Bromfenac 25 mg	4:10 (2:16, >6h)	>6h (5:10, >6h)	>6h (NE)
Bromfenac 10 mg	3:05 (1:40, 4:15)	6:05 (4:05, >6h)	>6h (NE)
Bromfenac 5 mg	2:05 (1:45, 4:20)	5:00 (3:00, >6h)	>6h (5:10, >6h)
Acetaminophen 1000 mg	2:29 (1:36, 3:25)	4:10(3:15, >6h)	>6h (NE)
Placebo	1:40 (1:25, 2:15)	3:00 (1:48, 3:25)	4:10 (3:05, 4:45)

NE: Not estimable.

CONFIDENTIAL: SBA Summary for Bromfenac Protocol AHR-20-SW

A Double-blind, Single-dose Evaluation of the Relative Analgesic Efficacy and Safety of Three Doses of Bromfenac (AHR-10282B; 100, 50, and 25 mg) and Two Doses of Ibuprofen (400 and 200 mg) in theTreatment of Pain Following Orthopedic Surgery: Final Report

IND DRUG:	Bromfenac	DOSES:	100, 50, 25 mg oral
REFERENCE DRUGS:	Ibuprofen	DOSE:	400 mg oral 200 mg oral
TOTAL PTS ENROLLED:200		DURATION OF DOSING: Single dose, 6 hr	
INVESTIGATOR:	Ake Boström, M.D., Karlstad, Sweden		

PURPOSE: The purpose of this study was to compare the efficacy and safety of single oral doses of bromfenac (100, 50, and 25 mg) and ibuprofen (400 and 200 mg) in the treatment of moderate to severe pain resulting from orthopedic surgery.

METHOD: This was a single-dose, double-blind, randomized, parallel study with 5 treatments. Study medication was administered within 72 hours after surgery provided pain intensity was moderate or severe. Pain intensity was assessed before dose, then both pain intensity and pain relief were assessed at 0.5 and 1 hour and then hourly up to 6 hours postdose. The following measurements of efficacy were derived from the patients' rating scores: hourly pain intensity difference (PID), sum of the pain intensity difference (SPID), peak PID, hourly pain relief, total pain relief (TOPAR), peak pain relief, hourly pain relief plus PID (PRID) and sum of the PRID (SPRID), hourly pain analog intensity difference (PAID), summed PAID (SPAID), total hours of 50% relief and hourly patient acceptability. The hourly measures of efficacy were calculated by using both extrapolated and unextrapolated methods. In the event of premature withdrawal or remedication, the baseline pain intensity and analog pain intensity scores were carried forward for all remaining timepoints. For the patient acceptability variable, the last observation was carried forward. The pain relief and pain-half-gone scores for all timepoints after remedication were assigned a value of 0. All efficacy results were analyzed as combined scores and by baseline pain intensity because of significant ($p \leq 0.10$) baseline pain intensity-by-treatment interaction. Therefore, meaningful interpretations of the results are restricted to the separate moderate and severe baseline intensity strata.

RESULTS: Bromfenac 100 mg provided the greatest analgesic efficacy of the three bromfenac doses for patients in the severe baseline pain intensity stratum. In general, bromfenac 100 mg was comparable to ibuprofen 400 mg for peak analgesic efficacy and provided longer duration of analgesia than ibuprofen 400 mg. However, ibuprofen 400 mg had a faster onset of pain relief than bromfenac 100 mg in the moderate baseline pain intensity stratum. With bromfenac 100 mg, the scores for 6-hour TOPAR, SPID, SPRID and SPAID were statistically better than the scores with ibuprofen 400 mg in the severe baseline pain intensity stratum.

A paradoxical relationship in the analgesic effectiveness for bromfenac 50 mg and 25 mg was seen in the severe baseline pain stratum.

For most efficacy variables in patients with severe baseline pain intensity, there was a statistically significant difference between one or more doses of bromfenac and the lower - but not the higher - dose of ibuprofen.

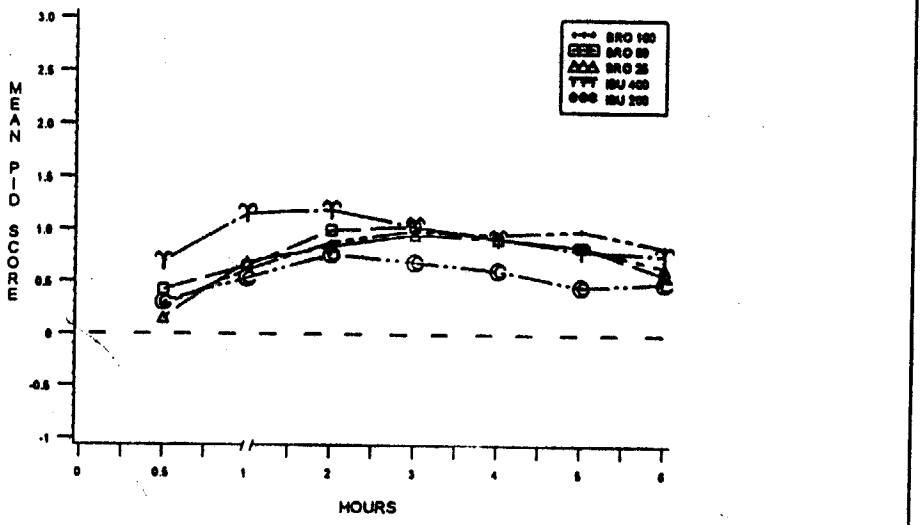
Overall, the percentages of patients who remedicated at less than 6 hours were lower with bromfenac than with ibuprofen. Among patients reporting severe baseline pain, a significantly lower percentage treated with either bromfenac 100 or 25 mg than with either bromfenac 50 mg or ibuprofen 200 mg remedicated within 3 hours.

One or more treatment-emergent study events (TESE) were reported by 7 patients (17.5%) who took bromfenac 100 mg, 5 (12.5%) who took bromfenac 50 mg, 10 (25%) who took bromfenac 25 mg, 9 (22.5%) who took ibuprofen 400 mg, and 9 (22.5%) who took ibuprofen 200 mg. The number of study events was not significantly different among the treatment groups for any COSTART body system or any preferred term. No patient was withdrawn because of a study event and no patient reported a serious study event.

CONCLUSIONS: In summary, the analgesic efficacy of bromfenac was demonstrated in patients suffering from pain associated with orthopedic surgery. The 100 mg dose was the most efficacious of the bromfenac treatments, and statistically superior to ibuprofen 400 mg in all primary variables in the severe-pain stratum. All treatments were equally well tolerated.

