Appendix I-Study Summary Sheets

In Vivo-Pivotal Studies

Supportive Studies-PK

NDA/IND# 20-535 Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.67
Study Type Metabolic study - ^{14}C-labeled Study# 792-A-102-US
Study Title A ^{14}C-labeled metabolic disposition study of bromfenac in healthy volunteers

Clinical Investigator	Philip Leese MD	Analytical Investigator	M.Osman
Site	Clinical Research Foundation-America Lenexa, KS	Site	Wyeth-Ayerst Research Princeton, NJ

Single Dose_X Multiple Dose Washout Period
Cross-Over Parallel Other Design
Fasted_X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? _8 Prior to dosing and_4 Post-dosing.
Volunteers_X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
volunteers	6	6/0	32	18-42	74	58-88

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch #
bromfenac	all	50 mg	capsule		

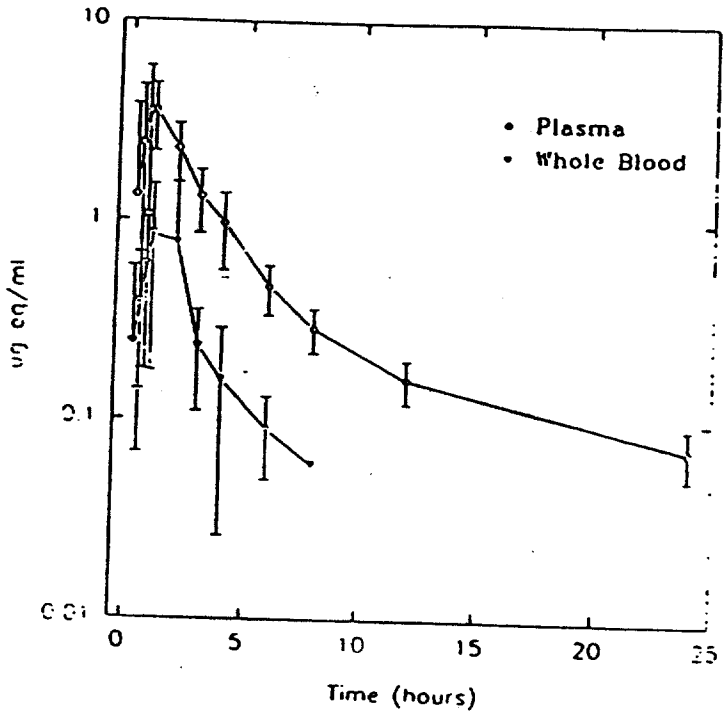
Sampling Times

Plasma	(10 mL) 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96 hours postdose
Whole Blood	samples as for plasma
Urine	0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 hours postdose
Feces	through 96 hours postdose
Assay Method	

Labeling Claims From Study

I After the ingestion of [^{14}C] bromfenac sodium, virtually all of the radioactivity in plasma is recovered as unchanged drug.
II. After 24 hours, an average of 80% of the radioactivity has been recovered.
III. Approximately 80% of radioactivity is excreted in the urine; neither unchanged bromfenac nor bromfenac conjugates have been recovered from urine.
IV. A cyclic amide metabolite and four glucuronide conjugates of aglycone metabolites account for most of the radioactivity recovered in the urine.
V. [Tradename] metabolites are eliminated primarily by the kidneys.

Radioactivity concentration in plasma and whole blood following a 50 mg dose of [^{14}C]bromfenac, as the sodium salt



Pharmacokinetic parameters of radioactivity in plasma following oral administration of 50 mg ^{14}C-bromfenac, as the sodium salt

Subject #	C_{max} (µg-equiv/ml)	t_{max} (hr)	AUC (µg-equiv hr/ml)	$t_{1/2}$ (hr)
1				
2				
3				
4				
5				
6				
Mean ± SD	4.87 ± 1.78	1.00 ± 0.52	12.50 ± 2.40	4.54 ± 0.61

Recovery of radioactivity in human urine following a 50 µCi dose of [^{14}C]bromfenac, as the sodium salt

Subject	Percent of dose recovered								
	0-2[a]	2-4	4-8	8-12	12-24	24-48	48-72	72-96	Total
1									
2									
3									
4									
5									
6									
Mean[b]	23.3	26.1	17.1	5.5	6.6	2.9	0.6	0.2	82.4

[a]Hour post-dose
[b]Subjects 1 and 5 were excluded due to unusually low and high recovery, respectively.

Recovery of radioactivity in human feces following a 50 µCi dose of [^{14}C]bromfenac, as the sodium salt

Subject[a]	Percent of dose recovered				
	Day 1	Day 2	Day 3	Day 4	Total
1					
2					
3					
4					
5					
6					
Mean[a]	1.54	4.51	7.78	0.52	13.22

[a]Subjects 1 and 5 were excluded due to unusually high and low radioactivity recovery
[b]No sample

Summary of recovery of radioactivity in humans following a 50 mg dose of [^{14}C]bromfenac, as the sodium salt

Subject	Percent of dose recovered				
	Day 1	Day 2	Day 3	Day 4	Total
2					
3					
4					
6					
Mean[a]	80.2	6.3	8.3	0.8	95.6

NDA/IND# 20-535/ Suppl/Amend.# Submission Date 29 Dec 94 Volume: 1.54-1.55
Study Type Absolute bioavailability/Food effect Study# 792-A-107-US
Study Title An absolute bioavailability study of bromfenac (intravenous and oral formulations) in healthy volunteers

Clinical Investigator	S Swan MD	Analytical Investigator
Site	Hennepin County Medical Center Minneapolis, MN	Site

Single Dose X Multiple Dose Washout Period 2 days
Cross-Over Parallel Other Design Incomplete block design
Fasted X Food Study X FDA High Fat Breakfast X
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
volunteers	24	23/1	31	20-42	75	49-94

Drug Dosage Forms

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg	capsule	49.8 mg	OVTF	
Na citrate	all		diluent		2TJV	
bromfenac	all	50 mg	IV - lyophilized	52.6 mg	2THD	

Sampling Times

Plasma(7mL): IV: 0 ,0.08, 0.17, 0.33, 0.5, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hrs post dose
oral: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hrs post dose
Urine (-)2-0 hrs before dose; 0-12 hrs postdose
Protein Binding 1 hr postdose - equilibrium dialysis

Assay Method:

Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

I. The mean systemic availability of oral doses of bromfenac administered as [Tradename] as compared with intravenous administration is approximately 67% in humans.
II. Food intake reduces peak plasma concentrations of bromfenac by approximately 75%, while the AUC is reduced by about 60%.

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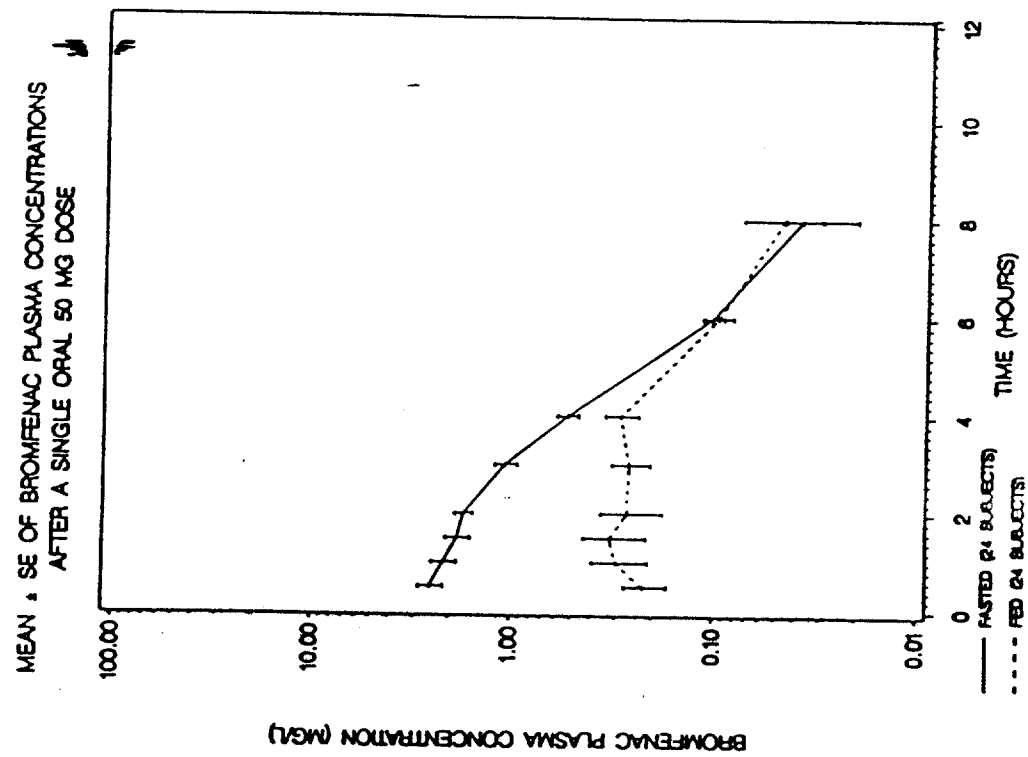

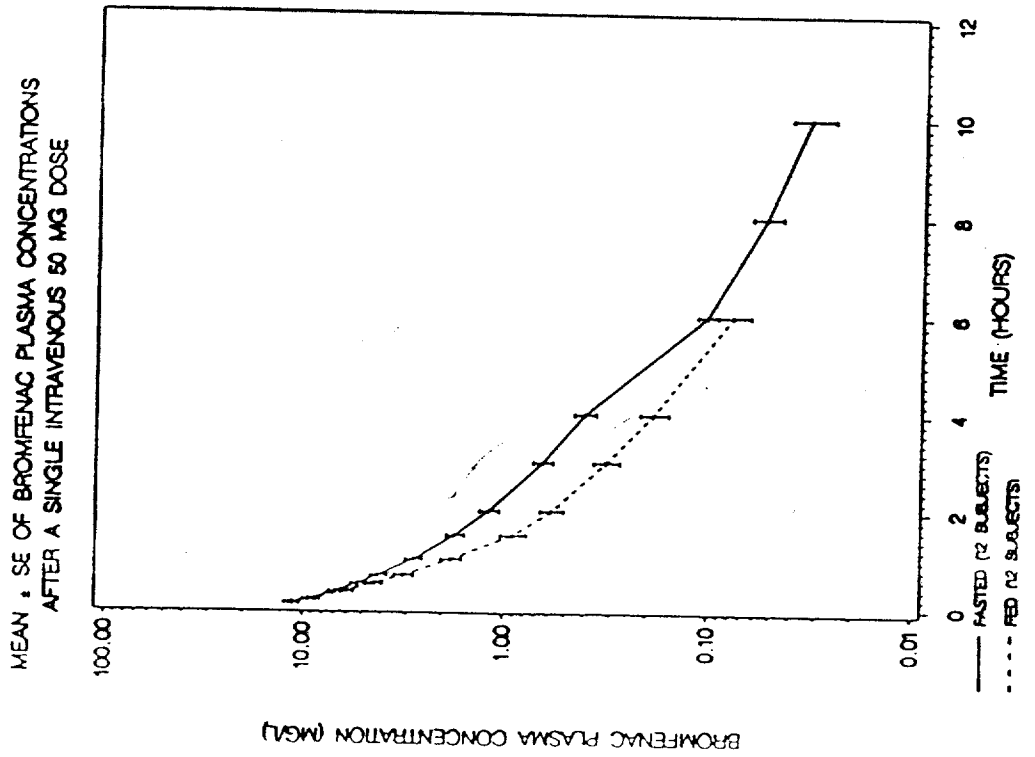

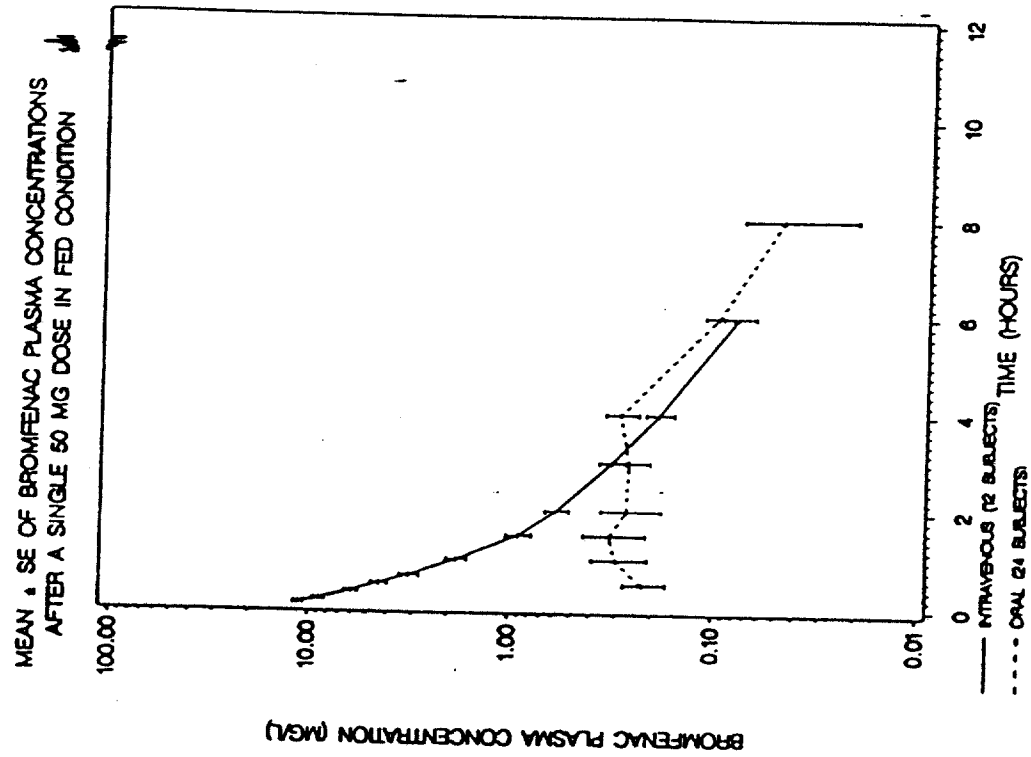

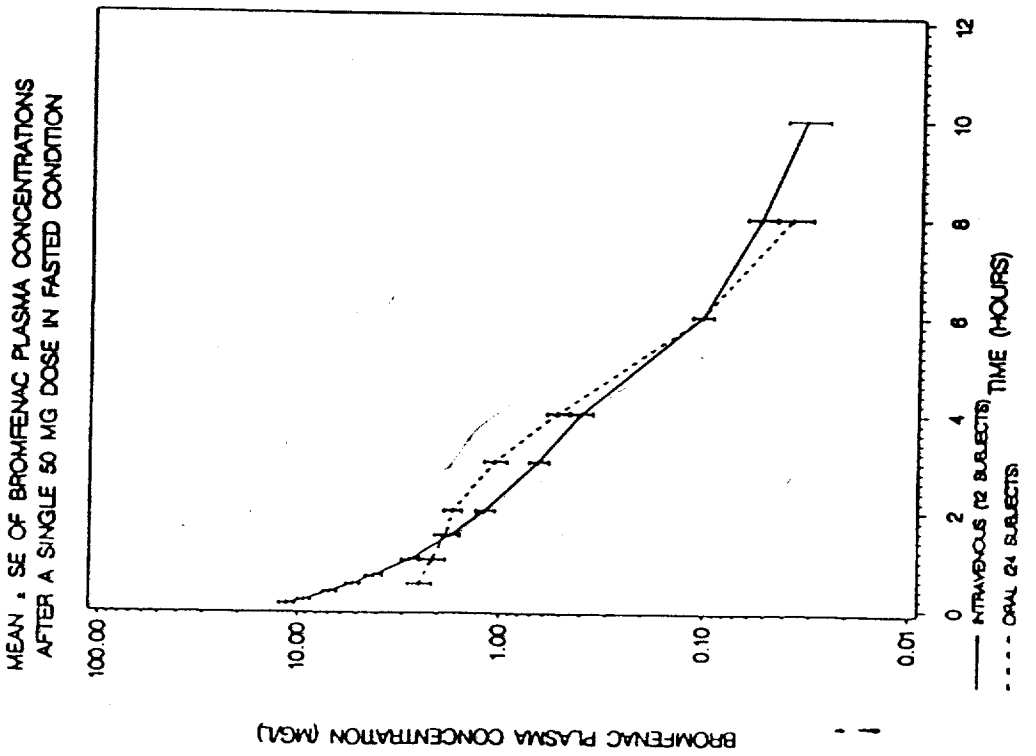

TABLE 6 - STATISTICAL COMPARISONS OF PHARMACOKINETIC PARAMETERS IN HEALTHY VOLUNTEERS RECEIVING A SINGLE 50 MG DOSE OF BROMFENAC

INVESTIGATOR 10713 - SUZANNE K. SWAN, M.D.

SUBJECT	CMAX (MG/L)	TMAX (H)	T1/2 (H)	AUC (MG*H/L)	CL/F* (L/H/K)	V λ_z/F* (L/K)	MRT (H)	λ_z (1/H)	F (%)	FRACTION UNBOUND (%)	AUC,U (MCG*H/ML)	CLR (ML/H)	FRACTION ELIMINATED (%)
INTRAVENOUS FASTED													
MEAN	11.6	0.09	2.5	9.7	0.08	0.2	1.51	0.34	100	0.11	10.4	10	0.17
S.D.	3.1	0.03	1.1	3.0	0.03	0.1	0.36	0.18	0	0.01	3.3	7	0.11
GEOMETRIC MEAN	11.2	0.09	2.3	9.2	0.07	0.2	1.47	0.31	100	0.11	9.9	9	0.17
INTRAVENOUS FED													
MEAN	11.2	0.08	2.0	7.0	0.11	0.3	1.17	0.41	100	0.12	8.1	53	0.60
S.D.	2.1	0.00	1.2	2.4	0.05	0.1	0.35	0.14	0	0.01	2.6	81	0.70
GEOMETRIC MEAN	11.0	0.08	1.8	6.6	0.10	0.3	1.12	0.38	100	0.12	7.8	33	0.46
CAPSULE FASTED													
MEAN	3.3	1.35	1.7	6.5	0.12	0.3	2.28	0.56	67	0.12	7.4	6	0.08
S.D.	1.4	0.87	1.1	2.7	0.04	0.1	0.55	0.27	20	0.02	2.9	6	0.11
GEOMETRIC MEAN	3.1	1.09	1.4	6.1	0.11	0.2	2.22	0.49	64	0.12	7.0	6	0.11
CAPSULE FED													
MEAN	0.6	2.79	1.6	1.7	0.56	1.4	4.03	0.52	27	0.14	2.3	5	0.13
S.D.	0.5	1.85	0.8	1.0	0.31	1.6	1.44	0.26	14	0.01	1.5	8	0.15
GEOMETRIC MEAN	0.4	2.14	1.5	1.4	0.48	1.0	3.78	0.47	24	0.14	2.0	12	0.21
P-VALUES FROM A ONE WAY ANALYSIS OF VARIANCE FOR INTRAVENOUS ADMINISTRATION USING LOG TRANSFORMED DATA													
SOURCE OF VARIATION													
TRD	.83	.33	.25	.04	.02	.30	.02	.25	-	.05	.10	.004	.01
P-VALUES FROM A TWO WAY ANALYSIS OF VARIANCE FOR ORAL ADMINISTRATION USING LOG TRANSFORMED DATA													
SOURCE OF VARIATION													
TRD	.001	.001	.73	.001	.001	.001	.001	.73	.001	.001	.001	.04	
SUBJECT(SEQUENCE)	.66	.26	.11	.50	.40	.32	.62	.11	-	.01	.32	-	
SEQUENCE	.13	.54	.48	.04	.19	.38	.40	.48	-	.64	.04	-	.22

NOTE: FOR INTRAVENOUS DOSING, BIOAVAILABILITY (F) IS EQUAL TO 1

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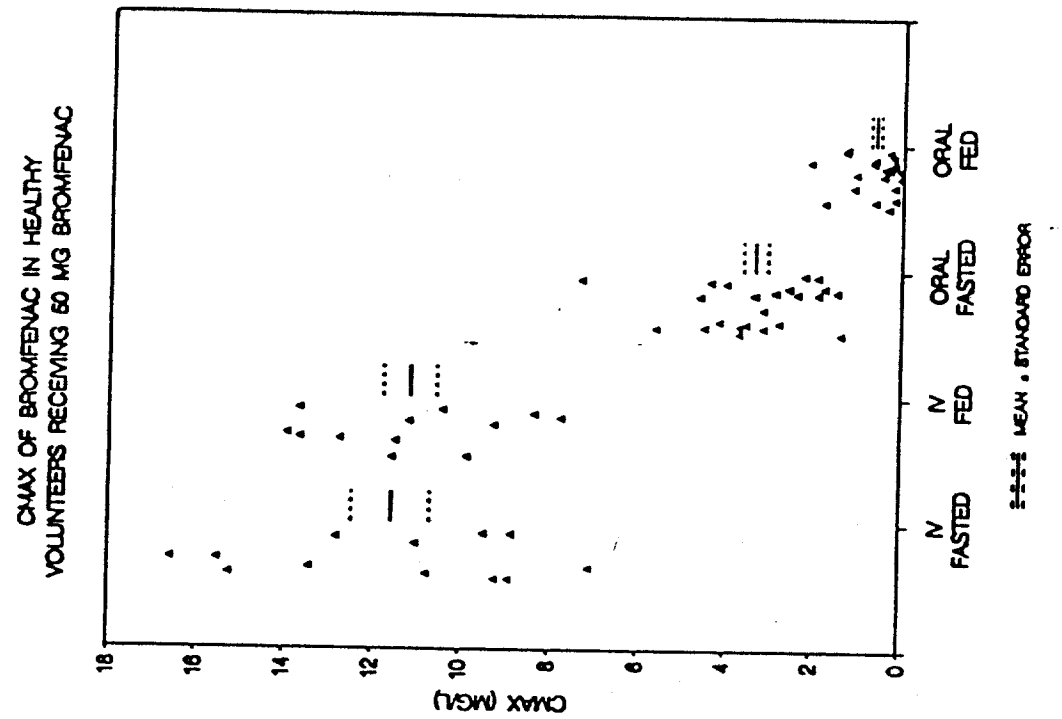
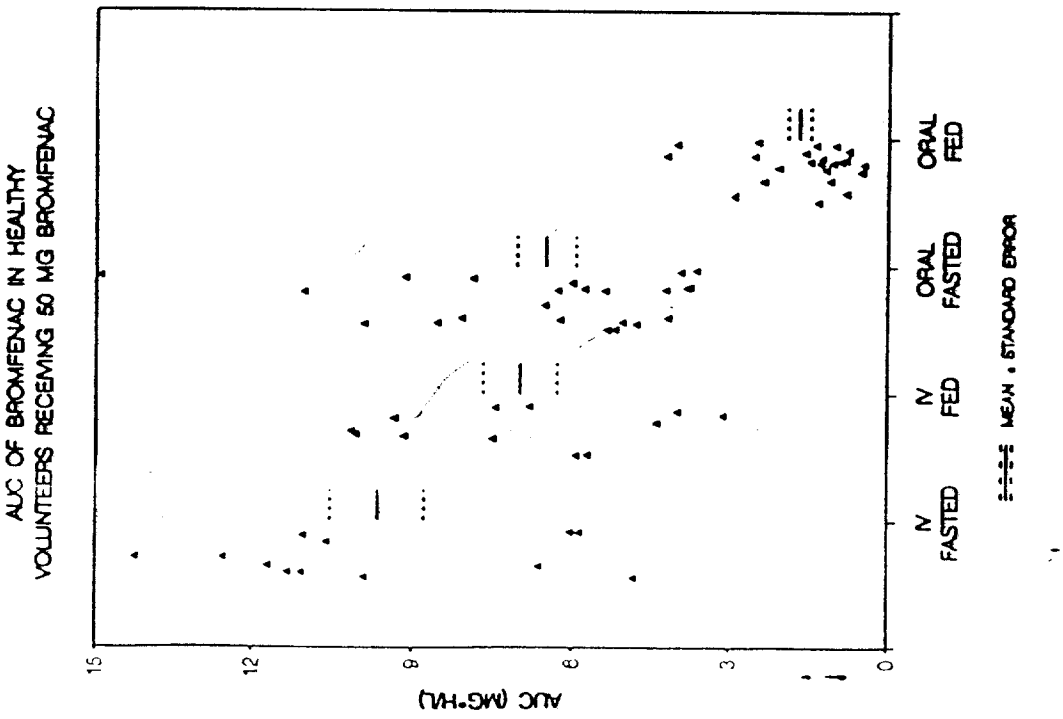




NDA/IND# 20-535 1 Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.65
Study Type Dose proportionality Study# 792-A-105-US
Study Title A dose proportionality study of bromfenac following single and multiple-dose administration to healthy male volunteers

Clinical Investigator W Keane MD
Site Drug Evaluation Unit
Hennepin County Med. Center
Minneapolis, MN

Analytical Investigator
Site

Single Dose X Multiple Dose X Washout Period 2 days
Cross-Over X Parallel Other Design
Fasted X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 8 Prior to dosing and 4 Post-dosing.
Healthy X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
healthy	24	24/0	28	18-42	75	57-87

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	5 mg (q8h)	capsule	5.01 mg	1TKA	
bromfenac	all	25, 50, 100 mg (q8h)	capsule	25.1 mg	OVTF	

Sampling Times

Plasma	single-dose:0,0.25,0.5,1,2,4,6,8 hrs; multiple-dose: 0,0.17,0.33,0.66,1,1.5,2,3,4,6,8,10,16 hrs
Whole Blood	single-dose: 0.5, 4 hrs post dose; multiple-dose: 0.33, 4 hrs post dose
Urine	pre-dose, 0-2, 2-8, 8-16 hrs postdose (not analyzed)
Protein Binding	0, 0.33, 2, 6, hrs postdose after multiple dosing - equilibrium dialysis
Assay Method	
Assay Sensitivity	
Assay Accuracy	

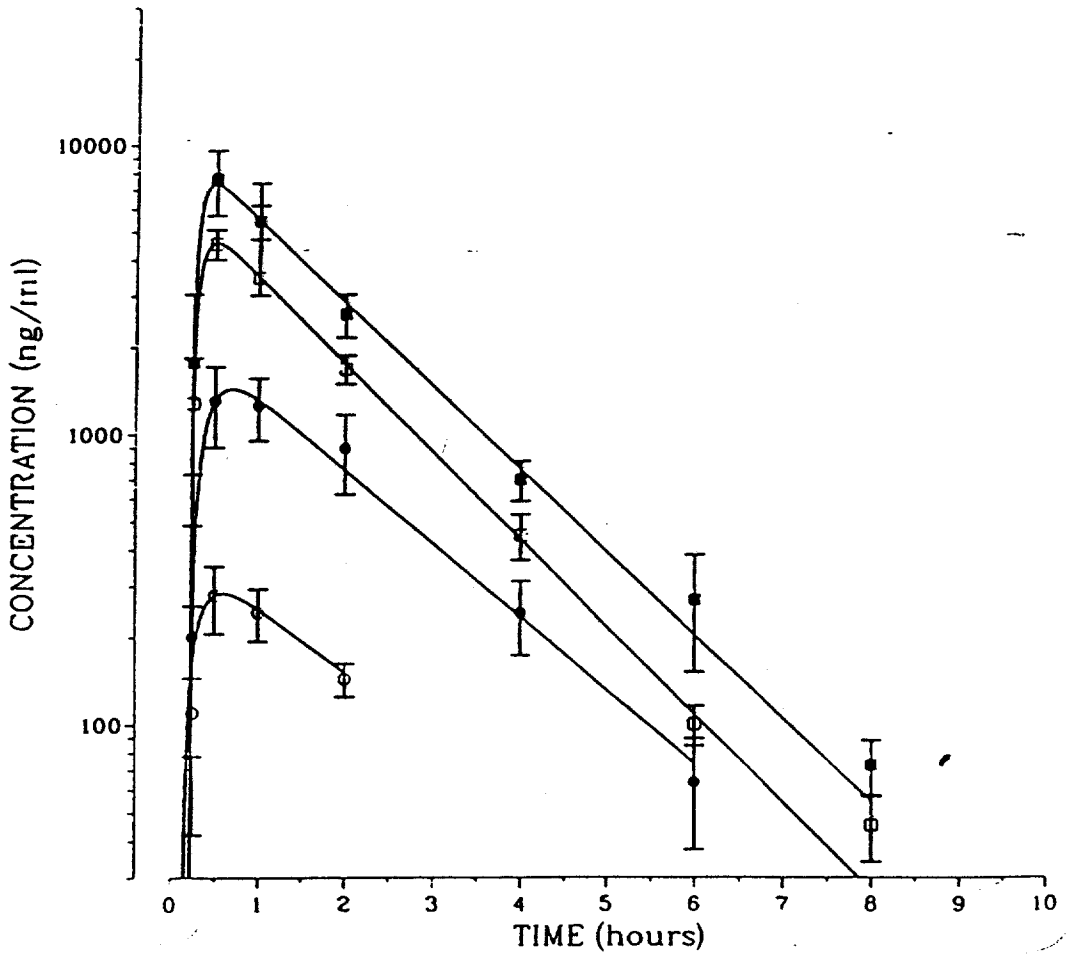
Labeling Claims From Study

1. The dose proportionality based on AUC (area under the plasma-concentration time curve) is linear between doses of 5 and 100 mg.

APPEARS THIS WAY
ON ORIGINAL

Figure 1

MEAN ± SE PLASMA CONCENTRATIONS OF BROMFENAC IN SUBJECTS RECEIVING SINGLE 5, 25, 50, OR 100 MG DOSES OF BROMFENAC



○ = 5 MG (n=6)
● = 25 MG (n=6)
□ = 50 MG (n=6)
■ = 100 MG (n=6)

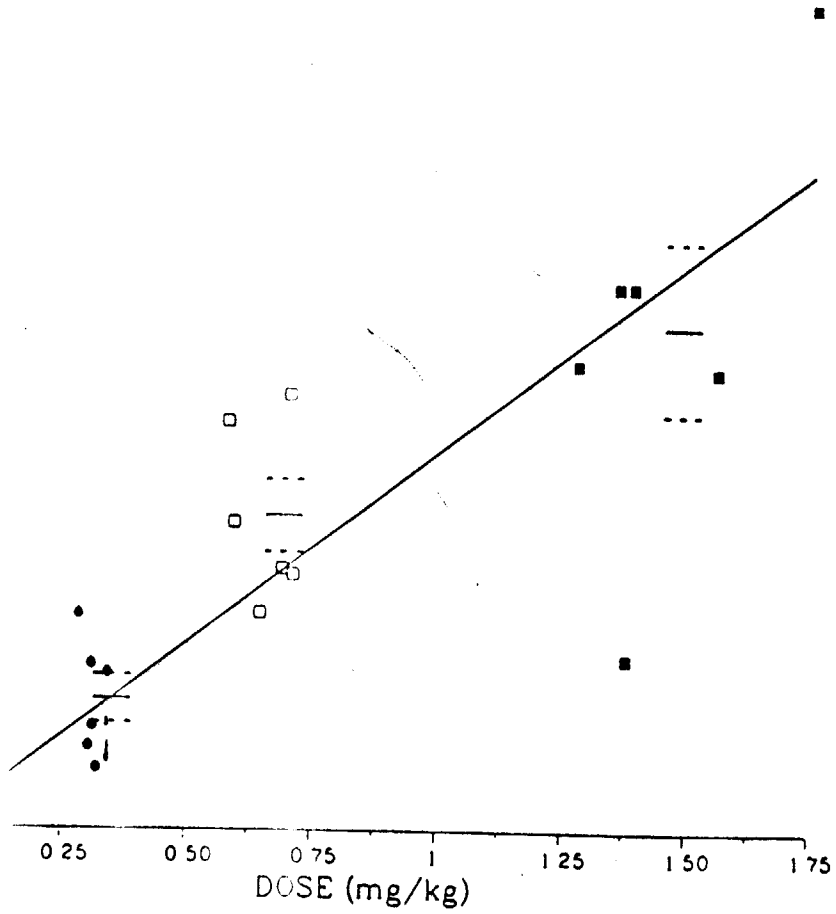
TABLE 4 PHARMACOKINETIC PROFILE OF SINGLE-DOSE BROMFENAC IN HEALTHY MALE SUBJECTS RECEIVING 5, 25, 50, OR 100 MG ORAL BROMFENAC DOSES

INVESTIGATOR 10504 WILLIAM F KEANE M D

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUC (MCG*H/ML)	AUCI	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ z (1/H)
5	2									
	8									
	12									
	16									
	18									
	24									
	MEAN	0.37	0.79	0.96	0.58	0.48	0.117	0.160	1.89	0.747
	S.D.	0.09	0.64	0.19	0.08	0.09	0.013	0.024	0.56	0.149
	GEOMETRIC MEAN	0.36	0.63	0.94	0.58	0.47	0.116	0.158	1.83	0.735
25	4									
	7									
	9									
	13									
	19									
	23									
	MEAN	1.86	0.92	1.13	3.29	3.18	0.115	0.181	2.19	0.662
	S.D.	0.92	0.58	0.37	1.46	1.46	0.057	0.091	0.79	0.189
	GEOMETRIC MEAN	1.63	0.79	1.09	3.01	2.89	0.104	0.164	2.09	0.637

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUC (MCG*H/ML)	AUCI	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ z (1/H)
50	1									
	5									
	10									
	15									
	20									
	22									
	MEAN	4.61	0.58	1.14	7.91	7.82	0.089	0.144	1.82	0.611
	S.D.	1.27	0.20	0.10	2.21	2.19	0.026	0.036	0.19	0.059
	GEOMETRIC MEAN	4.46	0.56	1.14	7.66	7.58	0.085	0.140	1.81	0.609
100	3									
	6									
	11									
	14									
	17									
	21									
	MEAN	7.90	0.58	1.15	12.68	12.54	0.140	0.220	1.89	0.614
	S.D.	4.74	0.20	0.15	5.35	5.32	0.087	0.097	0.14	0.089
	GEOMETRIC MEAN	6.84	0.56	1.14	11.52	11.39	0.125	0.206	1.88	0.609

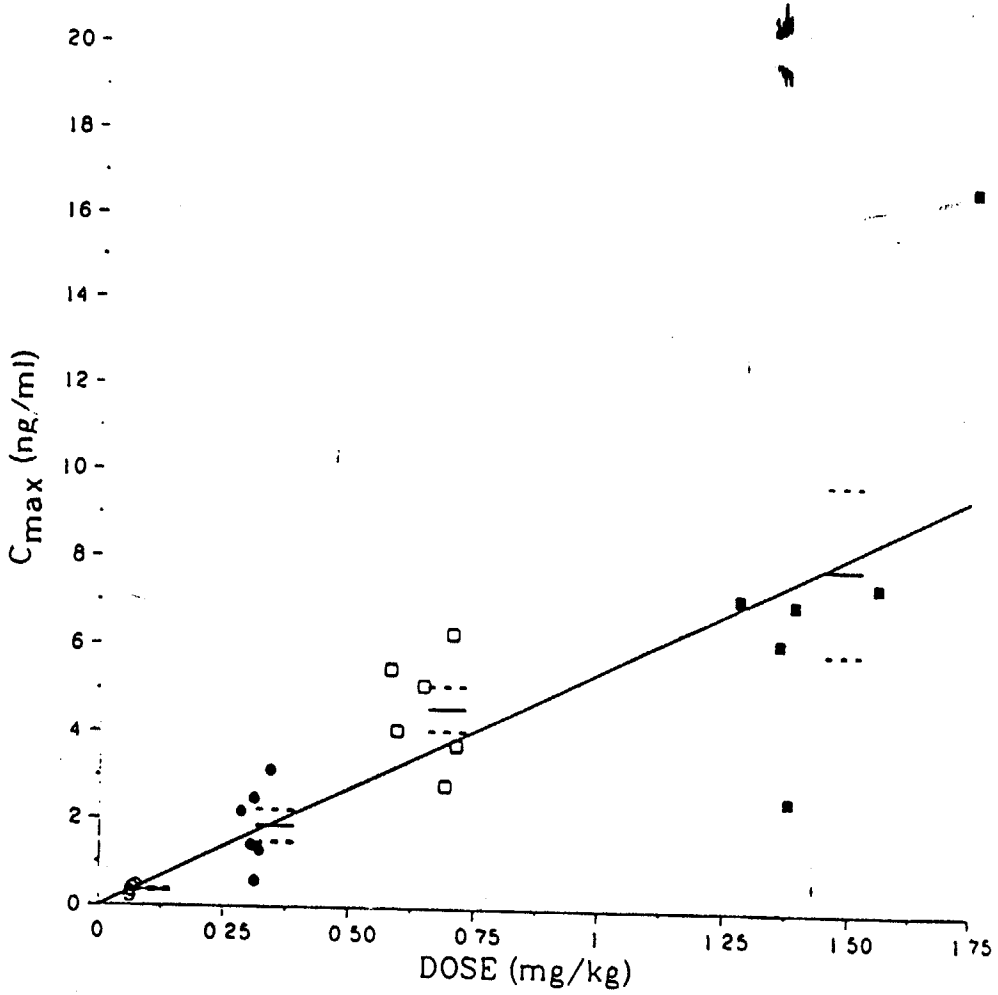
SINGLE DOSE BROMFENAC AUC



5 MG (n=6)
25 MG (n=6)
50 MG (n=6)
100 MG (n=6)

MEAN + SE

SINGLE DOSE BROMFENAC C_{max}



○ = 5 MG (n=6)
● = 25 MG (n=6)
□ = 50 MG (n=6)
■ = 100 MG (n=6)

MEAN + SE

Figure 4

MEAN ± SE PLASMA CONCENTRATIONS OF BROMFENAC
IN 24 SUBJECTS RECEIVING MULTIPLE (Q8H)
5, 25, 50, OR 100 MG BROMFENAC DOSES

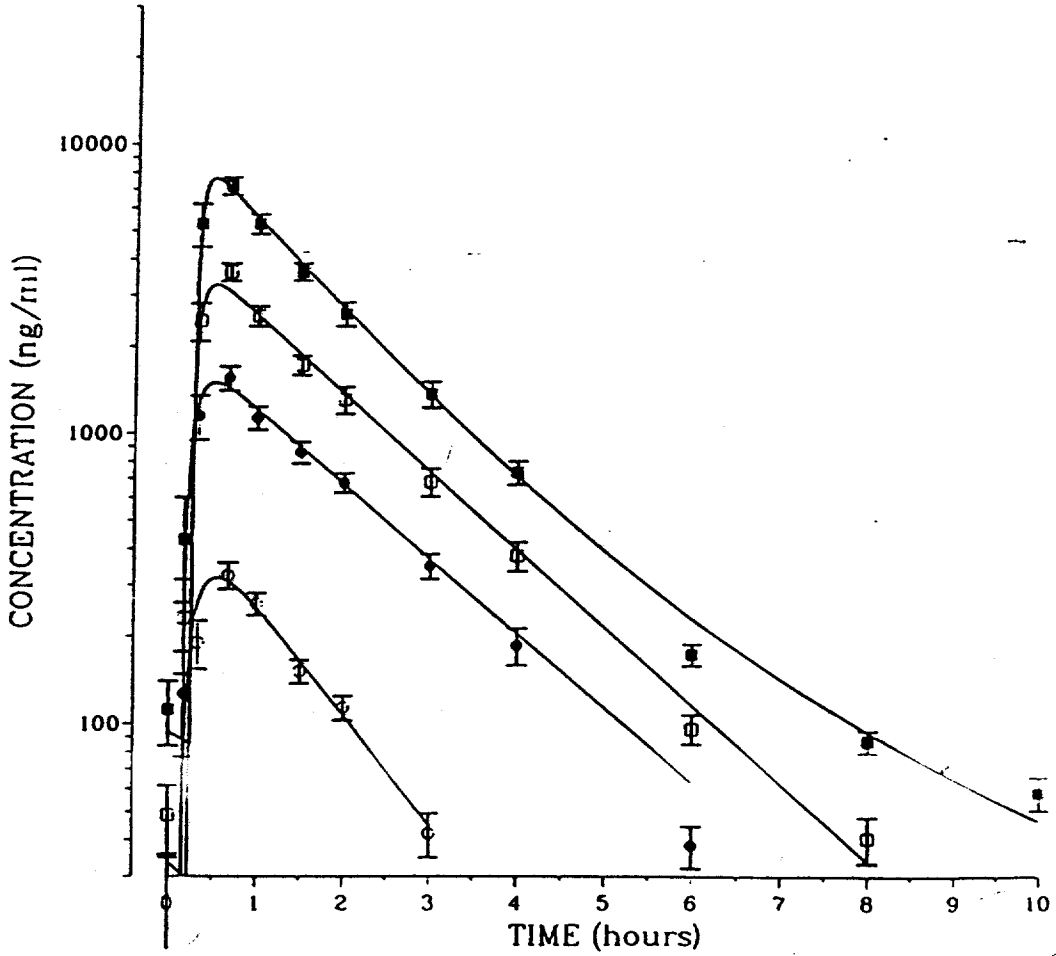


TABLE 10 · PHARMACOKINETIC PROFILE OF STEADY-STATE BROMFENAC (OBHI IN HEALTHY MALE SUBJECTS RECEIVING 5, 25, 50, AND 100 MG ORAL BROMFENAC DOSES

INVESTIGATOR 10504 WILLIAM F KEANE M D

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUC_BH (MCG-H/ML)	R	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ Z (1/H)
5	1									
	2									
	3									
	4									
	5									
	6									
	7									
	8									
	9									
	10									
	11									
	12									
	13									
	14									
	15									
	16									
	17									
	18									
	19									
	20									
	21									
	22									
	23									
	24									
	MEAN	0.37	0.91	0.95	0.53	1.0	0.150	0.191	1.68	0.844
	S.D.	0.15	0.50	0.36	0.22	-	0.065	0.092	0.36	0.348
	GEOMETRIC MEAN	0.33	0.79	0.89	0.48	1.0	0.138	0.176	1.64	0.782

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUCBH (MCG-H/ML)	R	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ Z (1/H)	FU (%)	CMAXU (NG/ML)	AUCU_BH (NG-H/ML)	RU	CLU/F (L/H/KG)	VAZU/F (L/KG)
25	1															
	2															
	3															
	4															
	5															
	6															
	7															
	8															
	9															
	10															
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	21															
	22															
	23															
	24															
	MEAN	1.85	0.88	1.27	2.89	6.2	0.126	0.208	1.91	0.668	0.14	2.63	4.09	1.0	90.0	147.2
	S.D.	0.74	0.55	0.72	0.86	3.2	0.040	0.084	0.46	0.245	0.01	1.04	1.24	-	29.4	55.8
	GEOMETRIC MEAN	1.72	0.75	1.13	2.77	5.7	0.120	0.196	1.86	0.614	0.14	2.42	3.91	1.0	85.4	139.1

TABLE 10 - PHARMACOKINETIC PROFILE OF STEADY STATE BROMFENAC (OBM) IN HEALTHY MALE SUBJECTS (CONT.) RECEIVING 5, 25, 50, AND 100 MG ORAL BROMFENAC DOSES

INVESTIGATOR 0504 - WILLIAM F. KEANE, M.D.

