CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-944

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-944 **SUBMISSION DATE:** 12/19/97
PRODUCT: Advil (ibuprofen) Chewable Tablets, 50 mg and 100 mg
SPONSOR: Whitehall Robins
5 Giralda Farms, Madison, NJ 07940-0871
TYPE OF SUBMISSION: Original Submission **REVIEWER:** Sue-Chih Lee, Ph.D.

SYNOPSIS:
The proposed drug product is developed for OTC use in children aged 2-11 for temporary fever reduction and relief of minor aches and pains due to the common cold, flu, sore throat, headaches and toothaches. These indications are identical to those of currently approved over-the-counter ibuprofen formulations: Children's Advil Suspension/NDA 20-589 (for ages 2-11) and Junior Strength Advil Tablets/NDA 20-267 (for ages 6-11).

Included in the Human Pharmacokinetic section of the NDA are a pivotal bioequivalence/food effect study (AF-95-03) and 3 pilot bioavailability studies. The pilot studies were not reviewed because tablets of different formulations were used in these studies. The pivotal study is a 4-way crossover study (Advil suspension/fast, Advil swallowable tablets/fast, Advil Chewable tablets/fast and Advil Chewable tablets/fed). The suspension, but not the swallowable tablets, is the formulation approved with supporting clinical data. This study indicates the chewable tablets are bioequivalent to the swallowable tablets (in terms of Cmax and AUC), but not to the suspension (Cmax did not meet the BE criteria). Tmax for the chewable tablets (1.87 hr) is further delayed when compared to that of the swallowable tablets (1.49 hr) or suspension (0.65 hr). The sponsor has conducted a clinical trial for the purpose of demonstrating the efficacy of the chewable tablets.

Food decreased the bioavailability of the chewable tablets (Cmax: -45%; AUC: -10%; Tmax: increased from 1.87 to 3.28 hrs). In a previous study with the 80 mg/5 mL suspension, food also decreased the bioavailability of ibuprofen but to a smaller extent (Cmax: -20%; AUC: -4.3%; Tmax increased from 0.9 to 1.3 hr).

COMMENTS:
1. There are no PK studies in children. Previous studies with other ibuprofen formulations have indicated that the pharmacokinetic characteristics of ibuprofen are similar between children and adults.

2. There is no PK study for the 50 mg Chewable tablets. Since the formulations for the 2 strengths are proportional, this is acceptable.

3. In the study, chewable tablets were chewed for 30 seconds before swallowing. The chewing time may be longer than what is normally seen in clinical settings.

4. The suspension, but not the swallowable tablets, is the formulation approved with supporting clinical data. Since the chewable tablets are not bioequivalent to the suspension, it is essential that the clinical trial demonstrates the efficacy of the chewable tablets.

5. The food used in the investigation of food effect conforms to the OGD recommended high fat meal, which has less calories than the OCPB recommended high fat meal.

6. The food effect study indicates food decreases the rate and extent of absorption of ibuprofen from the chewable tablets (Cmax: -45%; AUC: -10%; Tmax: increased from 1.87 to 3.28 hrs).

RECOMMENDATION:
From the Biopharmaceutics standpoint, the application is acceptable. Please convey comments #4 and 6 to the Medical Officer.

/S/ 6/8/98

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D. /S/ 6/8/98

CC:
NDA 20-944
HFD-550 (Div.File)
HFD-550 (CSO/Koerner)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

Table of Contents:

I. FORMULATION and DOSAGE REGIMEN:

This application covers 2 strengths of tablets: 50 mg (Children's Advil Chewable Tablets) and 100 mg (Junior Strength Advil Chewable Tablets). The formulations for the two strengths are proportionally similar. Each strength of tablets has two flavors: Grape-flavored and Fruit-flavored. The 100 mg chewable tablets are for children of 6 to 11 years old, and the 50 mg chewable tablets are for children of 2 to 11 years old. The dose is based on age/body weight.