Figure 1, Table 1. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPID AND PEAK PID

Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Brom 100 mg	26	1.98	4.87	1.15
Brom 50 mg	26	2.22	4.80	1.23
Brom 25 mg	26	1.92	4.50	1.15
Ibuprofen 400 mg	26	2.92	5.56	1.42
Ibuprofen 200 mg	26	1.67	3.35	1.12
p-value		0.1034	0.2974	0.5909
Root MSE		1.7337	3.6974	0.7504

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

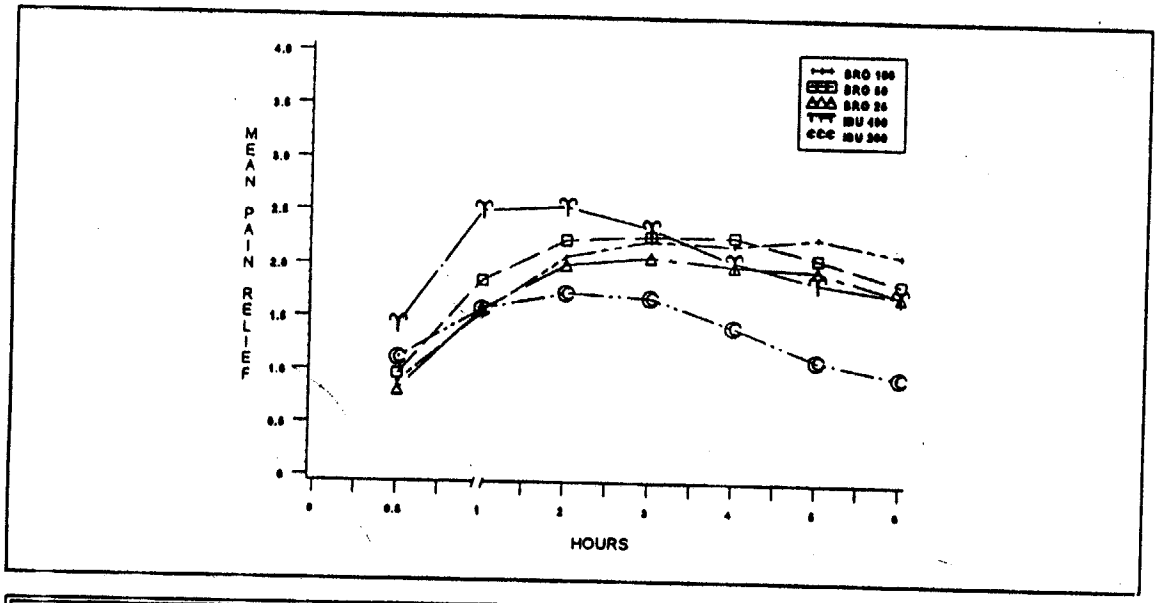
	Assessment Time Points (Hours)													
Treatment	1/2		1		2		3		4		5		6	
Bromfenac 100 mg	0.27 26 (a)	(0.60) B (c)	0.62 26	(0.70) B	0.88 26	(0.86)	1.00 21	(0.75)	0.96 20	(0.77)	1.00 20	(0.80)	0.85 19	(0.92)
Bromfenac 50 mg	0.42 26	(0.50) AB	0.65 26	(0.63) B	1.00 25	(0.69)	1.04 23	(0.66)	0.92 22	(0.74)	0.85 22	(0.78)	0.58 22	(0.81)
Bromfenac 25 mg	0.15 26	(0.54) B	0.69 26	(0.55) B	0.85 26	(0.73)	0.96 21	(0.82)	0.92 19	(0.84)	0.85 18	(0.78)	0.65 17	(0.80)
Ibuprofen 400 mg	0.69 26	(0.55) A	1.15 26	(0.83) A	1.19 25	(0.90)	1.04 22	(0.96)	0.92 20	(0.98)	0.81 19	(0.94)	0.77 16	(0.91)
Ibuprofen 200 mg	0.31 26	(0.62) B	0.54 26	(0.65) B	0.77 24	(0.86)	0.69 20	(0.93)	0.62 19	(0.80)	0.46 17	(0.71)	0.50 14	(0.71)
p-value Trt (b)	0.011		0.012		0.377		0.530		0.549		0.182		0.568	
Root MSE (b)	0.565		0.677		0.813		0.831		0.832		0.806		0.832	

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PID = u + T(i) + error

Figure 2, Table 2. Pain Relief (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL TOPAR AND PEAK RELIEF

Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak Pain RELIEF
Bromfenac 100 mg	26	4.79	11.42	2.54
Bromfenac 50 mg	26	5.23	11.63	2.73
Bromfenac 25 mg	26	4.63	10.49	2.58
Ibuprofen 400 mg	26	6.30	12.22	2.92
Ibuprofen 200 mg	26	4.32	8.18	2.19
p-value Trt		0.1954	0.2997	0.4382
Root MSE		3.1698	7.2744	1.4137

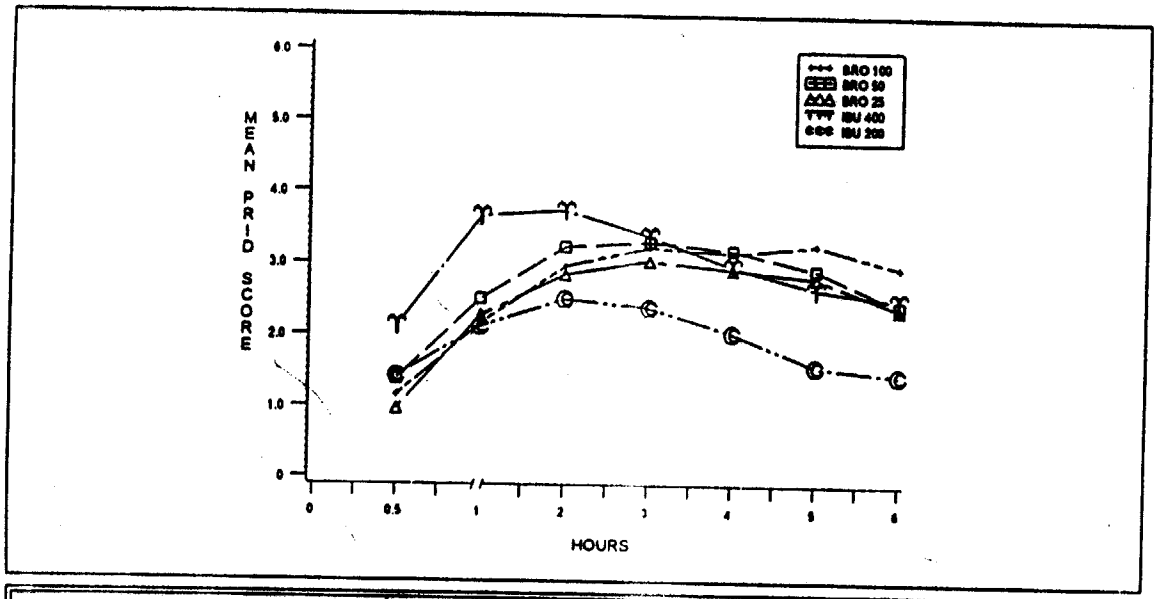
a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)						
	1/2	1	2	3	4	5	6
Bromfenac 100 mg	0.88 (0.95) 26 (a)	1.54 (1.21) 26 B (c)	2.08 (1.44) 26	2.23 (1.56) 21	2.19 (1.60) 20	2.27 (1.61) 20	2.12 (1.63) 19
Bromfenac 50 mg	0.96 (0.87) 26	1.85 (0.97) 26 B	2.23 (1.31) 25	2.27 (1.31) 23	2.27 (1.34) 22	2.08 (1.44) 22	1.85 (1.41) 22
Bromfenac 25 mg	0.81 (0.90) 26	1.58 (0.95) 26 B	2.00 (1.39) 26	2.08 (1.52) 21	2.00 (1.65) 19	1.96 (1.56) 18	1.73 (1.54) 17
Ibuprofen 400 mg	1.42 (1.27) 26	2.50 (1.50) 26 A	2.54 (1.50) 25	2.35 (1.65) 22	2.04 (1.78) 20	1.85 (1.71) 19	1.73 (1.80) 16
Ibuprofen 200 mg	1.12 (1.11) 26	1.58 (1.06) 26 B	1.73 (1.34) 24	1.69 (1.62) 20	1.42 (1.50) 19	1.12 (1.40) 17	0.96 (1.40) 14
p-value Trt (b)	0.221	0.015	0.322	0.563	0.335	0.083	0.103
Root MSE (b)	1.030	1.155	1.397	1.536	1.581	1.549	1.562