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUC8H (MCG*H/ML)	R	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ Z (1/H)	FU (%)	CMAXU (NG/ML)	AUCU_8H (NG*H/ML)	RU	CLU/F (L/H/KG)	VAZU/F (L/KG)
50	1															
	2															
	3															
	4															
	5															
	6															
	7															
	8															
	9															
	10															
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	20															
	21															
	22															
	23															
	24															
	MEAN	3.93	0.67	2.14	6.14	13.2	0.118	0.332	1.98	0.380	0.14	5.52	8.53	2.1	86.2	244.4
	S.D.	1.35	0.26	0.85	1.75	5.7	0.035	0.084	0.41	0.157	0.02	2.12	2.59	0.5	29.2	76.6
	GEOMETRIC MEAN	3.70	0.63	1.98	5.92	12.2	0.113	0.322	1.94	0.350	0.14	5.10	8.16	2.1	81.8	233.4

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUC8H (MCG*H/ML)	R	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ Z (1/H)	FU (%)	CMAXU (NG/ML)	AUCU_8H (NG*H/ML)	RU	CLU/F (L/H/KG)	VAZU/F (L/KG)
100	1															
	2															
	3															
	4															
	5															
	6															
	7															
	8															
	9															
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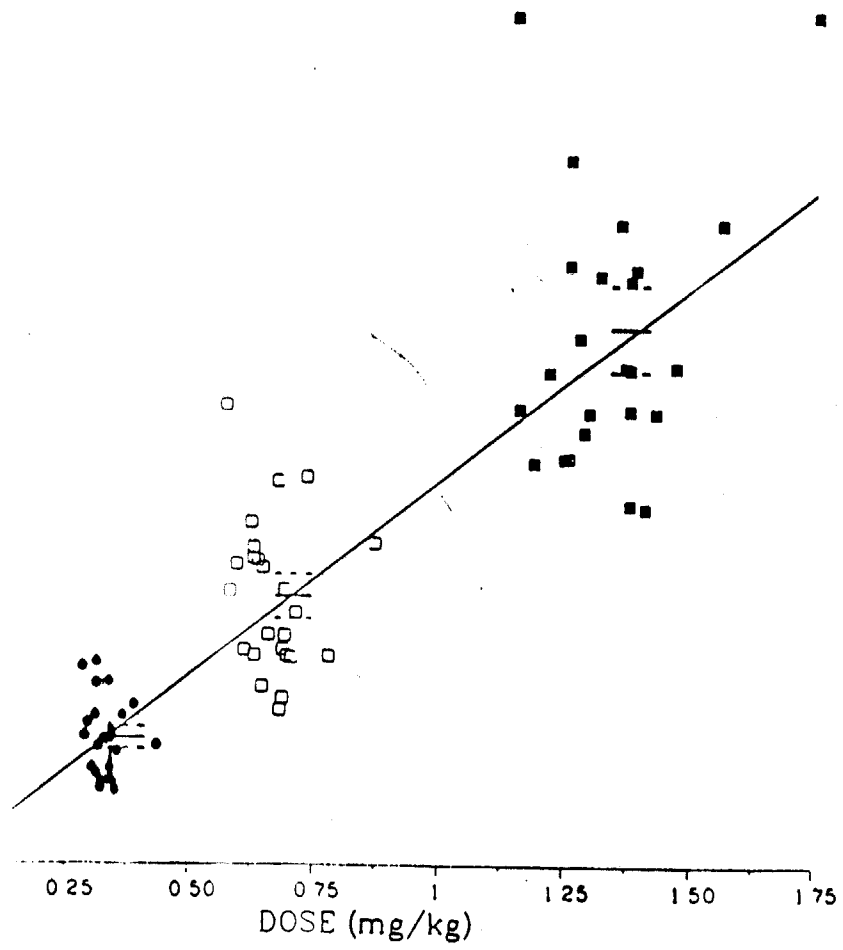
	24															
	MEAN	8.24	0.63	2.70	12.31	26.9	0.115	0.434	2.01	0.290	0.14	11.39	17.05	4.3	83.2	314.6
	S.D.	2.96	0.27	1.21	3.16	13.1	0.026	0.185	0.38	0.098	0.01	4.24	4.55	1.1	19.9	135.2
	GEOMETRIC MEAN	7.75	0.58	2.53	11.96	24.7	0.112	0.407	1.97	0.274	0.14	10.69	16.51	4.2	80.9	294.8

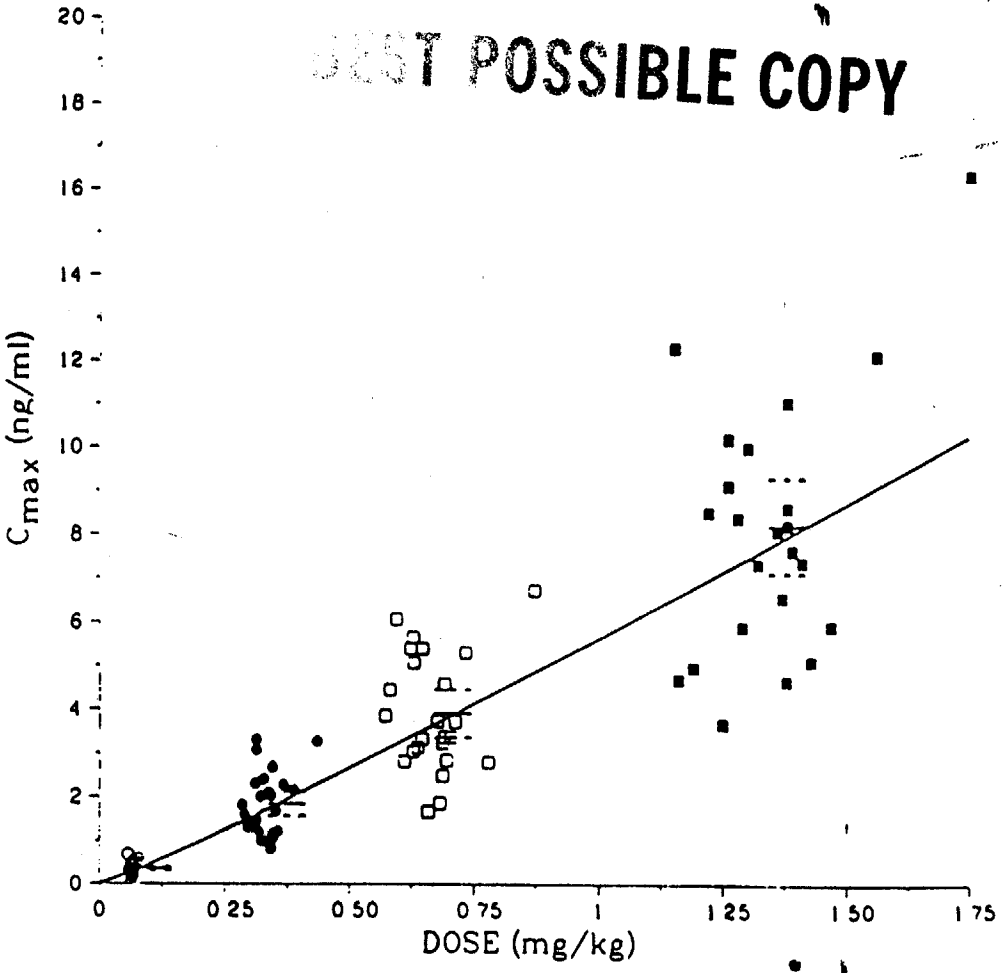
STEADY-STATE BROMFENAC AUC



5 MG (n=24)
25 MG (n=24)
50 MG (n=24)
100 MG (n=24)

MEAN AND 95% CONFIDENCE LIMITS, BASED ON WITHIN-SUBJECT STANDARD DEVIATION

STEADY-STATE BROMFENAC C_{max}



o = 5 MG (n=24)
• = 25 MG (n=24)
o = 50 MG (n=24)
▪ = 100 MG (n=24)

MEAN AND 95% CONFIDENCE LIMITS, BASED ON WITHIN-SUBJECT STANDARD DEVIATION

NDA/IND# 20-535 Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.97-1.98
Study Type Age/gender Study# 792-A-104-US
Study Title The effects of age and sex on the pharmacokinetics of bromfenac in healthy volunteers

Clinical Investigator P Wicht MD
Site Harris Labs
Clinical Res. Div III
Phoenix, AZ

Analytical Investigator D Hicks
Site Wyeth-Ayerst Res.
Princeton, NJ

Single Dose_X Multiple Dose_X Washout Period
Cross-Over Parallel_X Other Design
Fasted_X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? _10 Prior to dosing and_4 Post-dosing.
Volunteers___X Patients Young_X Elderly_X Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age(yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
young males	10	10/0	29	20-42	82	63-92
young females	10	0/10	29	19-40	61	43-84
young-elderly males	6	6/0	68	65-71	83	78-91
young-elderly females	6	0/6	67	65-68	70	58-76
elderly males	6	6/0	79	75-82	78	68-94
elderly females	6	0/6	81	76-85	63	51-73

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg (q12h)	capsule	50.4 mg	4023	

Sampling Times

Plasma (10mL) 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 hrs post single dose; also 24 hrs after multiple-dose
Urine collected 0-2, 2-4, 4-8, 8-12 hours postdose - but not analyzed
Protein Binding 0.75, 2, 4, 12 hours postdose - equilibrium dialysis

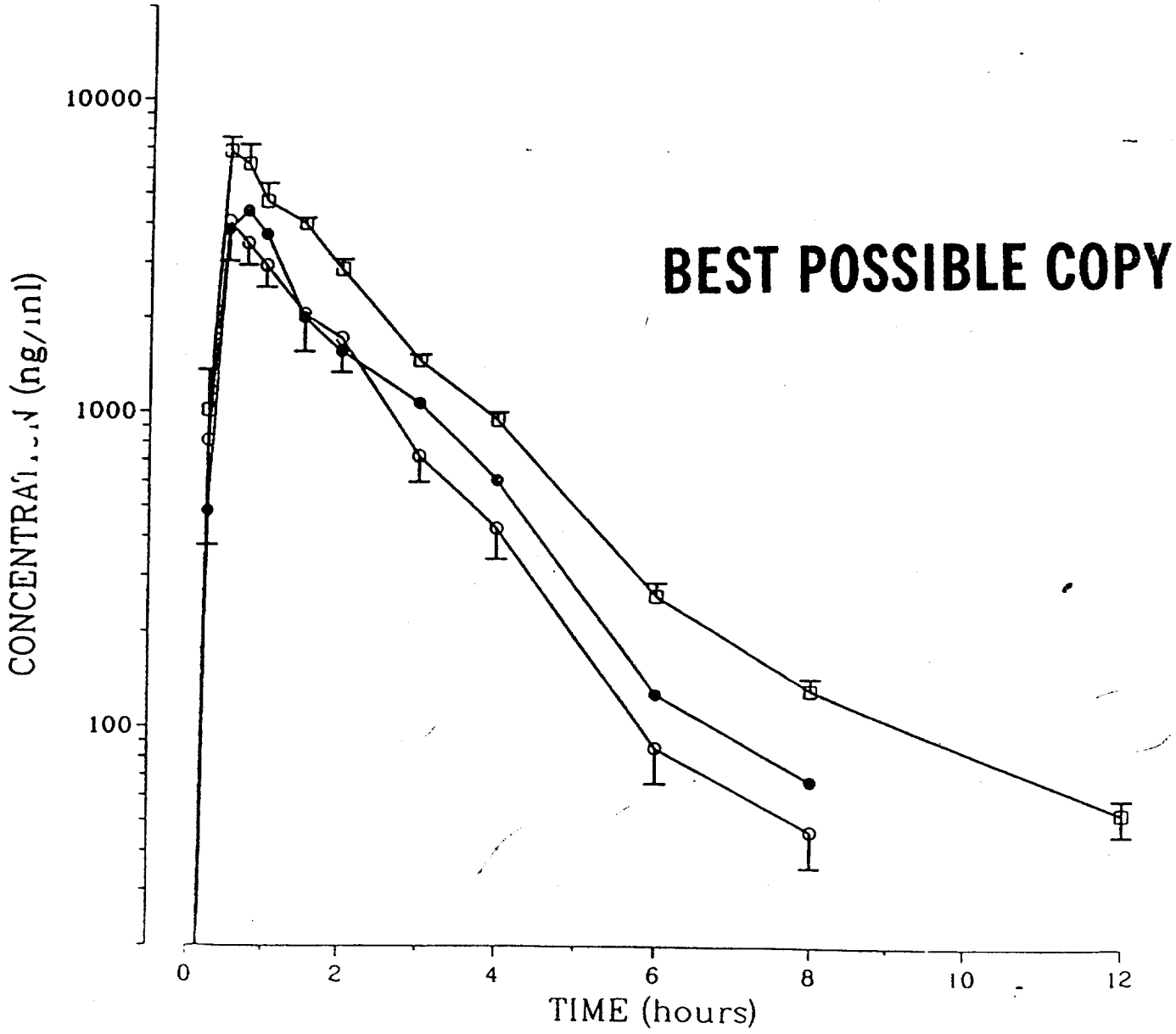
Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

I. No pharmacokinetic differences between males and females.
II. Differences in pharmacokinetics due to age observed but no dosage adjustment for elderly is required.

Figure 1

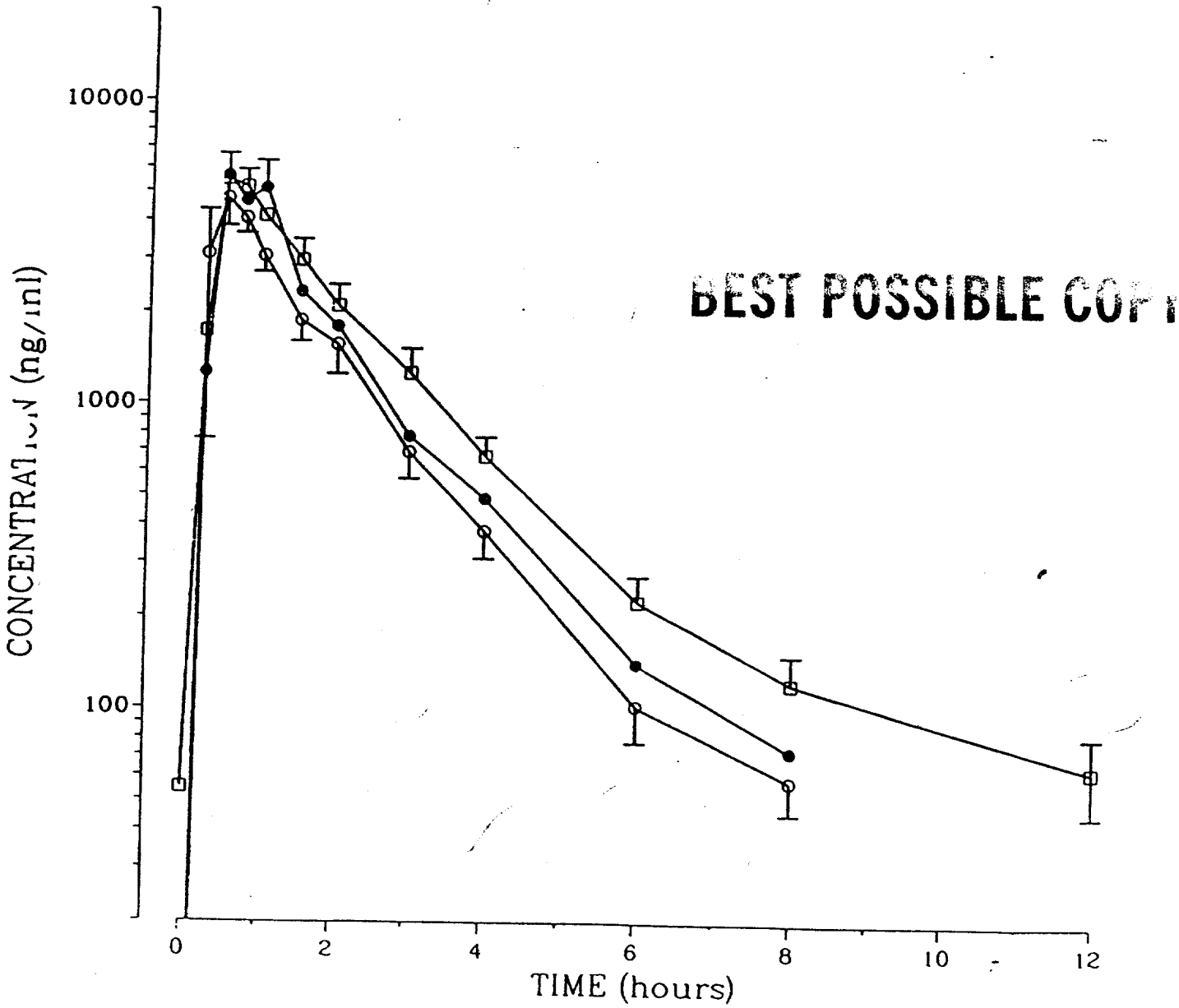
MEAN ± SE OF BROMFENAC PLASMA CONCENTRATIONS
IN THREE GROUPS OF MALE VOLUNTEERS
RECEIVING A SINGLE 50 MG ORAL DOSE OF BROMFENAC



○ = MALE - YOUNG 18-45 yr
● = MALE - YOUNG-ELDERLY 65-74 yr
□ = MALE - ELDERLY 75 yr and older

Figure 3

MEAN ± SE OF PLASMA CONCENTRATIONS OF BROMFENAC
IN THREE AGE GROUPS OF MALE VOLUNTEERS RECEIVING
50 MG ORAL DOSE OF BROMFENAC EVERY 12 HR FOR 4 DAYS



o = MALE - YOUNG 18-45 yr
• = MALE - YOUNG-ELDERLY 65-74 yr
□ = MALE - ELDERLY 75 yr and older

TABLE 3 - PHARMACOKINETIC PROFILE OF BROMFENAC IN THE PLASMA OF HEALTHY VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 12 HOURS

INVESTIGATOR 10405 - PAUL J. WICHT, M. D.

SUBJECT	CMAX (MCG/ML)	TMAX (H)	λ_z (1/H)	AUC_12H (MCG*H/ML)	T1/2 (H)	MRT (H)	CL/F (L/H/K)	V_z/F (L/K)	PERCENT BROMFENAC UNBOUND IN PLASMA 0.75H (%)	2H (%)	12H (%)	CLU/F (L/H/K)	CMAXU (NG/ML)
G MALES													
1													
GLE DOSE)													
017													
019													
020													
021													
023													
029													
035													
038													
039													
042													
MEAN	4.62	0.85	0.63	6.92	1.2	1.89	0.097	0.16	0.10	0.10	0.13	92.85	4.38
S.D.	1.82	0.61	0.19	1.99	0.4	0.52	0.029	0.04	0.03	0.02	0.03	23.34	1.55
GEOMETRIC MEAN	4.23	0.72	0.61	6.63	1.1	1.83	0.093	0.15	0.10	0.10	0.13	90.26	4.11
IPLE DOSING)													
017													
019													
020													
021													
023													
029													
035													
038													
039													
042													
MEAN	5.96	0.70	0.50	7.76	1.6	1.85	0.083	0.19	0.10	0.10	0.11	84.00	6.89
S.D.	2.12	0.51	0.16	1.71	0.8	0.84	0.019	0.08	0.02	0.02	0.02	23.86	2.53
GEOMETRIC MEAN	5.66	0.58	0.47	7.58	1.5	1.74	0.081	0.17	0.10	0.10	0.11	81.08	5.41

= 18 TO 45 YEARS
ELDERLY = 65 TO 74 YEARS
Y = 75 YEARS AND OLDER

TABLE 3 - PHARMACOKINETIC PROFILE OF BROMFENAC IN THE PLASMA OF HEALTHY VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 12 HOURS (CONT'D)

INVESTIGATOR 10405 - PAUL J. WICHT, M. D.

SUBJECT	CMAX	TMAX	λ_z	AUC_12H	T1/2	MRT	CL/F	V_z/F	PERCENT BROMFENAC UNBOUND IN PLASMA 0.75H	2H	12H	CLU/F	CMAXU
ELDERLY MALES	(MCG/ML)	(H)	(1/H)	(MCG*H/ML)	(H)	(H)	(L/H/K)	(L/K)	(%)	(%)	(%)	(L/H/K)	(NG/ML)
F DOSE)													
001													
002													
003													
005													
006													
016													
MEAN	4.85	0.71	0.52	7.94	1.4	2.23	0.085	0.16	0.09	0.10	0.14	81.42	4.31
S.D.	2.33	0.19	0.15	2.12	0.5	0.50	0.034	0.04	0.01	0.02	0.02	25.25	1.98
GEOMETRIC MEAN	4.20	0.69	0.50	7.65	1.4	2.18	0.080	0.16	0.09	0.10	0.14	78.35	3.82
PLE DOSING)													
001													
002													
003													
005													
006													
016													
MEAN	6.23	0.63	0.41	9.16	2.0	1.94	0.071	0.20	0.10	0.10	0.11	66.31	6.12
S.D.	2.55	0.21	0.15	2.67	1.1	0.23	0.020	0.10	0.02	0.02	0.02	14.78	1.99
GEOMETRIC MEAN	5.86	0.60	0.38	8.86	1.8	1.93	0.069	0.18	0.10	0.10	0.11	65.01	5.86

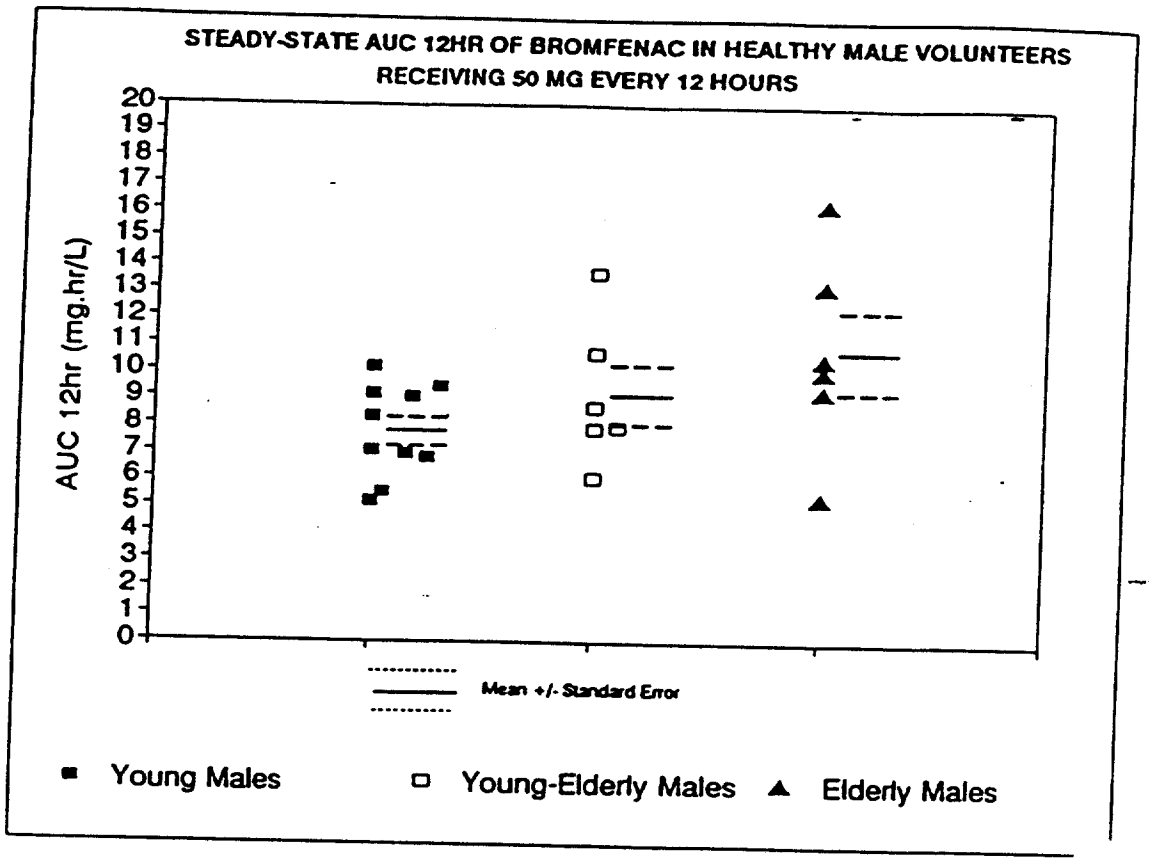
= 18 TO 45 YEARS
ELDERLY = 65 TO 74 YEARS
= 75 YEARS AND OLDER

TABLE 3 - PHARMACOKINETIC PROFILE OF BROMFENAC IN THE PLASMA OF HEALTHY VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 12 HOURS (CONT'D)

INVESTIGATOR 10405 - PAUL J. WICHT, M. D.

SUBJECT	CMAX	TMAX	λ_z	AUC_12H	T1/2	MRT	CL/F	V_z/F	PERCENT UNBOUND BROMFENAC IN PLASMA 0.75H	2H	12H	CLU/F	CMAXU
r MALES	(MCG/ML)	(H)	(1/H)	(MCG*H/ML)	(H)	(H)	(L/H/K)	(L/K)	(%)	(%)	(%)	(L/H/K)	(NG/ML)
E DOSE)													
013													
014													
015													
026													
034													
043													
MEAN	7.02	0.58	0.26	13.08	2.7	2.43	0.050	0.19	0.09	0.09	0.13	53.13	6.60
S.D.	1.74	0.13	0.03	2.02	0.3	0.23	0.005	0.02	0.02	0.01	0.03	11.95	1.69
GEOMETRIC MEAN	6.86	0.57	0.26	12.96	2.6	2.42	0.050	0.19	0.09	0.09	0.13	52.06	6.41
PLE DOSING)													
013													
014													
015													
026													
034													
043													
MEAN	5.99	0.63	0.21	10.80	3.4	2.56	0.066	0.32	0.10	0.09	0.11	68.85	5.91
S.D.	1.91	0.14	0.04	3.70	0.6	0.48	0.024	0.11	0.02	0.02	0.02	25.69	2.13
GEOMETRIC MEAN *	5.70	0.61	0.21	10.22	3.3	2.53	0.063	0.30	0.10	0.08	0.11	64.31	5.64

= 18 TO 45 YEARS
ELDERLY = 65 TO 74 YEARS
Y = 75 YEARS AND OLDER



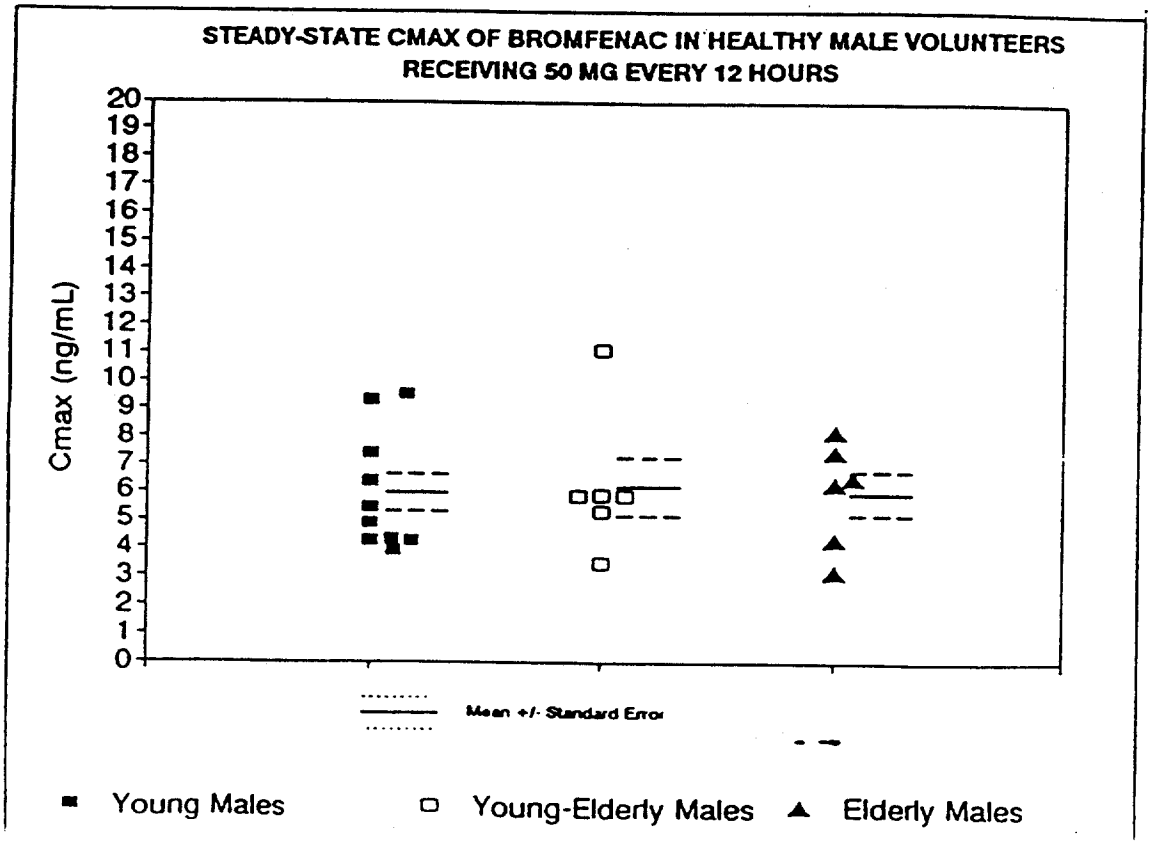
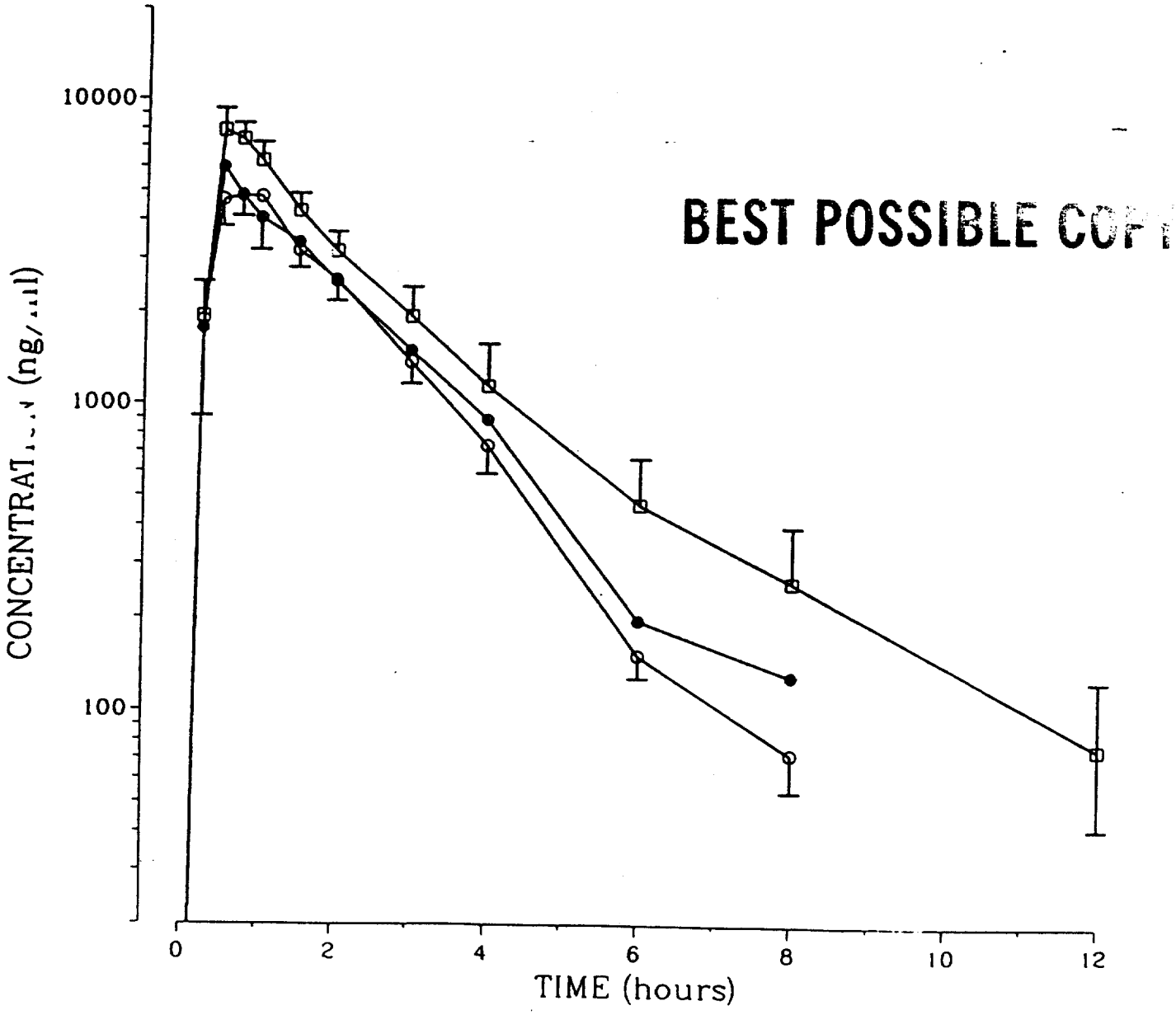


Figure 2

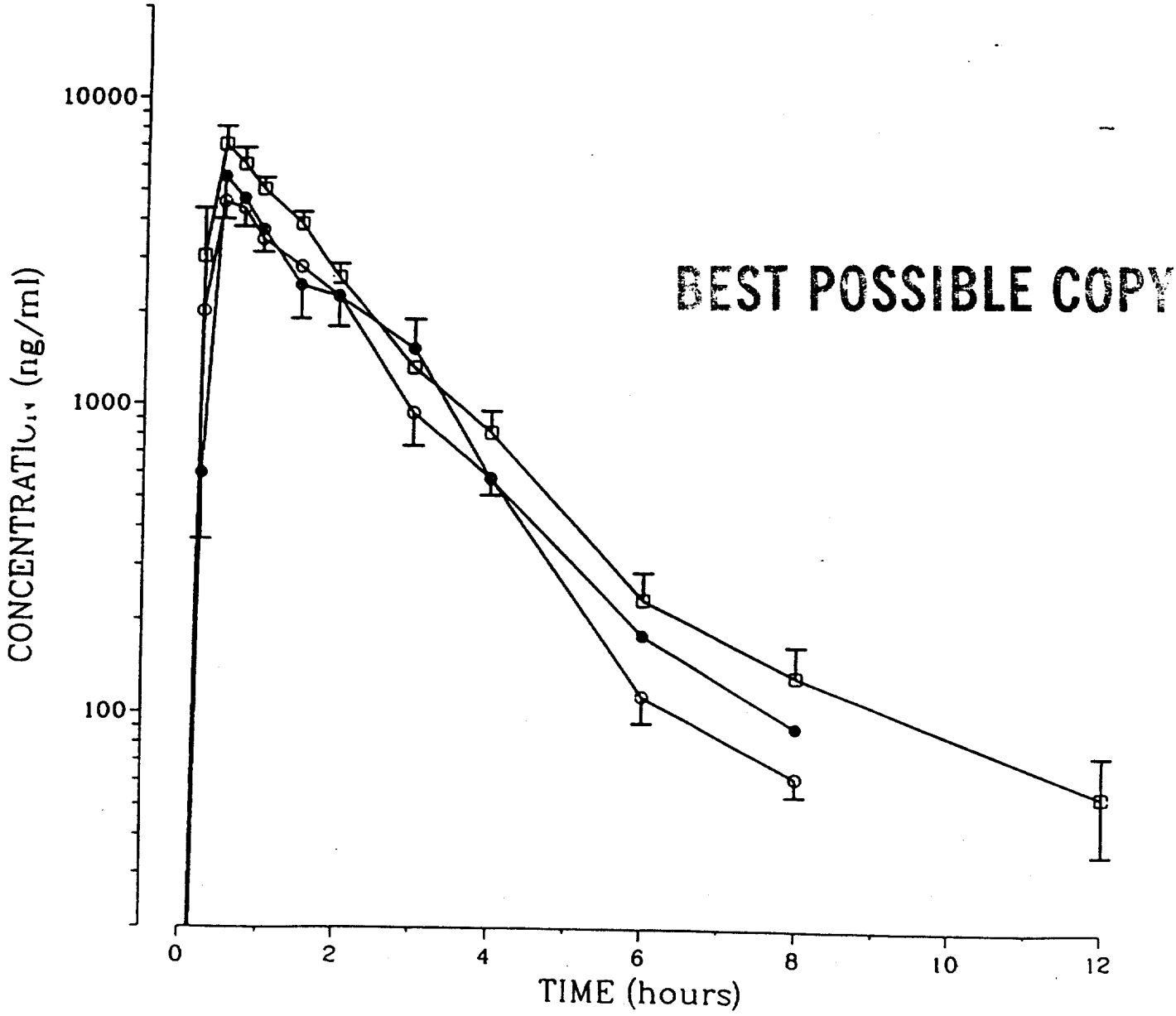
MEAN ± SE OF BROMFENAC PLASMA CONCENTRATIONS
IN THREE GROUPS OF FEMALE VOLUNTEERS
RECEIVING A SINGLE 50 MG ORAL DOSE OF BROMFENAC



○ = FEMALE YOUNG 18-45 yr
● = FEMALE- YOUNG-ELDERLY 65-74 yr

Figure 4

MEAN ± SE OF PLASMA CONCENTRATIONS OF BROMFENAC IN THREE AGE GROUPS OF FEMALE VOLUNTEERS RECEIVING 50 MG ORAL DOSE OF BROMFENAC EVERY 12 HR FOR 4 DAYS



o = FEMALE- YOUNG 18-45 yr
• = FEMALE- YOUNG-ELDERLY 65-74 yr

TABLE 3 - PHARMACOKINETIC PROFILE OF BROMFENAC IN THE PLASMA OF HEALTHY VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 12 HOURS (CONT'D)

INVESTIGATOR 10405 - PAUL J. WICHT, M. D.

	SUBJECT	CMAX	TMAX	λ_z	AUC_12H	T1/2	MRT	CL/F	$V_{\lambda z}$/F	PERCENT BROMFENAC UNBOUND IN PLASMA 0.75H	2H	12H	CLU/F	CMAXU
FEMALES		(MCG/ML)	(H)	(1/H)	(MCG*H/ML)	(H)	(H)	(L/H/K)	(L/K)	(%)	(%)	(%)	(L/H/K)	(NG/ML)
LE DOSE)														
	018													
	022													
	024													
	025													
	032													
	033													
	036													
	037													
	040													
	041													
	MEAN	6.22	0.90	0.56	10.80	1.5	2.06	0.083	0.18	0.10	0.09	0.15	82.27	6.64
	S.D.	2.48	0.29	0.19	2.59	0.8	0.53	0.021	0.13	0.03	0.02	0.04	21.94	3.89
	GEOMETRIC MEAN	5.77	0.86	0.52	10.51	1.3	2.00	0.080	0.15	0.10	0.09	0.15	79.70	5.75
IPLE DOSING)														
	018													
	022													
	024													
	025													
	032													
	033													
	036													
	037													
	040													
	041													
	MEAN	6.08	0.85	0.53	9.09	1.4	1.89	0.103	0.20	0.10	0.09	0.15	98.65	6.07
	S.D.	3.16	0.53	0.15	2.87	0.4	0.35	0.038	0.07	0.02	0.02	0.04	35.47	2.77
	GEOMETRIC MEAN	5.52	0.72	0.51	8.63	1.3	1.86	0.098	0.19	0.10	0.09	0.15	94.05	5.63

* 18 TO 45 YEARS
-ELDERLY = 65 TO 74 YEARS
LY = 75 YEARS AND OLDER

TABLE 3 - PHARMACOKINETIC PROFILE OF BROMFENAC IN THE PLASMA OF HEALTHY VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 12 HOURS (CONT'D)

INVESTIGATOR 10405 - PAUL J. WICHT, M. D.

SUBJECT	CMAX	TMAX	λz	AUC_12H	T1/2	MRT	CL/F	VλZ/F	PERCENT BROMFENAC UNBOUND IN PLASMA 0.75H	2H	12H	CLU/F	CMAXU
LDERLY FEMALES	(MCG/ML)	(H)	(1/H)	(MCG*H/ML)	(H)	(H)	(L/H/K)	(L/K)	(%)	(%)	(%)	(L/H/K)	(NG/ML)
DOSE)													
007													
008													
009													
010													
012													
027													
MEAN	6.28	1.21	0.40	11.44	2.1	2.36	0.070	0.19	0.09	0.09	0.13	75.60	5.56
S.D.	3.14	0.95	0.23	3.48	0.9	0.51	0.028	0.05	0.01	0.01	0.02	27.44	2.37
GEOMETRIC MEAN	5.58	0.97	0.36	10.97	1.9	2.31	0.066	0.18	0.09	0.09	0.13	72.22	5.08
PLE DOSING)													
007													
008													
009													
010													
012													
027													
MEAN	6.20	1.21	0.38	9.80	2.4	2.27	0.077	0.24	0.09	0.09	0.13	83.01	5.75
S.D.	2.61	1.05	0.26	1.90	1.1	0.41	0.023	0.08	0.01	0.01	0.03	28.84	2.56
GEOMETRIC MEAN	5.74	0.91	0.33	9.64	2.1	2.24	0.075	0.23	0.09	0.09	0.13	79.26	5.32

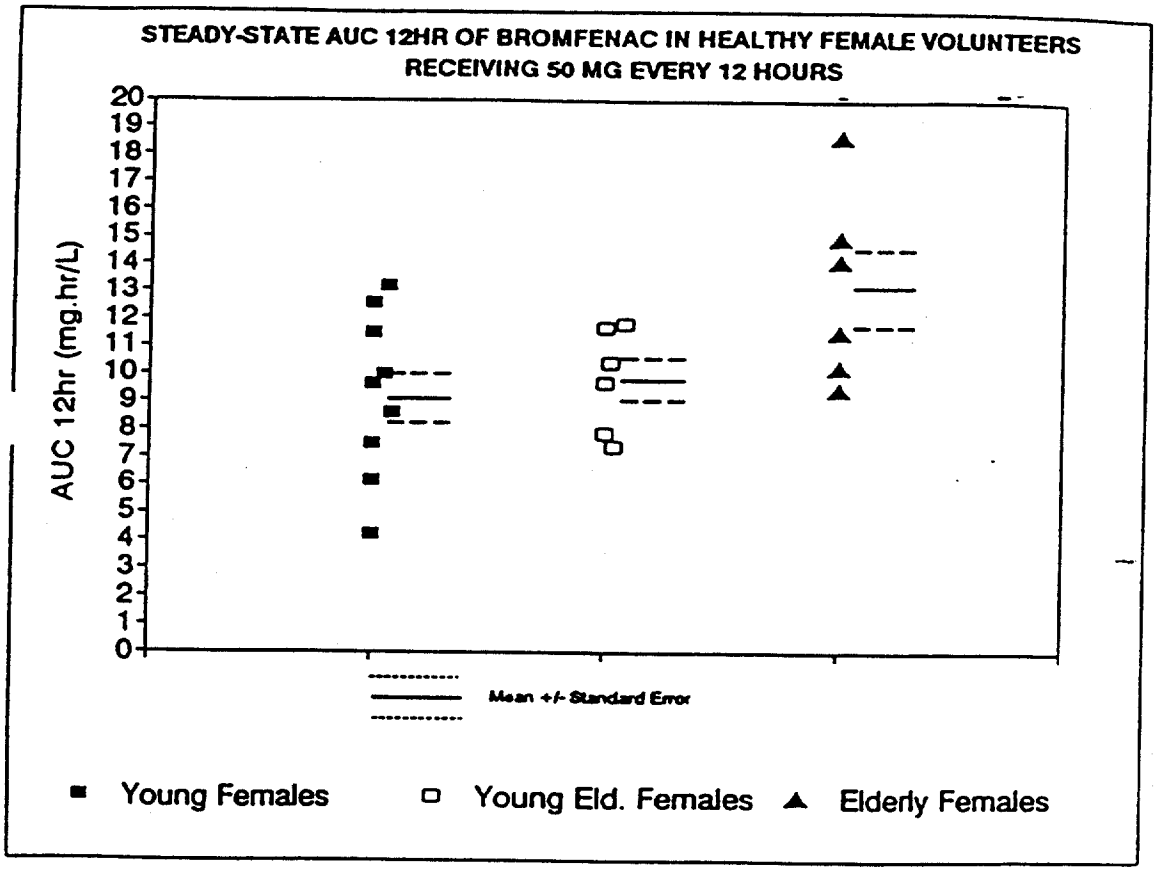
= 18 TO 45 YEARS
ELDERLY = 65 TO 74 YEARS
Y = 75 YEARS AND OLDER

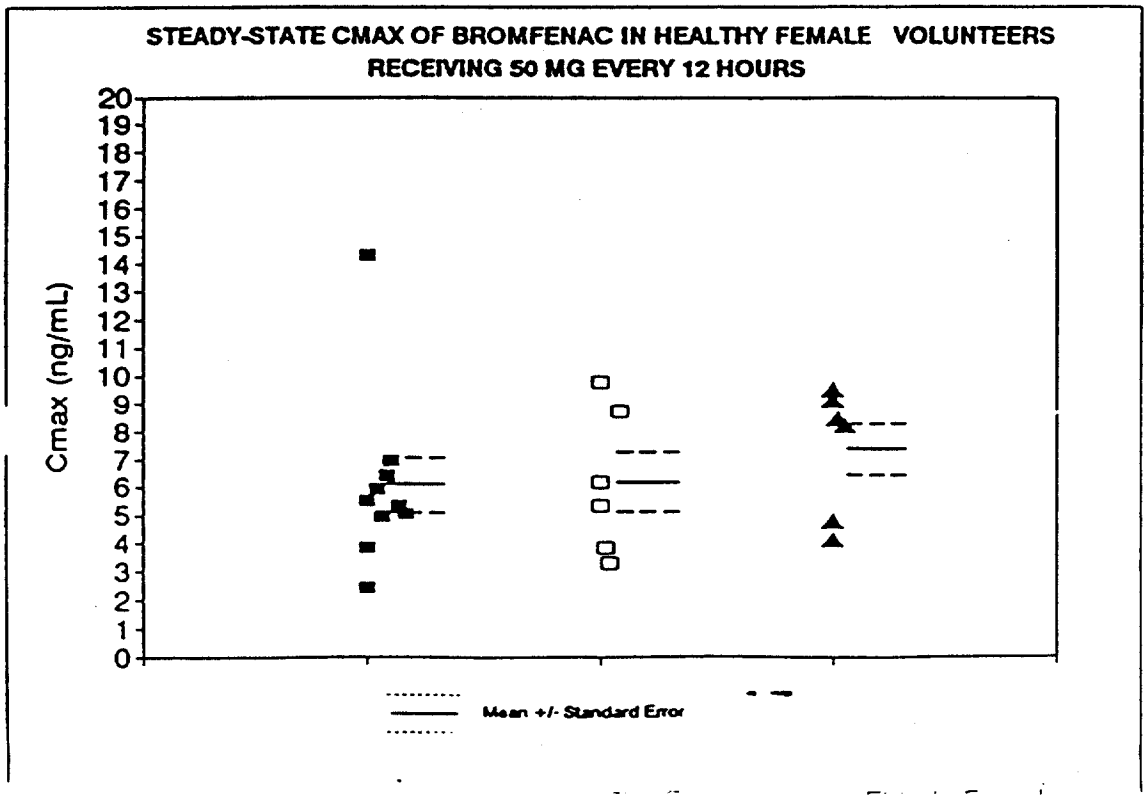
TABLE 3 - PHARMACOKINETIC PROFILE OF BROMFENAC IN THE PLASMA OF HEALTHY VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 12 HOURS (CONT'D)

INVESTIGATOR 10405 - PAUL J. WICHT, M. D.