Formulations:

Component	Quantity (mg)			
	100 mg Grape (WH-450-036)	100 mg Fruit (WH-450-038)	50 mg Grape (WH-450-037)	50 mg Fruit (WH-450-039)
Mannitol, USP				
Microcrystalline Cellulose, NF				
Sodium Starch Glycolate, NF				
Magnasweet				
Aspartame, NF				
Grape Flavoe				
D&C Red #30 Lake				
FD&C Blue #2 Lake				
FD&C Red #40 Lake				

D&C Red #27 Lake	
Magnesium Stearate, NF	
Silicon Dioxide, NF	
Total Tablet Weight	

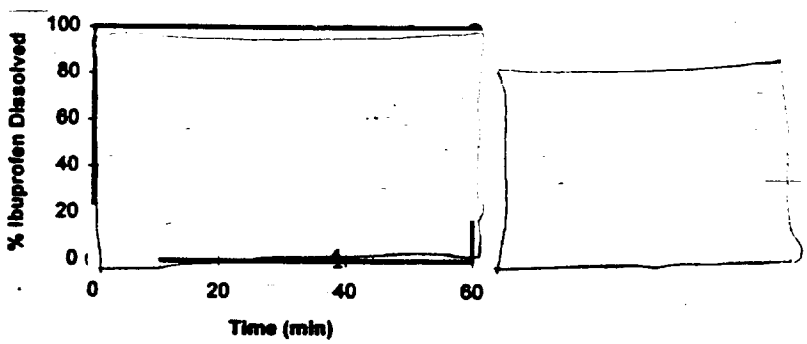
Dose:

Weight (lb)	Age (yr)	No. Of Tablets	
		100 mg Tablets	50 mg Tablets
Under 24	Under 2	Consult Doctor	Consult Doctor
24-35	2-3	Consult Doctor	2
36-47	4-5	Consult Doctor	3
48-59	6-8	2	4
60-71	9-10	2 ½	5
72-95	11	3	6

II. DISSOLUTION TEST METHOD AND SPECIFICATIONS

The proposed test method and test specifications are given below:

Media:
Apparatus:
Specification



III: HUMAN PHARMACOKINETIC STUDIES

A) List of studies not reviewed

The following pilot studies were not reviewed because these studiesdid not employ the to-be-marketed formulation.

1. Study AF-93-02:
   A single-Dose, Open-Label, Randomized, Three-Way Crossover Bioequivalence Study Comparing Chewable Ibuprofen Tablets to a Marketed Ibuprofen Suspension (Formerly WM-737)
   The tablets have a different formulation (WH# 450-23A) although [redacted] were used for the manufacture of these tablets.

2. Study WM-692:
   A Single-Dose, Open Label, Randomized, Three-Way Crossover Bioequivalence Study Comparing Chewable Ibuprofen Tablets to a Marketed Ibuprofen Suspension
   The tablets have a different formulation (WH# 450-24A) although [redacted] were used for the manufacture of these tablets.

3. Study WM-515:
   A Single-Dose, Two-Way Crossover Bioavailability Study of Two Pediatric Ibuprofen Formulations
   [redacted]

B) Study reviewed:

Study AF-95-03:

A Randomized, Single-Dose, Four-Way Crossover, Bioequivalence Food Effects Study Evaluating Whitehall-Robins Advil (ibuprofen) 100 mg Chewable Tablets (Vol. 1.9)

INVESTIGATOR AND LOCATION:

[redacted]

OBJECTIVES:

To evaluate the rate and extent of absorption of ibuprofen from Advil 100 mg chewable tablets administered under fasted and fed conditions compared to Children's Advil 20 mg/mL suspension and Advil 100 mg swallow tablets administered under fasted conditions.

TREATMENTS:

A. Advil 20 mg/mL suspension x 10 mL, fasted condition
B. 100 mg Advil swallow tablet x 2, fasted conditions
C. 100 mg Advil chewable tablets x 2, fasted conditions
D. 100 mg Advil chewable tablets x 2, fed conditions

STUDY DESIGN:

This is a single-center, randomized, open-label, single-dose, four-way cross-over study. A total

of 30 healthy, non-smoking males and females (mean wt: 66.5±9.4 kg; mean age: 26.7±5.9 yrs.) were enrolled. Five subjects did not complete the study (#2, 4, 7, 19 and 22). Subjects received a single dose of each of the 4 treatments (see above) with a washout period of 5-7 days.