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + error
(c) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPRID AND PEAK PRID

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 100 mg	26	6.77	16.29	3.69
Bromfenac 50 mg	26	7.45	16.43	3.96
Bromfenac 25 mg	26	6.55	14.99	3.73
Ibuprofen 400 mg	26	9.22	17.78	4.35
Ibuprofen 200 mg	26	5.99	11.53	3.31
p-value Trt		0.1455	0.2936	0.5053
Root MSE		4.8226	10.8602	2.1299

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)						
Treatment	1/2	1	2	3	4	5	6
Bromfenac 100 mg	1.15 (1.49) 26 (a)	2.15 (1.85) B (c)	2.96 (2.25) 26	3.23 (2.27) 21	3.15 (2.34) 20	3.27 (2.39) 20	2.96 (2.46) 19
Bromfenac 50 mg	1.38 (1.27) 26	2.50 (1.50) B	3.23 (1.92) 25	3.31 (1.91) 23	3.19 (2.04) 22	2.92 (2.17) 22	2.42 (2.16) 22
Bromfenac 25 mg	0.96 (1.34) 26	2.27 (1.40) B	2.85 (2.07) 26	3.04 (2.29) 21	2.92 (2.46) 19	2.81 (2.30) 18	2.38 (2.26) 17
Ibuprofen 400 mg	2.12 (1.77) 26	3.65 (2.30) A	3.73 (2.36) 25	3.38 (2.58) 22	2.96 (2.72) 20	2.65 (2.61) 19	2.50 (2.69) 16
Ibuprofen 200 mg	1.42 (1.68) 26	2.12 (1.66) B	2.50 (2.16) 24	2.38 (2.52) 20	2.04 (2.25) 19	1.58 (2.04) 17	1.46 (2.08) 14
p-value Trt (b)	0.078	0.011	0.321	0.537	0.399	0.100	0.232
Root MSE (b)	1.521	1.769	2.158	2.324	2.375	2.310	2.339

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PRID = u + T(i) + error

Table 4. Estimated Onset of Pain Relief (on-PR)

	PRID at 30 min			Estimated on-PR	
Treatment Group	Mean [a]	SD	n	Time (min)	95%-CI (min)
Bromfenac 100 mg	1.15	1.49	26	26	(17 - 54)
Bromfenac 50 mg	1.38	1.27	26	22	(16 - 34)
Bromfenac 25 mg	0.96	1.34	26	31	(20 - 71)
Ibuprofen 400 mg	2.12	1.77	26	14	(11 - 21)
Ibuprofen 200 mg	1.42	1.68	26	21	(14 - 40)

a Raw unadjusted mean of (unextrapolated) PRID scores.

Figure 4. Estimated Duration of Analgesia
(Time-to-Remedication)

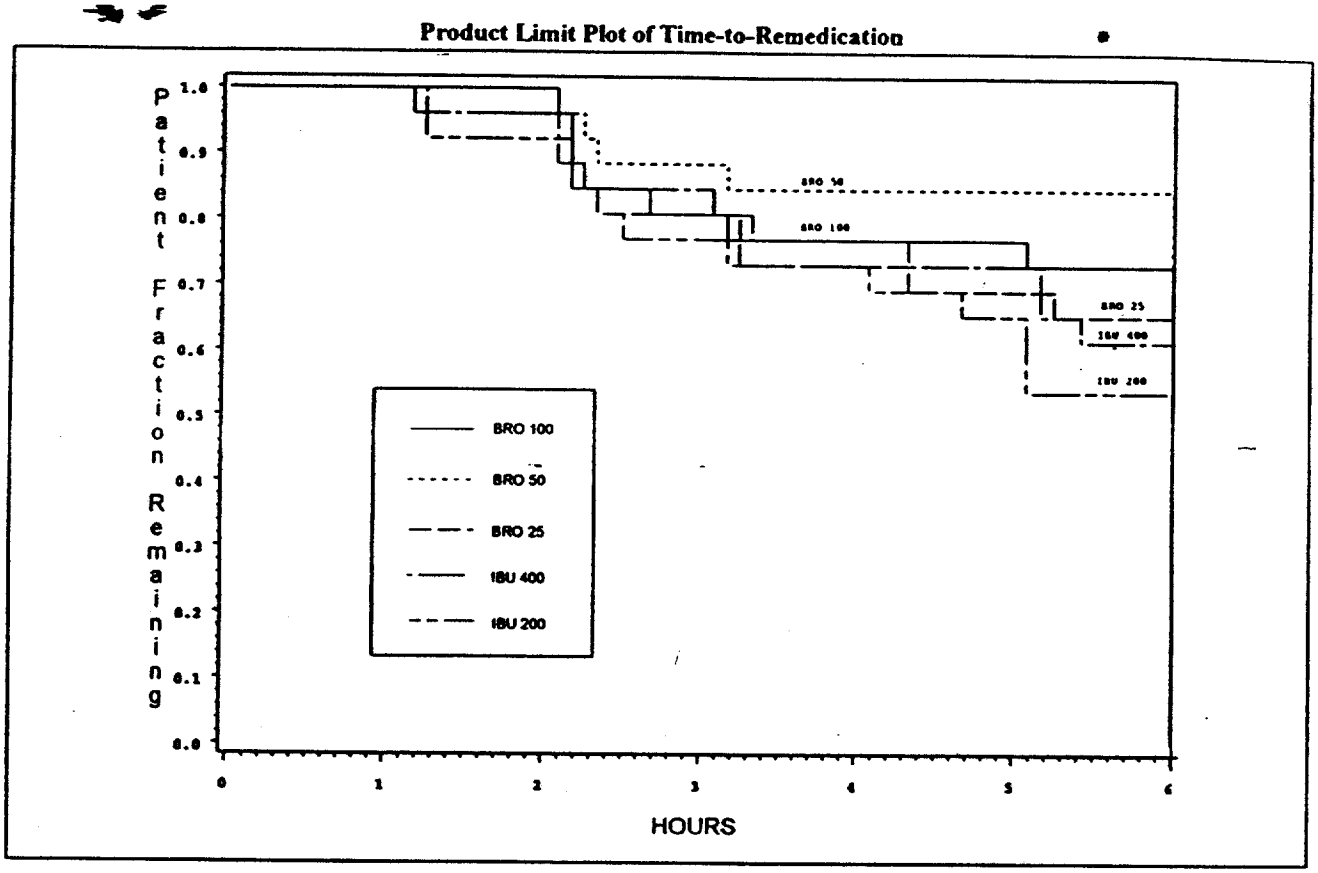


Table 5. Duration of Pain Relief (dur-PR)

Treatment Group	n	Calculated Time to Remedication	
		Mean [a] h:min	95% CI [b] h:min
Bromfenac 100 mg	26	5:54[c]	(5:06, > 6h)
Bromfenac 50 mg	26	> 6h	(5:36, >6h)
Bromfenac 25 mg	26	5:36	(4:48, >6h)
Ibuprofen 400 mg	26	5:36	(4:48, >6h)
Ibuprofen 200 mg	26	5:18	(4:24, >6h)

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied. No significant differences.