SUBJECT	CMAX	TMAX	λz	AUC_12H	T1/2	MRT	CL/F	$V_{\lambda z}$/F	PERCENT BROMFENAC UNBOUND IN PLASMA 0.75H	2H	12H	CLU/F	CMAXU
Y FEMALES	(MCG/ML)	(H)	(1/H)	(MCG*H/ML)	(H)	(H)	(L/H/K)	(L/K)	(%)	(%)	(%)	(L/H/K)	(NG/ML)
E DOSE)													
004													
011													
028													
030													
031													
044													
MEAN	8.86	0.71	0.33	16.31	2.2	2.40	0.055	0.17	0.09	0.08	0.13	63.94	8.00
S.D.	2.59	0.19	0.09	5.65	0.5	0.79	0.022	0.05	0.02	0.02	0.04	26.22	3.81
GEOMETRIC MEAN	8.52	0.69	0.32	15.37	2.1	2.31	0.052	0.16	0.09	0.08	0.12	59.85	7.42
IPLE DOSING)													
004													
011													
028													
030													
031													
044													
MEAN	7.36	0.63	0.27	13.18	2.8	2.25	0.064	0.25	0.09	0.07	0.13	70.46	6.85
S.D.	2.31	0.44	0.10	3.45	0.7	0.42	0.015	0.06	0.01	0.01	0.03	17.85	2.57
GEOMETRIC MEAN	7.01	0.53	0.26	12.82	2.7	2.22	0.062	0.24	0.09	0.07	0.13	68.48	6.39

= 18 TO 45 YEARS
-ELDERLY = 65 TO 74 YEARS
LY = 75 YEARS AND OLDER





NDA/IND# 20-53[illegible] Suppl/Amend.# Submission Date 29 Dec 94 Volume: 1.88
Study Type Food effect Study# 792-A-118-US
Study Title The duration of food effect on the bioavailability of bromfenac

Clinical Investigator R Fruncillo MD, PhD Analytical Investigator
Site Clinical Pharmacology Unit Site
Graduate Hospital
Philadelphia, PA

Single Dose X Multiple Dose Washout Period 2 days
Cross-Over X Parallel Other Design
Fasted X Food Study X FDA High Fat Breakfast X
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
volunteers	12	8/4	33	24-41	72	50-102

Drug Dosage Forms

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg	capsule	49.8 mg	OVTF	

Sampling Times

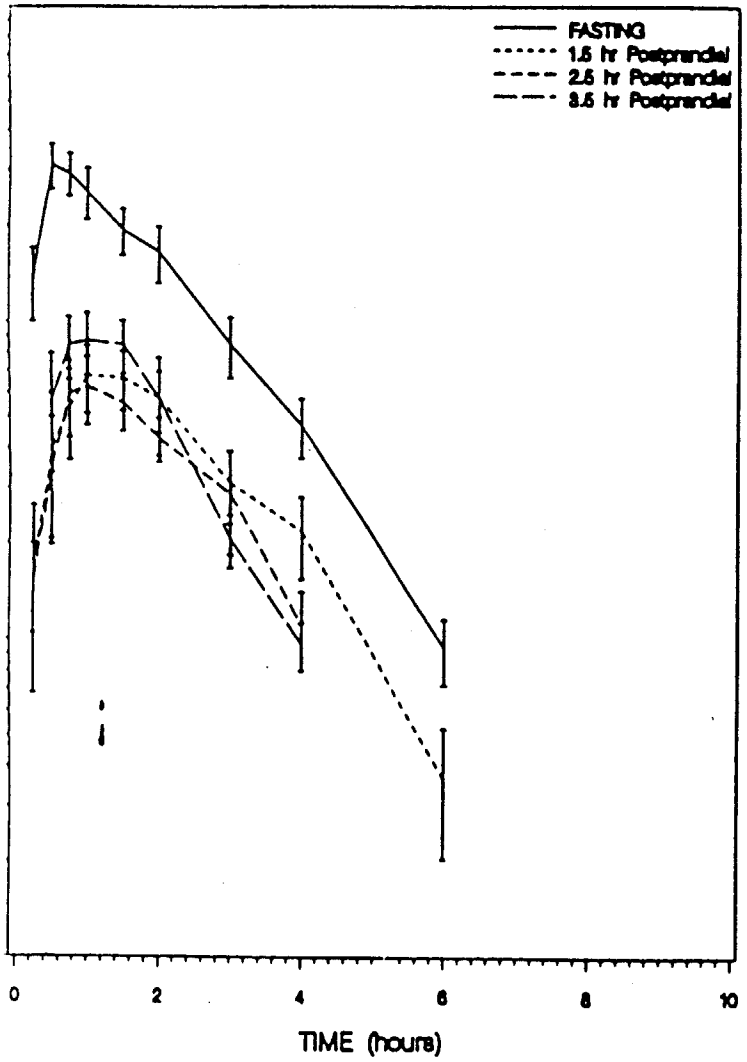
Plasma (7mL): 0 ,0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 hrs post dose
Protein Binding 1 hr postdose - equilibrium dialysis
Assay Method
Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

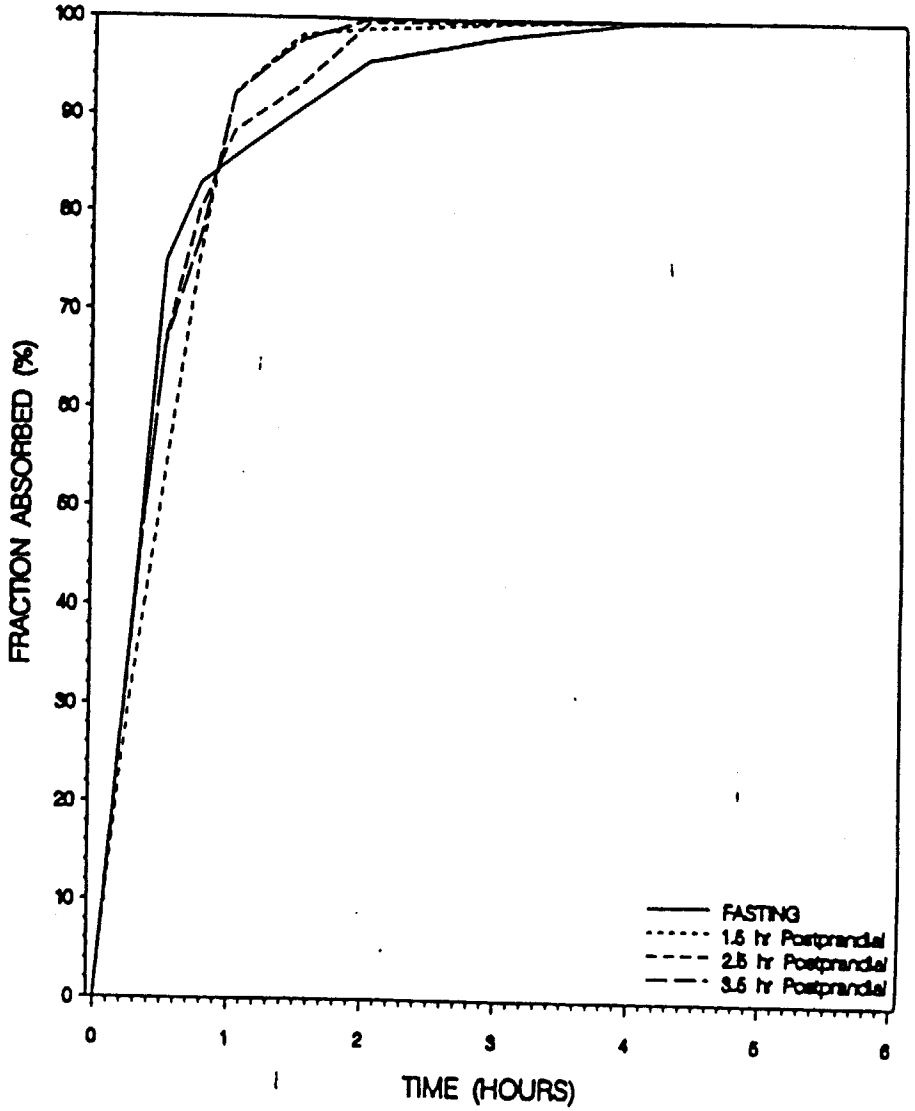
none - study was done to determine the duration of the decrease in concentration observed when bromfenac is administered with food

APPEARS THIS WAY
ON ORIGINAL

'A CONCENTRATIONS (MEAN AND SE) OF BROMFENAC
VOLUNTEERS RECEIVING A SINGLE 50 MG DOSE



FRACTION ABSORBED OF BROMFENAC IN VOLUNTEERS
RECEIVING A SINGLE 50 MG DOSE



TREATMENT: FASTING

INVESTIGATOR 11802 - R. FRUNCILLO, M.D., PH.D.

SUBJECT	CMAX (MG/L)	TMAX (H)	AUCT (MG*H/L)	AUC (MG*H/L)	CL/F (L/H/KG)	T1/2 (H)	MRT ORAL (H)	λz (1/H)	$V_{\lambda z}$/F (L/KG)	FU (%)	CMAXU (NG/ML)	AUCU (NG*H/ML)	CLU/F (ML/H/KG)	RATIO* CMAX (%)	RATIO* AUC (%)
001															
002															
003															
004															
005															
006															
007															
008															
009															
010															
011															
012															
MEAN	3.63	0.82	6.79	6.86	0.13	1.1	1.9	0.66	0.19	0.11	4.13	7.83	110.3	100.0	100.0
S.D.	1.45	0.50	3.27	3.29	0.05	0.4	0.5	0.21	0.06	0.01	1.61	3.70	45.5	0.0	0.0
GEOMETRIC MEAN	3.26	0.72	6.03	6.11	0.12	1.1	1.8	0.63	0.19	0.11	3.73	6.98	102.7	100.0	100.0

TREATMENT: 1.5 HOURS POSTPRANDIAL

INVESTIGATOR 11802 - R. FRUNCILLO, M.D., PH.D.

SUBJECT	CMAX (MG/L)	TMAX (H)	AUCT (MG*H/L)	AUC (MG*H/L)	CL/F (L/H/KG)	T1/2 (H)	MRT ORAL (H)	λz (1/H)	$V_{\lambda z}$/F (L/KG)	FU (%)	CMAXU (NG/ML)	AUCU (NG*H/ML)	CLU/F (ML/H/KG)	RATIO* CMAX (%)	RATIO* AUC (%)
001															
002															
003															
004															
005															
006															
007															
008															
009															
010															
011															
012															
MEAN	1.08	1.36	1.95	2.07	0.44	1.2	2.4	0.63	0.80	0.14	1.49	2.87	332.9	32.6	32.0
S.D.	0.69	0.98	1.27	1.25	0.23	0.3	0.7	0.13	0.65	0.01	0.97	1.89	194.6	19.9	14.5
GEOMETRIC MEAN	0.89	1.15	1.65	1.80	0 40	1.1	2.3	0.61	0.65	0.14	1.21	2.44	293.3	27.2	29.5

* RATIO TO THE FASTING TREATMENT

NOTE SUBJECT 12 EXCLUDED FROM STATISTICAL CALCULATIONS

TREATMENT: 2.5 HOURS POSTPRANDIAL

INVESTIGATOR 11802 - R. FRUNCILLO, M.D., PH.D.

SUBJECT	CMAX (NG/L)	TMAX (H)	AUCT (NG*H/L)	AUC (NG*H/L)	CL/F (L/H/KG)	T1/2 (H)	MRT ORAL (H)	λz (1/H)	V_{L}/F (L/KG)	FU (%)	CMAXU (NG/ML)	AUCU (NG*H/ML)	CLU/F (ML/H/KG)	RATIO* CMAX (%)	RATIO* AUC (%)
001															
002															
003															
004															
005															
006															
007															
008															
009															
010															
011															
012															
MEAN	0.89	1.30	1.60	1.68	0.61	0.9	2.1	0.79	0.79	0.13	1.16	2.19	493.1	27.5	26.5
S.D.	0.52	0.76	0.94	0.95	0.36	0.2	0.4	0.18	0.52	0.01	0.72	1.38	304.3	18.9	15.1
GEOMETRIC MEAN	0.72	1.13	1.29	1.38	0.52	0.9	2.0	0.78	0.67	0.13	0.91	1.75	409.9	22.0	22.6

TREATMENT: 3.5 HOURS POSTPRANDIAL

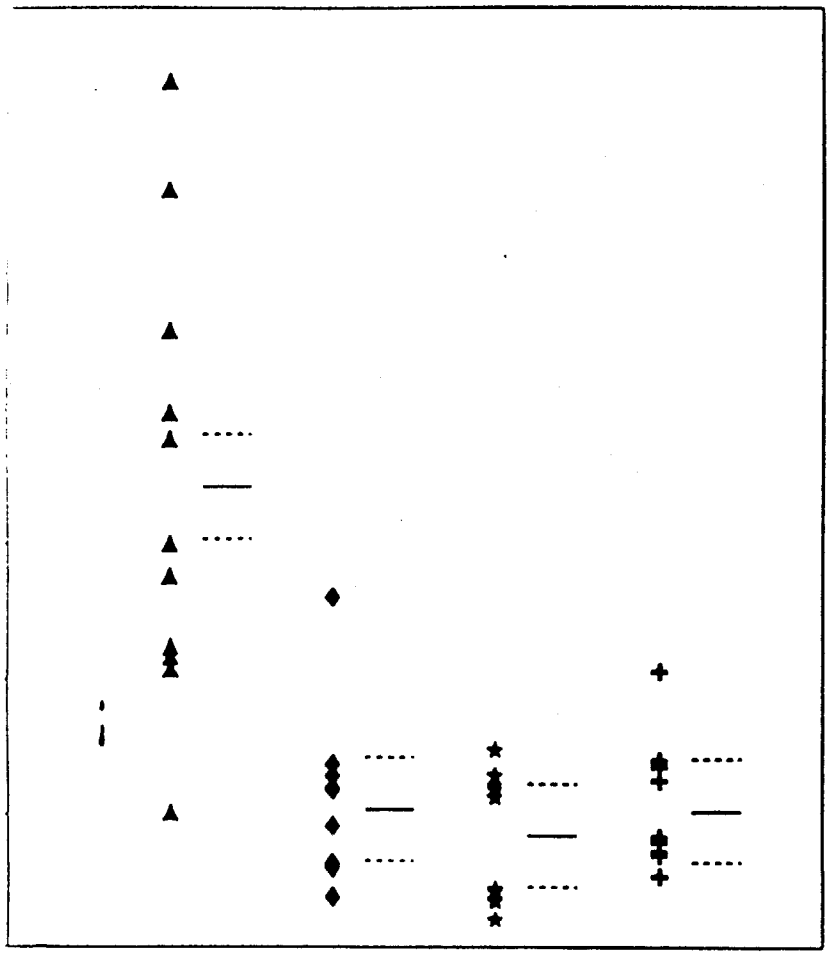
INVESTIGATOR 11802 - R. FRUNCILLO, M.D., PH.D.

SUBJECT	CMAX (NG/L)	TMAX (H)	AUCT (NG*H/L)	AUC (NG*H/L)	CL/F (L/H/KG)	T1/2 (H)	MRT ORAL (H)	λz (1/H)	V_{L}/F (L/KG)	FU (%)	CMAXU (NG/ML)	AUCU (NG*H/ML)	CLU/F (ML/H/KG)	RATIO* CMAX (%)	RATIO* AUC (%)
001															
002															
003															
004															
005															
006															
007															
008															
009															
010															
011															
012															
MEAN	1.27	1.16	1.91	2.05	0.40	1.1	2.1	0.74	0.66	0.11	1.43	2.36	352.5	44.4	35.5
S.D.	0.77	0.52	0.95	0.90	0.13	0.6	1.0	0.26	0.49	0.02	0.90	1.28	109.9	41.7	19.8
GEOMETRIC MEAN	1.06	1.06	1.71	1.90	0.38	1.0	2.0	0.69	0.55	0.11	1.19	2.13	336.1	32.4	31.1

* RATIO TO THE FASTING TREATMENT

NOTE: SUBJECT 12 EXCLUDED FROM STATISTICAL CALCULATIONS

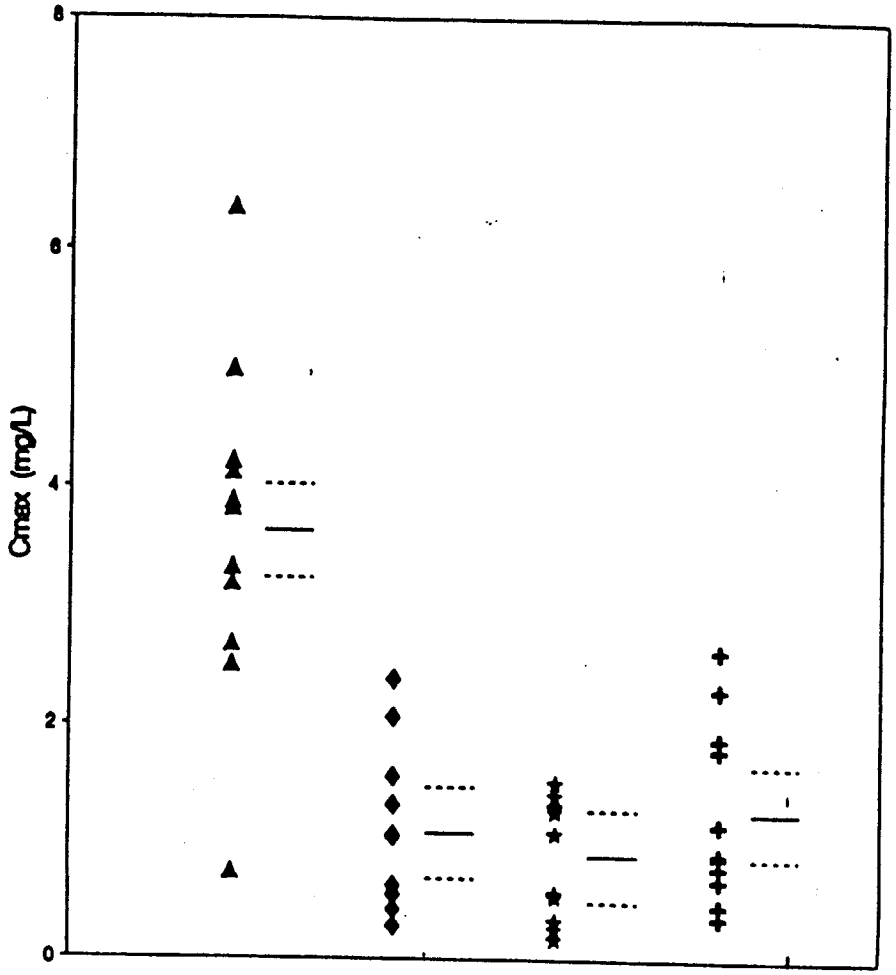
AUC OF BROMFENAC IN VOLUNTEERS RECEIVING
A SINGLE 60 MG DOSE



▲▲▲ Fasting
♦♦♦ 1.5 hr postprandial
★★★ 2.5 hr postprandial
+++ 3.5 hr postprandial

------ Mean & 90 %
—— Confidence Limits

Cmax OF BROMFENAC IN VOLUNTEERS RECEIVING
A SINGLE 60 MG DOSE



▲▲▲ Fasting
♦♦♦ 1.5 hr postprandial
★★★ 2.5 hr postprandial
+++ 3.5 hr postprandial

------ Mean & 90 %
—— Confidence Limits

NDA/IND# 20-535 Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.86-1.87
Study Type Food effect/Drug interaction - antacid Study# 792-A-108-US
Study Title The effect of food and antacid on the bioavailability of bromfenac in healthy men

Clinical Investigator R Fruncillo MD,PhD Analytical Investigator
Site Clinical Pharmacology Unit Site
Graduate Hospital
Philadelphia, PA

Single Dose X Multiple Dose Washout Period 2 days
Cross-Over X Parallel Other Design
Fasted X Food Study X FDA High Fat Breakfast
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
volunteers	20	20/0	29	18-45	78	59-96

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
aluminum hydroxide (Amphojel®)	all	2 tbsp	suspension			
bromfenac	all	50 mg	capsule	51.3 mg	1TKD	

Sampling Times

Plasma(5 mL) 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 hours postdose
Assay Method
Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

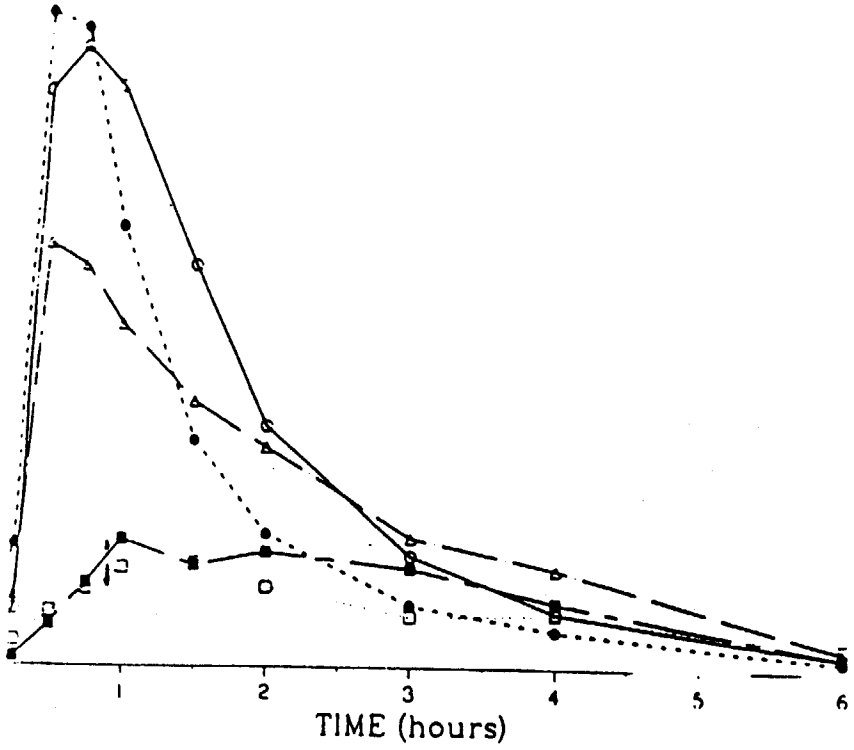
I. Food intake reduces peak plasma concentration of bromfenac by approximately 75%, while the AUC is reduced by about 60%.
II. The concomitant administration of aluminum hydroxide-containing antacid has no effect on the rate and extent of bromfenac absorption, but decreases the peak bromfenac concentration by 36%.

APPEARS THIS WAY
ON ORIGINAL

INFLUENCE OF FOOD ON MEAN PLASMA

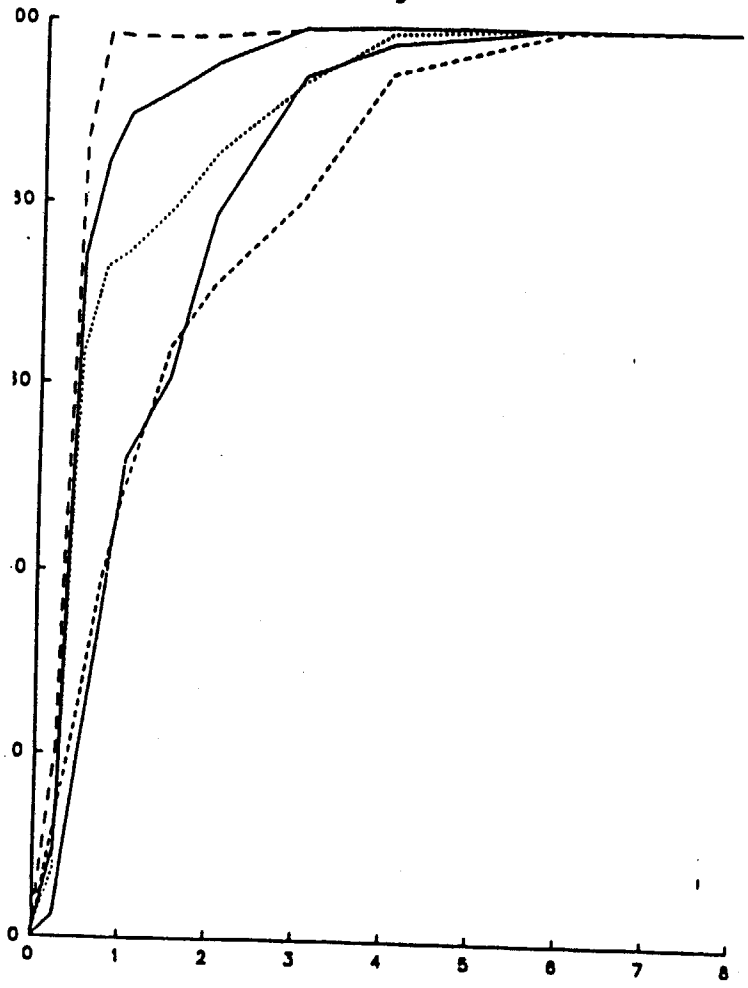
CONCENTRATIONS OF BROMFENAC FOLLOWING 50 MG DOSE

PROTOCOL 792A-108-US



○ = FASTING
● = 20 MINUTES PRIOR
□ = POSTPRANDIAL
■ = 60 MINUTES POSTPRANDIAL
△ = FASTING WITH AMPHOJEL

Mean Absorption of Bromfenac
In Subjects Receiving a Single
50 mg Dose



——Fasting
- - -20 Minutes Prior to a Meal
·····With a Meal
——60 Minutes After a Meal
·····Fasting with Amphojel

TREATMENT FASTING

SUBJECT	CMAX (MCG/ML)	TMAX (HR)	T1/2 (HR)	AUCT (MCG*HR/ML)	AUC (MCG*HR/ML)	MRT ORAL (HR)
1						
2						
103						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
MEAN	3.55	0.90	1.0	5.09	5.17	1.79
S.D.	1.88	0.59	0.3	2.90	2.91	0.31
GEOMETRIC MEAN	3.09	0.79	1.0	4.46	4.55	1.77

TREATMENT FASTING WITH AMPHOJEL

SUBJECT	CMAX (MCG/ML)	TMAX (HR)	T1/2 (HR)	AUCT (MCG*HR/ML)	AUC (MCG*HR/ML)	MRT ORAL (HR)	RATIO OF AMPHOJEL/FASTING CMAX (%)	RATIO OF AMPHOJEL/FASTING AUCT (%)	RATIO OF AMPHOJEL/FASTING AUC (%)
1									
2									
103									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
MEAN	2.25	1.26	1.1	4.36	4.43	2.30	73	97	97
S.D.	1.33	1.31	0.3	1.77	1.77	0.71	46	38	38
GEOMETRIC MEAN	1.90	0.87	1.0	4.03	4.11	2.21	61	90	90

TREATMENT 20 MINUTES PRIOR

SUBJECT	CMAX (MCG/ML)	TMAX (HR)	T1/2 (HR)	AUC T (MCG-HR/ML)	AUC (MCG-HR/ML)	MRT ORAL (HR)	RATIO OF PRIOR/FASTING CMAX (%)	RATIO OF PRIOR/FASTING AUC T (%)	RATIO OF PRIOR/FASTING AUC (%)
1									
2									
103									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
MEAN	3.65	0.60	1 2	3 87	3 99	1 66	122	88	90
S D	1 57	0.15	0 4	1 49	1 44	0 47	73	46	45
GEOMETRIC MEAN	3 27	0 58	1 1	3 57	3 73	1 60	106	80	82

TREATMENT POSTPRANDIAL

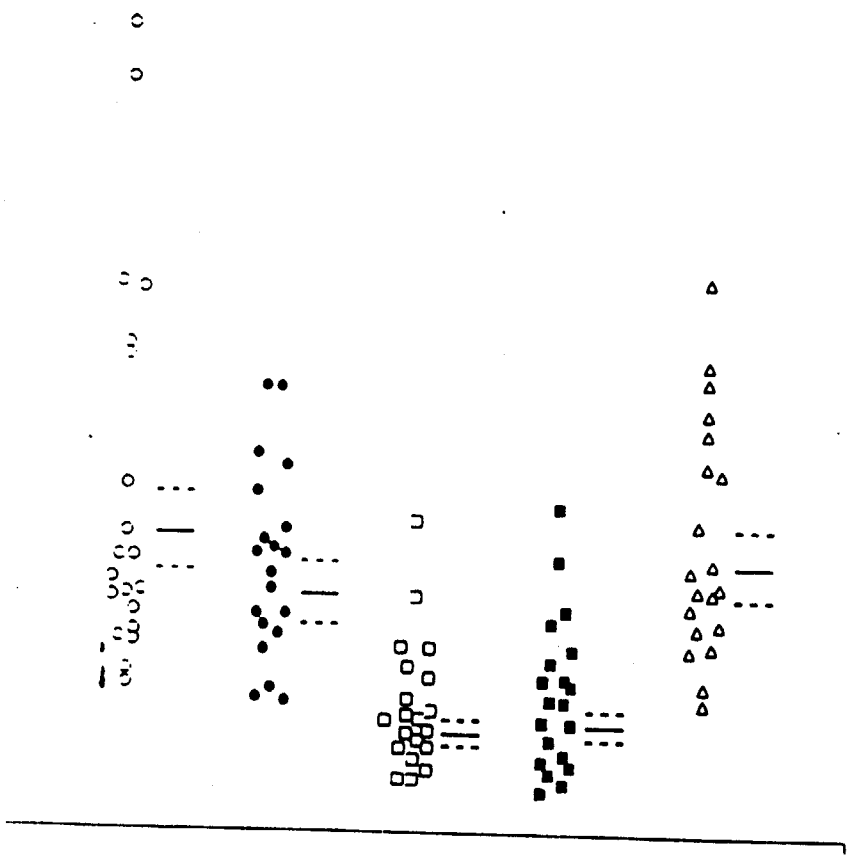
SUBJECT	CMAX (MCG/ML)	TMAX (HR)	T1/2 (HR)	AUC T (MCG-HR/ML)	AUC (MCG-HR/ML)	MRT ORAL (HR)	RATIO OF POSTPRANDIAL/FASTING CMAX (%)	RATIO OF POSTPRANDIAL/FASTING AUC T (%)	RATIO OF POSTPRANDIAL/FASTING AUC (%)
1									
2									
103									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
MEAN	1 05	2 19	1 1	1 75	1 87	2 73	37	41	43
S D	1 03	1 71	0 4	1 02	0 99	1 15	37	27	26
GEOMETRIC MEAN	0 78	1 64	1 0	1 50	1 66	2 55	25	34	37

TREATMENT 60 MINUTES POSTPRANDIAL

SUBJECT	CMAX (MCG/ML)	TMAX (HR)	T1/2 (HR)	AUCT (MCG·HR/ML)	AUC (MCG·HR/ML)	MRT ORAL (HR)	RATIO OF 60 MIN POST/FASTING CMAX (%)	RATIO OF 60 MIN POST/FASTING AUCT (%)	RATIO OF 60 MIN POST/FASTING AUC (%)
1									
2									
103									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
MEAN	1.01	1.80	1.3	1.96	2.10	3.02	34	42	45
S.D.	0.68	1.26	0.6	1.17	1.13	0.97	27	24	24
GEOMETRIC MEAN	0.80	1.50	1.2	1.63	1.82	2.89	26	36	40

COMPARISON OF BROMFENAC AUC_T

PROTOCOL 7921-108-US

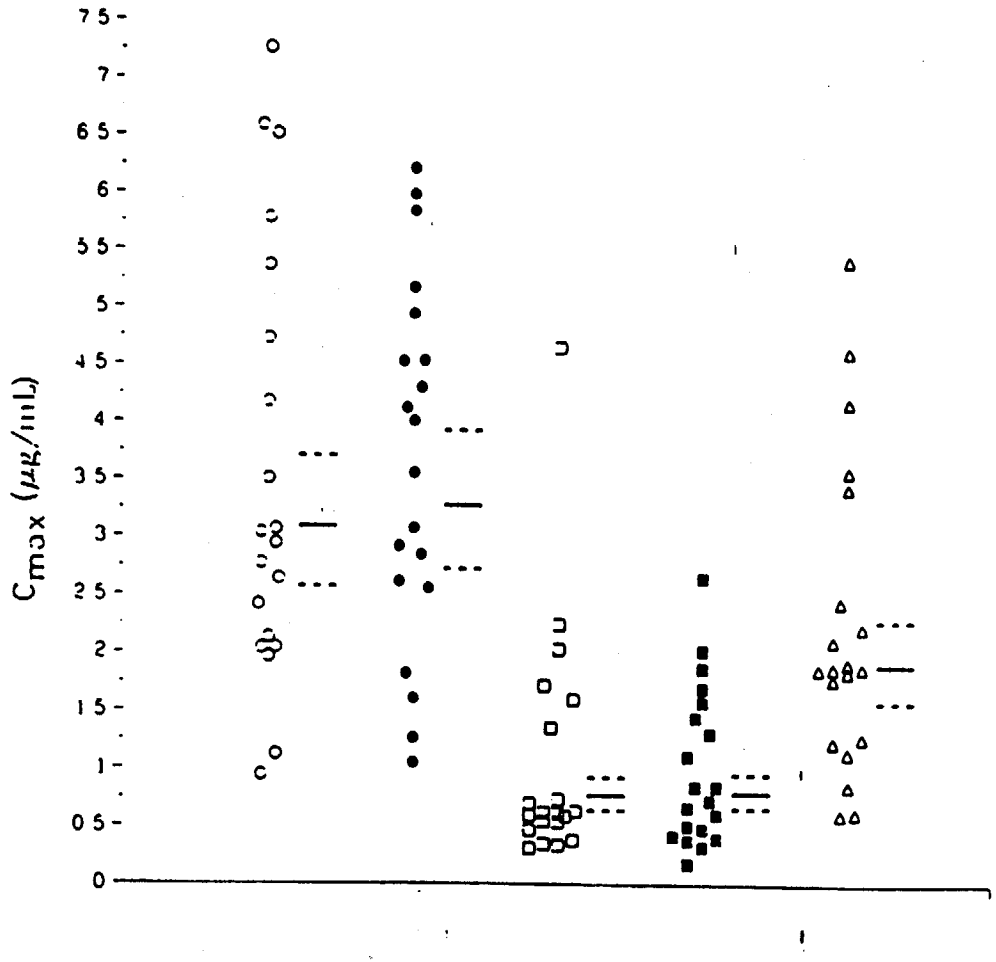


○ = FASTING
● = 20 MINUTES PRIOR
□ = POSTPRANDIAL
■ = 60 MINUTES POSTPRANDIAL
△ = FASTING WITH AMPHOJEL

⊣⊢ GEOMETRIC MEAN AND 95% CONFIDENCE LIMITS BASED ON LOG TRANSFORMED DATA

COMPARISON OF BOMFENAC C_{max}

PROTOCOL 792A-108-US



○ = FASTING
● = 20 MINUTES PRIOR
□ = POSTPRANDIAL
■ = 60 MINUTES POSTPRANDIAL
△ = FASTING WITH AMPHOJEL

⊣⊢ GEOMETRIC MEAN AND 95% CONFIDENCE LIMITS BASED ON LOG TRANSFORMED DATA

DEMOGRAPHIC ATTRIBUTES: SECTION III PATIENTS

Demographic Attribute	Bromfenac 50 mg fed (n=20)	Bromfenac 25 mg fasted (n = 21)	Bromfenac 25 mg fed (n = 20)	Placebo fed (n = 19)
Sex				
Male	7	11	10	4
Female	13	10	10	15
Age (years)				
Mean	24.2	22.8	24.5	24.3
Range	18-40	19-30	18-36	18-41
Standard deviation	6.3	3.2	6.2	6.2
Ethnic Origin				
Black	1	7	5	3
Hispanic	2	-	-	1
Oriental (Asian)	3	1	2	-
Other	-	2	-	-
White	14	11	13	15
Height (cm)				
Mean	168.5	170.8	174.3	168.3
Range	157-185	155-188	155-188	150-185
Standard deviation	7.3	10.6	8.8	8.5
Weight (kg)				
Mean	67.6	73.4	73.4	69.2
Range	48-114	44-129	59-110	43-130
Standard deviation	17.2	19.0	13.3	17.6

PLASMA CONCENTRATIONS OF BROMFENAC IN PATIENTS FOLLOWING SURGERY (CONT'D)

INVESTIGATOR 31102 - STEPHEN A. COOPER, D.M.D, PH.D.

SECTION: 1

		PLASMA CONCENTRATIONS (MCG/ML) (HOURS AFTER ADMINISTRATION)									
	SUBJECT	0	0.25	0.5	1	1.5	2	3	4	6	8
DOSE/FOOD: 50 MG - FED	303										
	305										
	309										
	315										
	316										
	325										
	327										
	328										
	340										
	341										
	347										
	348										
	350										
	355										
	359										
	362										
	363										
	370										
	372										
	377										
	MEAN	0.00	0.01	0.02	0.21	0.27	0.35	0.52	0.35	0.19	0.11
	S.D.	0.00	0.03	0.04	0.31	0.26	0.31	0.38	0.24	0.15	0.13

NOTE: '.' INDICATES VALUE NOT SAMPLED

PHARMACOKINETIC PARAMETERS OF BROMFENAC
IN PATIENTS FOLLOWING SURGERY

(CONT'D)

INVESTIGATOR 31102 - STEPHEN A. COOPER, D.M.D, PH.D.

SECTION 3

SUBJECT	CMAX (MCG/ML)	TMAX (HR)	AUCT (MCG*HR/ML)	AUC (MCG*HR/ML)	T_HALF (HR)	FU (%)	CMAX,U (NG/ML)	AUCT,U (NG*HR/ML)	AUC,U (NG*HR/ML)	WEIGHT (KG)	GENDER
DOSE/FOOD: 50 MG - FED											
303	- .-	- ..									
305											
309											
315											
316											
325											
327											
328											
340											
341											
347											
348											
350											
355											
359											
362											
363											
370											
372											
377											
MEAN	0.70	3.11	1.98	2.34	2.19	0.16	1.12	3.25	3.86	67.6	
S.D.	0.38	1.63	0.77	0.92	1.39	0.03	0.55	1.37	1.67	17.2	
GEOMETRIC MEAN	0.60	2.76	1.82	2.16	1.86	0.16	0.97	2.94	3.50	65.8	

NOTE: BECAUSE OF INSUFFICIENT DATA, NO PHARMACOKINETIC PARAMETERS WERE CALCULATED FOR SUBJECTS 37, 41, 57, 305, 313, 326, 336 AND 353.
BECAUSE OF INSUFFICIENT PLASMA CONCENTRATIONS, T_HALF WAS NOT CALCULATED FOR SUBJECTS 107, 362, AND 376.

PLASMA CONCENTRATIONS OF BROMFENAC
IN PATIENTS FOLLOWING SURGERY (CONT'D)

INVESTIGATOR 31102 - STEPHEN A. COOPER, D.M.D, PH.D.

SECTION: 3

DOSE/FOOD: 25 MG - FED

SUBJECT	PLASMA CONCENTRATIONS (MCG/ML) (HOURS AFTER ADMINISTRATION) 0	0.25	0.5	1	1.5	2	3	4	6	8
304										
312										
313										
319										
320										
321										
326										
330										
336										
337										
338										
344										
352										
353										
358										
365										
368										
373										
374										
379		....	[illegible]	[illegible]	0.05	0.00	0.07	0.19	0.37	0.13
MEAN	0.00	0.00	0.02	0.11	0.15	0.17	0.18	0.21	0.13	0.05
S.D.	0.00	0.00	0.04	0.20	0.18	0.17	0.13	0.18	0.12	0.05

NOTE: '.' INDICATES VALUE NOT SAMPLED

PHARMACOKINETIC PARAMETERS OF BROMFENAC IN PATIENTS FOLLOWING SURGERY (CONT'D)

INVESTIGATOR 31102 - STEPHEN A. COOPER, D.M.D, PH.D.

SECTION 1

	SUBJECT	CMAX (MCG/ML)	TMAX (HR)	AUCT <--(MCG*HR/ML)-->	AUC	T_HALF (HR)	FU (%)	CMAX,U (NG/ML)	AUCT,U <--(NG*HR/ML)-->	AUC,U	WEIGHT (KG)	GENDER
DOSE/FOOD 25	MG - FED											
	304											
	312											
	313											
	319											
	320											
	321											
	326											
	330											
	336											
	337											
	338											
	344											
	352											
	353											
	358											
	365											
	368											
	373											
	374											
	379											
	MEAN	0.33	3.09	1.03	1.29	1.75	0.16	0.55	1.72	2.15	73.4	
	S.D.	0.17	1.61	0.44	0.43	0.59	0.04	0.29	0.88	0.92	13.3	
	GEOMETRIC MEAN	0.28	2.68	0.87	1.20	1.66	0.16	0.46	1.41	1.90	72.4	

NOTE: BECAUSE OF INSUFFICIENT DATA, NO PHARMACOKINETIC PARAMETERS WERE CALCULATED FOR SUBJECTS 37, 41, 57, 305, 313, 326, 336 AND 353.
BECAUSE OF INSUFFICIENT PLASMA CONCENTRATIONS, T_HALF WAS NOT CALCULATED FOR SUBJECTS 107, 362, AND 374.

Table 12 (Continued)

PLASMA CONCENTRATIONS OF BROMFENAC
IN PATIENTS FOLLOWING SURGERY (CONT'D)

INVESTIGATOR 31102 - STEPHEN A. COOPER, D.M.D, PH.D.

PLASMA CONCENTRATIONS (MCG/ML)
(HOURS AFTER ADMINISTRATION)

SECTION: 3

DOSE/FOOD: 25 MG - FASTED

SUBJECT	0.00	0.11	0.33	0.66	0.89	0.75	0.45	0.24	0.08	0.04
306	0.01	0.28	0.65	0.73	0.74	0.51	0.30	0.18	0.08	0.04
307										
308										
311										
314										
329										
331										
332										
334										
335										
342										
343										
349										
356										
360										
364										
367										
369										
375										
376										
378										
MEAN										
S.D.										

NOTE: '.' INDICATES VALUE NOT SAMPLED

PHARMACOKINETIC PARAMETERS OF BROMFENAC IN PATIENTS FOLLOWING SURGERY (CONT'D)

INVESTIGATOR 31102 - STEPHEN A. COOPER, D.M.D, PH.D.

SECTION 3 SUBJECT	CMAX (MCG/ML)	TMAX (HR)	AUCT <--(MCG*HR/ML)-->	AUC	T_HALF (HR)	FU (%)	CMAX,U (NG/ML)	AUCT,U <--(NG*HR/ML)-->	AUC,U	WEIGHT (KG)	GENDER
DOSE/FOOD: 25 MG - FASTED											
306											
307											
308											
311											
314											
329											
331											
332											
334											
335											
342											
343											
349											
356											
360											
364											
367											
369											
375											
376											
378											
MEAN	1.24	1.74	2.50	2.71	2.20	0.13	1.66	3.34	3.62	73.4	
S.D.	0.77	0.85	1.39	1.35	2.86	0.01	1.05	1.86	1.79	19.0	
GEOMETRIC MEAN	0.98	1.54	2.11	2.43	1.48	0.13	1.31	2.81	3.23	71.3	

NOTE: BECAUSE OF INSUFFICIENT DATA, NO PHARMACOKINETIC PARAMETERS WERE CALCULATED FOR SUBJECTS 37, 41, 57, 305, 313, 326, 336 AND 353.
BECAUSE OF INSUFFICIENT PLASMA CONCENTRATIONS, T_HALF WAS NOT CALCULATED FOR SUBJECTS 107, 362, AND 374.