Chewable tablets were chewed for 30 seconds before swallowing. Fasted condition means at least a 10 hour overnight fast pre-dose. Tablets (or suspension) were taken with 240 mL of water under fasted conditions and with 240 mL of whole milk and a standardized breakfast under fed conditions. All subjects were refrained from food or liquid 4 hours after dose.

High fat meal used was:

Buttered English muffin, 1
American cheese, 1 slice
Hash brown, 1 serving
Whole milk, 240 mL
Fried egg, 1
Canadian bacon, 1 slice
Orange juice, 180 mL

The calorie content was 292 cal of carbohydrate (45%), 116 cal of protein (18%) and 240 cal of fat (37%), with a total calorie content of 650 cal.

Sample collections - Five mL of blood was drawn pre-dose and at 15, 30, 45, 60, 75, 90 minutes and 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose (17 samples).

ASSAY:

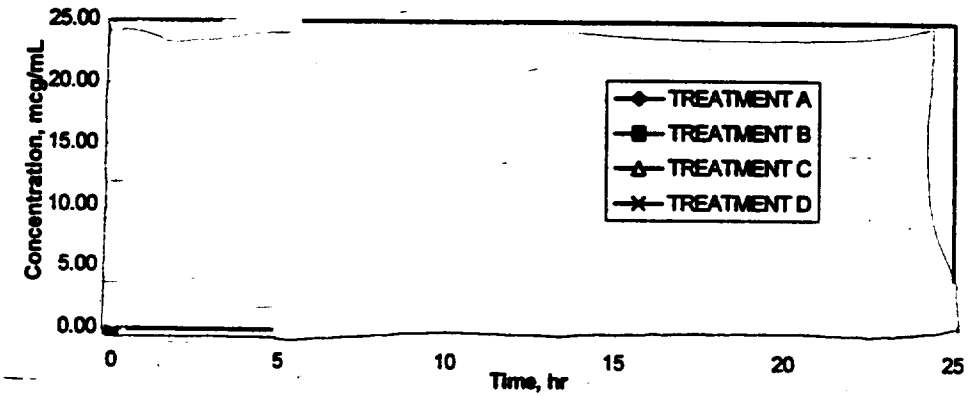
DATA ANALYSIS:

The following pharmacokinetic parameters were determined: $AUC_{0\text{-tldc}}$, AUC_{inf}, Cmax, Tmax, mean residence time, T1/2, Kel, $\log(AUC_{0\text{-tldc}})$, log(AUCI) and log(Cmax). Analysis of variance was used to determine the differences among treatments with effects for subjects, carry-over, period and treatment. A 90% two-sided confidence interval for the test/reference ratio was calculated according to [redacted] two one-sided t-tests for the following pairs:

Chewable, fasted vs. Suspension, fasted
Chewable, fasted vs. Swallowable, fasted
Chewable, fed vs. Chewable, fasted

RESULTS:

The mean plasma concentration-time profiles for the four treatments are presented below.



The mean (±SD) pharmacokinetic parameters for the 4 treatments are given in the following table. Cmax is higher for the suspension than for the swallowable or chewable tablets.

Table 1:

Treatment	Cmax	Tmax	AUC_{0-tldc}	AUC_{inf}	T1/2	Kel
Suspension fasted (A)	22.88 ±3.25	0.65 ±0.36	67.99 ±26.50	68.69 ±26.92	2.08 ±0.49	0.348 ±0.06
Swallowable tablets fasted (B)	19.78 ±4.13	1.49 ±0.74	72.42 ±28.08	73.44 ±29.82	2.19 ±0.75	0.338 ±0.07
Chewable tablets fasted (C)	19.74 3.87±	1.87 ±0.72	70.23 ±23.43	71.00 ±24.00	2.10 ±0.56	0.347 ±0.07
Chewable tablets fed (D)	10.87 ±3.27	3.28 ±2.19	63.24 ±23.37	63.91 ±24.48	2.68 ±0.96	0.288 ±0.09
C/A 90% CI*	76-91%			100-109%		
C/B 90% CI*	90-108%			94-102%		
D/C 90% CI*	50-60%			86-94%		

* Based on the log-transformed data.