CONFIDENTIAL: BROMFENAC AHR-20-SW (MODERATE PAIN)

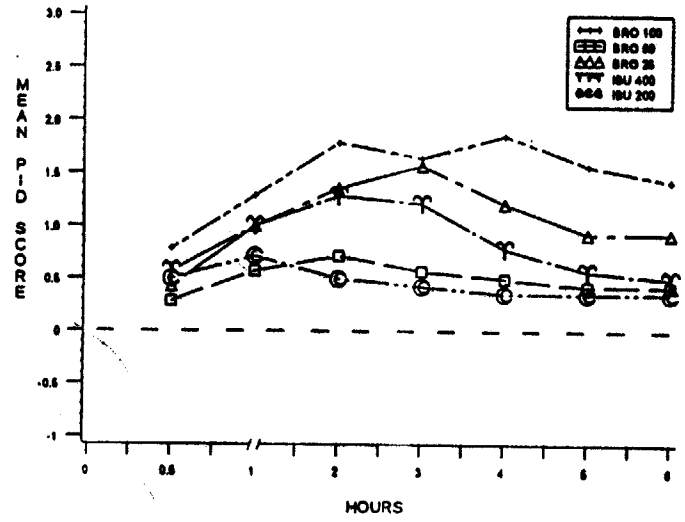
Table 6. Time-to-Remedication (Percentiles)

	----------Percentiles In Hours:minutes (95% C. I.)----------		
Treatment	25%	50% (Median)	75%
Bromfenac 100 mg	5:05 (2:10, >6hr)	>6hr (NE)	>6hr (NE)
Bromfenac 50 mg	>6hr (3:10, >6hr)	>6hr (NE)	>6hr (NE)
Bromfenac 25 mg	3:15 (2:15, >6hr)	>6hr (5:15, >6hr)	>6hr (NE)
Ibuprofen 400 mg	4:20 (2:15, >6hr)	>6hr (5:10, >6hr)	>6hr (NE)
Ibuprofen 200 mg	3:10 (2:10, 5:05)	>6hr (4:40, >6hr)	>6hr (NE)

NE: Not estimable.

Figure 5, Table 7. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPID AND PEAK PID

Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 100 mg	14	3.96A	8.93A	2.07A
Bromfenac 50 mg	14	1.57B	3.00C	1.00B
Bromfenac 25 mg	14	3.11A	6.50AB	1.64AB
Ibuprofen 400 mg	14	2.93AB	5.14BC	1.36AB
Ibuprofen 200 mg	14	1.50B	2.61C	0.93B
p-value		0.0044	0.0015	0.0121
Root MSE		1.9377	4.3807	0.9469

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission

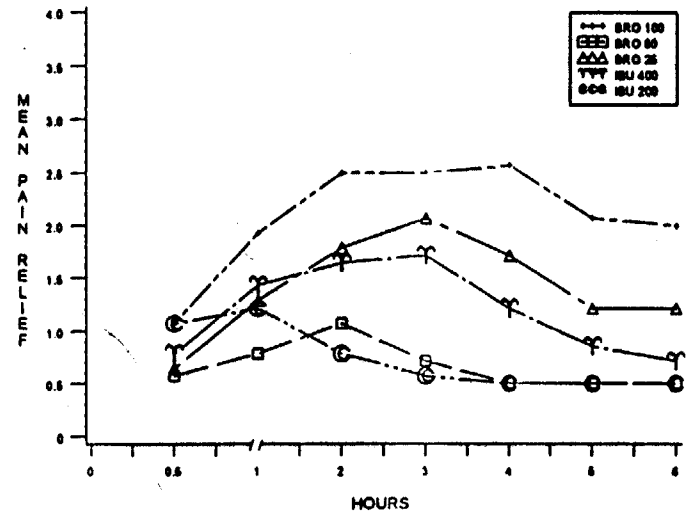
	Assessment Time Points (Hours)						
Treatment	1/2	1	2	3	4	5	6
Bromfenac 100 mg	0.79 (0.80) 14 (a)	1.29 (0.83) 14	1.79 (0.89) 13 A (c)	1.64 (1.01) 13 A	1.86 (1.03) 12 A	1.57 (0.94) 12 A	1.43 (1.09) 10 A
Bromfenac 50 mg	0.29 (0.47) 14	0.57 (0.65) 14	0.71 (0.99) 14 BC	0.57 (0.94) 5 BC	0.50 (0.85) 4 BC	0.43 (0.76) 4 B	0.43 (0.76) 4 B
Bromfenac 25 mg	0.43 (0.51) 14	1.00 (0.68) 14	1.36 (0.74) 13 AB	1.57 (0.85) 13 A	1.21 (1.12) 9 AB	0.93 (1.14) 7 AB	0.93 (1.14) 7 AB
Ibuprofen 400 mg	0.57 (0.76) 14	1.00 (0.88) 14	1.29 (0.91) 12 AB	1.21 (0.97) 10 AB	0.79 (0.97) 8 BC	0.57 (0.85) 6 B	0.50 (0.85) 4 B
Ibuprofen 200 mg	0.50 (0.76) 14	0.71 (0.99) 14	0.50 (0.76) 11 C	0.43 (0.94) 4 C	0.36 (0.93) 2 C	0.36 (0.93) 2 B	0.36 (0.93) 2 B
p-value Trt (b)	0.387	0.175	0.001	0.001	<0.001	0.005	0.023
Root MSE (b)	0.674	0.814	0.866	0.943	0.985	0.931	0.964

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PID = u + T(i) + error

Figure 6, Table 8. Pain Relief (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL TOPAR AND PEAK RELIEF