HOURLY MEAN PID SCORES: SECTION III
(VALID-FOR-EFFICACY, EXTRAPOLATED RESULTS)[a,b]

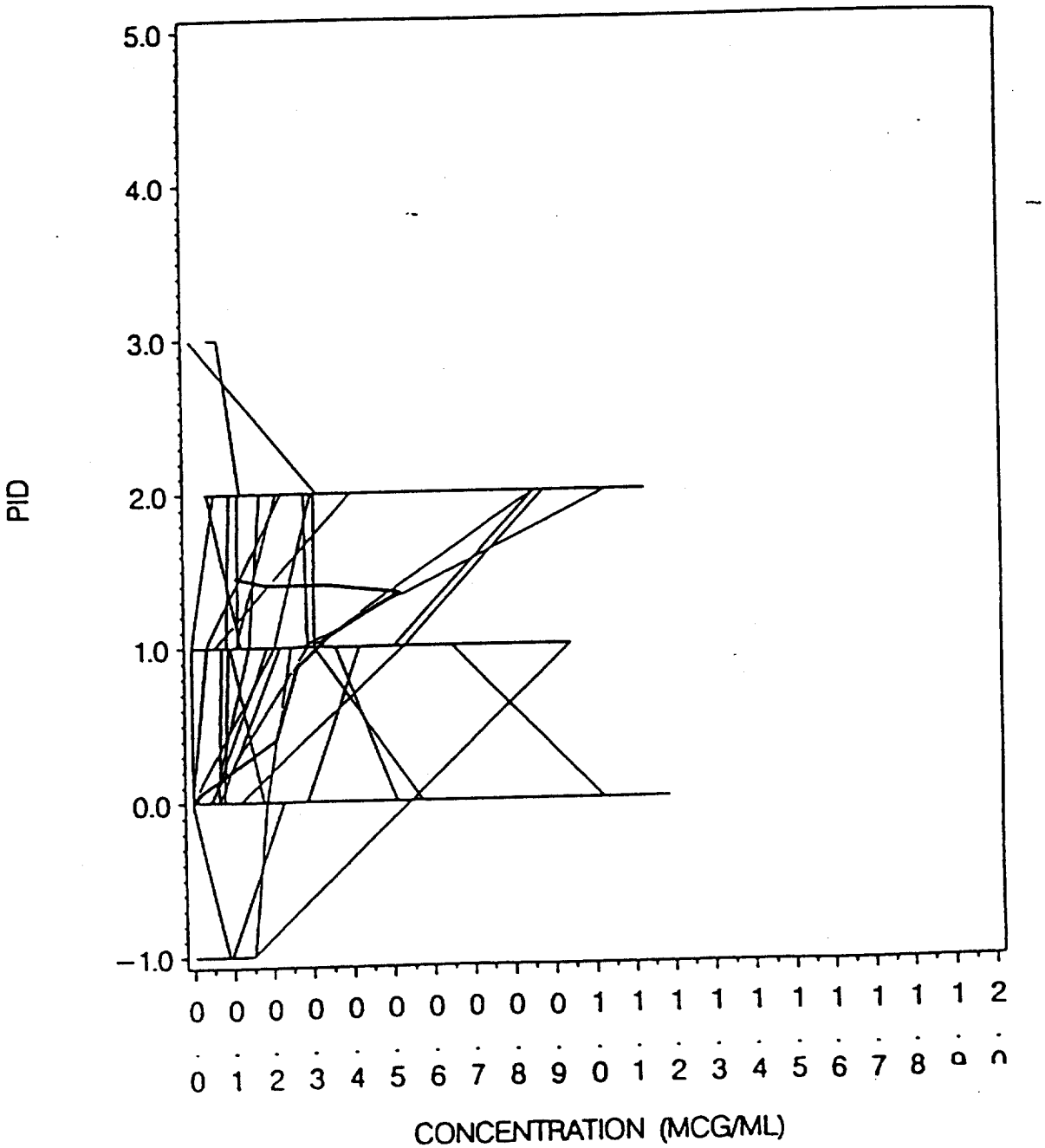
Treatment Group (Mean baseline pain intensity)	n	Hours 0.25	0.5	1	1.5	2	3	4	5	6	7	8
Bromfenac 50 mg fed (2.45)	20	20 0.01	20 0.07	20 0.40	20 0.86 BC	20 1.08 BC	18 1.35 B	17 1.40 B	17 1.40 B	17 1.39 B	16 1.50 B	16 1.44 B
Bromfenac 25 mg fasted (2.48)	21	21 0.01	21 0.16	21 0.69	21 1.22 C	21 1.41 C	21 1.60 B	21 1.84 B	21 1.60 B	20 1.64 B	19 1.51 B	19 1.41 B
Bromfenac 25 mg fed (2.40)	20	20 0.17	20 0.08	20 0.27	20 0.52 AB	20 0.92 B	15 1.19 B	14 1.38 B	14 1.33 B	14 1.29 B	14 1.25 B	14 1.15 B
Placebo fed (2.42)	19	19 0.05	19 0.03	19 0.11	19 0.18 A	19 0.11 A	10 0.30 A	6 0.34 A	6 0.11 A	3 0.06 A	2 0.11 A	2 0.11 A
Overall treatment p-value		0.6834	0.8862	0.0821	0.0006	0.0001	0.0001	0.0001	0.0001	0.0001	0.0002	0.0001
Root MSE		0.4641	0.5349	0.7166	0.7853	0.7806	0.7559	0.7568	0.7820	0.7813	0.8190	0.8391

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.

b: At each observation hour, n = number of patients with observed (unextrapolated) data. Means include data (unextrapolated or extrapolated) from all patients.

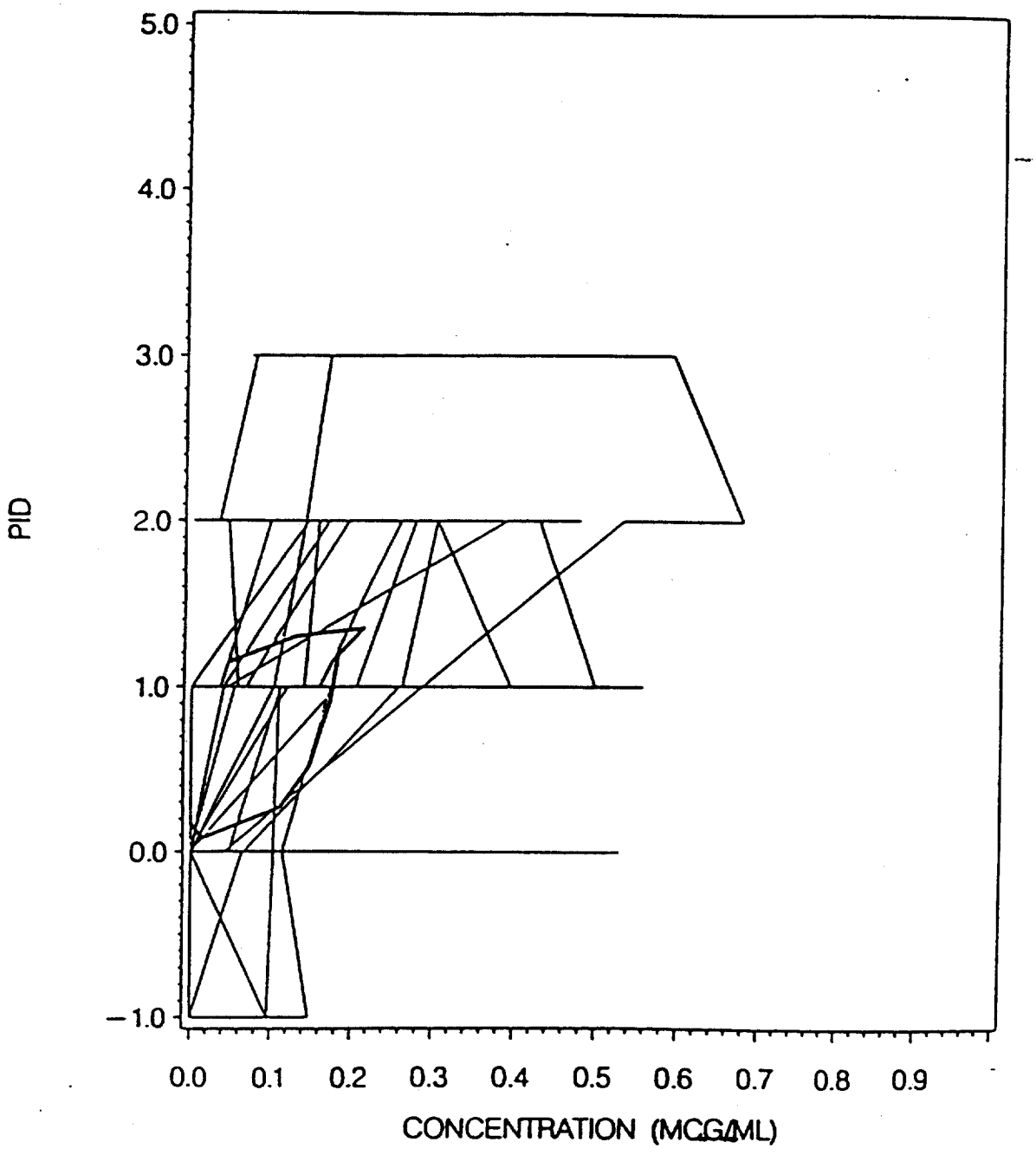
Supportive Figure 82

PID VS CONCENTRATION
FOR 50 MG FED GROUP (SECTION III)



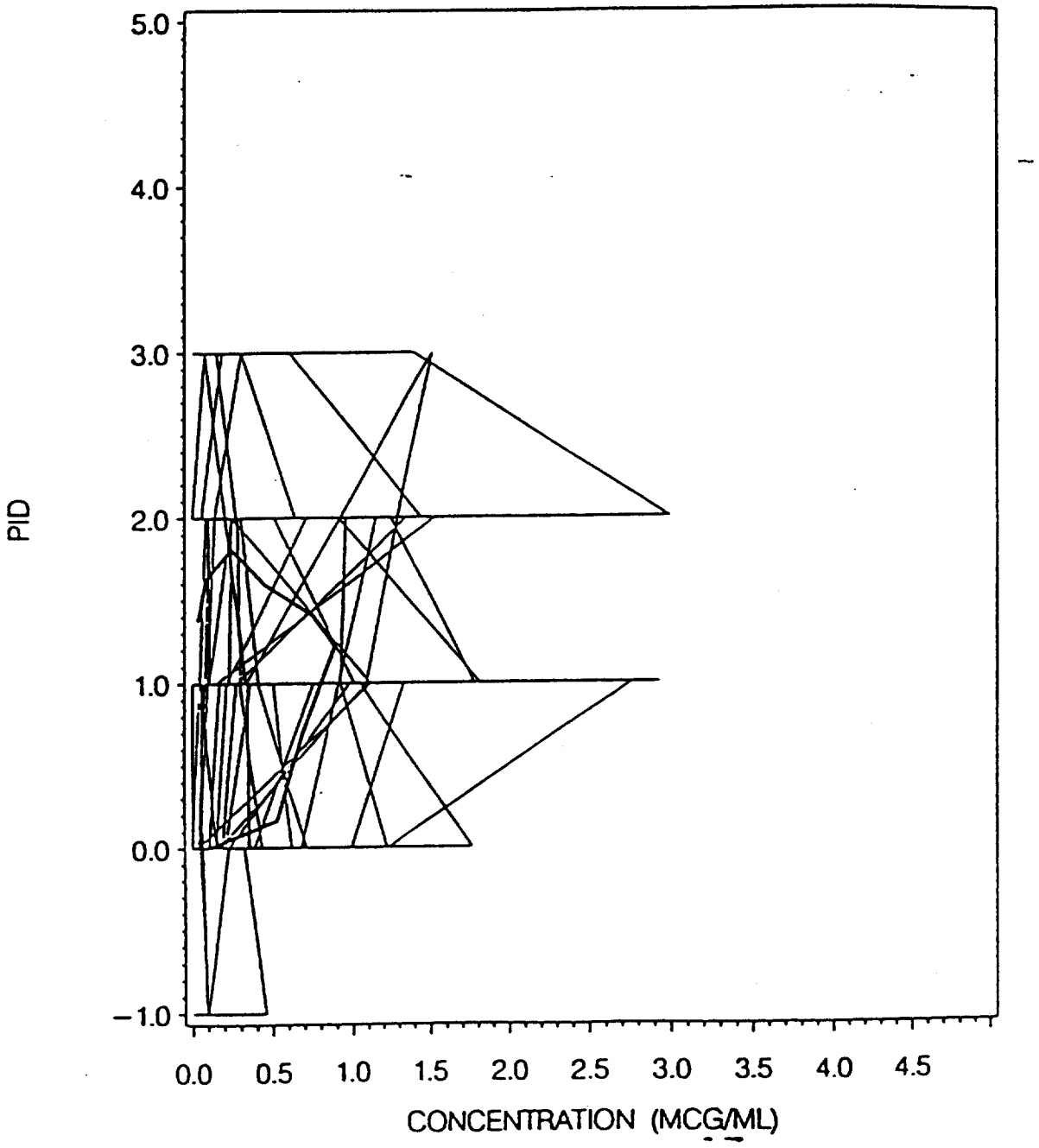
Supportive Figure 79

PID VS CONCENTRATION
FOR 25 MG FED GROUP (SECTION III)



Supportive Figure 76

PID VS CONCENTRATION
FOR 25 MG FASTED GROUP (SECTION III)



NDA/IND# 20-535/ Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.91-1.92
Study Type Renal disease Study# 792-A-101-US
Study Title: Pharmacokinetic evaluation of bromfenac in healthy adult subjects and in subjects with impaired renal function

Clinical Investigator and Site: M Rudnick MD, Clinical Pharmacology Unit, Graduate Hospital, Philadelphia, PA

Analytical Investigators and Sites: plasma- PH Burghart, Wyeth-Ayerst Research, Princeton, NJ

Single Dose_X Multiple Dose_ Washout Period
Cross-Over Parallel_X Other Design
Fasted_X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 10 Prior to dosing and_4 Post-dosing.
Volunteers_X Patients Young Elderly Renal X Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
normal	18	14/4	30	19-58	76	57-97
impaired	12	9/3	45	20-71	79	64-98
dialysis	10	7/3	48	39-56	73	61-100

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg	capsule	50.4 mg	4023	

Sampling Times

Plasma: (10 mL) 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hour postdose when not on dialysis
0, 1, 3, 4 hours after beginning of dialysis, which started 30 min post dose
Urine: 0-1, 1-3, 3-6, 6-12, 12-24 hour postdose
Dialysate: from total dialysate
Protein Binding: (5 mL) 0.75, 2, 4, 12 hours postdose

Assay Method

Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

I. In a study of the effects of mild to severe renal impairment, no significant differences were seen in the disposition of total and unbound bromfenac.
II. In subjects undergoing hemodialysis, unbound bromfenac clearance was not altered.
III. No dosage adjustment of Bromfenac is required in patients with mild to severe renal impairment; however, Bromfenac should be used with caution in such patients because NSAIDs may further decrease renal function in some patients with

Figure 1

Mean Plasma Concentrations of Bromfenac In Normals and Patients with Renal Disease

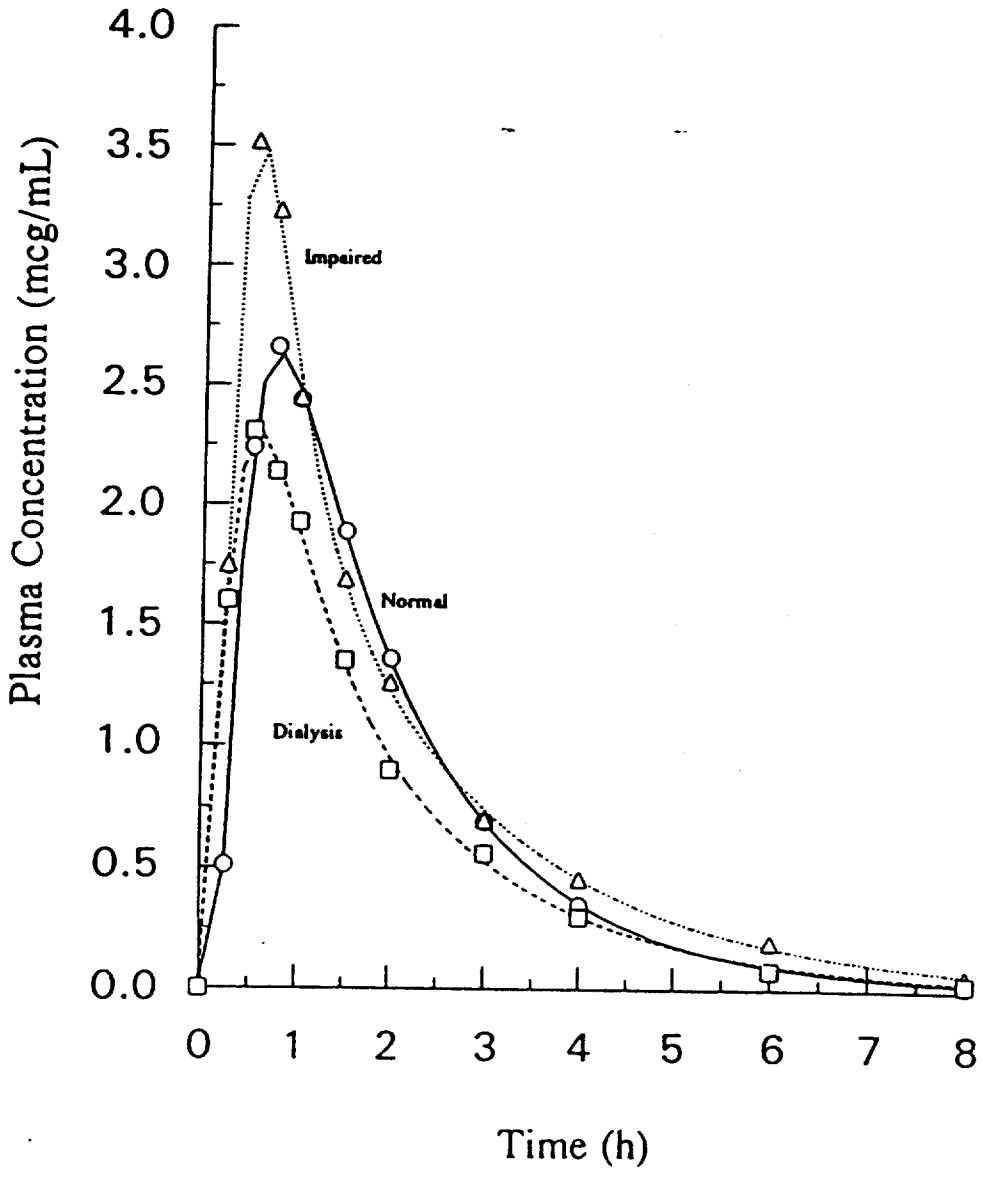


TABLE 5A - PHARMACOKINETIC PROFILE OF BROMFENAC IN SUBJECTS WITH VARYING DEGREES OF RENAL FUNCTION RECEIVING A SINGLE 50 MG ORAL DOSE OF BROMFENAC

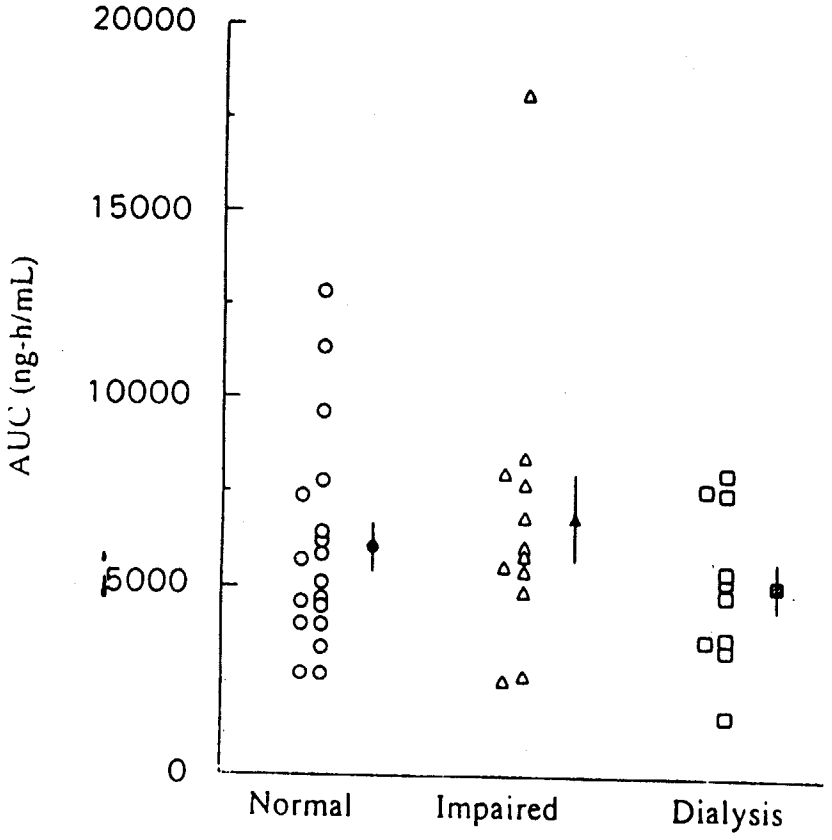
INVESTIGATOR 10115 - MICHAEL R. RUDNICK, M.D.

GROUP	SUB	CMAX (NG/ML)	TMAX (H)	T1/2 (H)	CL/F (L/H/KG)	TABS (H)	V Z/F (L/KG)	VSS/F (L/KG)	AUCT	AUC (NG-H/ML)	MRT (H)	FU (%)	CMAXU (NG/ML)	AUC U (NG-H/ML)	CLOU (L/H/KG)	V Z,U/F (L/KG)	VSS,U/F (L/KG)
NORMAL	14																
	15																
	16																
	17																
	18																
	19																
	21																
	22																
	23																
	24																
	25																
	26																
	27																
	35																
	36																
	37																
	38																
	39																
	MEAN	3424	0.8	0.9	0.13	0.588	0.17	0.149	5444	6062	1.2	0.17	5.5	9.7	79.0	101.6	90.8
	STD	1409	0.2	0.3	0.05	0.245	0.07	0.067	2542	2830	0.3	0.05	2.4	4.6	25.4	39.5	36.4
	GEOM	3134	0.7	0.9	0.12	0.542	0.15	0.136	4967	5520	1.1	0.16	5.1	8.9	74.6	94.1	84.5
IMPAIRED	1																
	2																
	3																
	4																
	7																
	9																
	10																
	20																
	28																
	29																
	31																
	40																
	MEAN	3898	0.7	1.8	0.12	0.563	0.32	0.224	6644	6866	1.7	0.16	6.3	10.9	72.2	178.8	130.4
	STD	2232	0.7	0.9	0.07	0.694	0.31	0.232	3707	4003	0.6	0.04	3.8	6.4	34.0	135.1	108.9
	GEOM	3201	0.6	1.6	0.11	0.380	0.24	0.171	5954	6058	1.6	0.16	5.1	9.7	65.5	150.0	106.2

GROUP	SUB	CMAX (NG/ML)	TMAX (H)	T1/2 (H)	CL/F (L/H/KG)	TABS (H)	V Z/F (L/KG)	VSS/F (L/KG)	AUCT	AUC (NG-H/ML)	MRT (H)	FU (%)	CMAXU (NG/ML)	AUC U (NG-H/ML)	CLOU (L/H/KG)	V Z,U/F (L/KG)	VSS,U/F (L/KG)
DIALYSIS	5																
	6																
	8																
	11																
	12																
	13																
	30																
	32																
	33																
	34																
	MEAN	3279	0.6	1.7	0.17	0.419	0.35	0.243	4630	5127	1.5	0.29	9.0	14.0	58.4	120.8	80.3
	STD	1950	0.4	1.0	0.11	0.298	0.22	0.161	2037	2095	0.7	0.08	5.4	4.9	33.7	63.8	34.3
	GEOM	2778	0.5	1.4	0.15	0.314	0.30	0.207	4187	4679	1.4	0.28	7.8	13.1	52.4	106.2	73.8

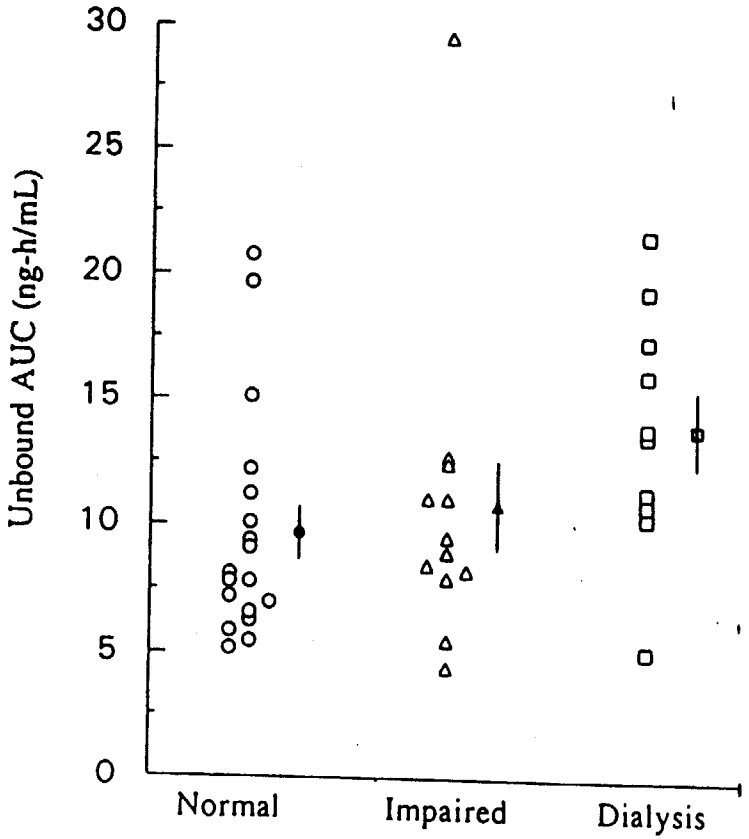
Individual Bromfenac AUC

(Mean +/- SE)

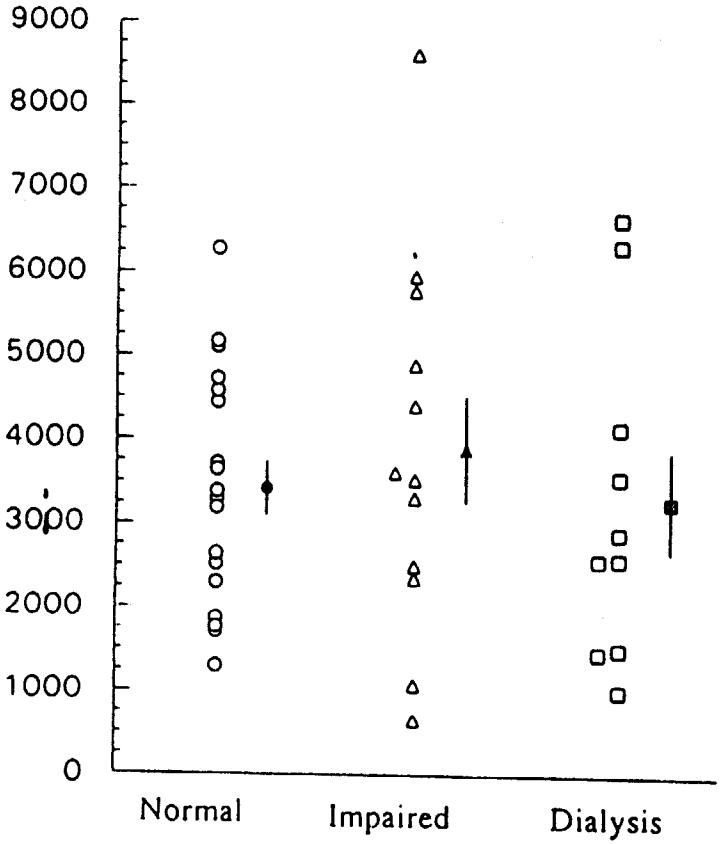


Individual Bromfenac Unbound AUC

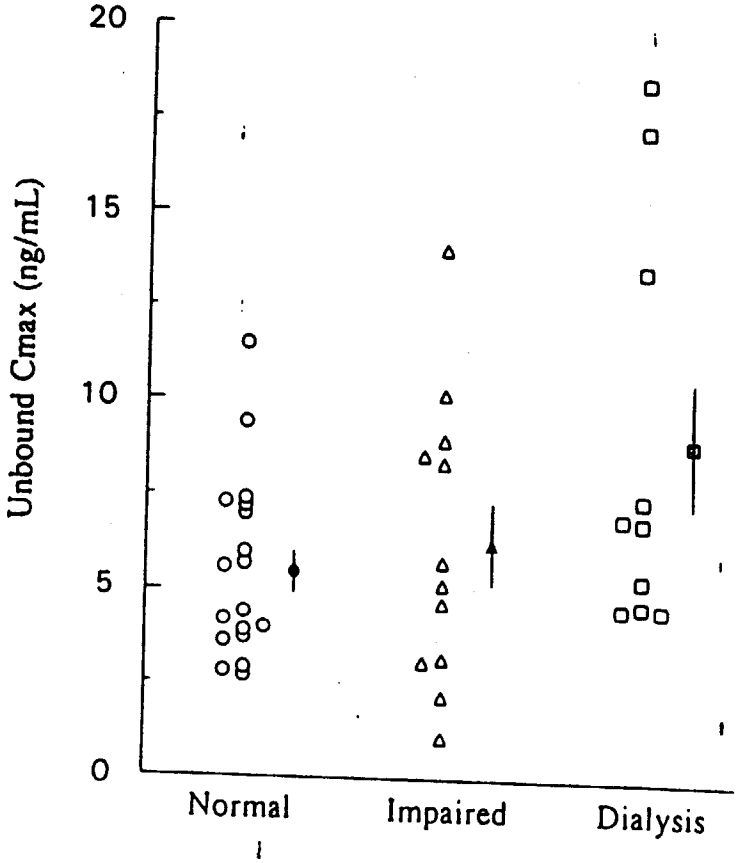
(Mean +/- SE)



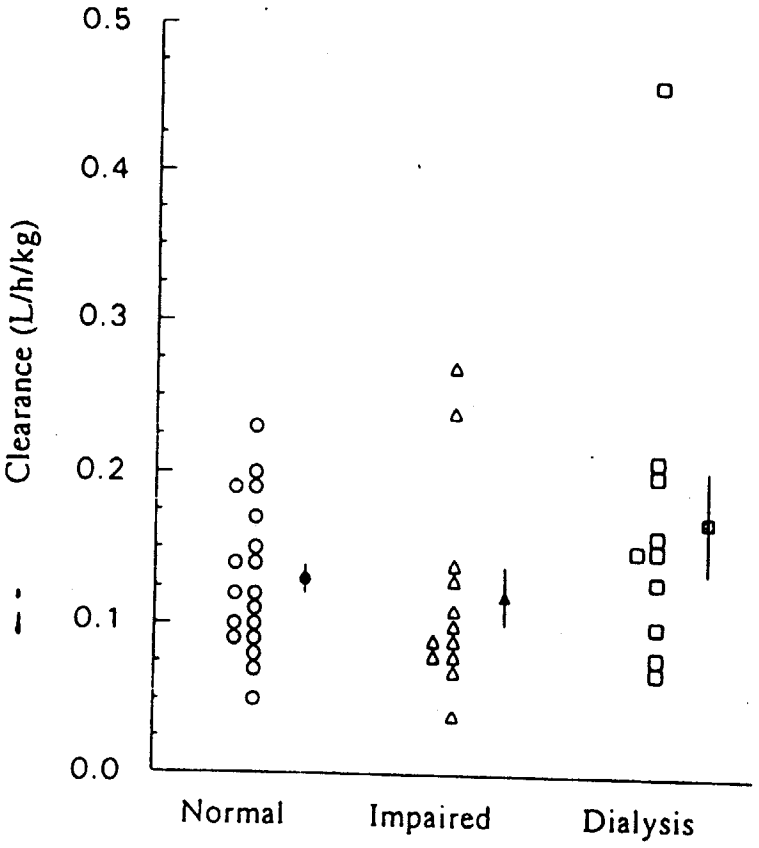
Individual Bromfenac Cmax
(Mean +/- SE)



Individual Bromfenac Unbound Cmax
(Mean +/- SE)



Individual Bromfenac Clearance
(Mean +/- SE)



Individual Bromfenac Unbound Clearance
(Mean +/- SE)

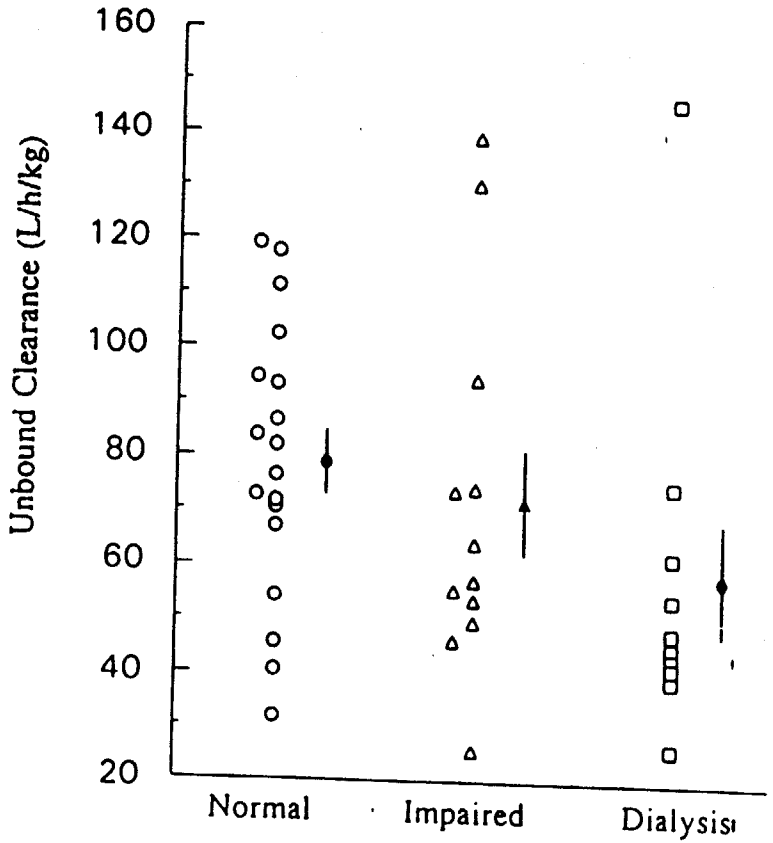


Figure 8

Relationship of Bromfenac Disposition and Renal Function

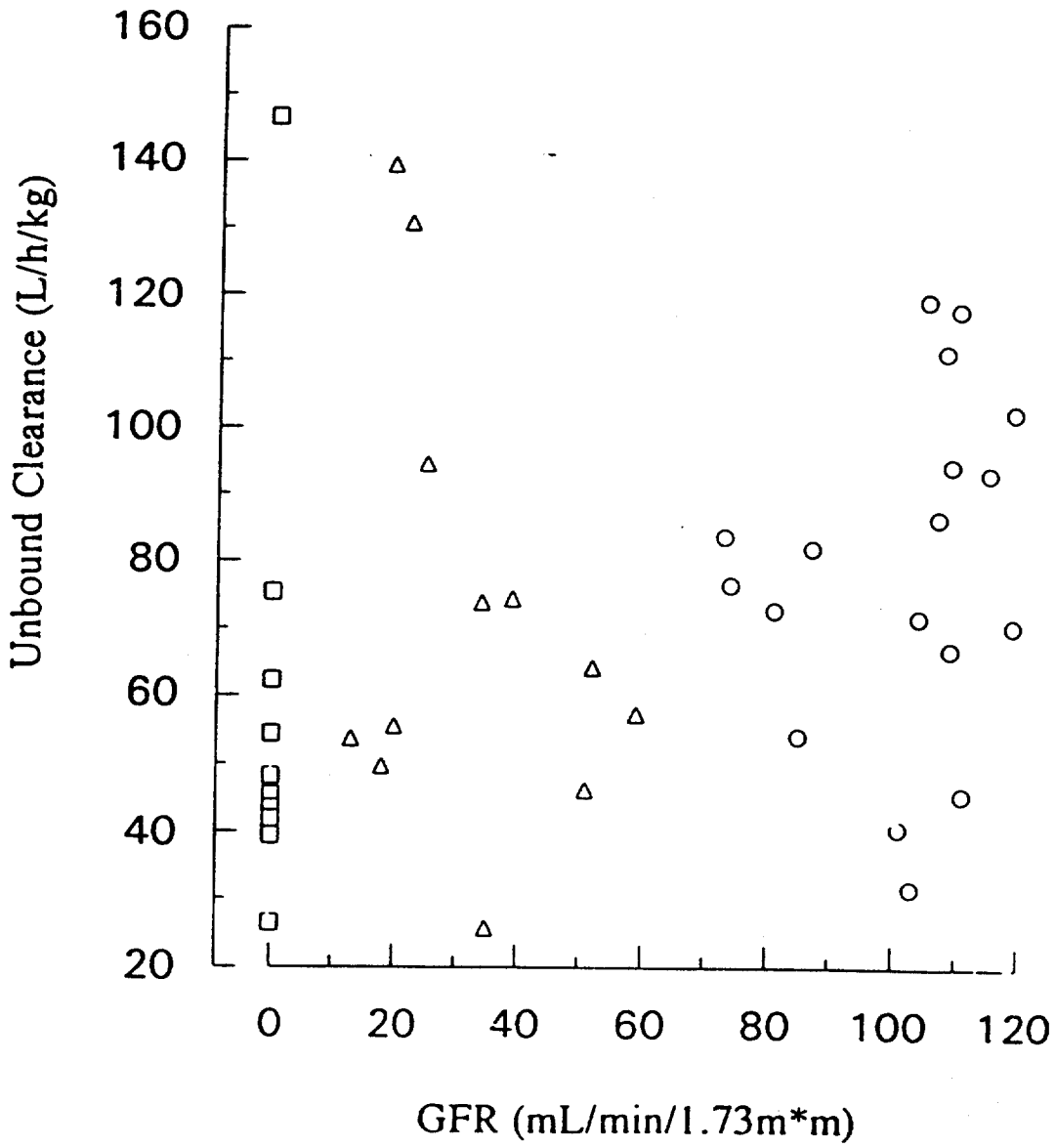


TABLE 7 - ARTERIAL AND VENOUS PLASMA CONCENTRATIONS OF BROMFENAC IN DIALYSIS SUBJECTS RECEIVING A SINGLE 50 MG ORAL DOSE OF BROMFENAC
(CONCENTRATION UNITS = NG/ML)

INVESTIGATOR 10115 - MICHAEL R. RUDNICK, M.D.

GROUP	SUBJECT	ARTERIAL 0 HOURS	VENOUS 0 HOURS	ARTERIAL 1 HOUR	VENOUS 1 HOUR	ARTERIAL 3 HOURS	VENOUS 3 HOURS	ARTERIAL 4 HOURS	VENOUS 4 HOURS
DIALYSIS	5								
	6								
	8								
	11								
	12								
	13								
	30								
	32								
	33								
	34								
	MEAN	1250.50	1380.20	520.40	608.60	479.00	507.30	384.10	384.90
	STD	1480.83	1552.13	382.86	463.94	432.71	472.38	327.23	348.07

A "BLANK" INDICATES A MISSING VALUE.

NDA/IND# 20-535. ___ Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.94-1.95
Study Type Hepatic disease Study# 792-A-103-US
Study Title A single-dose pharmacokinetic study of bromfenac in subjects with chronic stable liver disease in healthy adult subjects

Clinical Investigator Site: S Harris MD,PhD; South Florida Bioavailability Clinic; Coral Springs, FL
Analytical Investigators and Sites: plasma: D Hicks; Wyeth-Ayerst Res.; Princeton, NJ

Single Dose_X Multiple Dose Washout Period
Cross-Over Parallel_X Other Design
Fasted_X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers_X Patients Young Elderly Renal Hepatic_X

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
normal	16	12/4	47	35-65	71	47-99
hepatic	17*	13/4	49	35-64	75	45-143

* one subject was obese and excluded from summary statistics, although individual concentrations and pk parameters are presented in the report.

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg	capsule	50.4 mg	4023	

Sampling Times

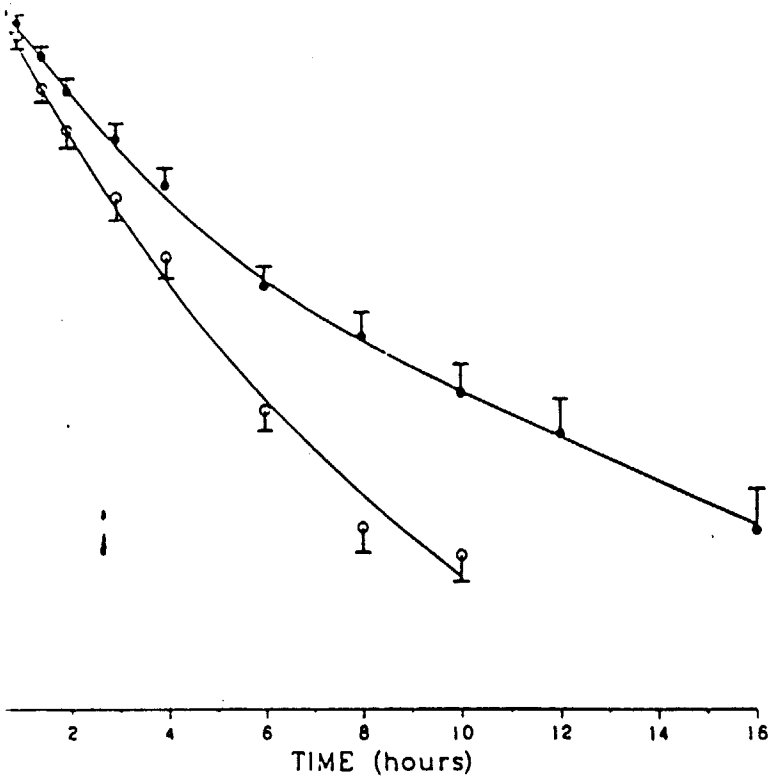
Plasma: (10 mL) 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 hours postdose
Urine: 0-24 hours postdose
Protein Binding: 0.75, 2, 4, 12 hours postdose - equilibrium dialysis
Assay Method

Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

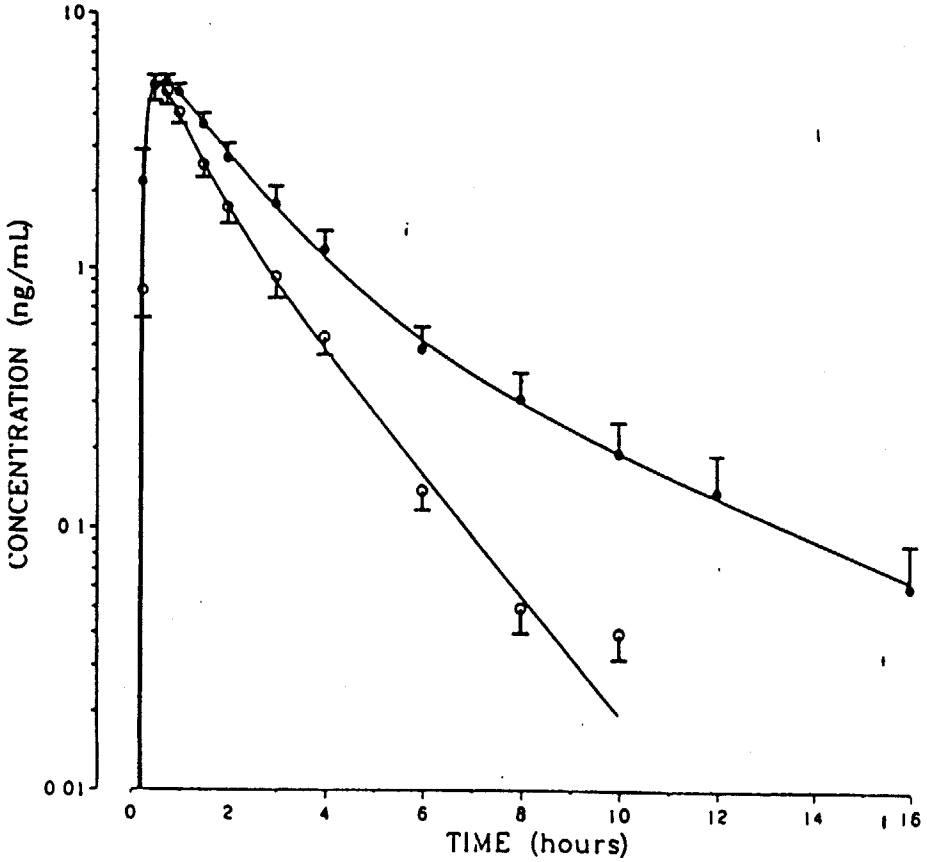
1. Dosage adjustment of 1/3 to 1/2 that of healthy volunteers is required in some hepatically impaired subjects especially if prothrombin time > 13.5 seconds.

MEAN + S E TOTAL BROMFENAC PLASMA CONCENTRATIONS
16 NORMAL HEALTHY AND 17 HEPATICALLY IMPAIRED SUBJECTS
RECEIVING A SINGLE DOSE OF 50 MG OF BROMFENAC
PROTOCOL 792A-103-US



o = NORMAL
• = HEPATIC

MEAN + S E UNBOUND BROMFENAC PLASMA CONCENTRATIONS
IN 16 NORMAL HEALTHY AND 17 HEPATICALLY IMPAIRED SUBJECTS
RECEIVING A SINGLE DOSE OF 50 MG OF BROMFENAC
PROTOCOL 792A-103-US



o = NORMAL
• = HEPATIC

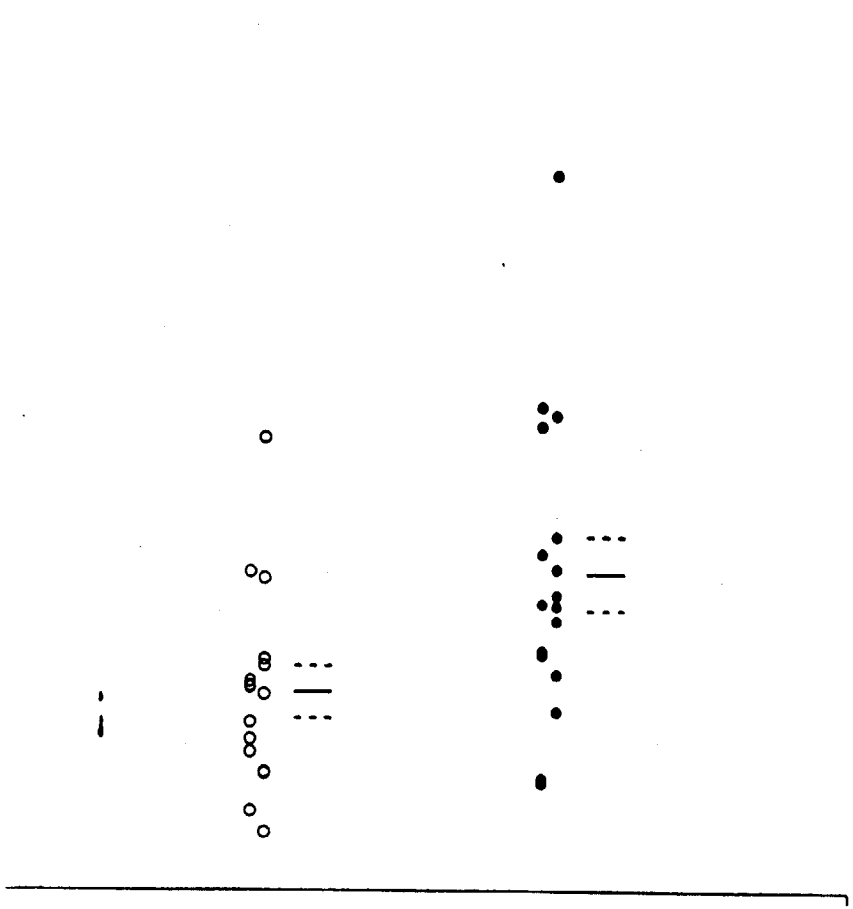
GROUP	SUBJECT	CMAX (MCG/ML)	TMAX (HR)	T1/2 (HR)	CL/F (L/HR/KG)	TABS (HR)	VSS/F (L/KG)	V Z/F (L/KG)	AUCT (MCG-HR/ML)	AUC (MCG-HR/ML)	MRT (HR)
NORMAL	11										
	12										
	13										
	14										
	16										
	17										
	18										
	25										
	26										
	27										
	28										
	29										
	30										
	31										
	32										
	33										
	MEAN	5.7	0.6	2.4	0.098	0.435	0.140	0.277	8.6	9.2	1.5
	S.D.	2.5	0.2	1.5	0.051	0.163	0.072	0.128	3.9	4.6	0.4
	GEOM	5.2	0.6	2.0	0.087	0.411	0.127	0.249	7.9	8.2	1.5

GROUP	SUBJECT	CMAX (MCG/ML)	TMAX (HR)	T1/2 (HR)	CL/F (L/HR/KG)	TABS (HR)	VSS/F (L/KG)	V Z/F (L/KG)	AUCT (MCG-HR/ML)	AUC (MCG-HR/ML)	MRT (HR)
IMPAIRED	1										
	2										
	3										
	4										
	5										
	6										
	7										
	8										
	9										
	10										
	15										
	19										
	20										
	21										
	22										
	23										
	24										
	MEAN #	6.1	0.6	3.3	0.062	0.406	0.130	0.253	13.4	14.7	2.5
	S.D.	1.6	0.3	1.5	0.035	0.296	0.044	0.100	6.5	7.2	1.2
	GEOM	5.9	0.5	3.0	0.055	0.316	0.124	0.235	12.1	13.1	2.3
	MEAN	6.1	0.6	3.3	0.060	0.419	0.125	0.244	13.3	14.7	2.5
	S.D.	1.6	0.3	1.5	0.035	0.291	0.046	0.103	6.4	7.0	1.2
	GEOM	5.8	0.5	3.0	0.052	0.329	0.118	0.224	12.0	13.2	2.3

GEOM GEOMETRIC MEAN # MEAN IS EXCLUDING SUBJECT 9

TOTAL BROMFENAC AUC

NORMAL vs. HEPATIC SUBJECTS

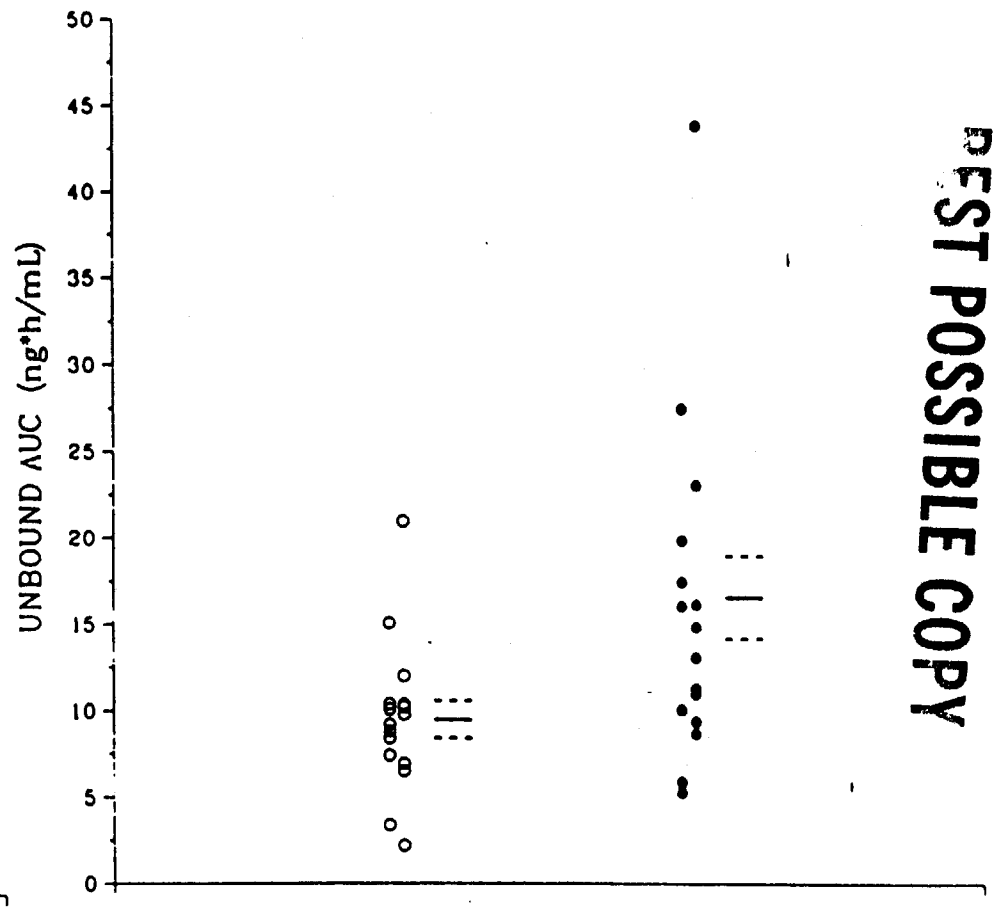


○ = NORMAL
● = HEPATIC

MEAN ± SE (N=16)

UNBOUND BROMFENAC AUC

NORMAL vs. HEPATIC SUBJECTS

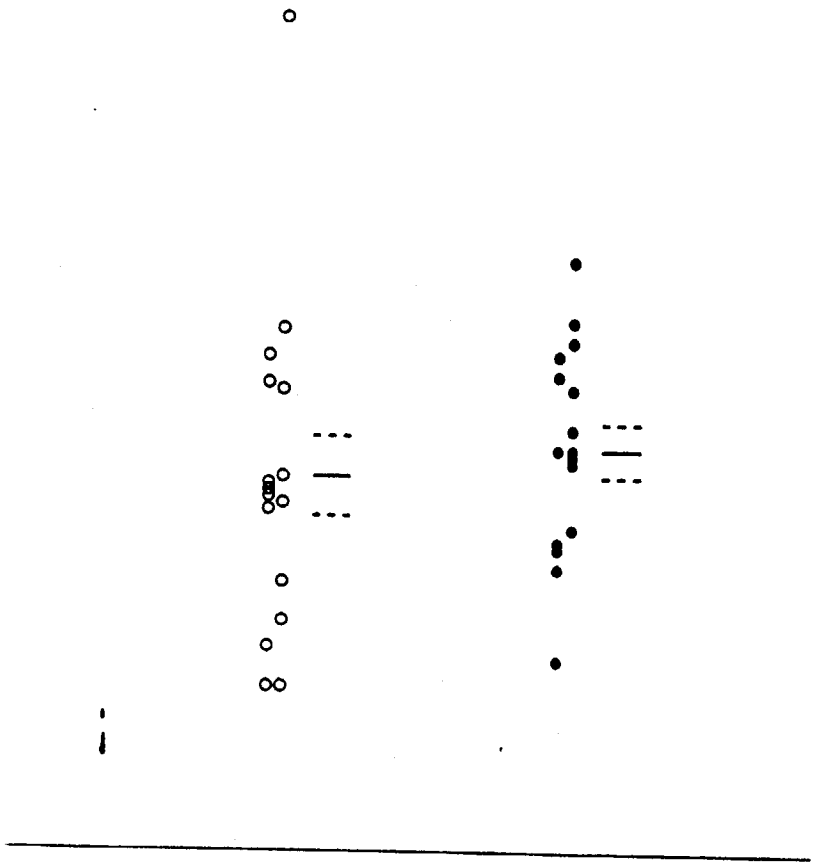


○ = NORMAL
● = HEPATIC

MEAN ± SE (N=16)

TOTAL BROMFENAC C_{max}

NORMAL vs HEPATIC SUBJECTS

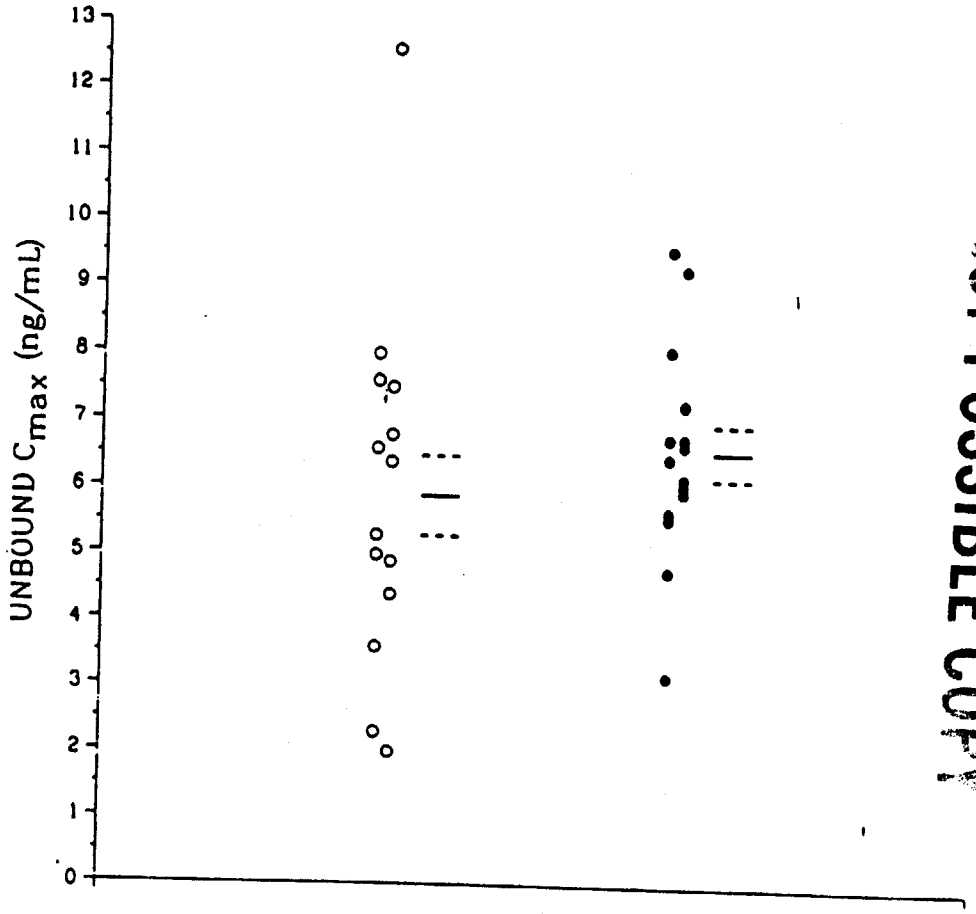


○ = NORMAL
● = HEPATIC

MEAN ± SE (N=16)

UNBOUND BROMFENAC C_{max}

NORMAL vs. HEPATIC SUBJECTS

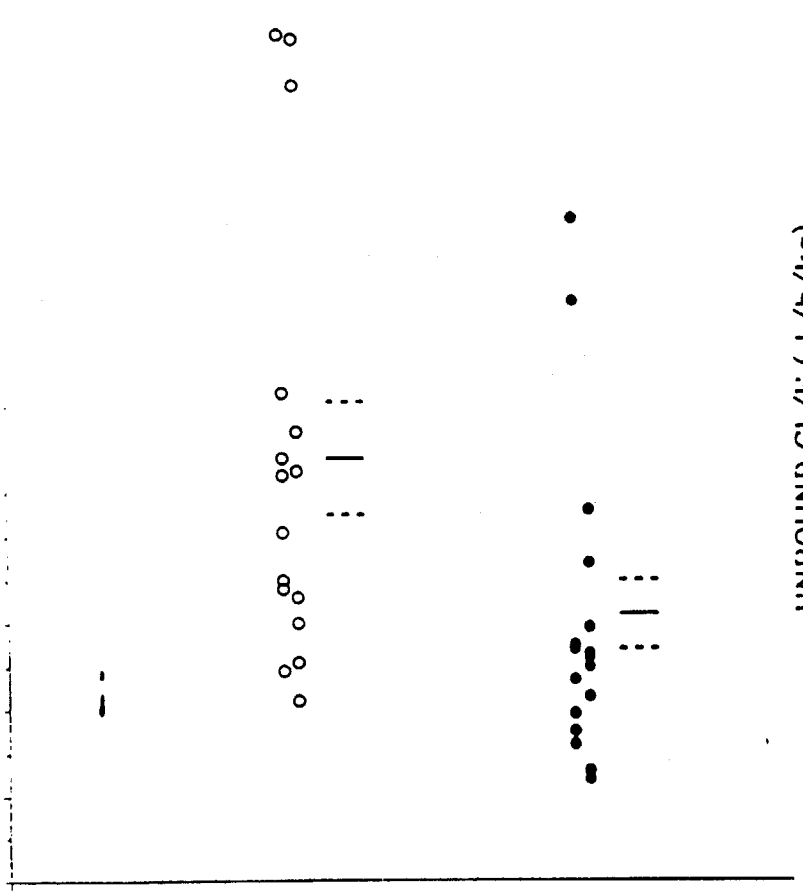


○ = NORMAL
● = HEPATIC

MEAN ± SE (N=16)

TOTAL BROMFENAC CL/F

NORMAL vs. HEPATIC SUBJECTS

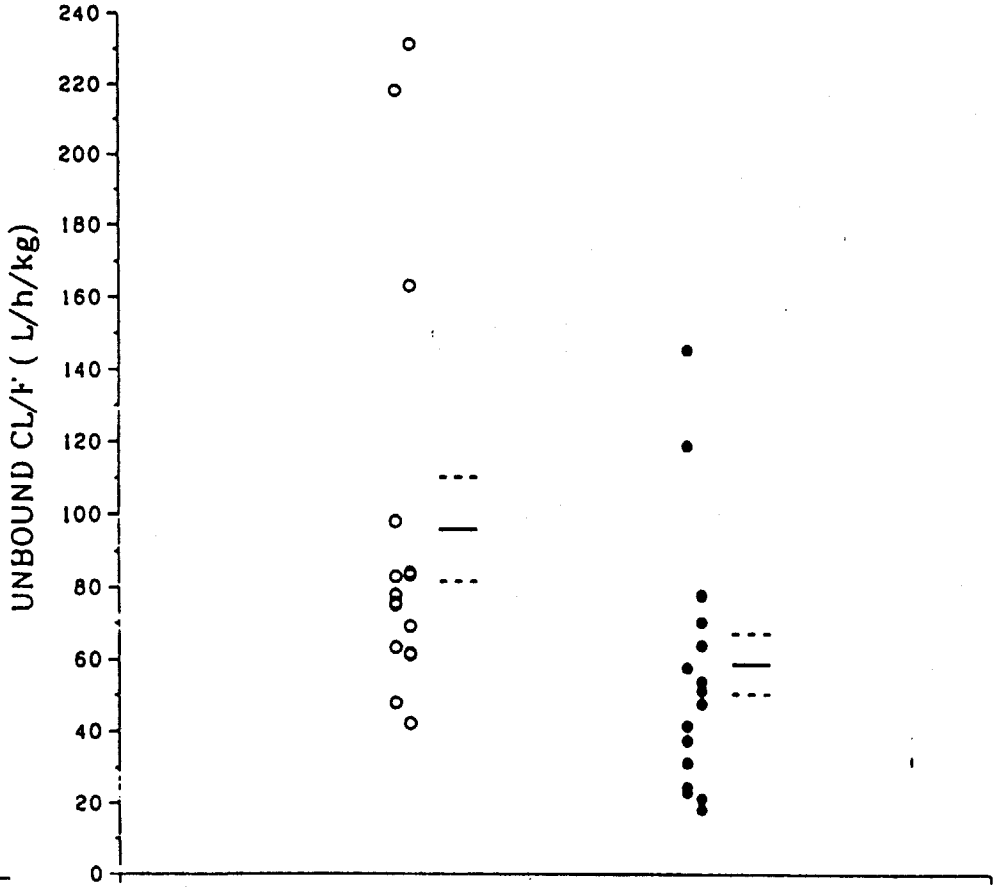


o = NORMAL
• = HEPATIC

MEAN + SE (N=16)

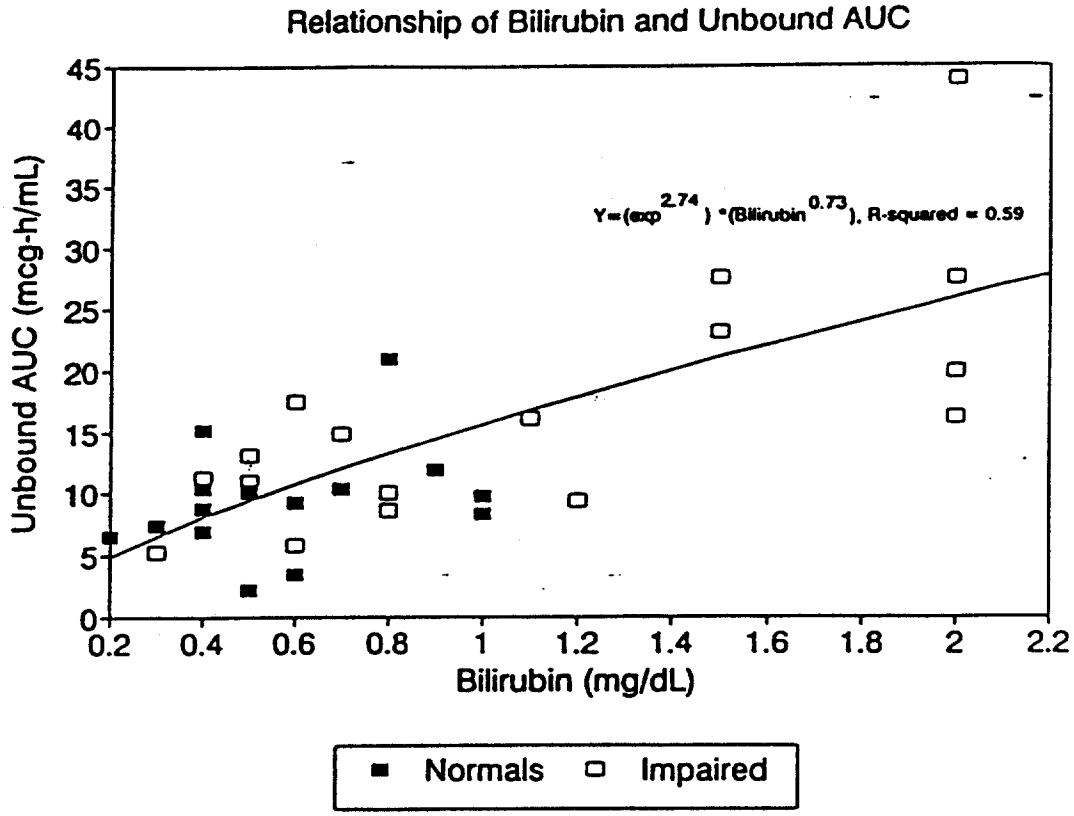
UNBOUND BROMFENAC CL/F

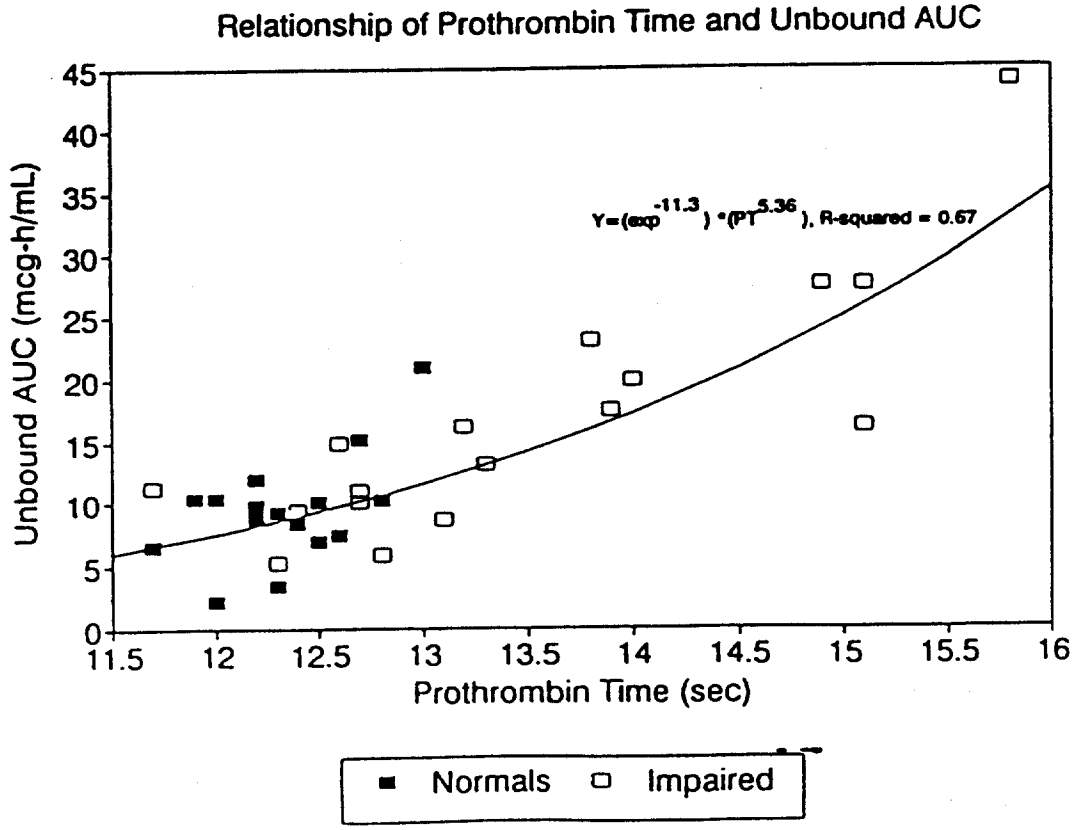
NORMAL vs. HEPATIC SUBJECTS



o = NORMAL
• = HEPATIC

MEAN + SE (N=16)





NDA/IND# 20-535/_____ Suppl/Amend.# Submission Date 29 Dec 94 Volume: 1.61-1.62
Study Type Bioavailability - clinical vs. trade Study# 792-A-119-US
Study Title A comparative bioavailability study of two oral bromfenac formulations

Clinical Investigator P. Leese MD Analytical Investigator
Site Innovex Inc Site
Lenexa, KS

Single Dose X Multiple Dose Washout Period 2 days
Cross-Over X Parallel Other Design
Fasted X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
volunteers	24*	21/3	27	19-39	73	49-95

* 27 volunteers completed study, data from first 24 was analyzed and 1 subject was excluded from final summary by outlier test

Drug Dosage Forms

Drug	TreatmentGroup	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	25 mg	capsule	24.9 mg	1TWG	
bromfenac	all	25 mg	capsule	25.1 mg	3TEV	
bromfenac	all	100 mg	capsule	99.2 mg	1VDF	
bromfenac	all	100 mg	capsule	102 mg	3TEX	

Sampling Times

Plasma(7 mL): 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 hrs post dose
Assay Method
Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

none - study done to verify that dosage forms used in clinical studies were bioequivalent to dosage form intended for market

FIGURE 1
MEAN ± SE OF BROMFENAC
PLASMA CONCENTRATIONS
IN 23 HEALTHY SUBJECTS
SINGLE 25 MG DOSE

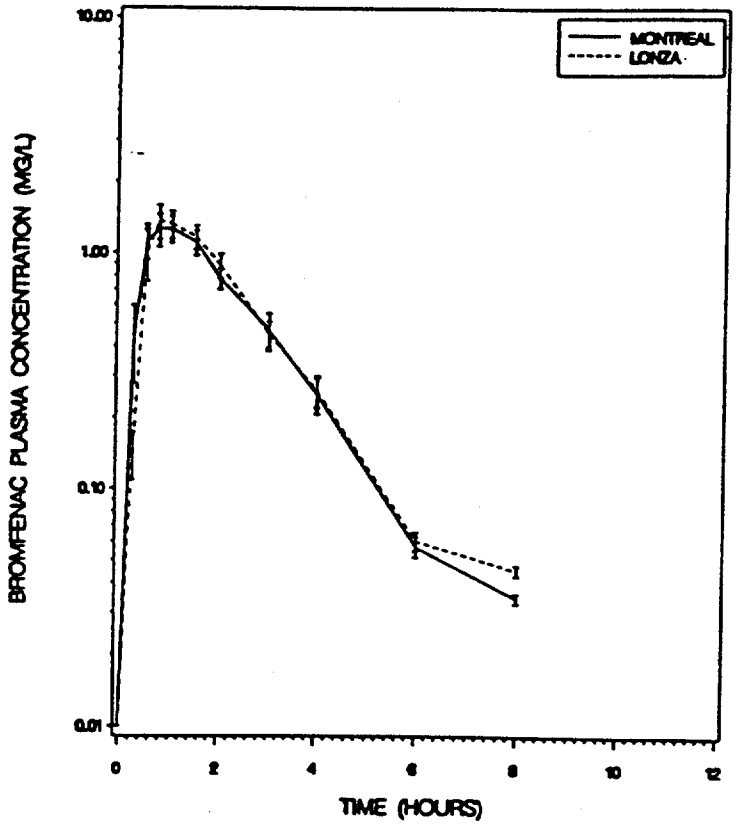


TABLE 3A - PHARMACOKINETIC PARAMETERS OF BROMFENAC IN HEALTHY SUBJECTS RECEIVING A SINGLE 25 MG DOSE

INVESTIGATOR 11902 - PHILIP LEESE . M.D

FORMULATION: MONTREAL

SUBJECT	CMAX (MG/L)	TMAX (H)	T1/2 (H)	AUCT --(MG*H/L)--	AUC	CL/F (L/H/K)	V_{ss} (L/K)	MRT (H)	λ_z (1/H)
16									
17									
18									
20									
21									
22									
23									
24									
25									
26									
27									
28									
101									
102									
103									
104									
105									
106									
107									
108									
109									
110									
111									
112									
113									
114									
115									
MEAN	1.9	1.25	1.0	3.04	3.14	0.12	0.17	2.1	0 74
S.D.	0.7	0.75	0.2	1.00	0.97	0.05	0.06	0.6	0.19
GEOMETRIC MEAN	1.8	1.06	0.9	2.89	3.00	0.12	0.16	2 0	0 74

NOTE: SUBJECTS 26, 27, 28 AND 110 WERE NOT INCLUDED IN THE SUMMARY STATISTICS

TABLE 3A - PHARMACOKINETIC PARAMETERS OF BROMFENAC IN HEALTHY SUBJECTS RECEIVING A SINGLE 25 MG DOSE

INVESTIGATOR 11902 - PHILIP LEESE . M.D

FORMULATION: LONZA

SUBJECT	CMAX (MG/L)	TMAX (H)	T1/2 (H)	AUCT --(MG*H/L)--	AUC	CL/F (L/H/K)	V_{ss} (L/K)	MRT (H)	λ_z (1/H)
16									
17									
18									
20									
21									
22									
23									
24									
25									
26									
27									
28									
101									
102									
103									
104									
105									
106									
107									
108									
109									
110									
111									
112									
113									
114									
115									
MEAN	2 2	1 24	1 1	3 19	3 27	0 12	0.18	2 1	0 74
S D	0 9	0 64	0 7	1 06	1 06	0 04	0 12	0 6	0 18
GEOMETRIC MEAN	2 0	1 10	1 0	3 01	3 10	0 11	0 16	2 1	0 70

NOTE: SUBJECTS 26, 27, 28 AND 110 WERE NOT INCLUDED IN THE SUMMARY STATISTICS

TABLE 7A - STATISTICAL COMPARISONS OF PHARMACOKINETIC PARAMETERS
IN HEALTHY SUBJECTS RECEIVING A SINGLE 25 MG DOSE OF BROMFENAC

INVESTIGATOR 11902 - PHILIP LEESE , M.D.

	CMAX (MG/L)	TMAX (H)	T1/2 (H)	AUCT --(MG*H/L)--	AUC	CL/F (L/H/K)	V_{ss} (L/K)	MRT (H)	λ_z (1/H)
MEAN	2.2	1.24	1.1	3.19	3.27	0.12	0.18	2.1	0.74
S.D.	0.9	0.64	0.7	1.06	1.06	0.04	0.12	0.6	0.18
GEOMETRIC MEAN	2.0	1.10	1.0	3.01	3.10	0.11	0.16	2.1	0.70
NTREAL									
MEAN	1.9	1.25	1.0	3.04	3.14	0.12	0.17	2.1	0.76
S.D.	0.7	0.75	0.2	1.00	0.97	0.05	0.06	0.6	0.19
GEOMETRIC MEAN	1.8	1.06	0.9	2.89	3.00	0.12	0.16	2.0	0.74

P-VALUES FROM THE CROSSOVER ANALYSIS OF VARIANCE ON LOG-TRANSFORMED PHARMACOKINETIC PARAMETERS

OURCE OF VARIATION									
EQUENCE	.48	.89	.42	.24	.26	.30	.16	.75	.42
UBJECT(SEQUENCE)	.001	.02	.35	.001	.001	.001	.10	.02	.36
ERIOD	.08	.17	.14	.24	.20	.20	.52	.81	.14
ORMULATION	.23	.81	.53	.35	.43	.43	.82	.60	.53

BIOEQUIVALENCE TESTING OF PHARMACOKINETIC PARAMETERS

	CMAX	TMAX	AUCT	AUC
OWER (%)	71	30	98	99
ATIO OF LEAST SQUARES GEOMETRIC MEANS * (%)	109	103	104	103
0% CONFIDENCE LIMITS AROUND THE RATIO OF THE GEOMETRIC MEANS * (%)	97 - 123	83 - 127	97 - 112	96 - 111
ATIO OF LEAST SQUARE ARITHMETIC MEANS	111	99	105	104
WO ONE-SIDED TESTS:				
P(R<0.8)	.001	.05	.001	.001
P(R>1.2)	.11	.04	.001	.001

BASED ON THE MEAN SQUARE ERROR AND LS MEANS FROM THE LOG-TRANSFORMED ANOVA

OTE: SUBJECTS 26, 27, 28 AND 110 WERE NOT INCLUDED IN THE SUMMARY STATISTICS OR THE ANOVA.
SUBJECT 110 WAS DELETED FROM STATISTICAL ANALYSIS BECAUSE OF A STATISTICALLY SIGNIFICANT RESIDUAL.

FIGURE 2
MEAN ± SE OF BROMFENAC
PLASMA CONCENTRATIONS
IN 23 HEALTHY SUBJECTS
SINGLE 100 MG DOSE

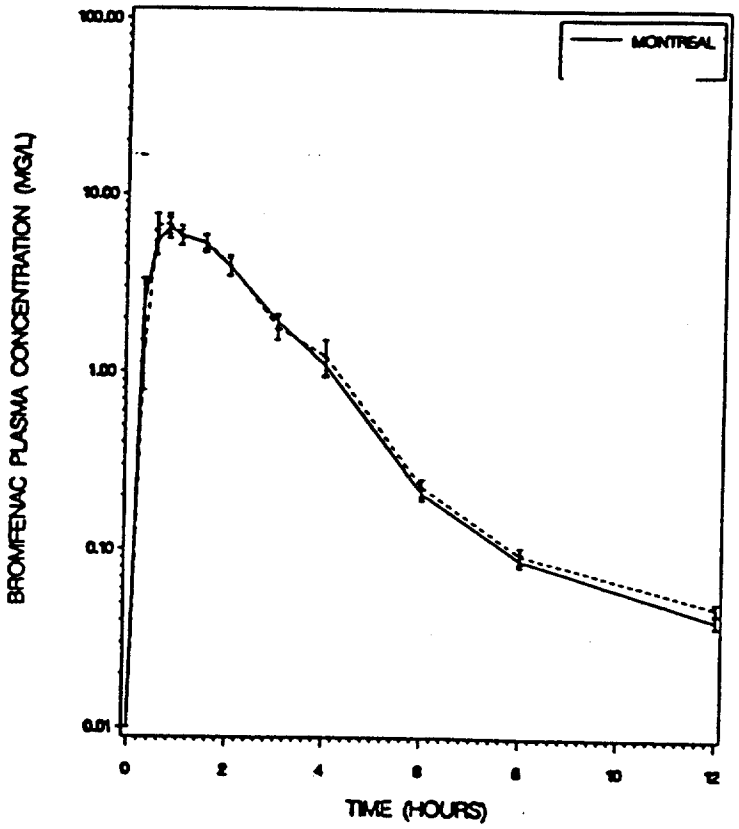


TABLE 38 - PHARMACOKINETIC PARAMETERS OF BRONFENAC IN HEALTHY SUBJECTS RECEIVING A SINGLE 100 MG DOSE

INVESTIGATOR 11902 - PHILIP LEESE . M.D.

FORMULATION: MONTREAL

SUBJECT	CMAX (MG/L)	TMAX (H)	T1/2 (H)	AUCT --(MG*H/L)--	AUC	CL/F (L/H/K)	V_{ss} (L/K)	MRT (H)	λ_z (1/H)
16									
17									
18									
20									
21									
22									
23									
24									
25									
26									
27									
28									- - -
101									
102									
103									
104									
105									
106									
107									
108									
109									
110									
111									
112									
113									
114									
115									
MEAN	9.4	1.20	1.6	15.14	15.26	0.10	0.22	2.1	0.49
S.D.	3.3	0.89	0.6	4.01	4.02	0.03	0.09	0.5	0.10
GEOMETRIC MEAN	8.9	1.04	1.5	14.67	14.79	0.09	0.21	2.0	0 46

NOTE: SUBJECTS 26, 27, 28 AND 110 WERE NOT INCLUDED IN THE SUMMARY STATISTICS

TABLE 38 - PHARMACOKINETIC PARAMETERS OF BRONFENAC IN HEALTHY SUBJECTS RECEIVING A SINGLE 100 MG DOSE

INVESTIGATOR 11902 - PHILIP LEESE . M.D.

FORMULATION: LONZA

SUBJECT	CMAX (MG/L)	TMAX (H)	T1/2 (H)	AUCT --(MG*H/L)--	AUC	CL/F (L/H/K)	V_{ss} (L/K)	MRT (H)	λ_z (1/H)
16									
17									
18									
20									
21									
22									
23									
24									
25									
26									
27									
28									
101									- - -
102									
103									
104									
105									- - -
106									
107									
108									
109									
110									
111									
112									
113									
114									
115									
MEAN	10 0	1 25	1 7	14 93	15 06	0 10	0 21	2 2	0 47
S.D.	3.7	1 02	0 6	4 29	4 33	0 04	0 06	0 7	0 17
GEOMETRIC MEAN	9 3	0 97	1 6	14 27	14 39	0 10	0 21	2 1	0 44

NOTE: SUBJECTS 26, 27, 28 AND 110 WERE NOT INCLUDED IN THE SUMMARY STATISTICS

TABLE 7B - STATISTICAL COMPARISONS OF PHARMACOKINETIC PARAMETERS
IN HEALTHY SUBJECTS RECEIVING A SINGLE 100 MG DOSE OF BROMFENAC

INVESTIGATOR 11902 - PHILIP LEESE , M.D.

		CMAX (MG/L)	TMAX (H)	T1/2 (H)	AUCT --(MG*H/L)--	AUC	CL/F (L/H/K)	V_{ss} (L/K)	MRT (H)	λ_z (1/H)
	MEAN	10.0	1.25	1.7	14.93	15.06	0.10	0.23	2.2	0.47
	S.D.	3.7	1.02	0.6	4.29	4.33	0.04	0.06	0.7	0.17
	GEOMETRIC MEAN	9.3	0.97	1.6	14.27	14.39	0.10	0.22	2.1	0.44
ORTREAL										
	MEAN	9.4	1.28	1.6	15.14	15.26	0.10	0.22	2.1	0.49
	S.D.	3.3	0.89	0.6	4.01	4.02	0.03	0.09	0.5	0.18
	GEOMETRIC MEAN	8.9	1.04	1.5	14.67	14.79	0.09	0.21	2.0	0.46

P-VALUES FROM THE CROSSOVER ANALYSIS OF VARIANCE ON LOG-TRANSFORMED PHARMACOKINETIC PARAMETERS

OURCE OF VARIATION									
EQUENCE	.61	.78	.92	.46	.46	.57	.45	.70	.92
UBJECT(SEQUENCE)	.001	.11	.001	.001	.001	.001	.001	.001	.001
ERIOD	.50	.57	.01	.29	.28	.28	.14	.70	.01
ORMULATION	.50	.69	.26	.66	.67	.67	.20	.54	.26

BIOEQUIVALENCE TESTING OF PHARMACOKINETIC PARAMETERS

	CMAX	TMAX	AUCT	AUC
OWER (%)	61	16	92	93
ATIO OF LEAST SQUARES GEOMETRIC MEANS * (%)	105	93	98	98
0% CONFIDENCE LIMITS AROUND THE RATIO OF THE GEOMETRIC MEANS * (%)	92 - 120	68 - 127	89 - 107	90 - 107
ATIO OF LEAST SQUARE ARITHMETIC MEANS	106	96	99	99
WO ONE-SIDED TESTS:				
P(R<0.8)	.001	.21	.001	.001
P(R>1.2)	.02	.13	.001	.001

BASED ON THE MEAN SQUARE ERROR AND LS MEANS FROM THE LOG-TRANSFORMED ANOVA

OTE: SUBJECTS 26, 27, 28 AND 110 WERE NOT INCLUDED IN THE SUMMARY STATISTICS OR THE ANOVA.
SUBJECT 110 WAS DELETED FROM STATISTICAL ANALYSIS BECAUSE OF A STATISTICALLY SIGNIFICANT RESIDUAL.

NDA/IND# 20-535, _____ Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.75-1.76
Study Type Drug interaction- methotrexate Study# 792-A-113-US
Study Title A pharmacokinetic evaluation of the potential interaction between bromfenac sodium (AHR-10282B) and methotrexate in patients with rheumatoid arthritis

Clinical Investigator J Doane MD Analytical Investigators
Site Sites

Single Dose Multiple Dose X Washout Period
Cross-Over X Parallel Other Design
Fasted X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers Patients X Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
RA patients	9	4/5	54	40-63	76	51-100

Drug Dosage Forms

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg q8h	capsule	49	1TBK	
methotrexate	all	5 - 15 mg q 7 days	tablets	patients supplied own medication		

Sampling Times

Plasma bromfenac: (5 mL) 0, 0.5, 1.5, 8 hrs post dose
Serum methotrexate: (7mL) 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48 hrs post dose
Urine methotrexate: 0-8, 8-16, 16-24, 24-48 hrs post dose
Assay Method

Assay Sensitivity

Assay Accuracy

Labeling Claims From Study

I. Coadministration of methotrexate has no effect on the pharmacokinetics of bromfenac.
II. Bromfenac has no effect on the pharmacokinetics of methotrexate.

FIGURE 1

PLASMA CONCENTRATIONS (MEAN AND SE) OF BROMFENAC IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING BROMFENAC WITH OR WITHOUT METHOTREXATE

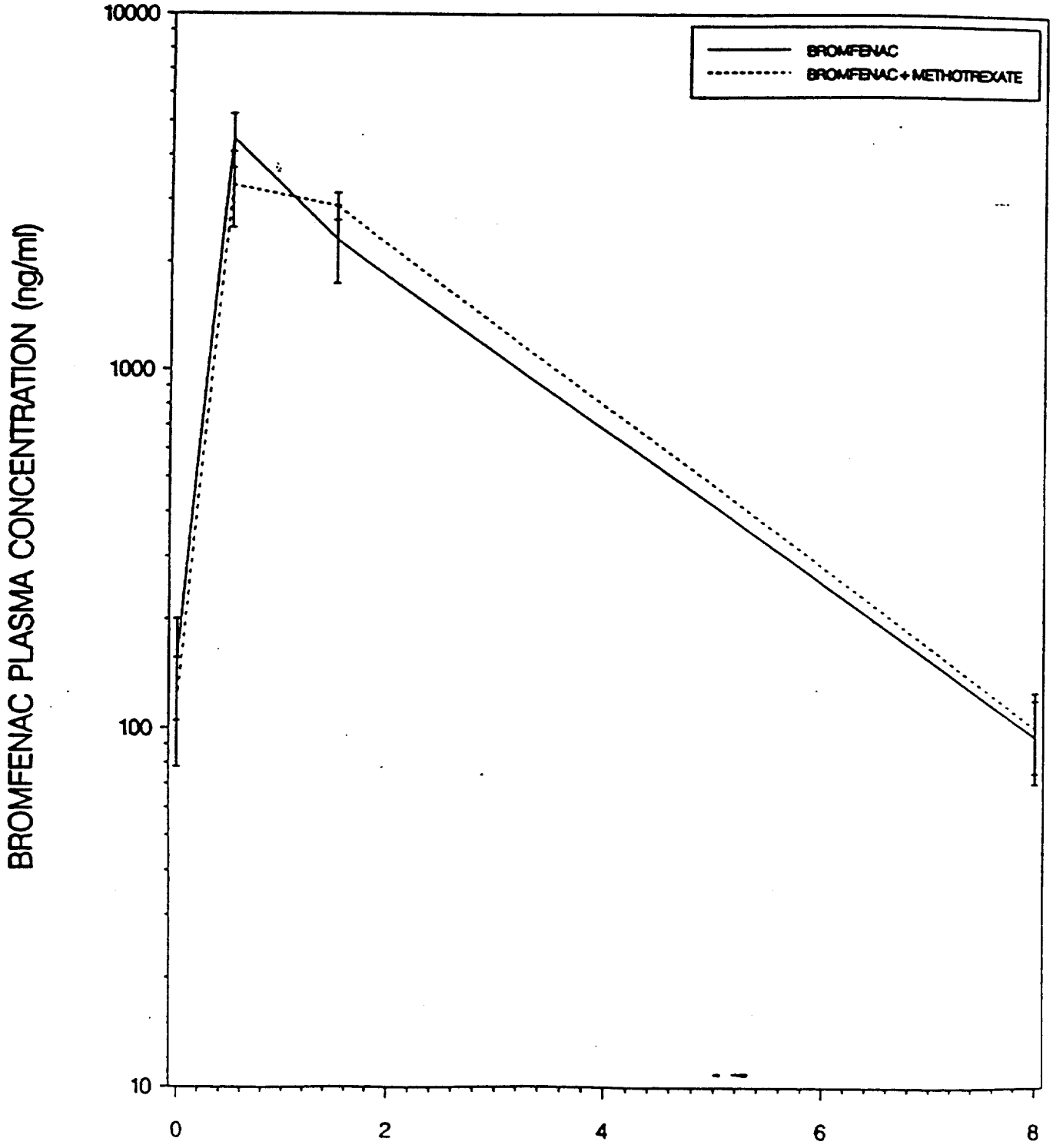


TABLE 3A - PHARMACOKINETIC PARAMETERS OF BROMFENAC IN PATIENTS RECEIVING BROMFENAC 50 MG EVERY 8 HOURS WITH OR WITHOUT THEIR REGULAR REGIMEN OF METHOTREXATE

INVESTIGATOR 11101 - J. DOWIE, M.D.