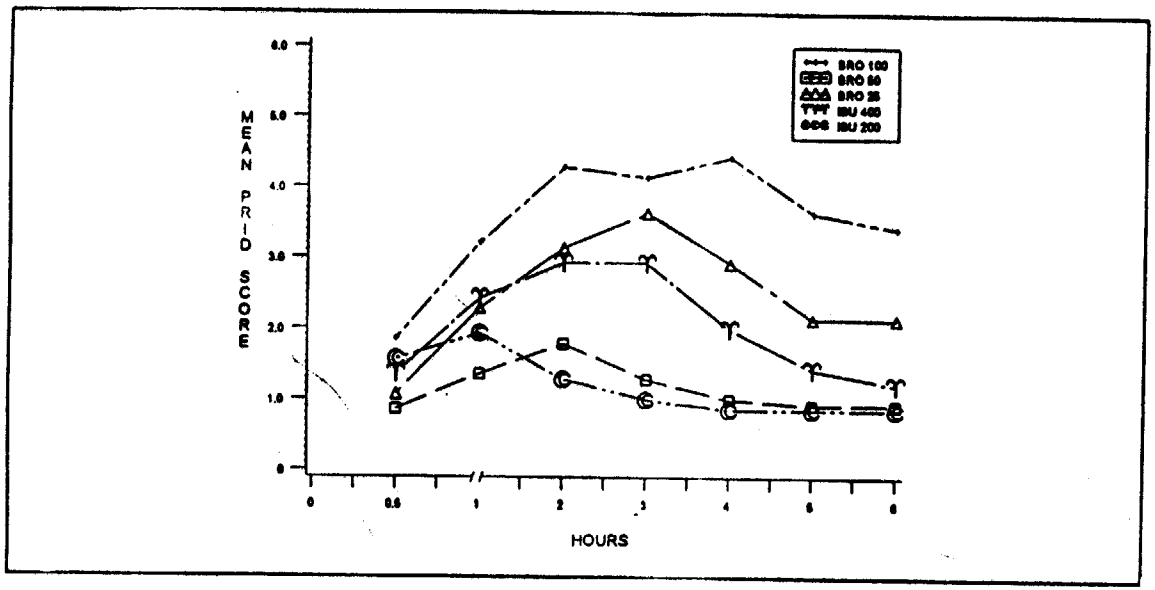
Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak Pain RELIEF
Bromfenac 100 mg	14	5.73A	12.63A	2.93A
Bromfenac 50 mg	14	2.30B	3.91C	1.50BC
Bromfenac 25 mg	14	4.11AB	8.68AB	2.36AB
Ibuprofen 400 mg	14	3.96AB	7.25BC	2.00BC
Ibuprofen 200 mg	14	2.52B	4.05C	1.43C
p-value		0.0028	0.0001	0.0068
Root MSE		2.4478	5.7285	1.1837

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)						
Treatment	1/2	1	2	3	4	5	6
Bromfenac 100 mg	1.07 (0.92) 14 (a)	1.93 (0.92) 14	2.50 (1.16) 13 A (c)	2.50 (1.29) 13 A	2.57 (1.34) 12 A	2.07 (1.33) 12 A	2.00 (1.47) 10 A
Bromfenac 50 mg	0.57 (0.65) 14	0.79 (0.70) 14	1.07 (1.21) 14 BC	0.71 (1.20) 5 B	0.50 (1.02) 4 C	0.50 (1.02) 4 B	0.50 (1.02) 4 B
Bromfenac 25 mg	0.64 (0.74) 14	1.29 (0.99) 14	1.79 (1.12) 13 AB	2.07 (1.27) 13 A	1.71 (1.54) 9 AB	1.21 (1.53) 7 AB	1.21 (1.53) 7 AB
Ibuprofen 400 mg	0.79 (0.89) 14	1.43 (1.09) 14	1.64 (1.28) 12 ABC	1.71 (1.38) 10 A	1.21 (1.37) 8 BC	0.86 (1.29) 6 B	0.71 (1.27) 4 B
Ibuprofen 200 mg	1.07 (1.07) 14	1.21 (1.12) 14	0.79 (1.12) 11 C	0.57 (1.28) 4 B	0.50 (1.29) 2 C	0.50 (1.29) 2 B	0.50 (1.29) 2 B
p-value Trt (b)	0.400	0.051	0.002	<0.001	<0.001	0.011	0.017
Root MSE (b)	0.866	0.976	1.179	1.286	1.322	1.300	1.325

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + error
(c) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 7, Table 9. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 100 mg	14	9.70A	21.55A	4.93A
Bromfenac 50 mg	14	3.88C	6.91C	2.50BC
Bromfenac 25 mg	14	7.21AB	15.18AB	4.00AB
Ibuprofen 400 mg	14	6.89ABC	12.39BC	3.36ABC
Ibuprofen 200 mg	14	4.02BC	6.66C	2.36C
p-value		0.0030	0.0001	0.0094
Root MSE		4.3230	0.0540	2.0934

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)													
	1/2		1		2		3		4		5		6	
Bromfenac 100 mg	1.86 14 (a)	(1.66)	3.21 14	(1.67)	4.29 13	(2.02) A (c)	4.14 13	(2.25) A	4.43 12	(2.34) A	3.64 12	(2.24) A	3.43 10	(2.53) A
Bromfenac 50 mg	0.86 14	(1.03)	1.36 14	(1.28)	1.79 14	(2.15) BC	1.29 5	(2.13) BC	1.00 4	(1.84) C	0.93 4	(1.73) B	0.93 4	(1.73) B
Bromfenac 25 mg	1.07 14	(1.21)	2.29 14	(1.64)	3.14 13	(1.83) AB	3.64 13	(2.10) A	2.93 9	(2.64) AB	2.14 7	(2.66) AB	2.14 7	(2.66) AB
Ibuprofen 400 mg	1.36 14	(1.60)	2.43 14	(1.91)	2.93 12	(2.16) AB	2.93 10	(2.34) AB	2.00 8	(2.32) BC	1.43 6	(2.14) B	1.21 4	(2.12) B
Ibuprofen 200 mg	1.57 14	(1.79)	1.93 14	(2.06)	1.29 11	(1.86) C	1.00 4	(2.22) C	0.86 2	(2.21) C	0.86 2	(2.21) B	0.86 2	(2.21) B
p-value Trt (b)	0.415		0.081		0.001		<0.001		<0.001		0.008		0.018	
Root MSE (b)	1.483		1.731		2.010		2.207		2.287		2.215		2.274	

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PRID = u + T(i) + error

Table 10. Estimated Onset of Pain Relief (on-PR)

	PRID at 30 min			Estimated on-PR	
Treatment Group	Mean [a]	SD	n	Time (min)	95%-CI (min)
Bromfenac 100 mg	1.86	1.66	14	16	(11 - 33)
Bromfenac 50 mg	0.86	1.03	14	35	(21 - 114)
Bromfenac 25 mg	1.07	1.21	14	28	(17 - 80)
Ibuprofen 400 mg	1.36	1.60	14	22	(13 - 69)
Ibuprofen 200 mg	1.57	1.79	14	19	(12 - 55)

a Raw unadjusted mean of (unextrapolated) PRID scores.