TREATMENT	SUBJECT	CMAX (MG/L)	TMAX (H)	AUC_8H (MG*H/L)	T1/2 (H)	MRT ORAL (H)	CL/F (L/H/KG)	λz (1/H)	V z/F (L/KG)	RATIO* CMAX (%)	RATIO* AUC (%)
BROMFENAC	001										
	002										
	003										
	004										
	005										
	006										
	007										
	008										
	009										
	MEAN	4.89	0.7	8.72	1.4	2.2	0.09	0.50	0.19	100.0	100.0
	S.D.	2.16	0.4	4.27	0.3	0.7	0.03	0.07	0.09	0.0	0.0
	GEOMETRIC MEAN	4.28	0.6	7.90	1.4	2.1	0.09	0.49	0.17	100.0	100.0
BROMFENAC + METHOTREXATE	001										
	002										
	003										
	004										
	005										
	006										
	007										
	008										
	009										
	MEAN	4.15	1.1	9.09	1.3	2.4	0.08	0.54	0.15	109.3	119.9
	S.D.	1.60	0.5	2.15	0.3	0.6	0.01	0.09	0.03	88.9	51.6
	GEOMETRIC MEAN	3.88	0.9	8.84	1.3	2.4	0.08	0.53	0.14	90.6	111.9

RATIO OF (BROMFENAC AND METHOTREXATE) TO (BROMFENAC)

TABLE 5A - STATISTICAL COMPARISONS OF LOG-TRANSFORMED BROMFENAC PHARMACOKINETIC PARAMETERS IN PATIENTS RECEIVING BROMFENAC 50 MG EVERY 8 HOURS WITH OR WITHOUT THEIR REGULAR REGIMEN OF METHOTREXATE

INVESTIGATOR 11301 - J. DOANE, M.D.

TREATMENT		CMAX (MG/L)	TMAX (H)	AUC_8H (MG*H/L)	T1/2 (H)	MRT ORAL (H)	CL/F (L/H/KG)	Z (1/H)	V Z/F (L/KG)
BROMFENAC									
	MEAN	4.89	0.7	8.72	1.4	2.2	0.09	0.50	0.19
	S.D.	2.16	0.4	4.27	0.3	0.7	0.03	0.07	0.09
	GEOMETRIC MEAN	4.28	0.6	7.90	1.4	2.1	0.09	0.49	0.17
BROMFENAC + METHOTREXATE									
	MEAN	4.15	1.1	9.09	1.3	2.4	0.08	0.54	0.15
	S.D.	1.60	0.5	2.15	0.3	0.6	0.01	0.09	0.03
	GEOMETRIC MEAN	3.88	0.9	8.84	1.3	2.4	0.08	0.53	0.14
P-VALUES FOR THE EFFECT OF TREATMENT FROM THE TWO-WAY ANALYSIS OF VARIANCE		.631	.081	.404	.239	.098	.404	.240	.336

BIOEQUIVALENCE TESTING OF BROMFENAC PHARMACOKINETIC PARAMETERS OBSERVED WITH OR WITHOUT METHOTREXATE

	CMAX	TMAX	AUC
POWER (%)	13	14	24
RATIO OF LEAST SQUARES GEOMETRIC MEAN (%)	91	144	112
90% LOG-TRANSFORMED CONFIDENCE LIMITS (%)	63-131	103-203	88-142
RATIO OF LEAST SQUARES ARITHMETIC MEAN (%)	85	146	104
APPROXIMATE 90% CONFIDENCE LIMITS AROUND THE RATIO OF THE ARITHMETIC MEANS (%)	59-111	103-189	79-129
THE P-VALUES FROM TWO ONE-SIDED T TESTS			
P(R<80%)	.37	.01	.06
P(R>120%)	.02	.86	.14

Bromfenac

TABLE 5A

GMR-23511

FIGURE 2

SERUM CONCENTRATIONS (MEAN AND SE) OF METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING METHOTREXATE WITH OR WITHOUT BROMFENAC

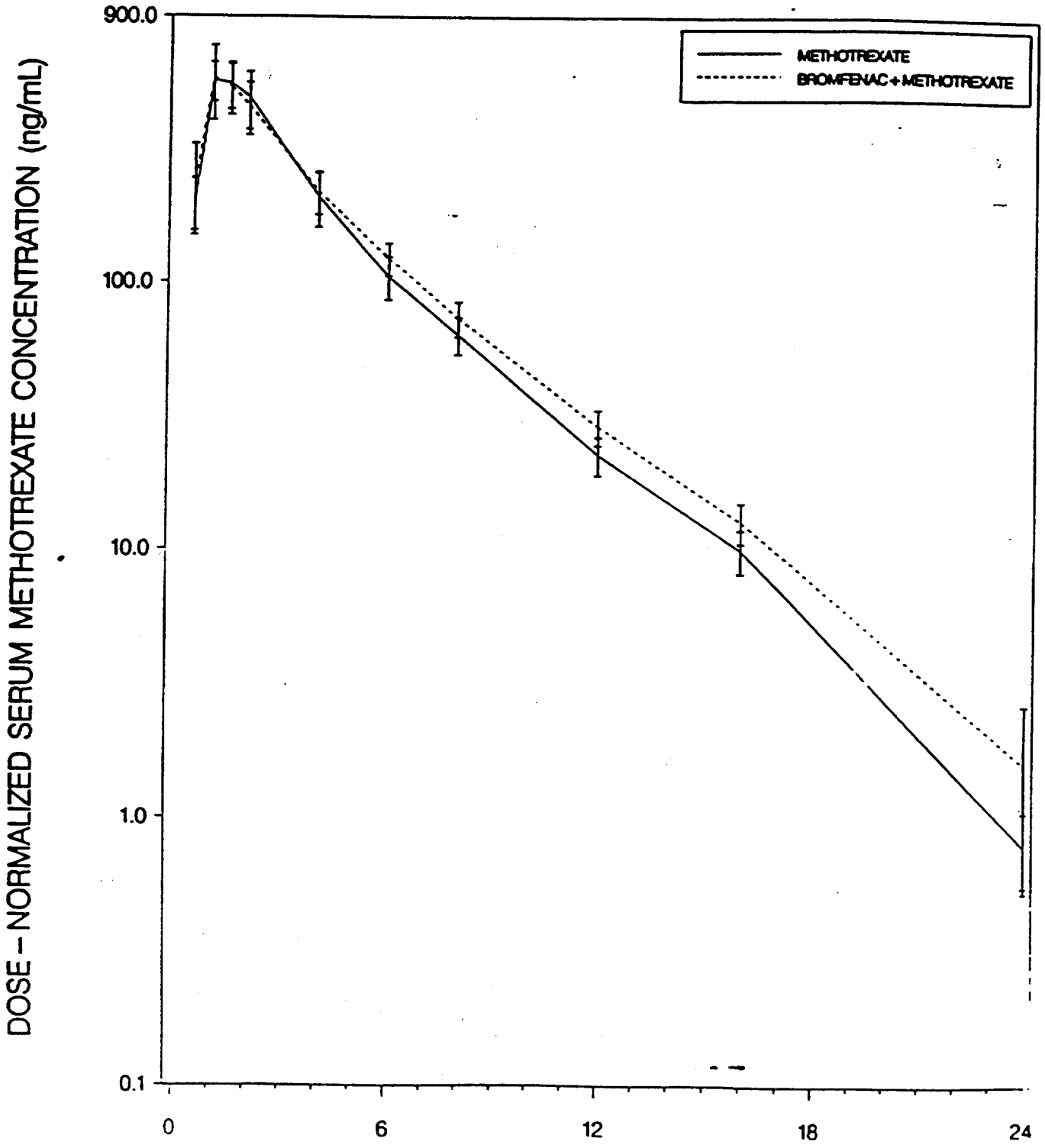


TABLE 3B - PHARMACOKINETIC PARAMETERS OF METHOTREXATE IN PATIENTS RECEIVING THEIR REGULAR REGIMEN OF METHOTREXATE WITH OR WITHOUT BROMFENAC 50 MG EVERY 8 HOURS

INVESTIGATOR 11301 - J. BRAUN, M.D.

TREATMENT	SUBJECT	CMAX (UG/L)	TMAX (H)	AUC (UG*H/L)	T1/2 (H)	MRT ORAL (H)	CL/F (L/H/KG)	Z (1/H)	V Z/F (L/KG)	CLR (ML/H/KG)	FE*F (%)	RATIO* CMAX (%)	RATIO* AUC (%)
METHOTREXATE	001												
	002												
	003												
	004												
	005												
	006												
	007												
	008												
	MEAN	287.1	1.3	1017.5	3.0	4.2	0.14	0.23	0.57	97.4	72.7	100.0	100.0
	S.D.	82.7	0.4	300.2	0.5	0.5	0.05	0.03	0.17	34.5	13.9	0.0	0.0
	GEOMETRIC MEAN	273.3	1.3	961.3	3.0	4.2	0.13	0.23	0.55	92.0	71.6	100.0	100.0
BROMFENAC + METHOTREXATE	001												
	002												
	003												
	004												
	005												
	006												
	007												
	008												
	MEAN	281.4	1.1	1082.6	3.3	4.6	0.13	0.22	0.59	79.8	57.6	99.3	106.4
	S.D.	87.2	0.4	312.1	0.8	1.0	0.06	0.05	0.19	53.0	14.8	19.7	9.3
	GEOMETRIC MEAN	266.6	1.1	1019.6	3.2	4.5	0.12	0.21	0.57	67.7	56.0	97.5	106.1

* RATIO OF (METHOTREXATE AND BROMFENAC) TO (METHOTREXATE)
NOTE: SUBJECT 9 EXCLUDED FROM STATISTICAL ANALYSIS

Bromfenac

TABLE 3B

GMR-23511

TABLE 5B - STATISTICAL COMPARISONS OF LOG-TRANSFORMED METHOTREXATE PHARMACOKINETIC PARAMETERS IN PATIENTS RECEIVING THEIR REGULAR REGIMEN OF METHOTREXATE WITH OR WITHOUT BROMFENAC 50 MG EVERY 8 HOURS

INVESTIGATOR 11301 J. DOANE, M.D.

TREATMENT		CMAX,D (UG/L)	TMAX (H)	AUC,D (UG*H/L)	T1/2 (H)	MRT ORAL (H)	CL/F (L/H/KG)	Z (1/H)	V Z/F (L/KG)	CLR (ML/H/KG)	FE*F (%)
METHOTREXATE											
	MEAN	592.3	1.3	2082.6	3.0	4.2	0.14	0.23	0.57	97.4	72.7
	S.D.	314.4	0.4	1061.5	0.5	0.5	0.05	0.03	0.17	34.5	13.9
	GEOMETRIC MEAN	500.6	1.3	1760.6	3.0	4.2	0.13	0.23	0.55	92.0	71.6
BROMFENAC + METHOTREXATE											
	MEAN	590.8	1.1	2192.4	3.3	4.6	0.13	0.22	0.59	79.8	57.6
	S.D.	340.5	0.4	1031.2	0.8	1.0	0.06	0.05	0.19	53.0	14.8
	GEOMETRIC MEAN	488.2	1.1	1867.3	3.2	4.5	0.12	0.21	0.57	67.7	56.0

P-VALUES FOR THE EFFECT OF TREATMENT FROM THE TWO-WAY ANALYSIS OF VARIANCE

.742 .392 .098 .133 .040 .098 .134 .681 .070 .088

BIOEQUIVALENCE TESTING OF METHOTREXATE PHARMACOKINETIC PARAMETERS OBSERVED WITH OR WITHOUT BROMFENAC

	CMAX,D	TMAX	AUC,D
POWER (%)	57	12	99
RATIO OF LEAST SQUARES GEOMETRIC MEAN (%)	98	83	106
90% LOG-TRANSFORMED CONFIDENCE LIMITS (%)	85-112	56-122	100-112
RATIO OF LEAST SQUARES ARITHMETIC MEAN (%)	100	86	105
APPROXIMATE 90% CONFIDENCE LIMITS AROUND THE RATIO OF THE ARITHMETIC MEANS (%)	89-111	50-122	99-111
THE P-VALUES FROM TWO ONE-SIDED T TESTS			
P(R<80%)	.01	.39	.001
P(R>120%)	.01	.06	.001

NOTE: SUBJECT 9 EXCLUDED FROM STATISTICAL ANALYSIS

Bromfenac

TABLE 5B

GMR-23511

FIGURE 3

SERUM CONCENTRATIONS (MEAN AND SE) OF 7-OH METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING METHOTREXATE WITH OR WITHOUT BROMFENAC

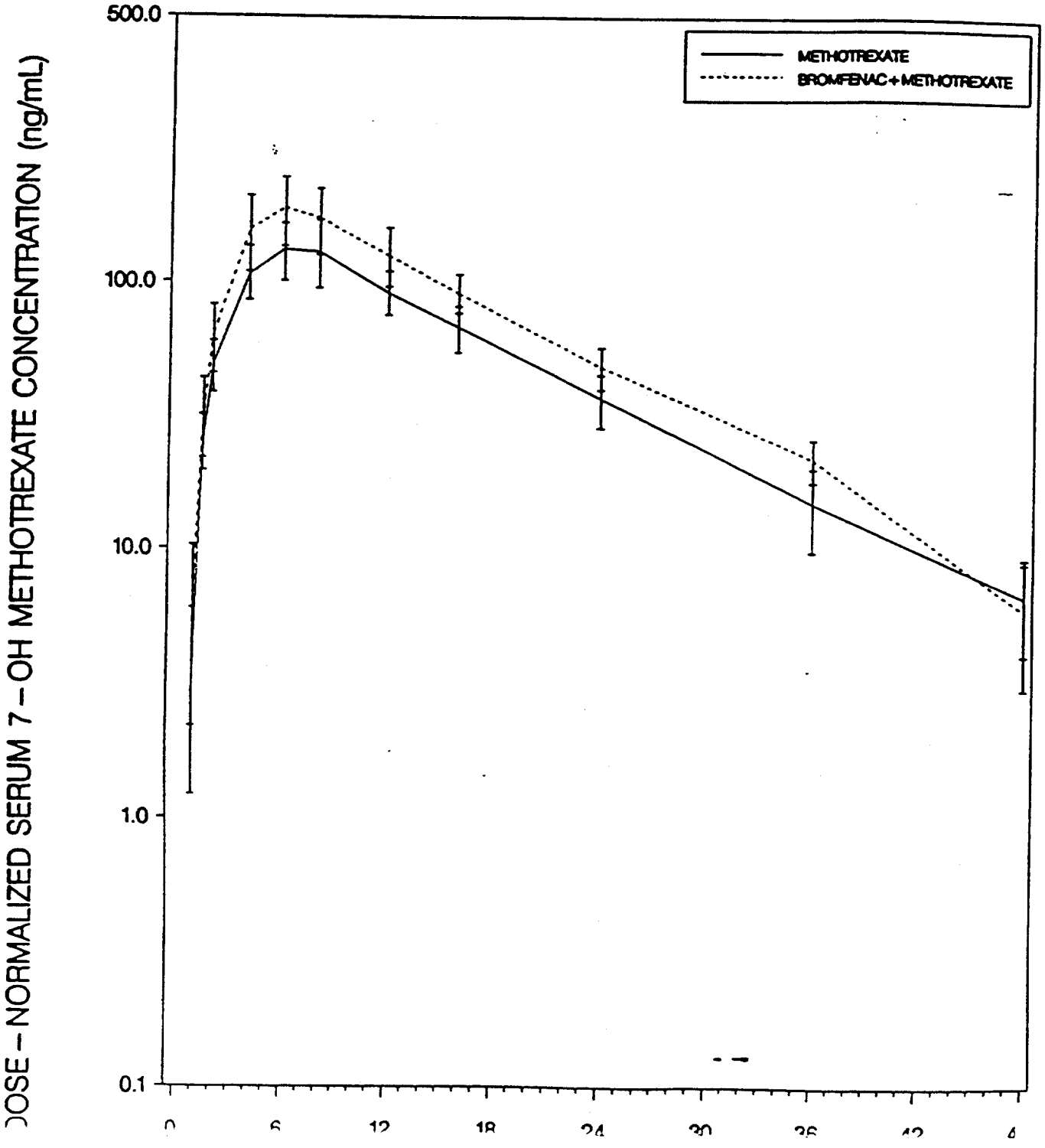


TABLE 3C - PHARMACOKINETIC PARAMETERS OF METHOTREXATE AND 7-OH METHOTREXATE IN PATIENTS RECEIVING THEIR REGULAR REGIMEN OF METHOTREXATE WITH OR WITHOUT BROMFENAC 50 MG EVERY 8 HOURS

INVESTIGATOR 11301 J. ROAIE, M.D.

TREATMENT	SUBJECT	CMAX_M (UG/L)	TMAX_M (H)	AUC_M (UG*H/L)	T1/2_M (H)	K_M (1/H)	CLR_M (ML/H/KG)	AUCM/AUCP RATIO*	RATIO* CMAX_M (%)	RATIO* AUC_M (%)
METHOTREXATE	001									
	002									
	003									
	004									
	005									
	006									
	007									
	008									
	MEAN	68.5	6.0	1241.3	10.2	0.07	12.2	1.21	100.0	100.0
	S.D.	43.4	1.1	664.1	2.8	0.02	5.5	0.55	0.0	0.0
	GEOMETRIC MEAN	59.3	5.9	1068.9	9.9	0.07	11.3	1.11	100.0	100.0
BROMFENAC + METHOTREXATE	001									
	002									
	003									
	004									
	005									
	006									
	007									
	008									
	MEAN	80.4	5.8	1575.8	10.5	0.07	10.0	1.42	124.1	133.6
	S.D.	36.7	1.3	667.3	2.6	0.02	6.7	0.44	28.0	32.6
	GEOMETRIC MEAN	71.8	5.6	1393.6	10.2	0.07	8.4	1.37	121.3	130.4

* RATIO OF (METHOTREXATE AND BROMFENAC) TO (METHOTREXATE)
+ RATIO OF (7-OH METHOTREXATE) TO (METHOTREXATE)
NOTE: SUBJECT 9 EXCLUDED FROM STATISTICAL ANALYSIS

Bromfenac

TABLE 3C

GMR-23511

TABLE 5C - STATISTICAL COMPARISONS OF LOG-TRANSFORMED 7-OH METHOTREXATE PHARMACOKINETIC PARAMETERS IN PATIENTS RECEIVING THEIR REGULAR REGIMEN OF METHOTREXATE WITH OR WITHOUT BROMFENAC 50 MG EVERY 8 HOURS

INVESTIGATOR 11301 - J. LOAINE, M.D.

TREATMENT		CMAX_M,D (UG/L)	TMAX_M (H)	AUC_M,D (UG*H/L)	T1/2_M (H)	K_M (1/H)	CLR_M (ML/H/KG)	AUCM/AUCP RATIO
METHOTREXATE								
	MEAN	132.0	6.0	2386.7	10.2	0.07	12.2	1.21
	S.D.	73.4	1.1	1191.8	2.8	0.02	5.5	0.55
	GEOMETRIC MEAN	108.5	5.9	1957.5	9.9	0.07	11.3	1.11
BROMFENAC + METHOTREXATE								
	MEAN	163.9	5.8	3102.0	10.5	0.07	10.0	1.42
	S.D.	92.4	1.3	1397.4	2.6	0.02	6.7	0.44
	GEOMETRIC MEAN	131.6	5.6	2552.3	10.2	0.07	8.4	1.37
P-VALUES FOR THE EFFECT OF TREATMENT FROM THE TWO-WAY ANALYSIS OF VARIANCE		.052	.517	.015	.555	.554	.048	.044

BIOEQUIVALENCE TESTING OF 7-OH METHOTREXATE PHARMACOKINETIC PARAMETERS OBSERVED WITH OR WITHOUT BROMFENAC

	CMAX_M,D	TMAX_M	AUC_M,D
POWER (%)	48	56	47
RATIO OF LEAST SQUARES GEOMETRIC MEAN (%)	121	95	130
90% LOG-TRANSFORMED CONFIDENCE LIMITS (%)	104-142	83-109	111-153
RATIO OF LEAST SQUARES ARITHMETIC MEAN (%)	124	96	130
APPROXIMATE 90% CONFIDENCE LIMITS AROUND THE RATIO OF THE ARITHMETIC MEANS (%)	100-149	82-110	114-145
THE P-VALUES FROM TWO ONE-SIDED T TESTS			
P(R<80%)	.01	.04	.001
P(R>120%)	.62	.01	.87

NOTE: SUBJECT 9 EXCLUDED FROM STATISTICAL ANALYSIS

Bromfenac

TABLE 5C

GMR-23511

NDA/IND# 20-535/. Suppl/Amend.# Submission Date29 Dec 94 Volume 1.73-1.74
Study Type Drug interaction- warfarin Study# 792-A-112-US
Study Title A pharmacokinetic and pharmacodynamic evaluation of the potential interaction between bromfenac and warfarin in normal volunteers

Clinical Investigator P Leese MD Analytical Investigators
Site Clinical Research Sites
Foundation-America
Lenexa, KS

Single Dose Multiple Dose X Washout Period
Cross-Over X Parallel Other Design
Fasted X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
volunteers	15	15/0	28	18-43	75	60-101

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg q8h	capsule	49	1TBK	
Coumadin®	all	5 mg*	tablets			
Coumadin®	all	2.5 mg*	tablets			

* dose adjusted to maintain prothrombin time in pharmacological range

Sampling Times

Plasma (5 mL) 0, 0.5, 1, 2, 4, 8 hrs post dose for bromfenac; 0, 1, 2, 4, 8, 12, 24 hrs post dose for warfarin
Protein Binding(5 mL) 0.5, 2, 4 hrs for bromfenac
4, 12, 24 hrs for warfarin

Assay Method

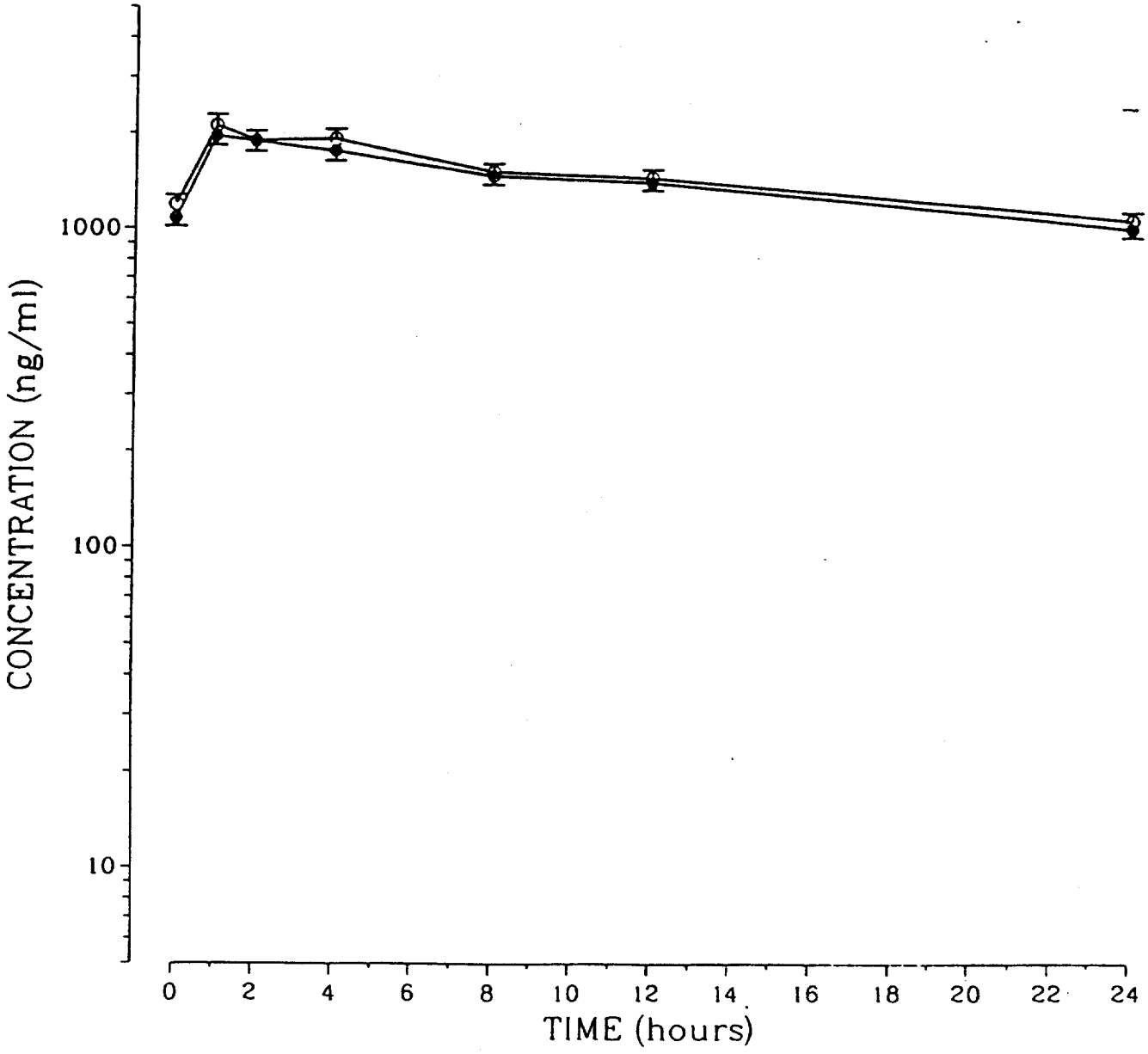
Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

I. Coadministration of bromfenac has no effect on warfarin pharmacokinetics or its anticoagulant effect.
II. Warfarin has no effect on the pharmacokinetics of bromfenac.

Figure 2A

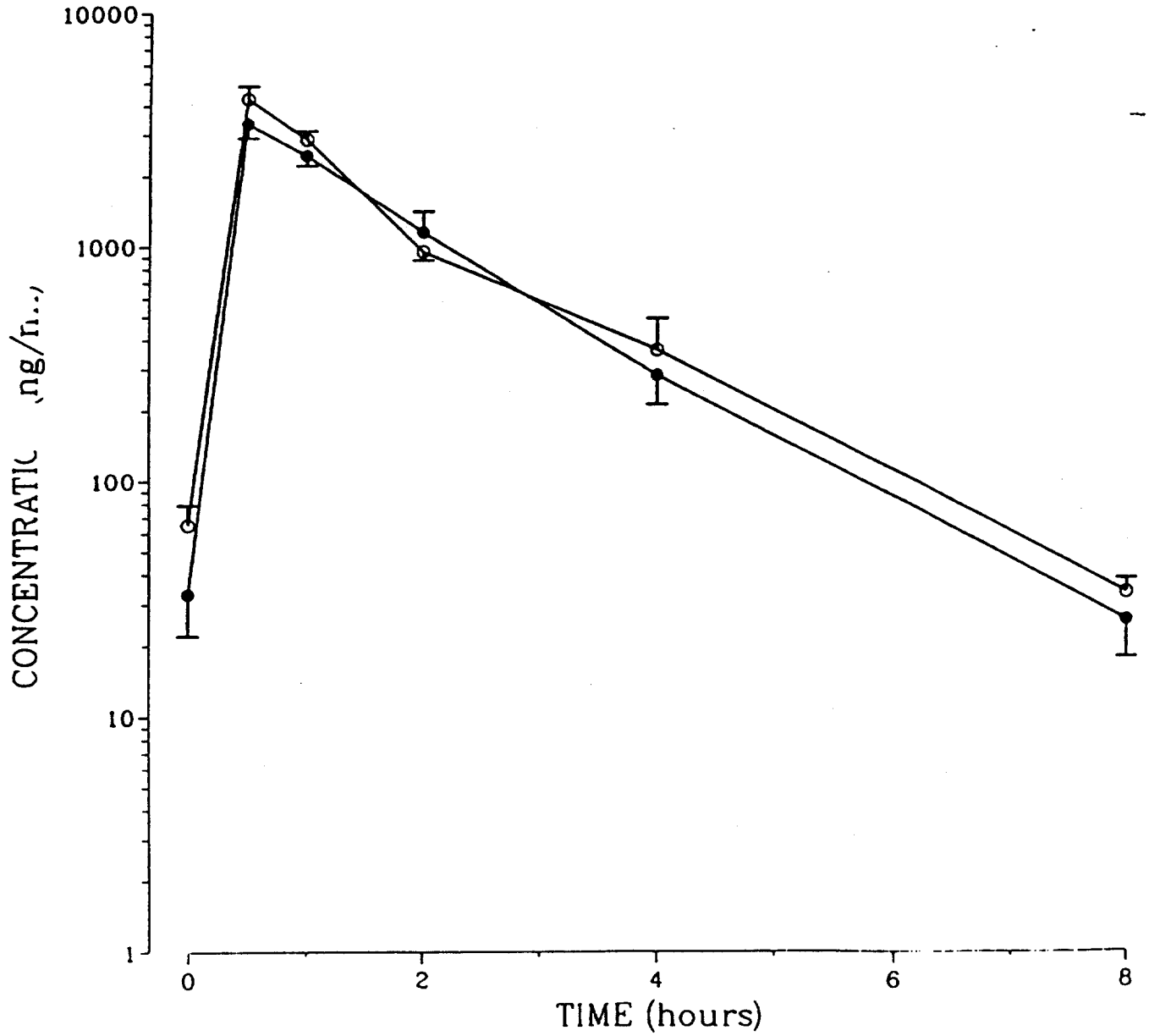
MEAN ± SE STEADY STATE PLASMA CONCENTRATIONS OF RACEMIC WARFARIN IN VOLUNTEERS WITH AND WITHOUT BROMFENAC



o = WITH BROMFENAC

Figure 1

MEAN ± SE STEADY STATE PLASMA CONCENTRATIONS OF BROMFENAC
IN VOLUNTEERS RECEIVING 50 MG DOSE EVERY 8 HOURS
WITH AND WITHOUT WARFARIN



○ – WITH WARFARIN

TABLE 3A - STEADY-STATE BROMFENAC PHARMACOKINETIC PARAMETERS IN HEALTHY MALE VOLUNTEERS WITHOUT ADMINISTRATION OF WARFARIN

INVESTIGATOR 11204 - PHILIP LEESE, M.D.

CMAX (NG/ML)	TMAX (H)	λ Z (1/H)	AUCT (NG.H/ML)	AUC 8H (NG.H/ML)	T 1/2 (H)	MRT ORAL (H)	CL/F (L/H/K)	V λ Z (L/K)	PERCENT FREE 30M	PERCENT FREE 2H	PERCENT FREE 4H	CL.U/F (L/H/K)	CMAX.U (NG/ML)

TABLE 3B - STEADY STATE BROMFENAC PHARMACOKINETIC PARAMETERS IN HEALTHY MALE VOLUNTEERS WITH ADMINISTRATION OF WARFARIN

INVESTIGATOR 11204 - PHILIP LEESE, M.D.

CMAX (NG/ML)	TMAX (H)	λ_2 (1/H)	AUCT (NG H/ML)	AUC 8H (NG.H/ML)	T 1/2 MRT ORAL (H)	CL/F (L/H/K)	$V\lambda_2$ (L/K)	RATIO• CMAX (%)	RATIO• AUC (%)	PERCENT FREE 30M	PERCENT FREE 2H	PERCENT FREE 4H	CL.U/F (L/H/K)	CMAX.U (NG/ML)

•NOTE RATIO OF (BROMFENAC + WARFARIN) TO (BROMFENAC ALONE)

TABLE 5 - STATISTICAL COMPARISONS OF STEADY-STATE BROMFENAC PHARMACOKINETIC PARAMETERS IN HEALTHY MALE VOLUNTEERS WITH AND WITHOUT ADMINISTRATION OF WARFARIN

INVESTIGATOR 11204 - PHILIP LEESE, M. D.

	CMAX (NG/ML)	TMAX (H)	λ Z (1/H)	AUCT (NG H/ML)	AUC 8H	T1/2 (H)	MRT (H)	CL/F (L/H/K)	VλZ (L/H)	<---RATIO---> CMAX (%)	AUCT (%)	<--PERCENT FREE--> 30 M (%)	2H (%)	4H (%)	CL.U/F (L/H/K)	CMAX.U (NG/ML)
WARFARIN																
	3959	0.8	0.68	5536	5621	1.07	1.68	0.141	0.21	100	100	0.16	0.16	0.14	91.1	6.32
	1290	0.4	0.16	2049	2006	0.24	0.47	0.061	0.09	0	0	0.02	0.02	0.02	34.4	2.11
IC	3724	0.7	0.66	5222	5327	1.04	1.62	0.132	0.20	100	100	0.16	0.16	0.14	86.2	5.96
RFARIN																
	4749	0 9	0 59	6254	6287	1.23	1.71	0.119	0.20	127	119	0.16	0.16	0.15	76.2	7.46
	1817	0 9	0 16	1716	1679	0.24	0.52	0.039	0.06	42	33	0.02	0.02	0.02	22.1	2.53
IC	4453	0.7	0.58	6037	6083	1.20	1.65	0.114	0.20	120	114	0.16	0.15	0.15	73.5	7.06
P-VALUES FROM THE TWO-WAY ANALYSIS OF VARIANCE																
	02	.006	17	.03	.02	.17	.006	.01	.003	-	-	.12	.08	.26	.02	005
	09	99	.08	.10	.11	.08	.74	.10	.93	-	-	.84	.67	26	.06	05

BIOEQUIVALENCE TESTING OF BROMFENAC PHARMACOKINETIC PARAMETERS OBSERVED WITH AND WITHOUT WARFARIN

	CMAX	TMAX	AUC 8H
(%)	41	31	54
OF LEAST SQUARES GEOMETRIC MEANS (%)	120	100	116
G TRANSFORMED CONFIDENCE LIMITS (%)	105 - 136	85 - 117	103 - 129
OF ARITHMETIC MEANS (%)	120	113	113
IMATE 90% CONFIDENCE LIMITS	107 - 133	86 - 140	102 - 124
VALUES FROM TWO ONE-SIDED T TESTS			
R>1 2)	001	.06	001
R<0 8)	.50	.37	21

RATIO OF (TREATMENT) TO (BROMFENAC ALONE)

TABLE 7A - STEADY-STATE WARFARIN PHARMACOKINETIC PARAMETERS IN HEALTHY MALE VOLUNTEERS WITHOUT ADMINISTRATION OF BROMFENAC (CONT'D)

INVESTIGATOR 11204 - PHILIP LEESE, M.D.

SUBJECT	CMAX (NG/ML)	TMAX (H)	AUC 24H (MCG•H/ML)	CL/F (L/H/K)	PERCENT FREE 4H	PERCENT FREE 12H	PERCENT FREE 24H	CLU (L/H/K)	CMAX,U (NG/ML)
002									
005									
006									
009									
011									
014									
016									
018									
019									
021									
022									
023									
024									
025									
026									
MEAN	2036	1.6	33.7	.00282	0.95	0.95	1.04	.29800	19.9
S.D.	528	0.8	7.7	.00063	0.13	0.15	0.13	.06956	6.1
GEOMETRIC MEAN	1971	1.4	32.8	.00275	0.94	0.94	1.03	.29044	19.0

NOTE: PERCENT FREE AT 4 HOURS IS MISSING FOR SUBJEC 11

TABLE 7B - STEADY-STATE PHARMACOKINETIC PARMAMETERS OF WARFARIN IN HEALTHY MALE VOLUNTEERS WITH ADMINISTRATION OF BROMFENAC EVERY 8 HOURS (CONT'D)

INVESTIGATOR 11204 - PHILIP LEESE, M.D.

SUBJECT	CMAX (NG/ML)	TMAX (H)	AUC 24H (MCG•H/ML)	CL/F (L/H/K)	RATIO• CMAX	RATIO• AUCT	PERCENT FREE 4H	PERCENT FREE 12H	PERCENT FREE 24H	CLU (L/H/K)	CMAX,U (NG/ML)
002											
005											
006											
009											
011											
014											
016											
018											
019											
021											
022											
023											
024											
025											
026											
MEAN	2224	1.7	35.3	.00269	110	105	0.90	0.95	1.01	.28564	20.0
S.D.	696	1.2	8.2	.00063	23	8	0.13	0.11	0.10	.07268	7.4
GEOMETRIC MEAN	2120	1.4	34.4	.00262	108	105	0.89	0.94	1.01	.27638	18.8

•NOTE: RATIO OF (WARFARIN + BROMFENAC) TO (WARFARIN ALONE)

TABLE 9 - STATISTICAL COMPARISONS OF STEADY-STATE WARFARIN PHARMACOKINETIC PARAMETERS IN HEALTHY MALE VOLUNTEERS WITH AND WITHOUT ADMINISTRATION OF BROMFENAC EVERY 8 HOURS (CONT'D)

INVESTIGATOR 11204 - PHILIP LEESE, M. D.

		CMAX (NG/ML)	TMAX (H)	AUC 24H (MCG.H/ML)	CL/F (L/H/K)	RATIO* CMAX (%)	RATIO* AUC 24H (%)	PERCENT FREE 4 H (%)	PERCENT FREE 12 H (%)	PERCENT FREE 24 H (%)	CL.U/F (L/H/K)	CMAX.U (NG/ML)
BROMFENAC	MEAN	2036	1.6	33.7	.00282	100	100	0.95	0.95	1.04	.29800	19.9
	S.D.	528	0.8	7.7	.00063	0	0	0.13	0.15	0.13	.06956	6.1
	GEOMETRIC MEAN	1971	1.4	32.8	.00275	100	100	0.94	0.94	1.03	.29044	19.0
MFENAC	MEAN	2224	1.7	35.3	.00269	110	105	0.90	0.95	1.01	.28564	20.0
	S.D.	696	1.2	8.2	.00063	23	8	0.13	0.11	0.10	.07268	7.4
	GEOMETRIC MEAN	2120	1.4	34.4	.00262	108	105	0.89	0.94	1.01	.27638	18.8
P-VALUES FROM THE TWO-WAY ANALYSIS OF VARIANCE												
SUBJECT		.001	.91	.001	.001	-	-	.36	.001	.02	001	.002
TREATMENT		.17	.84	.02	.02	-	-	.37	.91	.46	.14	.70

BIOEQUIVALENCE TESTING OF WARFARIN PHARMACOKINETIC PARAMETERS OBSERVED WITH AND WITHOUT BROMFENAC

	CMAX	TMAX	AUC 24H
	91	12	99
LEAST SQUARES GEOMETRIC MEANS (%)	108	95	105
TRANSFORMED CONFIDENCE LIMITS (%)	100 - 115	71 - 128	102 - 107
ARITHMETIC MEANS (%)	109	104	105
ATE 90% CONFIDENCE LIMITS (%)	101 - 117	67 - 141	102 - 108
LUES FROM TWO ONE-SIDED T TESTS			
1.2)	.001	.20	.001
0.8)	.05	.29	.001

ATIO OF (TREATMENT) TO (WARFARIN ALONE).

TABLE 9 - STATISTICAL COMPARISONS OF STEADY-STATE WARFARIN PHARMACOKINETIC PARAMETERS IN HEALTHY MALE VOLUNTEERS WITH AND WITHOUT ADMINISTRATION OF BROMFENAC EVERY 8 HOURS

INVESTIGATOR 11204 - PHILIP LEESE, M. D.

		CMAX (NG/ML)	TMAX (H)	AUC 24H (MCG.H/ML)	CL/F (L/H/K)	RATIO* CMAX (%)	RATIO* AUC 24H (%)
R ISOMER							
WITHOUT BROMFENAC	MEAN	1174	1.6	20.5	.00471	100	100
	S.D.	330	0.8	5.6	.00109	0	0
	GEOMETRIC MEAN	1126	1.4	19.6	.00459	100	100
WITH BROMFENAC	MEAN	1349	2.1	22.9	.00423	115	112
	S.D.	452	2.0	6.4	.00106	24	8
	GEOMETRIC MEAN	1276	1.6	21.9	.00411	113	112
P-VALUES FROM THE TWO-WAY ANALYSIS OF VARIANCE							
	SUBJECT	.001	.94	.001	.001	-	-
	TREATMENT	.03	.73	.001	.001	-	-

BIOEQUIVALENCE TESTING OF WARFARIN PHARMACOKINETIC PARAMETERS OBSERVED WITH AND WITHOUT BROMFENAC

	CMAX	TMAX	AUC 24H
	92	10	99
EAST SQUARES GEOMETRIC MEANS (%)	113	110	112
ANSFORMED CONFIDENCE LIMITS (%)	106 - 121	77 - 156	109 - 115
RITHMETIC MEANS (%)	115	133	112
E 90% CONFIDENCE LIMITS (%)	106 - 124	80 - 187	109 - 115
ES FROM TWO ONE-SIDED T TESTS			
2)	.001	.10	.001
8)	.22	.63	.001

*NOTE. RATIO OF (TREATMENT) TO (WARFARIN ALONE).

Bromfenac

Protocol 792-A-112-US
Table 9

GMR-23253

TABLE 9 - STATISTICAL COMPARISONS OF STEADY-STATE WARFARIN PHARMACOKINETIC PARAMETERS IN HEALTHY MALE VOLUNTEERS WITH AND WITHOUT ADMINISTRATION OF BROMFENAC EVERY 8 HOURS (CONT'D)

INVESTIGATOR 11204 - PHILIP LEESE, M. D.

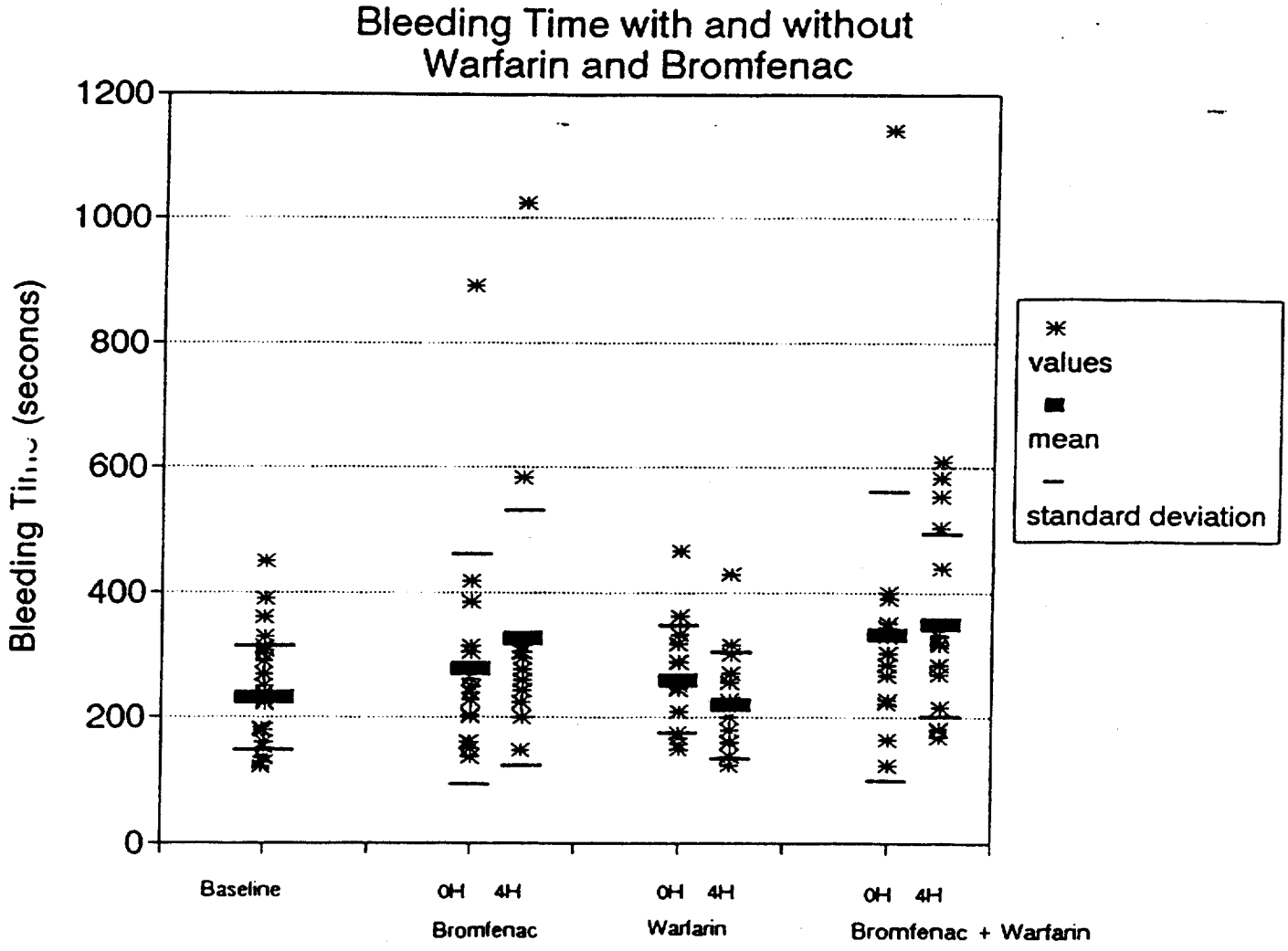
		CMAX (NG/ML)	TMAX (H)	AUC 24H (MCG.H/ML)	CL/F (L/H/K)	RATIO* CMAX (%)	RATIO* AUC 24H (%)
S ISOMER							
WITHOUT BROMFENAC	MEAN	863	1.5	13.2	.00719	100	100
	S.D.	216	0.5	2.7	.00183	0	0
	GEOMETRIC MEAN	840	1.4	13.0	.00694	100	100
WITH BROMFENAC	MEAN	879	1.5	12.5	.00763	102	95
	S.D.	259	1.1	2.4	.00191	22	9
	GEOMETRIC MEAN	843	1.3	12.3	.00736	100	94
	P-VALUES FROM THE TWO-WAY ANALYSIS OF VARIANCE						
	SUBJECT	.001	.82	.001	.001	-	-
	TREATMENT	.96	.61	.02	.02	-	-

BIOEQUIVALENCE TESTING OF WARFARIN PHARMACOKINETIC PARAMETERS OBSERVED WITH AND WITHOUT BROMFENAC

	CMAX	TMAX	AUC 24H
	90	16	99
LEAST SQUARES GEOMETRIC MEANS (%)	100	91	94
TRANSFORMED CONFIDENCE LIMITS (%)	93 - 108	72 - 116	91 - 97
ARITHMETIC MEANS (%)	102	100	94
TE 90% CONFIDENCE LIMITS (%)	94 - 109	69 - 131	91 - 97
UES FROM TWO ONE-SIDED T TESTS			
2)	.001	.20	.001
.8)	.003	.20	.001

*NOTE RATIO OF (TREATMENT) TO (WARFARIN ALONE).

Figure 7



NDA/IND# 20-535/_ _ _ _ Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.71
Study Type Drug interaction - cimetidine Study# 792-A-110-US
Study Title A pharmacokinetic evaluation of the potential interaction between bromfenac and cimetidine in normal volunteers

Clinical Investigator	Richard Fruncillo MD,PhD	Analytical Investigators
Site	Clinical Pharmacology Unit	Sites
	Graduate Hospital	
	Philadelphia, PA	

Single Dose Multiple Dose X Washout Period
Cross-Over X Parallel Other Design
Fasted X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
volunteers	24	24/0	28	18-45	77	56-98

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg q8h	capsule	49.8 mg	OVTF	
cimetidine	all	400 mg q12h	tablets			

Sampling Times

Plasma (7 mL) 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 hrs postdose
Urine 0-2, 2-4, 4-8, 8-24 hrs postdose (bromfenac not analyzed)
Assay Method

Assay Sensitivity

Assay Accuracy

Labeling Claims From Study

I. The concomitant administration of cimetidine caused a moderate increase in bromfenac concentrations. The clearance of bromfenac was decreased by 17% in subjects taking cimetidine.
II. Bromfenac has no effect on the pharmacokinetics of cimetidine.

FIGURE 1
Mean Bromfenac Plasma Concentrations in Healthy Male Volunteers Receiving Bromfenac 50 mg Every 8 Hours With and Without Cimetidine 400 mg Every 12 Hours

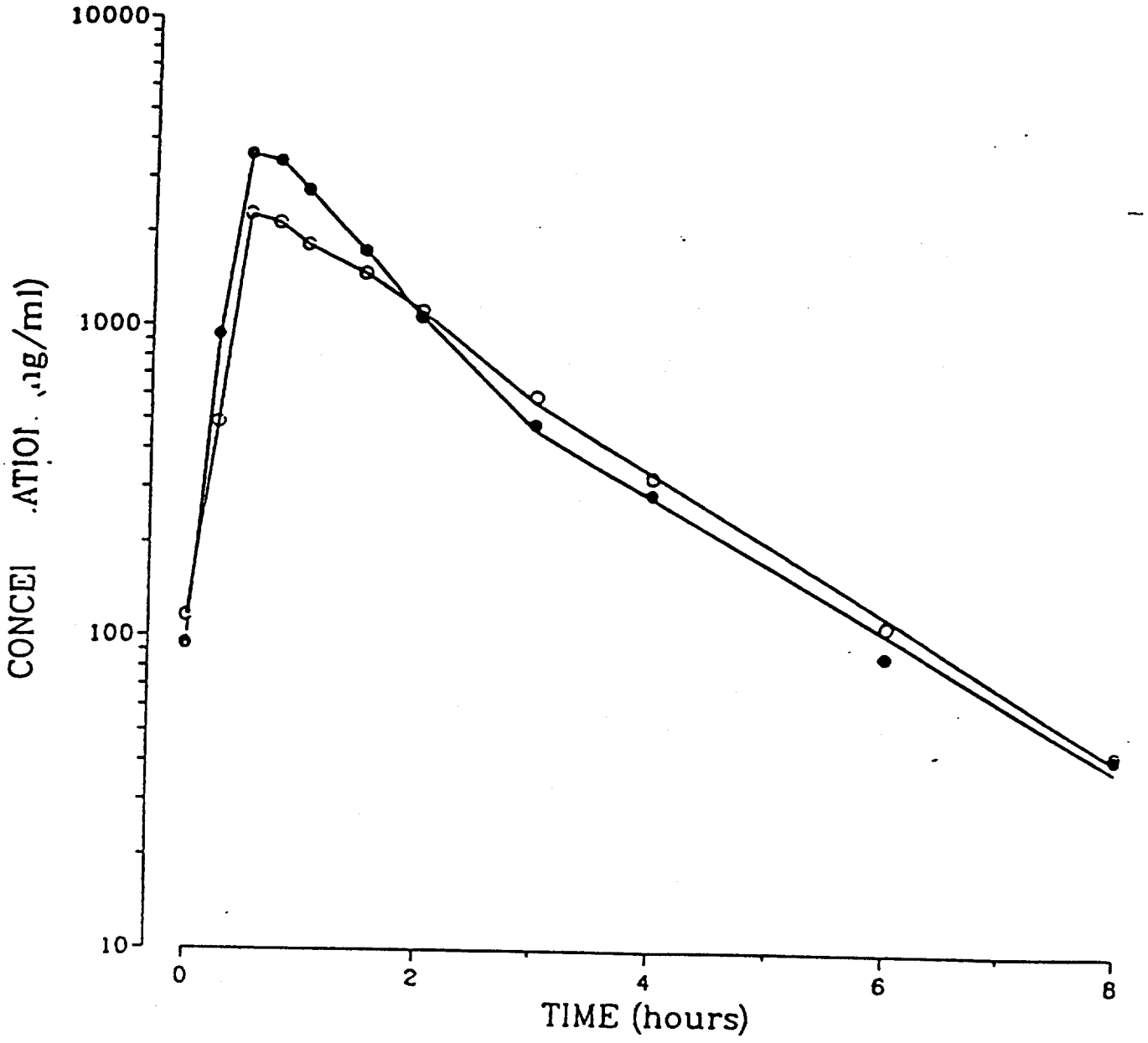


TABLE 3A - PHARMACOKINETIC PROFILE OF BROMFENAC IN HEALTHY MALE VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 8 HOURS WITH AND WITHOUT CIMETIDINE 400 MG EVERY 12 HOURS

INVESTIGATOR #11004 - RICHARD J. FRUNCILLO M.D., PH.D.

TREATMENT: BROMFENAC

SUBJECT	CMAX (MCG/ML)	TMAX (H)	λ_z (1/H)	AUCT (MCG*H/ML)	T1/2 (H)	MRT (H)	CLW/F (L/H/K)	$V_{\lambda z}$/F (L/K)	****RATIO OF**** TREATMENT **TO BROMFENAC** CMAX (%)	AUCT (%)
001										
002										
003										
004										
005										
006										
007										
008										
009										
010										
011										
012										
013										
014										
015										
016										
017										
018										
019										
020										
021										
022										
023										
024										
MEAN	2.78	0.91	0.52	4.73	1.5	2.12	0.158	0.34	100	100
S.D.	0.95	0.61	0.15	1.97	0.6	0.87	0.053	0.20	0	0
GEOMETRIC MEAN	2.61	0.78	0.50	4.40	1.4	2.02	0.149	0.30	100	100

Bromfenac

Protocol 792A-110-US

GMR-21864

TABLE 3A · PHARMACOKINETIC PROFILE OF BROMFENAC IN HEALTHY MALE VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 8 HOURS WITH AND WITHOUT CIMETIDINE 400 MG EVERY 12 HOURS (CONT'D)

INVESTIGATOR #11004 · RICHARD J. FRUNCILLO M.D., PH.D.

TREATMENT: BROMFENAC + CIMETIDINE

SUBJECT	CMAX (MCG/ML)	TMAX (H)	λz (1/H)	AUCT (MCG·H/ML)	T1/2 (H)	MRT (H)	CLW/F (L/H/K)	Vλz/F (L/K)	••••RATIO OF•••• TREATMENT ••TO BROMFENAC•• CMAX (%)	AUCT (%)
001										
002										
003										
004										
005										
006										
007										
008										
009										
010										
011										
012										
013										
014										
015										
016										
017										
018										
019										
020										
021										
022										
023										
024										
MEAN	4.43	0.74	0.47	5.71	1.6	1.81	0.131	0.30	184	127
S.D.	1.45	0.35	0.10	2.23	0.3	0.30	0.049	0.13	119	42
GEOMETRIC MEAN	4.20	0.67	0.46	5.33	1.5	1.79	0.123	0.27	161	121

TABLE 5A - STATISTICAL COMPARISONS OF BROMFENAC PHARMACOKINETIC PARAMETERS IN HEALTHY MALE VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 8 HOURS WITH AND WITHOUT CIMETIDINE 400 MG EVERY 12 HOURS

INVESTIGATOR 11004 - RICHARD FRUNCILLO, M.D., PH.D.

TREATMENT		CMAX (MCG/ML)	TMAX (H)	λz (1/HR)	AUCT (MCG*HR/ML)	T1/2 (H)	MRT (H)	CLW/F (L/H/K)	$V\lambda z/F$ (L/K)
BROM. #	MEAN	2.78	0.91	0.52	4.73	1.5	2.12	0.158	0.34
	S.D.	0.95	0.61	0.15	1.97	0.6	0.87	0.053	0.20
	GEOMETRIC MEAN	2.61	0.78	0.50	4.40	1.4	2.02	0.149	0.30
BROM. + CIMET. #	MEAN	4.43	0.74	0.47	5.71	1.6	1.81	0.131	0.30
	S.D.	1.45	0.35	0.10	2.23	0.3	0.30	0.049	0.13
	GEOMETRIC MEAN	4.20	0.67	0.46	5.33	1.5	1.79	0.123	0.27

P-VALUES FROM AN ANOVA FOR A TWO-PERIOD CROSSOVER DESIGN

SOURCE OF VARIATION								
SEQUENCE	.53	.45	.07	.98	.07	.31	.68	.32
SUBJECT WITHIN SEQUENCE	.30	.52	.27	<.001	.48	.21	<.001	.40
TREATMENT	<.001	.24	.13	.01	.64	.08	.006	.38
PERIOD	.12	.02	.96	.91	.79	.87	.68	.76
STATISTICAL POWER	.35	.23	-	.73	-	-	-	-
UNTRANSFORMED TWO ONE-SIDED TESTS								
$P(R \leq 0.8)$	<.001	.46	-	<.001	-	-	-	-
$P(R \geq 1.2)$	>.99	.01	-	.54	-	-	-	-
RATIO OF ARITHMETIC MEANS AND LOCKE'S CONFIDENCE LIMITS								
RATIO OF MEANS (%)	160	82	-	121	-	-	-	-
95% C.L.	132-193	59-117	-	105 - 139	-	-	-	-
90% C.L.	136-186	62-110	-	108 - 136	-	-	-	-
GEOMETRIC MEAN RATIO AND ORDINARY CONFIDENCE LIMITS								
MEAN RATIO (%)	161	87	-	121	-	-	-	-
95% C.L.	130-199	66-113	-	106 - 138	-	-	-	-
90% C.L.	135-192	70-108	-	109 - 135	-	-	-	-

BROM - BROMFENAC 50 MG EVRY 8 HOURS
BROM + CIMET - BROMFENAC 50 MG EVERY 8 HOURS + CIMETIDINE 400 MG EVERY 12 HOURS

Bromfenac
Protocol 792A-110-US
GMR-2186

FIGURE 2
Mean Cimetidine Plasma Concentrations in Healthy Male Volunteers Receiving Cimetidine 400 mg Every 12 Hours With and Without Bromfenac 50 mg Every 8 Hours

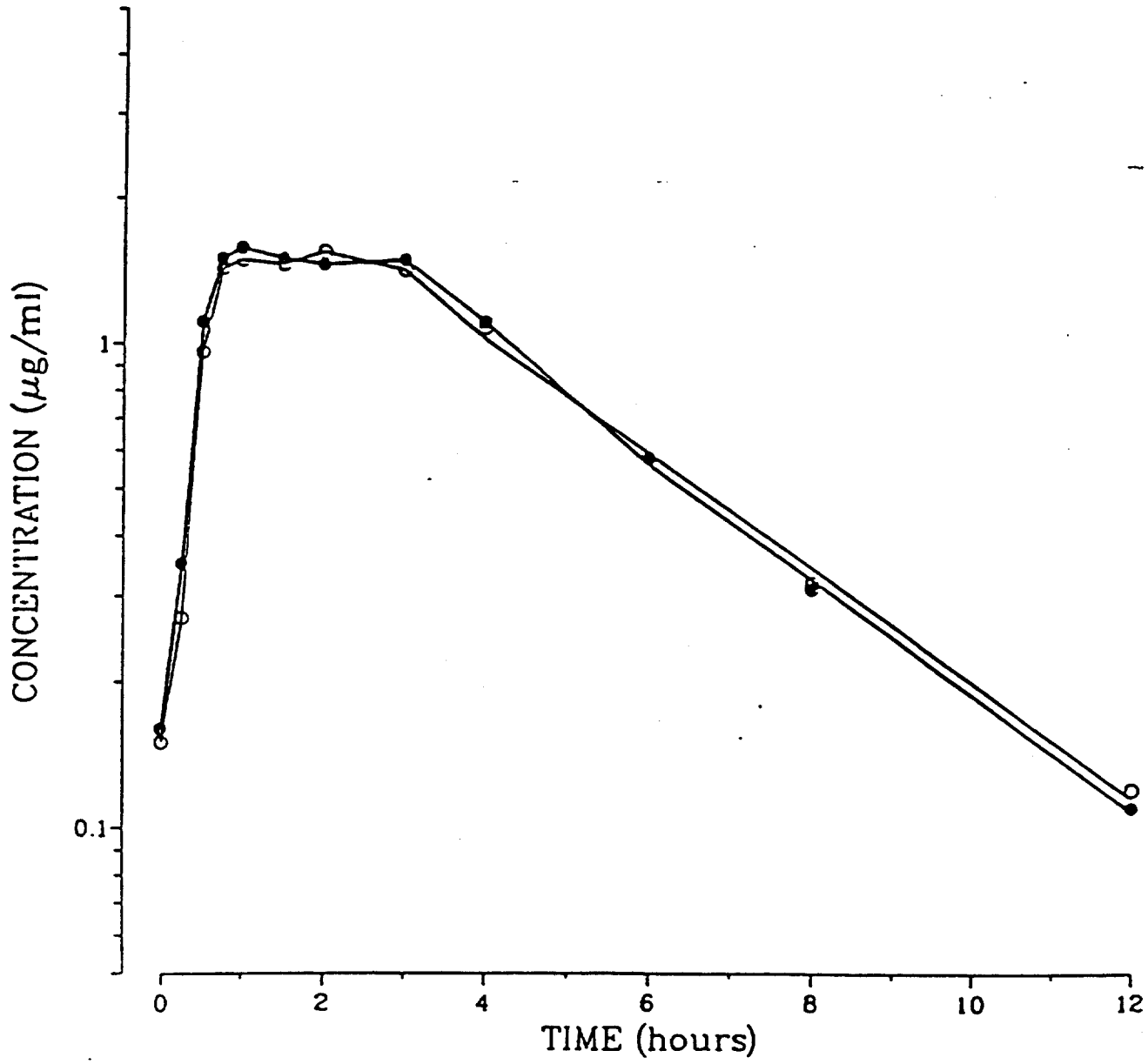


TABLE 38 - PHARMACOKINETIC PROFILE OF CIMETIDINE IN HEALTHY MALE VOLUNTEERS RECEIVING CIMETDIDNE 400 MG EVERY 12 HOURS WITH AND WITHOUT BROMFENAC 50 MG EVERY 8 HOURS

INVESTIGATOR #11004 - RICHARD J. FRUNCILLO M.D., PH.D.

TREATMENT: CIMETIDINE

SUBJECT	CMAX (MCG/ML)	TMAX (H)	λZ (1/H)	AUCT (MCG•H/ML)	T1/2 (H)	MRT (H)	CLW/F (L/H/K)	VλZ/F (L/K)	CLR (L/H)	FE (%)	••••RATIO OF•••• TREATMENT ••TO CIMETIDINE• CMAX (%)	AUCT (%)
001												
002												
003												
004												
005												
006												
007												
008												
009												
010												
011												
012												
013												
014												
015												
016												
017												
018												
019												
020												
021												
022												
023												
024												
MEAN	1.98	1.52	0.26	8.33	2.8	4.64	0.658	2.64	24.19	0.50	100	100
S.D.	0.53	0.84	0.06	1.53	0.9	0.73	0.175	1.14	4.67	0.10	0	0
GEOMETRIC MEAN	1.92	1.30	0.26	8.20	2.7	4.59	0.639	2.48	.	.	100	100

Bromfenac

Protocol 792A-110-US

GMR-21864

TABLE 38 - PHARMACOKINETIC PROFILE OF CIMETIDINE IN HEALTHY MALE VOLUNTEERS RECEIVING CIMETDIDNE 400 MG EVERY 12 HOURS WITH AND WITHOUT BROMFENAC 50 MG EVERY 8 HOURS (CONT'D)

INVESTIGATOR #11004 - RICHARD J. FRUNCILLO M.D., PH.D.

TREATMENT: BROMFENAC + CIMETIDINE

SUBJECT	CMAX (MCG/ML)	TMAX (H)	λz (1/H)	AUCT (MCG•H/ML)	T1/2 (H)	MRT (H)	CLW/F (L/H/K)	VλZ/F (L/K)	CLR (L/H)	FE (%)	••••RATIO OF•••• TREATMENT ••TO CIMETIDINE• CMAX (%)	AUCT (%)
001												
002												
003												
004												
005												
006												
007												
008												
009												
010												
011												
012												
013												
014												
015												
016												
017												
018												
019												
020												
021												
022												
023												
024												
MEAN	1.94	1.66	0.27	8.52	2.7	4.46	0.633	2.49	23.18	0.48	102	104
S.D.	0.43	1.10	0.05	1.35	0.7	0.63	0.118	0.91	6.59	0.12	27	15
GEOMETRIC MEAN	1.90	1.35	0.26	8.42	2.6	4.42	0.622	2.36	.	.	99	103

Bromfenac

Protocol 792A-110-US

GMR-2184

TABLE 58 - STATISTICAL COMPARISONS OF CIMETIDINE PHARMACOKINETIC PARAMETERS IN HEALTHY MALE VOLUNTEERS RECEIVING CIMETIDINE 400 MG EVERY 12 HOURS WITH AND WITHOUT BROMFENAC 50 MG EVERY 8 HOURS

INVESTIGATOR 11004 - RICHARD FRUNCILLO, M.D., PH.D.

TREATMENT		CMAX (MCG/ML)	TMAX (H)	λz (H)	AUCT (MCG*HR/ML)	T1/2 (H)	MRT (H)	CLW/F (L/H/K)	$V_{\lambda z}$/F (L/K)
CIMET. #	MEAN	1.98	1.52	0.26	8.33	2.8	4.64	0.658	2.64
	S.D.	0.53	0.84	0.06	1.53	0.9	0.73	0.175	1.14
	GEOMETRIC MEAN	1.92	1.30	0.26	8.20	2.7	4.59	0.639	2.48
BROM. + CIMET. #	MEAN	1.94	1.66	0.27	8.52	2.7	4.46	0.633	2.49
	S.D.	0.43	1.10	0.05	1.35	0.7	0.63	0.118	0.91
	GEOMETRIC MEAN	1.90	1.35	0.26	8.42	2.6	4.42	0.622	2.36

P-VALUES FROM AN ANOVA FOR A TWO-PERIOD CROSSOVER DESIGN

SOURCE OF VARIATION								
SEQUENCE	.08	.44	.14	.09	.10	.09	.26	.07
SUBJECT WITHIN SEQUENCE	.003	.24	.02	<.001	.17	<.001	<.001	.003
TREATMENT	.68	.61	.71	.37	.60	.29	.27	.43
PERIOD	.24	.41	.62	.77	.71	.12	.64	.51
STATISTICAL POWER	.99	.18	-	1.00	-	-	-	-
UNTRANSFORMED TWO ONE-SIDED TESTS								
P(R≤0.8)	<.001	.05	-	<.001	-	-	-	-
P(R≥1.2)	<.001	.26	-	<.001	-	-	-	-
RATIO OF ARITHMETIC MEANS AND LOCKE'S CONFIDENCE LIMITS								
RATIO OF MEANS (%)	98	109	-	102	-	-	-	-
95% C.L.	89-108	76-152	-	97-108	-	-	-	-
90% C.L.	91-106	81-144	-	98-107	-	-	-	-
GEOMETRIC MEAN RATIO AND ORDINARY CONFIDENCE LIMITS								
MEAN RATIO (%)	99	104	-	103	-	-	-	-
95% C.L.	89-110	73-147	-	97-109	-	-	-	-
90% C.L.	91-108	78-139	-	98-108	-	-	-	-

CIMET - CIMETIDINE 400 MG EVERY 12 HOURS
BROM + CIMET - BROMFENAC 50 MG EVERY 8 HOURS + CIMETIDINE 400 MG EVERY 12 HOURS

Bromfenac

Protocol 792A-110-US

GMR-21864

BEST POSSIBLE COPY

NDA/IND# 20-535. Suppl/Amend.# Submission Date29 Dec 94 Volume 1.77-1.79
Study Type Drug interaction- phenytoin Study# 792-A-114-US
Study Title A pharmacokinetic and evaluation of the potential interaction between bromfenac and phenytoin in normal subjects

Clinical Investigator W. Keane MD Analytical Investigator
Site Drug Evaluation Unit Site
Minneapolis, MN

Single Dose Multiple Dose X Washout Period
Cross-Over X Parallel Other Design
Fasted X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
volunteers	12	12/0	27	18-38	74	60-87

Drug Dosage Forms

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg q8h	capsule	49	1TBK	
Dilantin®	all	adjusted*	capsule	(30 mg)		
Dilantin®	all	adjusted*	capsule	(100 mg)		

* dose adjusted to maintain phenytoin concentration of 7 to 14 mg/L

Sampling Times

Plasma: (5 mL) bromfenac 0, 0.5, 1, 2, 4, 6, 8 hrs post dose
Serum: (5 mL phenytoin 0, 1, 2, 4, 6, 8, 12, 16, 24 hrs post dose
Protein Binding unbound phenytoin concentrations were measured in serum samples collected
Assay Method

Assay Sensitivity

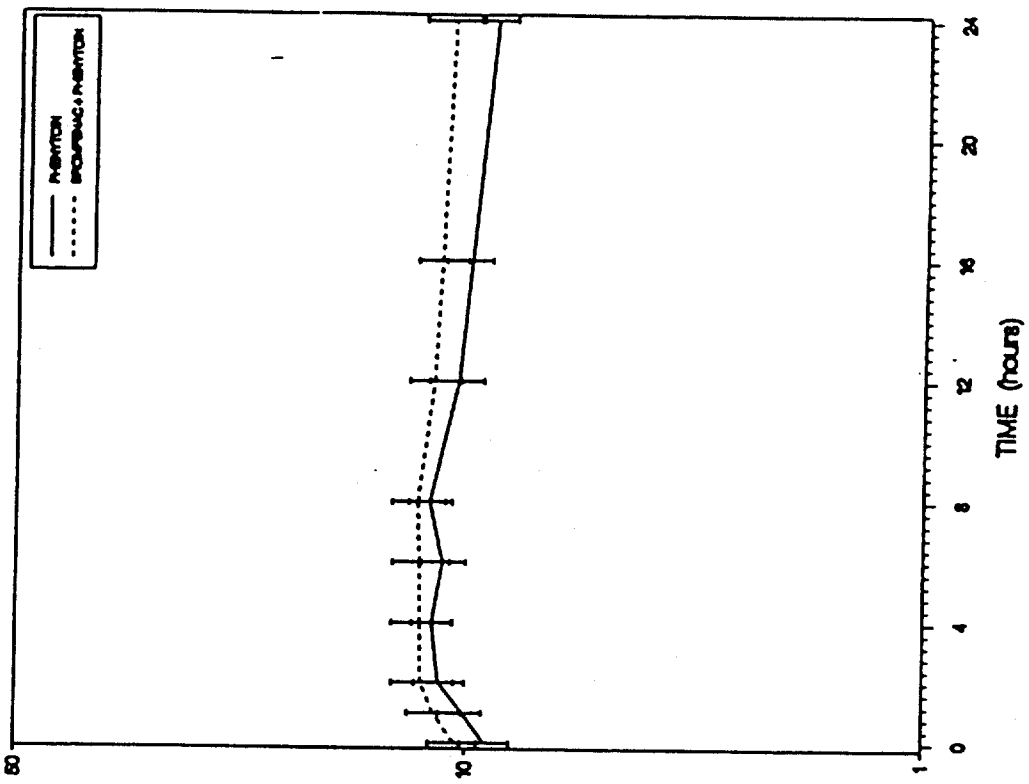
Assay Accuracy

Labeling Claims From Study

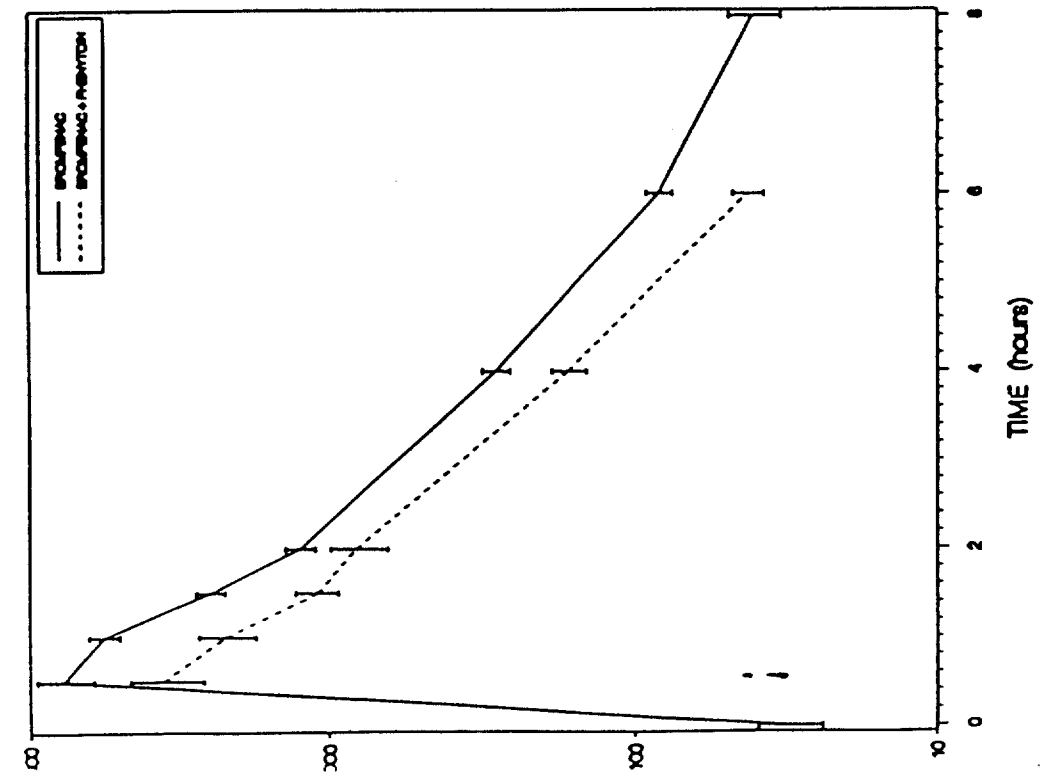
I. As with other drugs metabolized by the cytochrome P450 pathways, phenytoin reduced the plasma levels of bromfenac by about 50%.

II. Bromfenac has no effect on the pharmacokinetics of phenytoin.

SERUM CONCENTRATIONS (MEAN AND SE) OF PHENYTOIN
IN VOLUNTEERS RECEIVING PHENYTOIN
WITH OR WITHOUT BROMFENAC



SMA CONCENTRATIONS (MEAN AND SE) OF BROMFENAC
IN VOLUNTEERS RECEIVING BROMFENAC
WITH OR WITHOUT PHENYTOIN



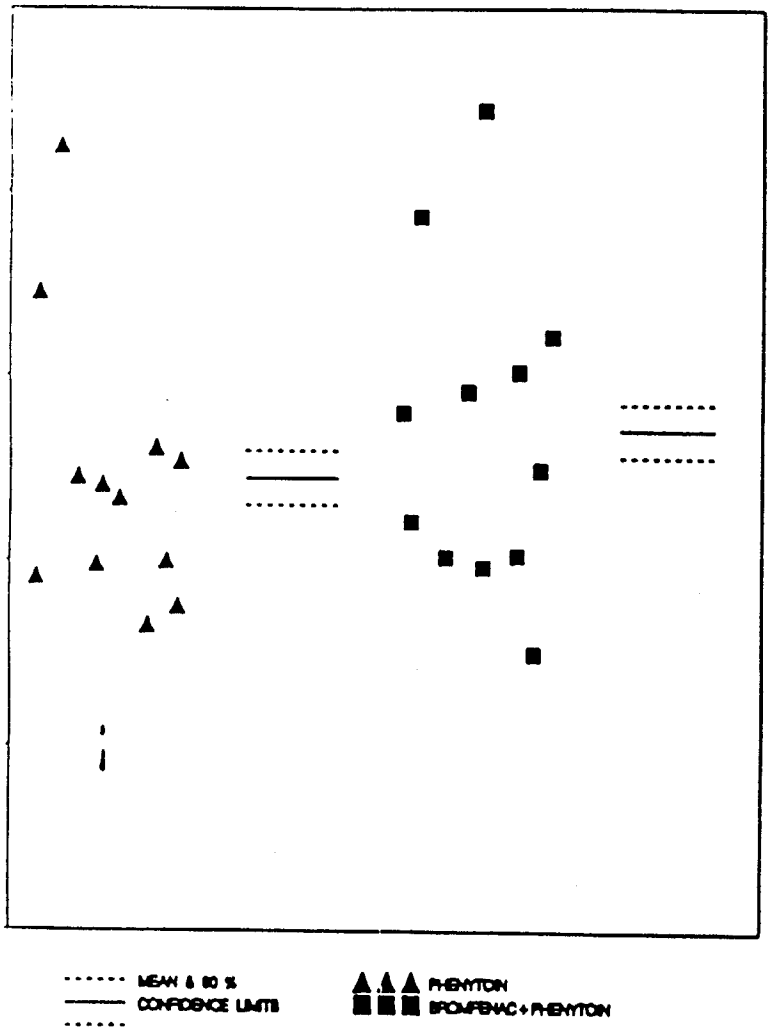
TREATMENT	SUBJECT	CMAX (NG/L)	TMAX (H)	T1/2 (H)	AUC_8H (NG*H/L)	CL/F (L/H/KG)	KE (1/H)	MRT ORAL (H)	VSS/F (L/KG)	RATIO* CMAX (%)	RATIO* AUCT (%)	FU (%)	UNBOUND CMAX (NG/ML)	UNBOUND CL/F (L/H/KG)
BROMFENAC	001													
	002													
	003													
	004													
	008													
	009													
	011													
	012													
	013													
	014													
	015													
	016													
	MEAN	4 00	0 7 1 5		6.61	0.11	0.51	1 7	0.22	100 0	100 0	0 10	4 74	110 3
	S D.	1.65	0.2 0 5		1.41	0.03	0 16	0.2	0 05	0 0	0 0	0 01	1 90	28 7
	GEOMETRIC MEAN	4.54	0 6 1 4		6.46	0.11	0.49	1 7	0 21	100 0	100 0	0-10	4 46	107 0
BROMFENAC + PHENYTOIN	001													
	002													
	003													
	004													
	008													
	009													
	011													
	012													
	013													
	014													
	015													
	016													
	MEAN	2 77	0 8 1 2		3 79	0.22	0.62	1 7	0 39	59 1	57 1	0 09	2 62	244 8
	S D.	1.52	0 5 0 1		1 38	0 14	0 15	0 4	0 33	30 1	17 7	0 01	1 52	174 0
	GEOMETRIC MEAN	2 29	0 7 1 2		3 49	0 19	0 60	1 7	0 33	50 5	54 0	0 09	2 11	211 1

* RATIO OF (BROMFENAC AND PHENYTOIN) TO (BROMFENAC)

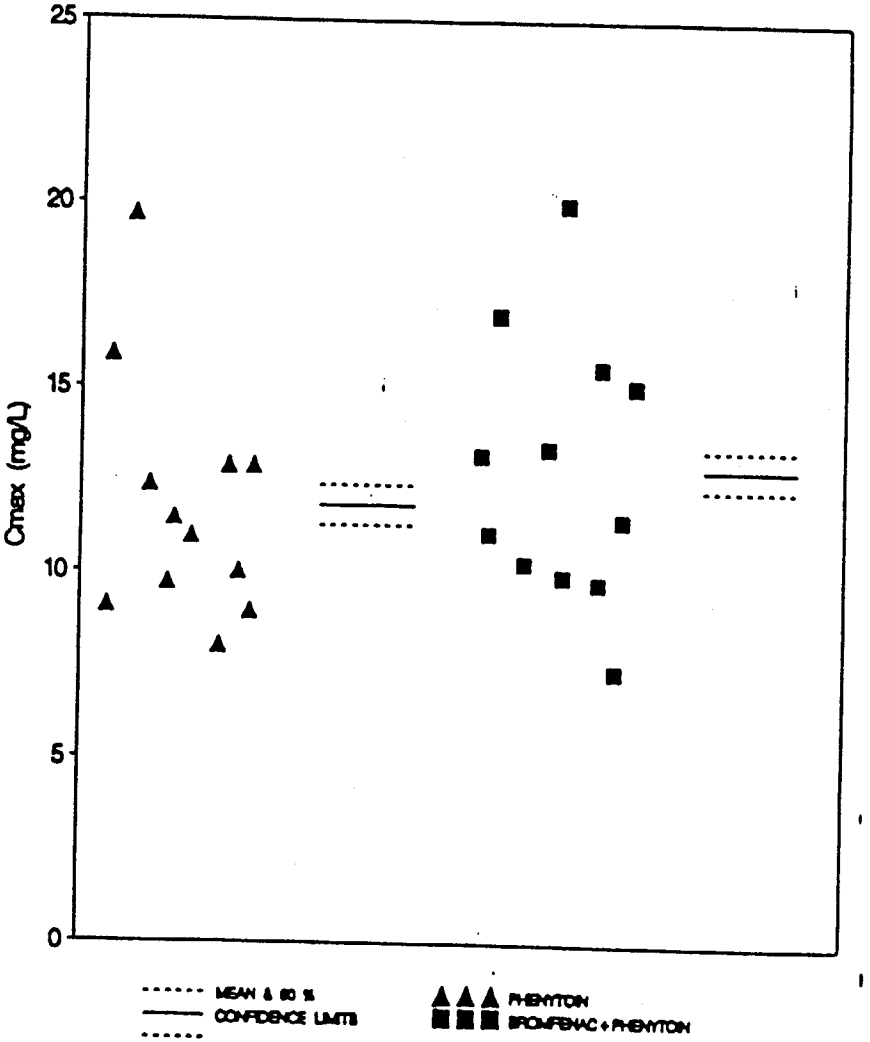
TREATMENT	SUBJECT	CMAX (NG/L)	TMAX (H)	AUC_24H (NG*H/L)	VMAX (MG/KG/DAY)	KM (MG/L)	CPSS (MG/L)	RATIO* CMAX (%)	RATIO* AUCT (%)
PHENYTOIN	001								
	002								
	003								
	004								
	008								
	009								
	011								
	012								
	013								
	014								
	015								
	016								
	MEAN	11 05	5 5	265 0	6 57	5 10	8 86	100 0	100 0
	S D	3 29	2 8	74 5	0 50	0 56	2 81	0 0	0 0
	GEOMETRIC MEAN	11 48	4 9	236 2	6 55	5 27	8 51	100 0	100 0
BROMFENAC + PHENYTOIN	001								
	002								
	003								
	004								
	008								
	009								
	011								
	012								
	013								
	014								
	015								
	016								
	MEAN	12 06	5 8	270 9	6 25	5 44	10 65	108 :	110 7
	S D	1 53	3 1	85 2	0 57	0 62	1 91	12 1	15 6
	GEOMETRIC MEAN	12 41	4 9	259 2	6 21	5 41	10 06	109 1	109 9

* RATIO OF (BROMFENAC AND PHENYTOIN) TO (PHENYTOIN)