Figure 8. Estimated Duration of Analgesia
(Time-to-Remedication)

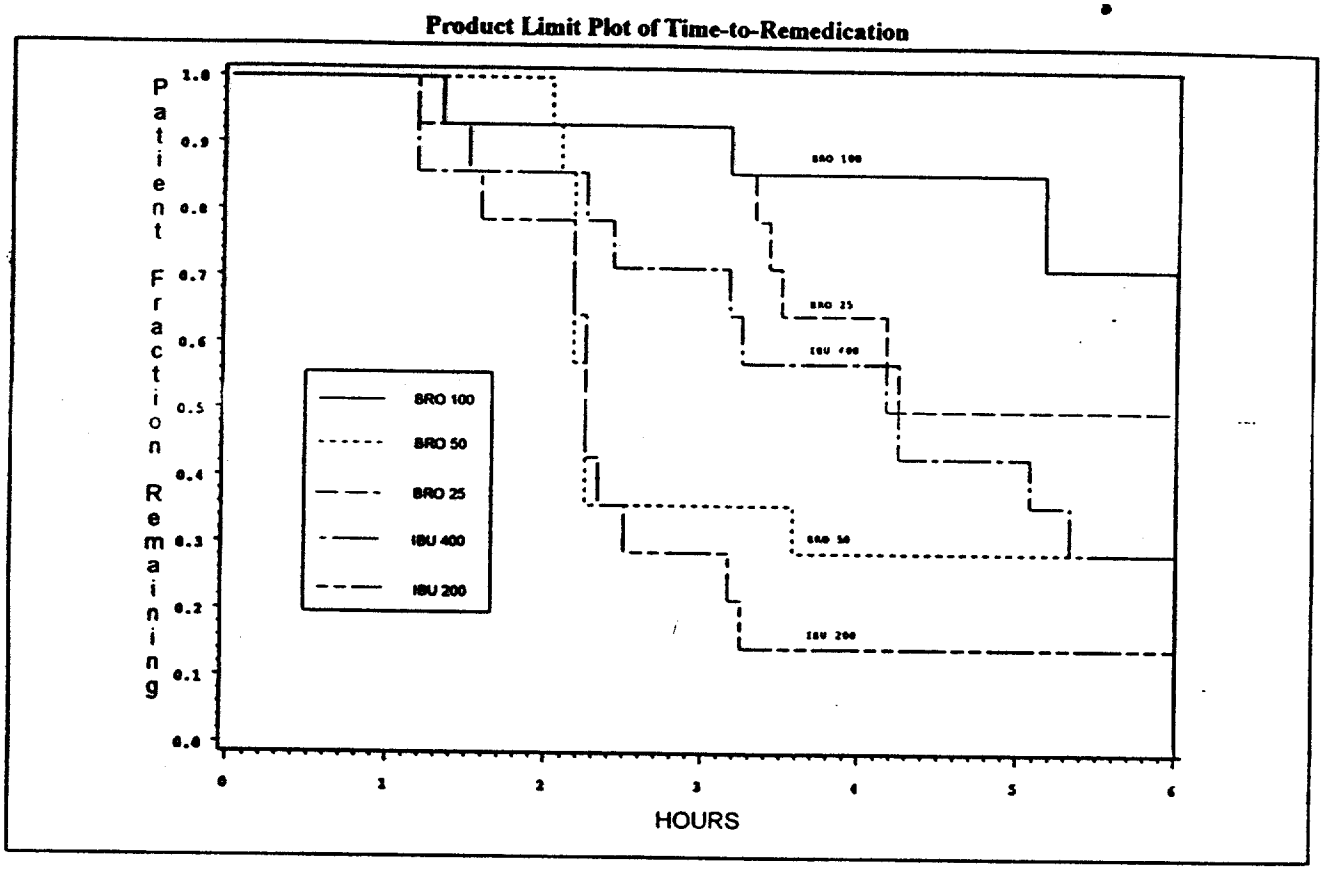


Table 11. Duration of Pain Relief (dur-PR)

Treatment Group	n	Calculated Time to Remedication	
		Mean [a] h:min	95% CI [b] h:min
Bromfenac 100 mg	14	> 6h (A)[c]	(5:06, >6h)
Bromfenac 50 mg	14	3:42 (BC)	(2:30, 4:48)
Bromfenac 25 mg	14	5:06 (AB)	(4:06, >6h)
Ibuprofen 400 mg	14	4:18 (BC)	(3:12, 5:24)
Ibuprofen 200 mg	14	2:54 (C)	(2:00, 3:54)

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77)
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

Table 12. Time-to-Remedication (Percentiles)

	----------Percentiles In Hours:minutes (95% C. I.)----------		
Treatment	25%	50% (Median)	75%
Bromfenac 100 mg	5:10 (3:10, >6hr)	>6hr (5:10, >6hr)	>6hr (NE)
Bromfenac 50 mg	2:10 (2:05, 2:15)	2:15 (2:10, >6hr)	>6hr (2:15, >6hr)
Bromfenac 25 mg	3:25 (3:10, >6hr)	5:38 (3:25, >6hr)	>6hr (4:15, >6hr)
Ibuprofen 400 mg	2:25 (1:10, 4:15)	4:13 (2:25, >6hr)	>6hr (4:10, >6hr)
Ibuprofen 200 mg	2:10 (1:30, 2:15)	2:15 (2:10, 3:10)	3:10 (2:15, >6hr)

NE: Not estimable.

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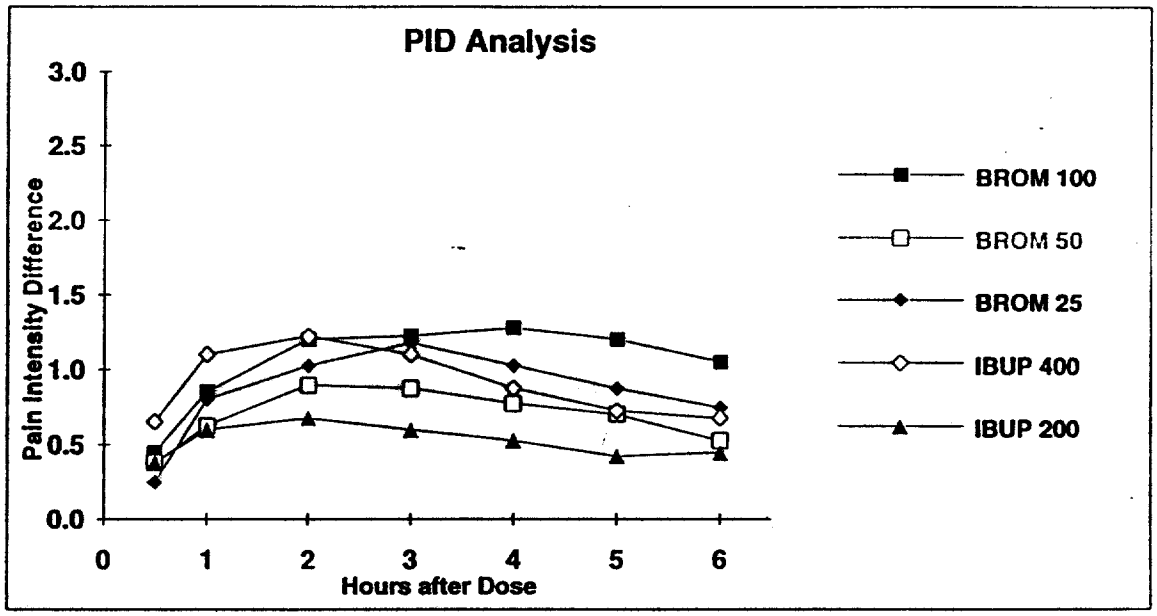