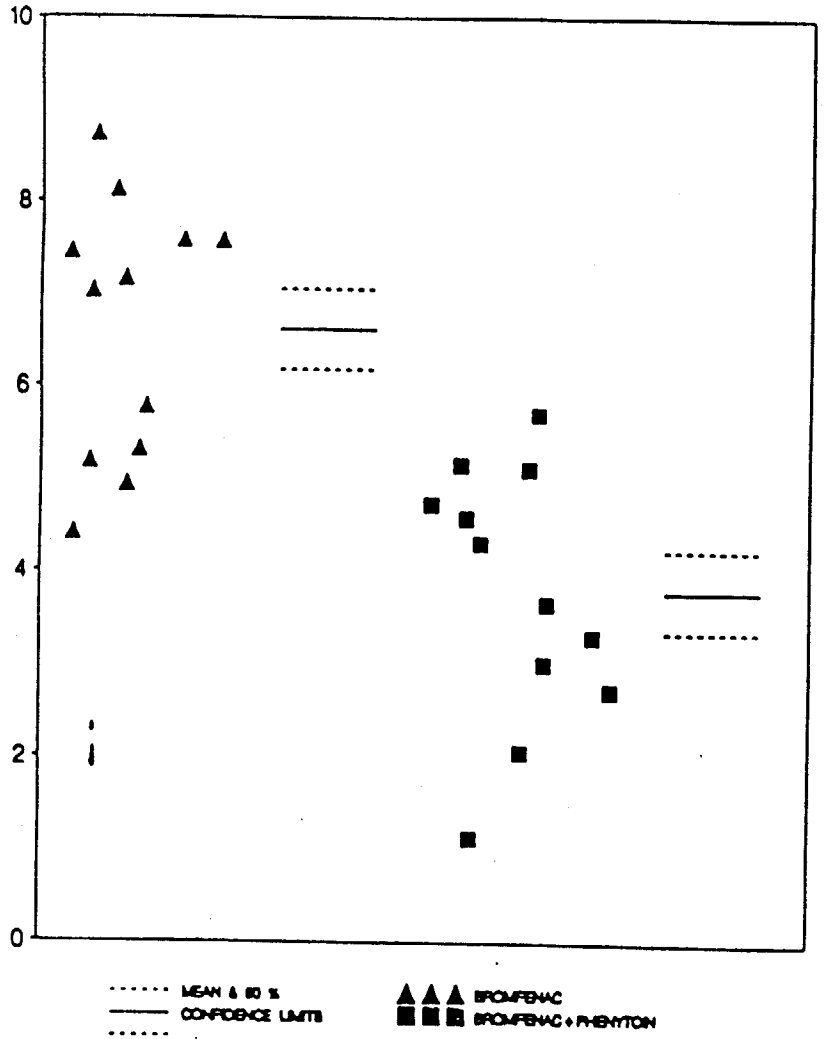
AUC OF PHENYTOIN IN VOLUNTEERS RECEIVING PHENYTOIN WITH OR WITHOUT BROMFENAC



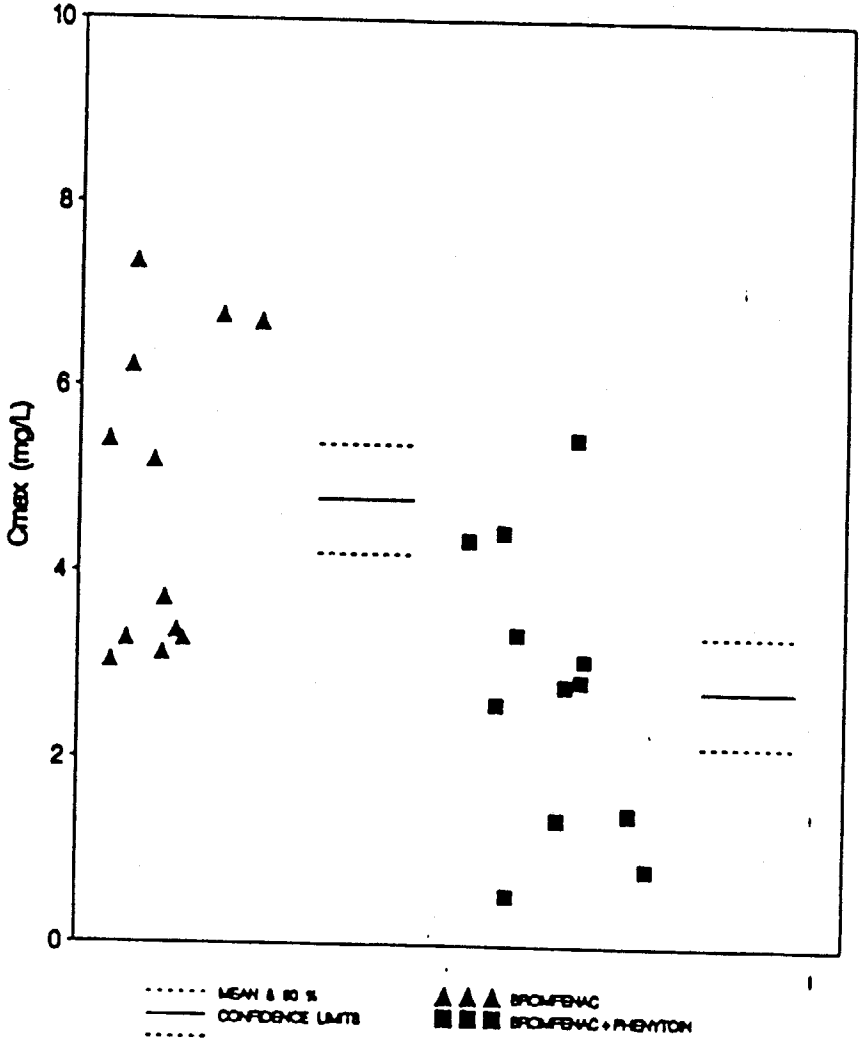
Cmax OF PHENYTOIN IN VOLUNTEERS RECEIVING PHENYTOIN WITH OR WITHOUT BROMFENAC



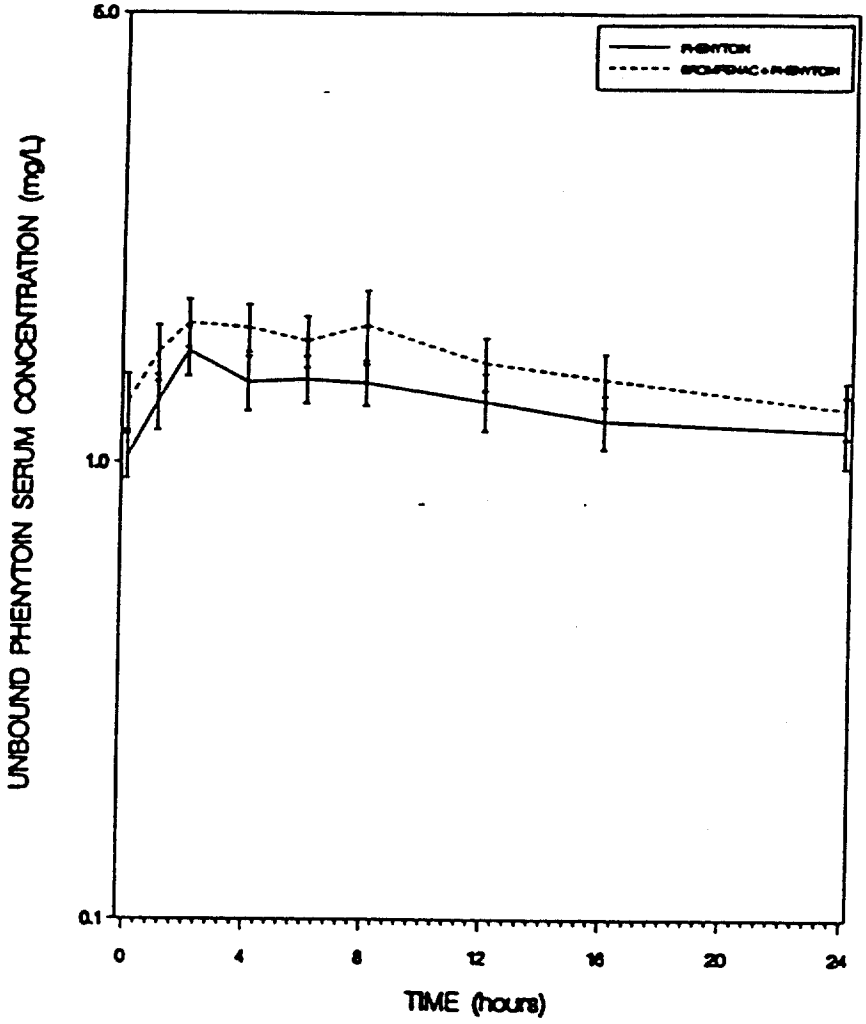
AUC OF BROMFENAC IN VOLUNTEERS RECEIVING BROMFENAC WITH OR WITHOUT PHENYTOIN



Cmax OF BROMFENAC IN VOLUNTEERS RECEIVING BROMFENAC WITH OR WITHOUT PHENYTOIN

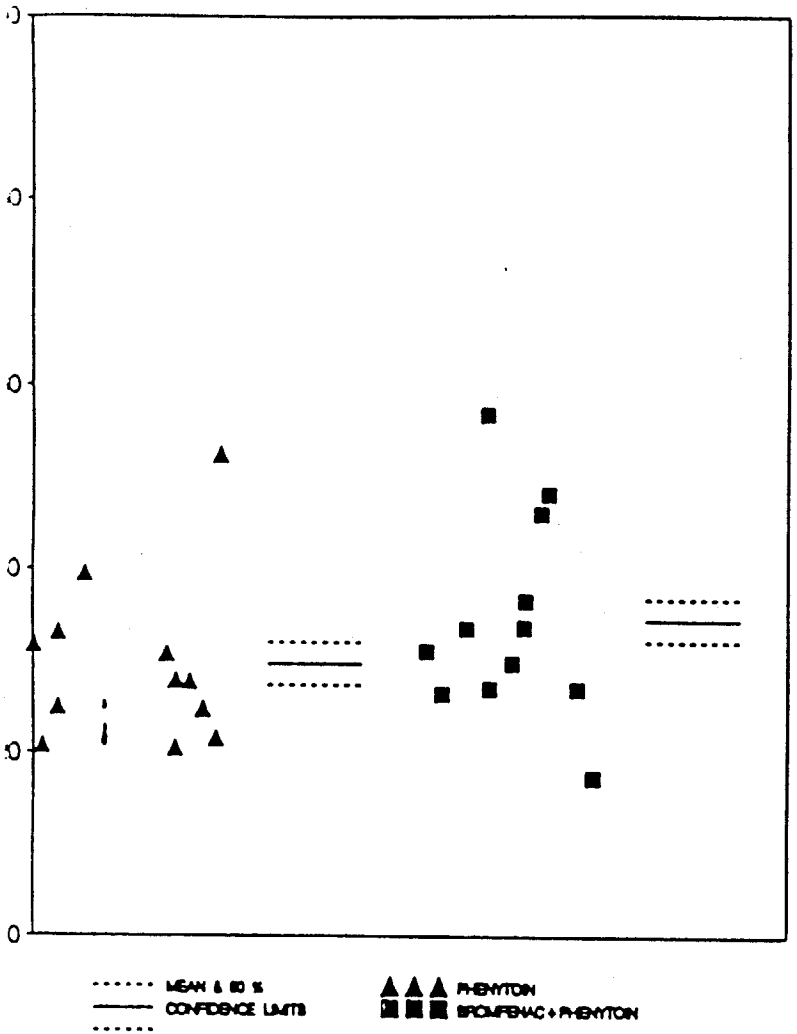


SERUM CONCENTRATIONS (MEAN AND SE) OF UNBOUND PHENYTOIN IN VOLUNTEERS RECEIVING PHENYTOIN WITH OR WITHOUT BROMFENAC

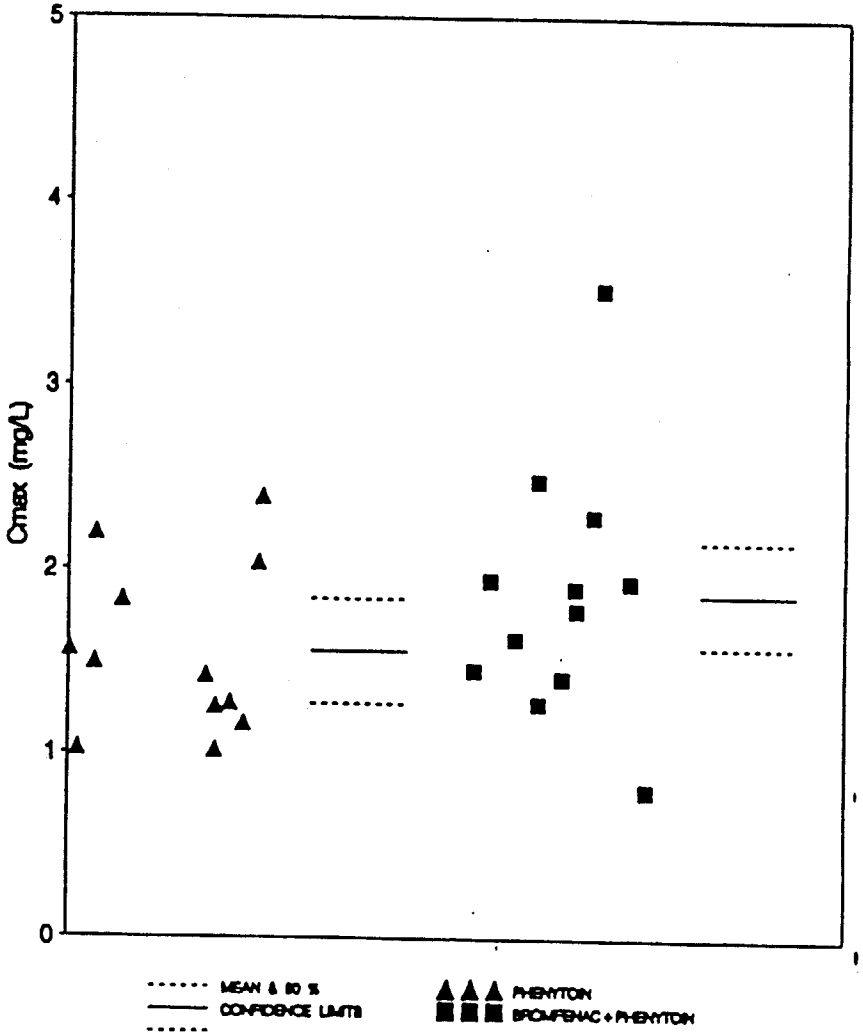


TREATMENT	SUBJECT	CMAXU (MG/L)	TMAXU (H)	AUC_24HU (MG*H/L)	CSSU (MG/L)	FU (%)	RATIO* (CMAXU) (%)	RATIO* AUCTU (%)
PHENYTOIN	001							
	002							
	003							
	004							
	008							
	009							
	011							
	012							
	013							
	014							
	015							
	016							
	MEAN	1.56	5.7	29.63	1.12	12.2	100.0	100.0
	S.D.	0.46	6.1	9.13	0.50	0.1	0.0	0.0
	GEOMETRIC MEAN	1.50	4.2	28.58	1.04	12.2	100.0	100.0
BROMFENAC + PHENYTOIN	001							
	002							
	003							
	004							
	008							
	009							
	011							
	012							
	013							
	014							
	015							
	016							

AUC OF UNBOUND PHENYTOIN IN VOLUNTEERS RECEIVING PHENYTOIN WITH OR WITHOUT BROMFENAC



Cmax OF UNBOUND PHENYTOIN IN VOLUNTEERS RECEIVING PHENYTOIN WITH OR WITHOUT BROMFENAC



NDA/IND# 20-53._____ Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.68-1.69
Study Type Drug interaction - glyburide Study# 792-A-109-US
Study Title The pharmacokinetic evaluation of the potential interaction between bromfenac sodium and glyburide in diabetic subjects

Clinical Investigator Stuart Harris MD, PhD Analytical Investigators
Site South Florida Sites
Bioavailability Clinic
Miami, FL

Single Dose_ Multiple Dose_X Washout Period
Cross-Over_X Parallel Other Design
Fasted X* Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? _10 Prior to dosing and_ Post-dosing.
* bromfenac given 2 hours after breakfast, glyburide given with breakfast

Volunteers Patients_X Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
diabetic	11	10/1	51	36-64	87	69-111

Drug Dosage Forms

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg	capsule	49.0 mg	1TBK	
bromfenac placebo	all		capsule		2TCV	
Micronase®	all	10 mg	tablet	5 mg		

Sampling Times

Plasma bromfenac: (5 mL) 0, 0.5, 1, 1.5, 2, 4, 6 hrs after dose; glyburide: (5 mL) 0, 1, 2, 3, 4, 6, 8, 10, 12, 16 hrs after dose

Protein Binding glyburide: 1, 2 hr after dose - equilibrium dialysis
Assay Method

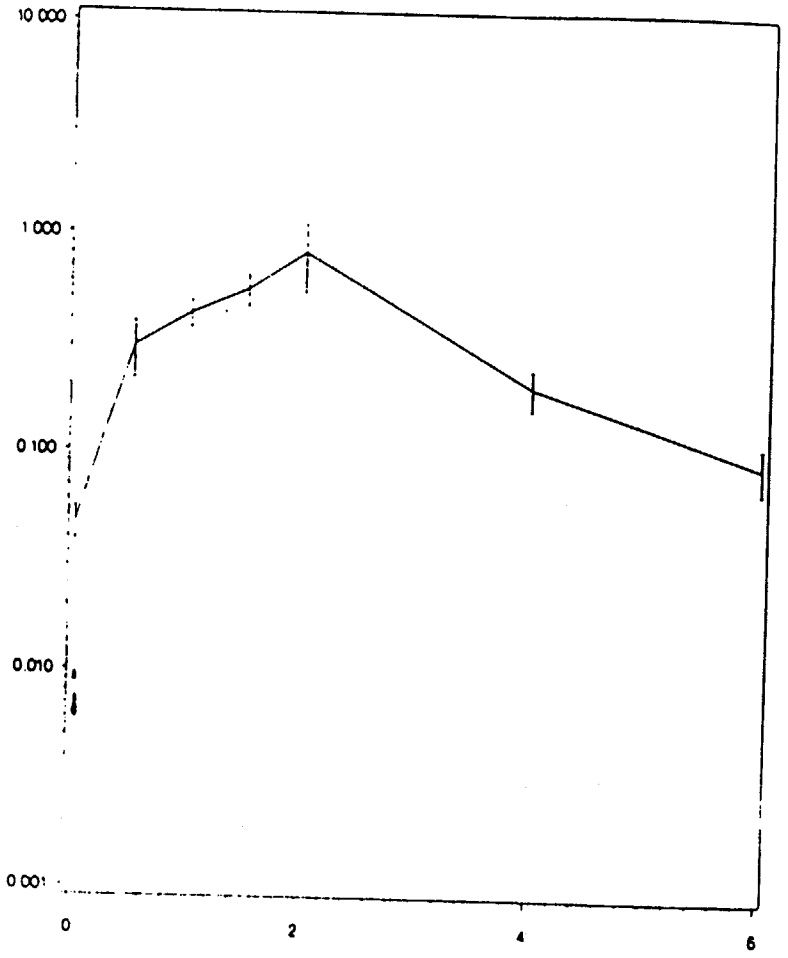
Assay Sensitivity

Assay Accuracy

Labeling Claims From Study

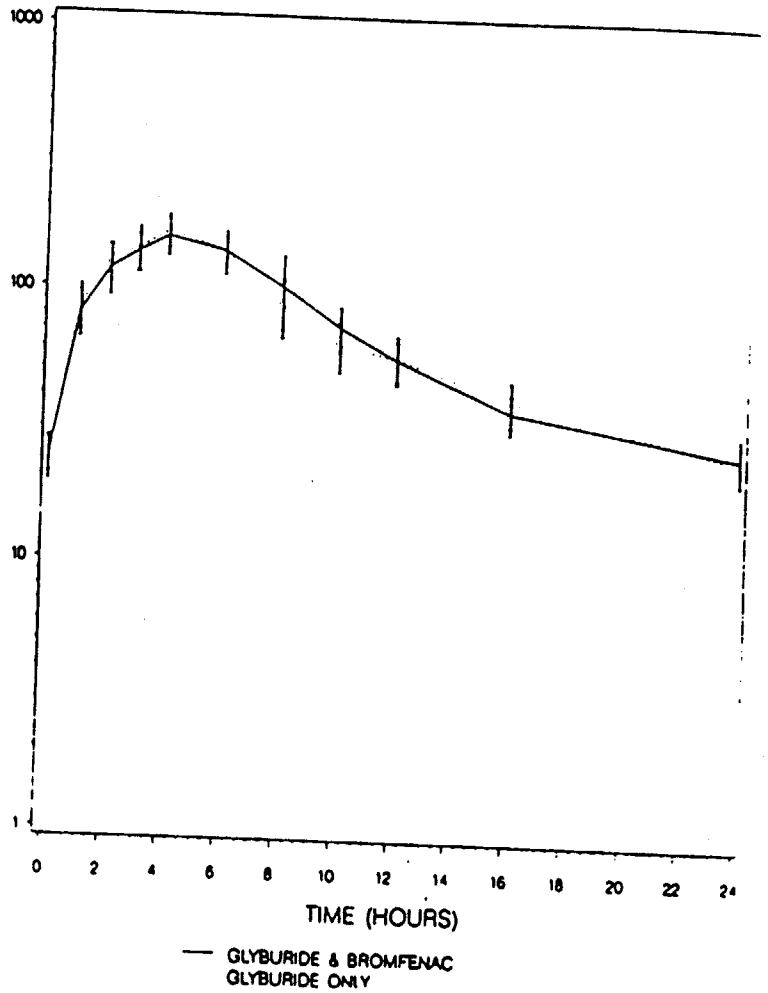
Coadministration of bromfenac has no effect on the pharmacokinetics and pharmacodynamics of glyburide.

MEAN +/- SE OF BROMFENAC PLASMA CONCENTRATIONS
IN VOLUNTEERS RECEIVING 50 MG BROMFENAC
WITH 10 MG GLYBURIDE



GLYBRUIDE PLASMA CONCENTRATION (MCG/L)

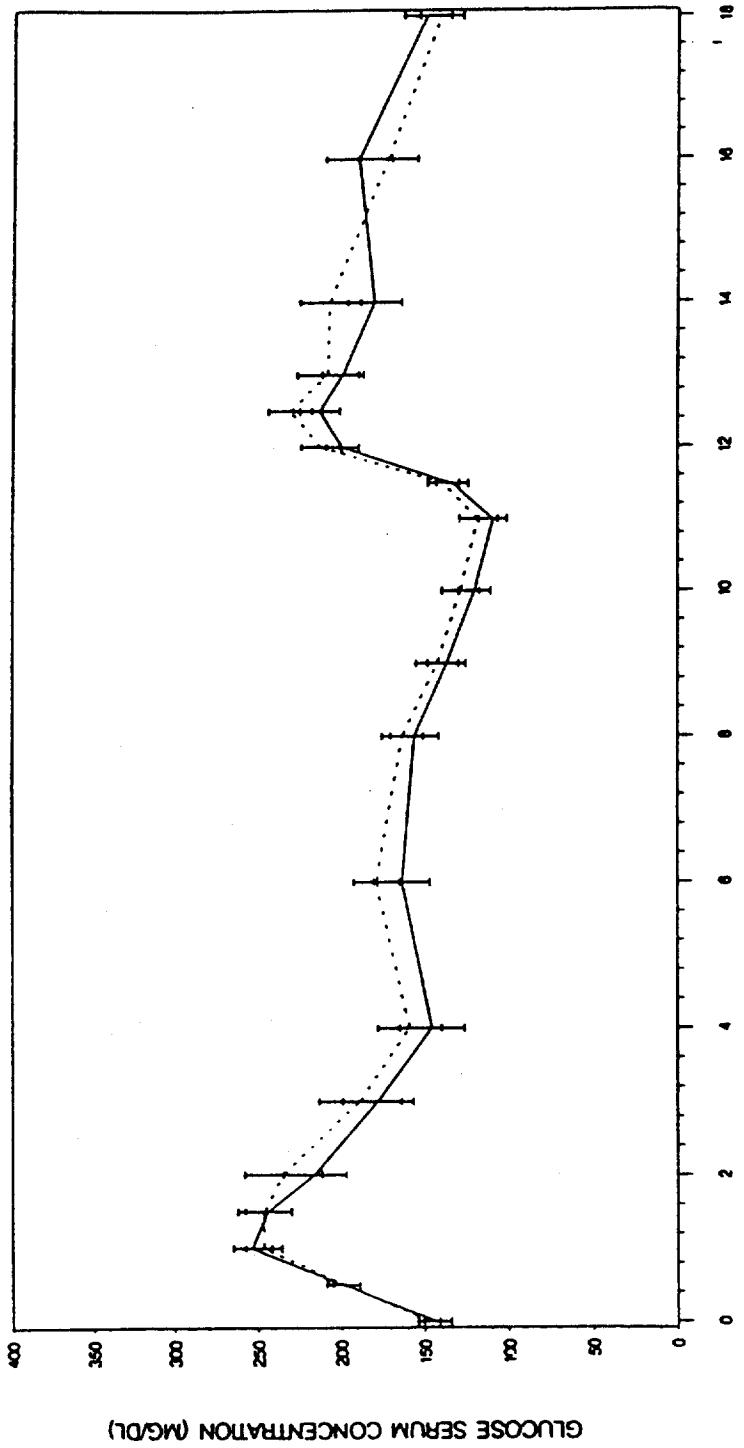
MEAN +/- SE OF GLYBURIDE PLASMA CONCENTRATIONS
IN VOLUNTEERS RECEIVING 10 MG GLYBURIDE ONCE A DAY
WITH AND WITHOUT 50 MG BROMFENAC



TIME (HOURS)

— GLYBURIDE & BROMFENAC
GLYBURIDE ONLY

MEAN +/- SE OF GLUCOSE CONCENTRATIONS
IN VOLUNTEERS RECEIVING 10 MG GLYBURIDE
WITH AND WITHOUT BROMFENAC



TREATMENT	SUBJECT	CMAX (MCG/L)	TMAX (H)	AUC_24H (MCG*H/L)	CL/F (L/H/K)	RATIO* CMAX (%)	RATIO* AUCT (%)	FRACTION UNBOUND 1 HOUR (%)	FRACTION UNBOUND 2 HOUR (%)	MEAN FRACTION UNBOUND (%)	CMAX,U (MCG/L)	AUC_24H,U (MCG*H/L)	CL,U/F (L/H/K)
GLYBURIDE ONLY	009												
	010												
	011												
	012												
	101												
	102												
	103												
	104												
	105												
	106												
	107												
	108												
	MEAN	222	3.8	1696	0.076	100	100	0.11	0.12	0.11	0.25	1.93	67
	S.D.	73	2.0	515	0.027	0	0	0.03	0.01	0.01	0.08	0.58	25
	GEOMETRIC MEAN	211	3.3	1614	0.072	100	100	0.11	0.12	0.11	0.24	1.83	64
	MEAN*	225	4.1	1674	0.078	100	100	0.11	0.12	0.11	0.26	1.92	68
	S.D.*	75	1.9	534	0.028	0	0	0.03	0.01	0.01	0.09	0.61	25
	GEOMETRIC* MEAN *	213	3.7	1588	0.074	100	100	0.11	0.12	0.11	0.24	1.81	64

TREATMENT	SUBJECT	CMAX (MCG/L)	TMAX (H)	AUC_24H (MCG*H/L)	CL/F (L/H/K)	RATIO* CMAX (%)	RATIO* AUCT (%)	FRACTION UNBOUND 1 HOUR (%)	FRACTION UNBOUND 2 HOUR (%)	MEAN FRACTION UNBOUND (%)	CMAX,U (MCG/L)	AUC_24H,U (MCG*H/L)	CL,U/F (L/H/K)
BROMFENAC & GLYBURIDE	009	...	. .										
	010												
	011												
	012												
	101												
	102												
	103												
	104												
	105												
	106												
	107												
	108												
	MEAN	222	4.4	1686	0.078	100	100	0.11	0.11	0.11	0.24	1.84	70
	S.D.	95	1.8	634	0.025	27	19	0.01	0.01	0.01	0.10	0.67	21
	GEOMETRIC MEAN	204	4.1	1578	0.074	97	98	0.11	0.11	0.11	0.22	1.73	67
	MEAN*	228	4.6	1730	0.076	101	103	0.11	0.11	0.11	0.25	1.89	69
	S.D.*	97	1.7	646	0.026	27	16	0.01	0.01	0.01	0.10	0.69	22
	GEOMETRIC* MEAN *	209	4.4	1618	0.072	98	102	0.11	0.11	0.11	0.23	1.77	66

TREATMENT	SUB	CMAX (MG/L)	TMAX (H)	AUC_24H (MCG*H/L)	CL/F (L/H/K)	RATIO* CMAX (%)	RATIO* AUCT (%)	FRACTION UNBOUND 1 HOUR (%)	FRACTION UNBOUND 2 HOUR (%)	MEAN FRACTION UNBOUND (%)	CMAX,U (MCG/L)	AUC_24H,U (MCG*H/L)	CLV,U/F (L/H/K)
GLYBURIDE ONLY													
	MEAN	221.7	3.8	1696	0.076	100	100	0.11	0.12	0.11	0.251	1.928	67
	S.D.	72.63	2.0	515	0.027	0	0	0.03	0.01	0.01	0.084	0.581	25
	GEOMETRIC MEAN	210.8	3.3	1614	0.072	100	100	0.11	0.12	0.11	0.239	1.831	64
BROMFENAC & GLYBURIDE													
	MEAN	221.9	4.4	1686	0.078	100	100	0.11	0.11	0.11	0.243	1.845	70
	S.D.	95.06	1.8	634	0.025	27	19	0.01	0.01	0.01	0.098	0.670	21
	GEOMETRIC MEAN	204.2	4.1	1578	0.074	97	98	0.11	0.11	0.11	0.224	1.734	67

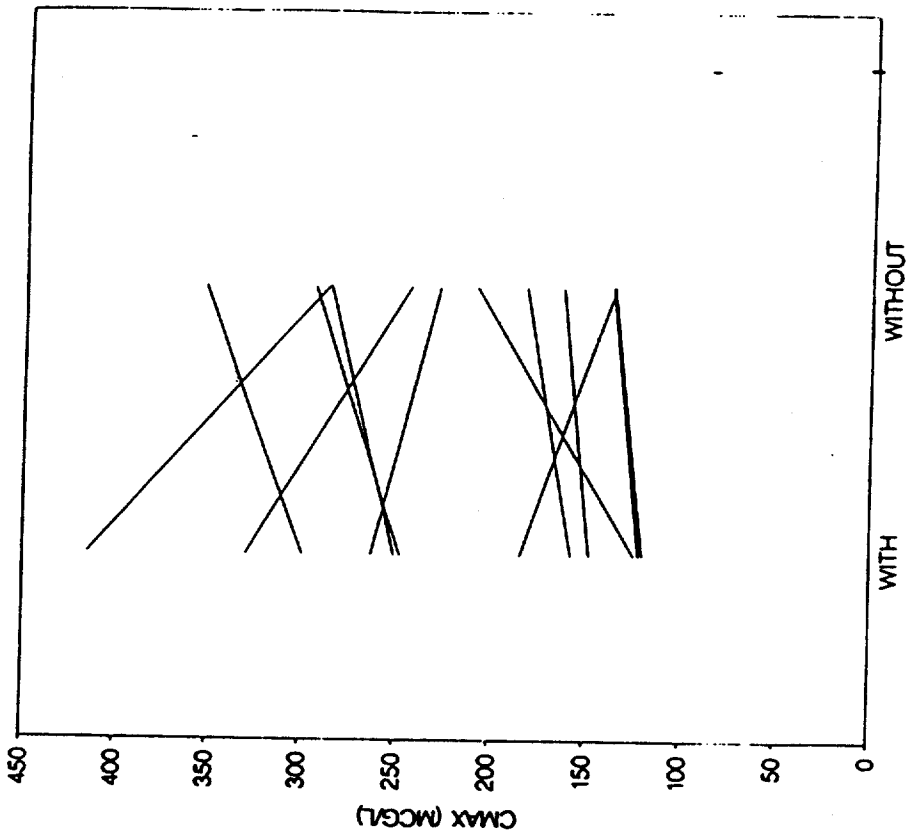
P-VALUES FROM THE TWO-WAY ANALYSIS OF VARIANCE PERFORMED ON LOG TRANSFORMED DATA

SUBJECT	.001	.01	.001	.001	.50	.50	.71	.70	.75	.007	002	.004
TREATMENT	.68	.15	.71	.71	.68	.71	.95	.11	.43	.49	.48	.48

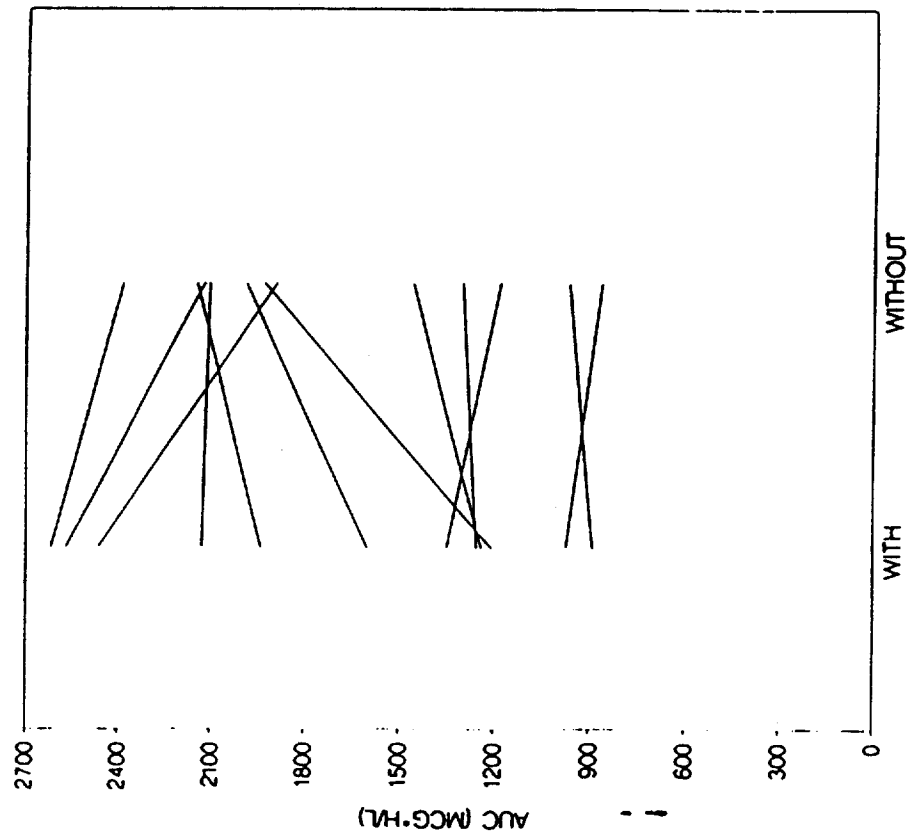
BIOEQUIVALENCE TESTING OF GLYBURIDE PHARMACOKINETIC PARAMETERS OBSERVED WITH AND WITHOUT BROMFENAC

	CMAX	TMAX	AUCT	CMAX,U	AUC_24H,U
POWER (%)	56	24	76	43	57
RATIO OF LEAST SQUARES GEOMETRIC MEAN (%)	97	122	98	94	95
90% LOG TRANSFORMED CONFIDENCE LIMITS (%)	85 - 111	97 - 153	88 - 109	80 - 110	83 - 108
RATIO OF LEAST SQUARES ARITHMETIC MEAN (%)	100	115	99	97	96
APPROXIMATE 90% CONFIDENCE LIMITS AROUND THE RATIO OF THE ARITHMETIC MEANS (%)	85 - 115	95 - 136	88 - 110	81 - 112	83 - 109
THE P-VALUES FROM TWO ONE-SIDED T TESTS					
P(R>1.2)	.02	.35	.004	01	004
P(R<0.8)	.02	006	.006	05	03

CMAX OF GLYBURIDE IN
VOLUNTEERS RECEIVING 10 MG GLYBURIDE
WITH AND WITHOUT 50 MG BROMFENAC



AUC OF GLYBURIDE IN
VOLUNTEERS RECEIVING 10 MG GLYBURIDE
WITH AND WITHOUT 50 MG BROMFENAC



NDA/IND# 20-535/____ Suppl/Amend.# Submission Date29 Dec 94 Volume 1.82-1.84
Study Type Drug interaction- digoxin Study# 792-A-116-US
Study Title The effects of bromfenac on serum digoxin concentrations

Clinical Investigator William Mullican MD Analytical Investigators
Site GFi Pharmaceutical- Sites
Services, Inc.
Evansville, IN

Single Dose Multiple Dose_X Washout Period
Cross-Over_X Parallel Other Design
Fasted X. Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? _10 Prior to dosing and_4 Post-dosing.
Volunteers_ Patients X Young Elderly X Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
cardiac patients	12	6/6	65	50-70	75	58-94

Drug Dosage Forms

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg q8h	capsule	49.8	OVTF	
digoxin	all	0.188 - 0.5 mg q 24h	tablets	patients supplied own tablets		

Sampling Times

Plasma bromfenac: (5 mL) 0, 0.5, 1, 2, 4, 6, 8 hrs post dose
Serum digoxin: (5 mL) 0, 1, 2, 4, 6, 8, 12, 16, 24 hrs post dose
Urine digoxin: 0-2, 2-4, 4-8, 8-12, 12-16, 16-24 hrs post dose
Assay Method

Assay Sensitivity

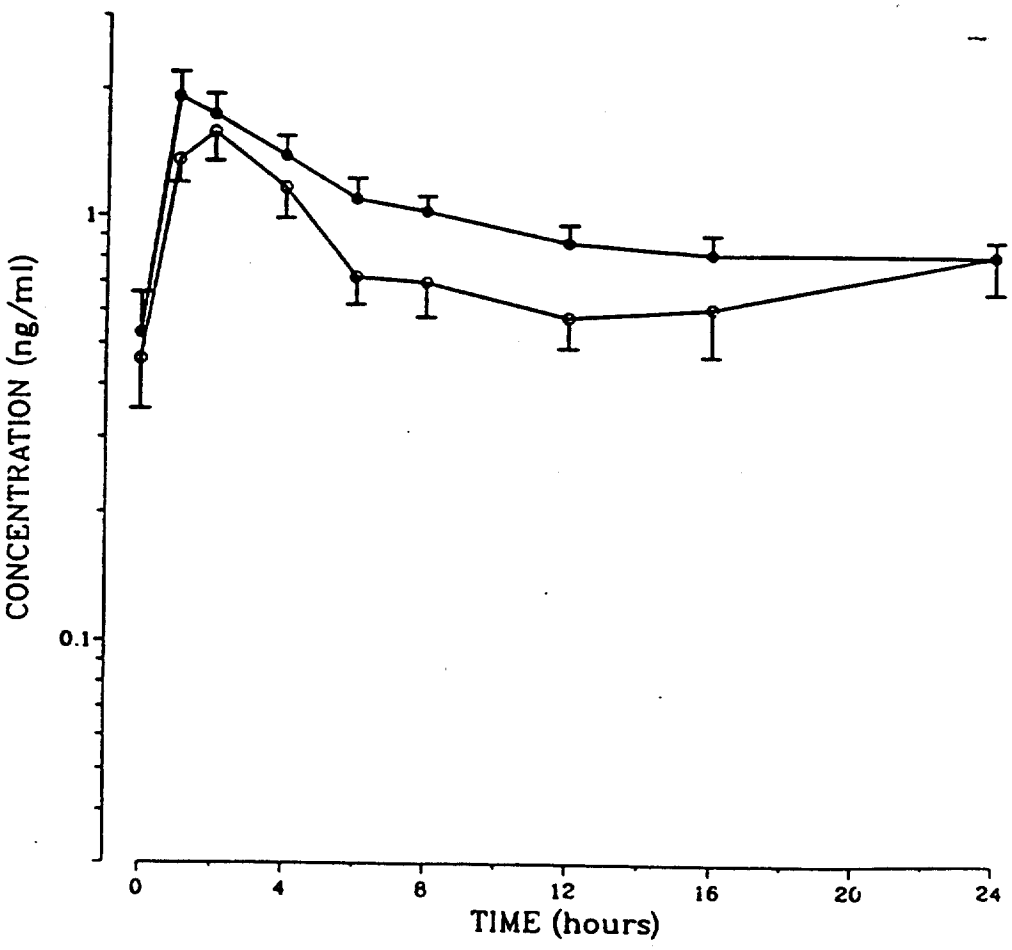
Assay Accuracy

Labeling Claims From Study

1. Coadministration of bromfenac has no effect on the pharmacokinetics of digoxin.

Figure 2

MEAN ± SE STEADY STATE SERUM CONCENTRATIONS OF DIGOXIN IN VOLUNTEERS RECEIVING THEIR REGULAR REGIMEN OF DIGOXIN WITH AND WITHOUT BROMFENAC 50 MG EVER 8 HOURS



o = DIGOXIN
• = DIGOXIN + BROMFENAC

TREATMENT	SUBJECT	CMAX (MCG/ML)	TMAX (H)	λ_z (1/H)	AUC_8H (MCG*H/ML)	T1/2 (H)	MRT ORAL (H)	CL/F (L/H/K)	VZ/F (L/K)
BROMFENAC + DIGOXIN	001								
	002								
	003								
	004								
	005								
	006								
	007								
	008								
	009								
	010								
	011								
	012								
	MEAN	3.73	1.08	0.57	7 75	1.3	2 43	0.10	0 17
	S.D.	1 98	0.36	0.13	2 72	0 3	0.51	0.03	0 05
	GEOMETRIC MEAN	3.36	1.02	0.56	7 33	1.2	2 38	0 09	0 17

TREATMENT	SUBJECT	CMAX (NG/ML)	TMAX (H)	AUC_24H (NG*H/ML)	CL/F (L/H/K)	CLR (L/H/K)	FE/F (%)	RATIO-CMAX (%)	RATIO-AUCT (%)
DIGOXIN	001								
	002								
	003								
	004								
	005								
	006								
	007								
	008								
	009								
	010								
	011								
	012								
	MEAN	1.71	3.7	17.88	0.24	0.229	80.87	100	100
	S.D.	0.80	6.5	8 50	0.13	0.191	16.55	0	0
	GEOMETRIC MEAN	1.57	2.1	15.81	0.22	0.183	79 19	100	100
BROMFENAC + DIGOXIN	001								
	002								
	003								
	004								
	005								
	006								
	007								
	008								
	009								
	010								
	011								
	012								
	MEAN	2 04	1 3	21 38	0 24	0 208	85 34	124	140
	S D	0 88	0 5	10 82	0 23	0 123	17 61	34	88
	GEOMETRIC MEAN	1 87	1 2	18 19	0 19	0 184	83 47	119	115

* RATIO OF (DIGOXIN AND BROMFENAC) TO (DIGOXIN)

TREATMENT		CMAX (NG/ML)	TMAX (H)	AUC_24H (NG*H/ML)	CL/F (L/H/K)	CLR (L/H/K)	FE/F (%)
DIGOXIN							
	MEAN	1 71	3 7	17 88	0 24	0 229	80 9
	S D	0 80	6 5	8 50	0 13	0 191	16 5
	GEOMETRIC MEAN	1 57	2 1	15 81	0 22	0 183	79 2
BROMFENAC + DIGOXIN							
	MEAN	2.04	1 3	21 38	0 24	0 208	85 3
	S D	0.88	0 5	10 82	0 23	0 123	17 6
	GEOMETRIC MEAN	1 87	1 2	18 19	0 19	0 184	83 5
P-VALUES FOR THE EFFECT OF TREATMENT FROM THE TWO-WAY ANALYSIS OF VARIANCE		04	06	51	51	97	42

BIOEQUIVALENCE TESTING OF DIGOXIN PHARMACOKINETIC PARAMETERS OBSERVED WITH AND WITHOUT BROMFENAC

POWER (%)	57	10	13
RATIO OF LEAST SQUARES GEOMETRIC MEAN (%)	119	57	115
90% LOG TRANSFORMED CONFIDENCE LIMITS (%)	104 - 137	36 - 91	79 - 167
RATIO OF LEAST SQUARES ARITHMETIC MEAN (%)	119	34	120
APPROXIMATE 90% CONFIDENCE LIMITS AROUND THE RATIO OF THE ARITHMETIC MEANS (%)	107 - 132	58 - 126	95 - 144
THE P-VALUES FROM TWO ONE-SIDED T TESTS			
P(R>1 2)	.001	81	008
P(R<0 8)	47	06	49

	SUBJECT	HEART RATE (BEATS/MIN)			PR INTERVAL (MSEC)			QRS INTERVAL (MSEC)			QT INTERVAL (MSEC)		
		0 HOUR	2 HOUR	6 HOUR	0 HOUR	2 HOUR	6 HOUR	0 HOUR	2 HOUR	6 HOUR	0 HOUR	2 HOUR	6 HOUR
DIGOXIN													
	001												
	002												
	003												
	004												
	005												
	006												
	007												
	008												
	009												
	010												
	011												
	012												
	MEAN	65	63	73	208	210	208	68	67	65	370	378	365
	S D	13	12	14	23	27	27	14	13	9	32	34	28
	GEOMETRIC MEAN	64	62	72	207	208	206	66	65	64	369	377	364
BROMFENAC + DIGOXIN													
	001												
	002												
	003												
	004												
	005												
	006												
	007												
	008												
	009												
	010												
	011												
	012												
	MEAN	62	61	69	212	210	208	65	62	62	370	377	363
	S D	12	12	15	19	24	27	15	13	13	36	38	40
	GEOMETRIC MEAN	61	59	68	211	209	206	63	60	60	368	376	361

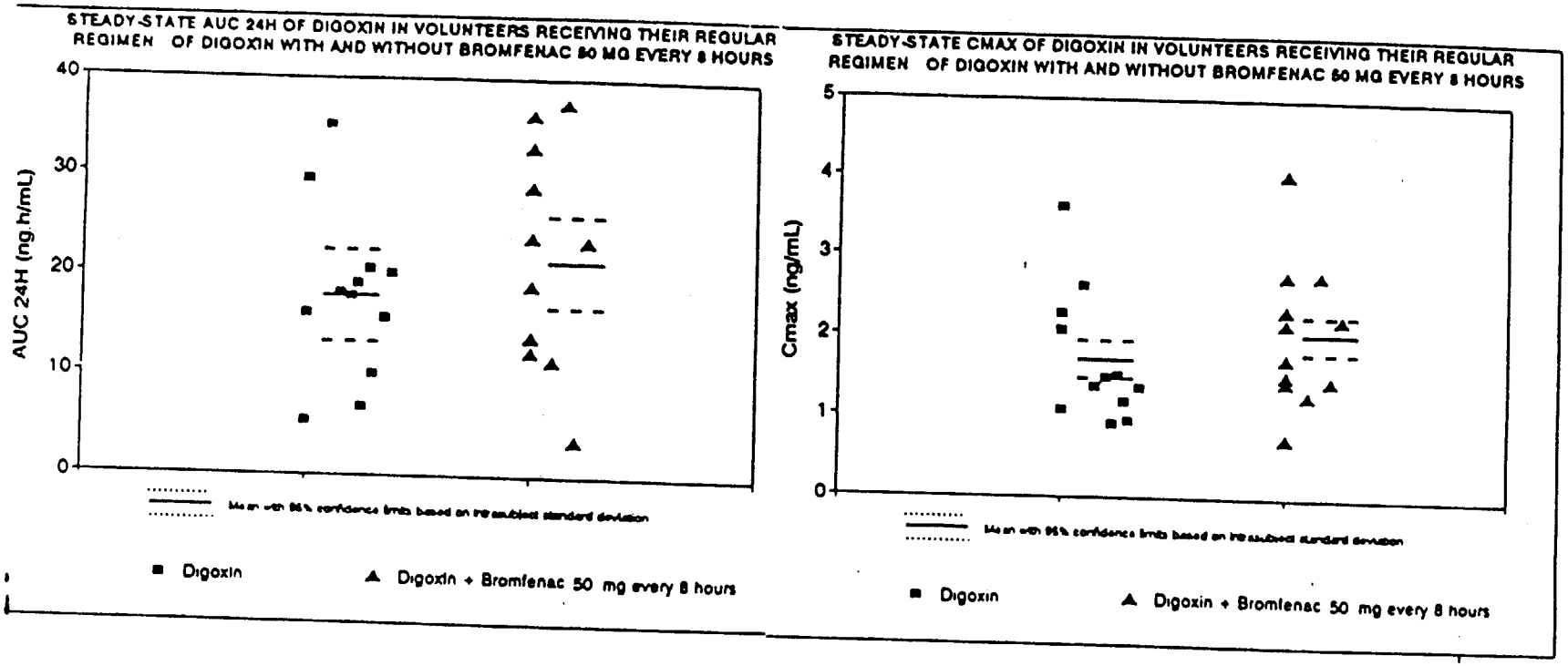


TABLE E.1
DISSOLUTION INFORMATION[a]: PROPOSED MARKET FORMULATIONS

Date of Test	Dosage Form Strength	Batch Number [formulation]	Collection Times	-- % Released[b] -- Range	Mean% Dissolved	% C.V.
September 1993	bromfenac sodium 100 mg capsule	A93D050[d] [0930209D]	5 minutes:		39.9	22.5
			10 minutes:		87.0	17.0
			15 minutes:		97.9	9.7
			20 minutes:		100.3	4.9
			30 minutes:		101.9	1.7
August 1993	bromfenac sodium 50 mg capsule	A93D046[c] [0930208D]	5 minutes:		47.4	17.4
			10 minutes:		94.6	9.4
			15 minutes:		102.4	2.9
			20 minutes:		103.5	2.8
			30 minutes:		103.6	2.8
September 1993	bromfenac sodium 25 mg capsule	A93D052[d] [0930207D]	5 minutes:		51.1	44.6
			10 minutes:		91.1	15.0
			15 minutes:		101.9	2.6
			20 minutes:		102.7	2.5
			30 minutes:		103.0	2.4

TABLE E.2
DISSOLUTION INFORMATION[a]: TEST FORMULATIONS

Date of Test	Dosage Form Strength	Batch No. [formulation] SOM[b] [Source][c]	Collection Times	% Released[d] Range	Mean% Dissolved	% C.V.
April 1992	bromfenac sodium	1VDF[f]	15 minutes:		85.2	14.6
	100 mg capsule	[0929964D]	30 minutes:		98.6	3.1
		W-AR	45 minutes:		100.8	1.1
		[W-A Canada]	60 minutes:		101.0	0.8
April 1992	bromfenac sodium	1VDE[e]	15 minutes:		79.9	15.5
	50 mg capsule	[0929945D]	30 minutes:		96.2	2.6
		W-AR	45 minutes:		98.1	1.2
		[W-A Canada]	60 minutes:		98.4	1.0
February 1991	bromfenac sodium	0VTF[e]	15 minutes:		80.1	16.9
	50 mg capsule	[0929945D]	30 minutes:		95.5	5.8
		W-AR	45 minutes:		97.3	4.9
			60 minutes:		97.4	4.9
March 1991	bromfenac sodium	1TBK	15 minutes		84.5	11.4
	50 mg capsule	[0929945D]	30 minutes		97.8	2.5
		W-AR	45 minutes		98.4	2.3
			60 minutes		98.5	2.2
March 1991	bromfenac sodium	AHR 4023	15 minutes		74.8	44.5
	50 mg capsule	0929848D	30 minutes		101.3	7.7
		Robins	45 minutes		101.3	7.6
			60 minutes		100.7	7.8
December 1991	bromfenac sodium	1TWG[f]	15 minutes:		96.8	8.3
	25 mg capsule	[0929944D]	30 minutes:		102.3	1.8
		W-AR	45 minutes:		102.9	1.0
		[W-A Canada]	60 minutes:		101.9	2.0