	0.5	1	2	3	4	5	6	SPID3	SPID
BROM 100	0.45 (0.71)	0.85 (0.80)	1.20 (0.97)	1.23 (0.89)	1.28 (0.96)	1.20 (0.88)	1.05 (1.01)	3.08 (2.37)	6.60 (4.74)
	40 NS	40 AB	39 A	34 A	32 A	32 A	29 A	40 A	40 A
BROM 50	0.38 (0.49)	0.63 (0.63)	0.90 (0.81)	0.88 (0.79)	0.78 (0.80)	0.70 (0.79)	0.53 (0.78)	2.28 (1.76)	4.28 (3.74)
	40 NS	40 B	39 AB	28 AB	26 BC	26 BC	26 B	40 AB	40 BC
BROM 25	0.25 (0.54)	0.80 (0.61)	1.03 (0.77)	1.18 (0.87)	1.03 (0.95)	0.88 (0.91)	0.75 (0.93)	2.73 (1.93)	5.38 (4.32)
	40 NS	40 AB	39 AB	34 A	28 AB	25 AB	24 AB	40 A	40 AB
IBUP 400	0.65 (0.62)	1.10 (0.84)	1.23 (0.89)	1.10 (0.96)	0.88 (0.97)	0.73 (0.91)	0.68 (0.89)	3.20 (2.24)	5.48 (4.39)
	40 NS	40 A	37 A	32 A	28 BC	25 BC	20 AB	40 A	40 AB
IBUP 200	0.38 (0.67)	0.60 (0.78)	0.68 (0.83)	0.60 (0.93)	0.53 (0.85)	0.43 (0.78)	0.45 (0.78)	1.76 (2.15)	3.16 (4.11)
	40 NS	40 B	35 B	24 B	21 C	19 C	16 B	40 B	40 C
p	0.059	* 0.020 *	* 0.026 *	* 0.011 *	* 0.005 *	* 0.002 *	* 0.027 *	* 0.015 *	* 0.006 *
rmse	0.61	0.74	0.86	0.89	0.91	0.86	0.88	2.10	4.27

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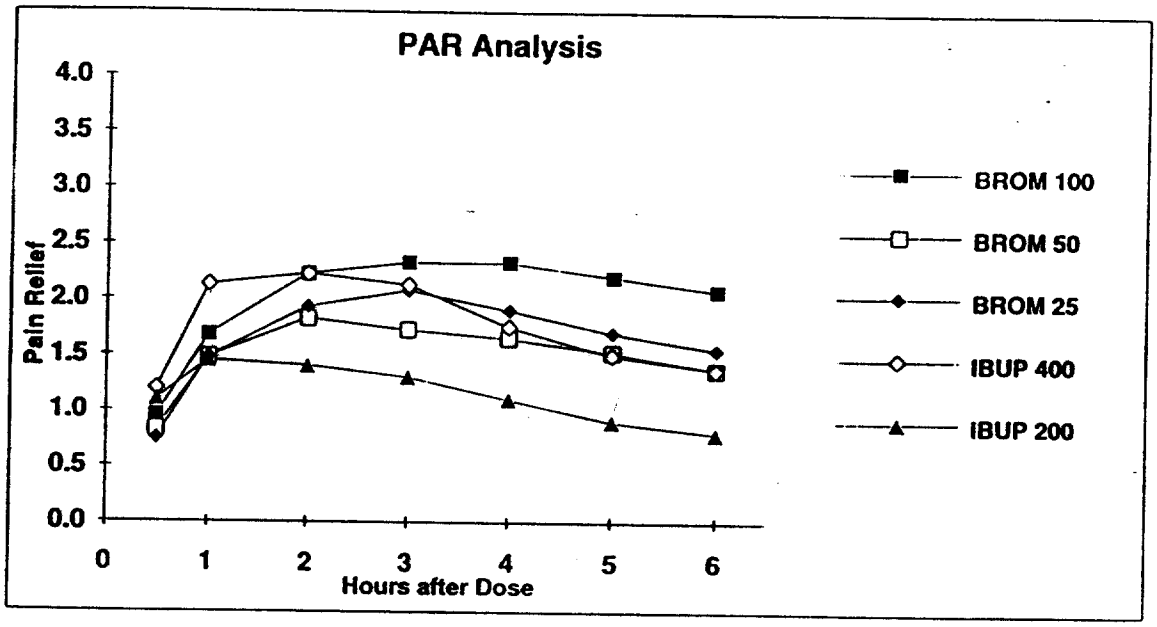

	0.5	1	2	3	4	5	6	TOTPAR3	TOTPAR
BROM 100	0.95 (0.93)	1.68 (1.12)	2.23 (1.35)	2.33 (1.46)	2.33 (1.51)	2.20 (1.51)	2.08 (1.56)	5.86 (3.48)	12.46 (7.48)
	40 NS	40 AB	39 A	34 A	32 A	32 A	29 A	40 NS	40 A
BROM 50	0.83 (0.81)	1.48 (1.01)	1.83 (1.38)	1.73 (1.47)	1.65 (1.49)	1.53 (1.50)	1.38 (1.43)	4.70 (3.27)	9.25 (7.18)
	40 NS	40 B	39 AB	28 AB	26 AB	26 BC	26 BC	40 NS	40 AB
BROM 25	0.75 (0.84)	1.48 (0.96)	1.93 (1.29)	2.08 (1.42)	1.90 (1.60)	1.70 (1.57)	1.55 (1.54)	5.11 (3.19)	10.26 (7.33)
	40 NS	40 B	39 AB	34 A	28 A	25 AB	24 AB	40 NS	40 A
IBUP 400	1.20 (1.18)	2.13 (1.45)	2.23 (1.48)	2.13 (1.57)	1.75 (1.68)	1.50 (1.63)	1.38 (1.69)	6.01 (3.91)	10.64 (8.13)
	40 NS	40 A	37 A	32 A	28 AB	25 BC	20 BC	40 NS	40 A
IBUP 200	1.10 (1.08)	1.45 (1.08)	1.40 (1.34)	1.30 (1.59)	1.10 (1.48)	0.90 (1.37)	0.80 (1.36)	3.98 (3.61)	6.78 (7.39)
	40 NS	40 B	35 B	24 B	21 B	19 C	16 C	40 NS	40 B
p	0.217	* 0.042 *	* 0.044 *	* 0.023 *	* 0.013 *	* 0.006 *	* 0.007 *	0.058	* 0.017 *
rmse	0.98	1.14	1.37	1.50	1.55	1.52	1.52	3.50	7.51

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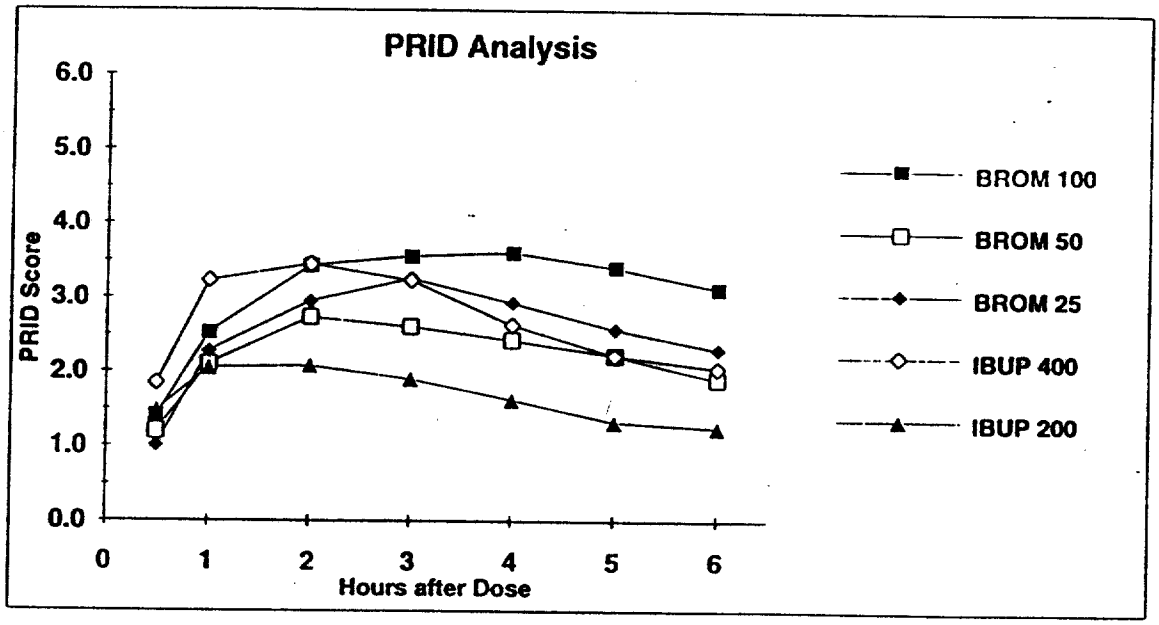

	0.5	1	2	3	4	5	6	SPRID3	SPRID
BROM 100	1.40 (1.57)	2.53 (1.84)	3.43 (2.24)	3.55 (2.28)	3.60 (2.39)	3.40 (2.32)	3.13 (2.46)	8.94 (5.69)	19.06 (11.87
	40 NS	40 AB	39 A	34 A	32 A	32 A	29 A	40 A	40 A
BROM 50	1.20 (1.20)	2.10 (1.52)	2.73 (2.10)	2.60 (2.19)	2.43 (2.22)	2.23 (2.22)	1.90 (2.12)	6.98 (4.83)	13.53 (10.55
	40 NS	40 B	39 AB	28 AB	26 BC	26 BC	26 BC	40 AB	40 BC
BROM 25	1.00 (1.28)	2.28 (1.47)	2.95 (1.97)	3.25 (2.22)	2.93 (2.49)	2.58 (2.42)	2.30 (2.38)	7.84 (4.94)	15.64 (11.33
	40 NS	40 B	39 AB	34 A	28 AB	25 AB	24 AB	40 AB	40 AB
IBUP 400	1.85 (1.73)	3.23 (2.22)	3.45 (2.30)	3.23 (2.48)	2.63 (2.60)	2.23 (2.50)	2.05 (2.55)	9.21 (6.02)	16.11 (12.33
	40 NS	40 A	37 A	32 A	28 ABC	25 BC	20 BC	40 A	40 AB
IBUP 200	1.48 (1.69)	2.05 (1.78)	2.08 (2.12)	1.90 (2.48)	1.63 (2.28)	1.33 (2.10)	1.25 (2.12)	5.74 (5.65)	9.94 (11.36)
	40 NS	40 B	35 B	24 B	21 C	19 C	16 C	40 B	40 C
p	0.132	* 0.024 *	* 0.027 *	* 0.014 *	* 0.007 *	* 0.003 *	* 0.010 *	* 0.028 *	* 0.009 *
rmse	1.51	1.79	2.15	2.33	2.40	2.32	2.33	5.44	11.50

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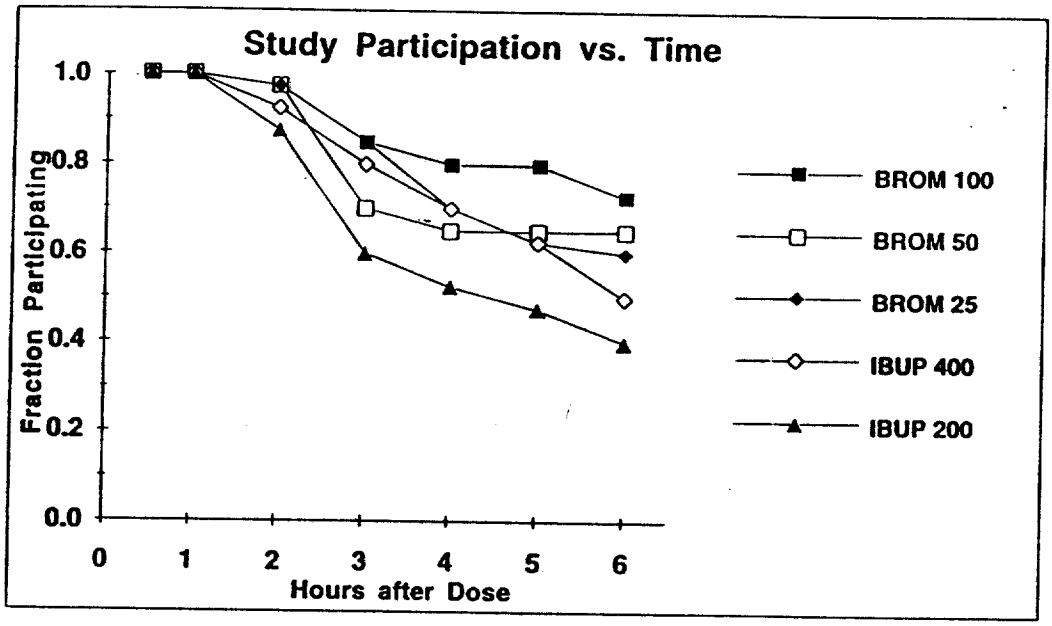

	0.5	1	2	3	4	5	6	ATIME
BROM 100	1.00 (0.00) 40	1.00 (0.00) 40	0.98 (0.02) 39	0.85 (0.06) 34	0.80 (0.06) 32	0.80 (0.06) 32	0.73 (0.07) 29	5.15 (1.58) 40 A
BROM 50	1.00 (0.00) 40	1.00 (0.00) 40	0.98 (0.02) 39	0.70 (0.07) 28	0.65 (0.08) 26	0.65 (0.08) 26	0.65 (0.08) 26	4.63 (1.92) 40 AB
BROM 25	1.00 (0.00) 40	1.00 (0.00) 40	0.98 (0.02) 39	0.85 (0.06) 34	0.70 (0.07) 28	0.63 (0.08) 25	0.60 (0.08) 24	4.75 (1.68) 40 A
IBUP 400	1.00 (0.00) 40	1.00 (0.00) 40	0.93 (0.04) 37	0.80 (0.06) 32	0.70 (0.07) 28	0.63 (0.08) 25	0.50 (0.08) 20	4.55 (1.78) 40 AB
IBUP 200	1.00 (0.00) 40	1.00 (0.00) 40	0.88 (0.05) 35	0.60 (0.08) 24	0.53 (0.08) 21	0.48 (0.08) 19	0.40 (0.08) 16	3.88 (2.02) 40 B
p	1.000	1.000	0.188	* 0.036 *	0.121	0.057	* 0.031 *	* 0.035 *
rmse								1.80

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	a-OPAR	a-DUPAR
BROM 100	21 16 - 33	** ** - **
BROM 50	25 19 - 37	** 4.00 - **
BROM 25	30 21 - 50	** 4.67 - **
IBUP 400	16 13 - 23	6.00 4.67 - **
IBUP 200	20 15 - 32	4.50 2.82 - **
p	0.132	