Chewable (fasted) vs. Suspension (fasted):

Based on the log-transformed data, the 90% CI for AUC_{inf} (100-109%) is within the range of 90-125% whereas the 90% CI for Cmax (76-91%) is beyond the acceptable range for declaring bioequivalence (Table 1). Besides, the Tmax for the chewable tablets (1.87 hr) is delayed when compared to the suspension (0.65 hr). Therefore, chewable tablets are not bioequivalent to the suspension.

Chewable (fasted) vs. Swallowable (fasted):

The 90% CI for both the Cmax and AUC_{inf} (Table 1) are within the bioequivalence criteria of 90-125%. However, the chewable tablets reached Cmax at a later time (1.87 hr) than the

swallowable tablets (1.49 hr).

Food effect on the bioavailability of the chewable tablets:
Administration of the chewable tablets with food decreased AUC_{inf} by approximately 10% and lowered the Cmax by approximately 45%. Co-administration with food also prolonged the Tmax significantly, increasing the time needed to reach Cmax by 75% (1.87 vs. 3.28 hrs, respectively).

Conclusion:
The suspension (but not the swallowable tablets) was the formulation approved with supporting clinical data. Since the chewable tablets are not bioequivalent to the suspension formulation, the sponsor should demonstrate the efficacy of the chewable tablets through clinical trials.

Adverse events:
There are 10 events (8 events of nausea or abdominal cramps and 2 events of headache) considered to be possibly due to the drug.

COMMENT:
The high fat meal used in the study is that recommended previously by the Office of Generic Drugs and is lower in fat and total calories as compared to that recommended in the current draft guidance on food effect studies.

TABLE 1

SUBJECT DEMOGRAPHICS AND RANDOMIZATION SCHEME

Subject No.	Regimen Period 1 2 3 4	Age (yrs)	Height▲ (cm)	Weight (kg)	Frame	Gender	Race
1	D B C A	28	187	81.7	Small	Male	Caucasian
* 2	B A D C	38	168	69.7	Small	Male	Caucasian
3	A C B D	20	167	60.4	Small	Female	Caucasian
* 4	C D A B	25	159	51.0	Small	Female	Caucasian
5	A C B D	40	161	51.6	Small	Female	Caucasian
6	C D A B	27	175	62.6	Small	Male	Caucasian
* 7	D B C A	25	180	77.3	Medium	Male	Caucasian
8	B A D C	23	174	75.6	Medium	Male	Caucasian
9	C D A B	21	157	52.5	Medium	Female	Caucasian
10	D B C A	21	187	78.3	Medium	Male	Caucasian
11	B A D C	27	185	69.0	Medium	Male	Caucasian
12	A C B D	19	169	67.7	Medium	Male	Caucasian
13	B A D C	33	157	60.8	Small	Male	Hispanic
14	C D A B	31	178	72.3	Medium	Male	Caucasian
15	D B C A	22	171	64.1	Small	Male	Caucasian
16	A C B D	37	170	59.0	Small	Female	Caucasian
17	D B C A	19	184	74.3	Medium	Male	Caucasian
18	B A D C	23	182	79.6	Medium	Male	Caucasian
* 19	A C B D	21	169	58.9	Medium	Female	Caucasian
20	C D A B	25	170	55.5	Small	Female	Caucasian
21	C D A B	24	188	67.2	Small	Male	Caucasian
* 22	B A D C	25	ǂ 172	55.5	Medium	Female	Caucasian
23	D B C A	31	177	80.1	Medium	Male	Caucasian
24	A C B D	31	163	62.2	Medium	Female	Caucasian
25	B A D C	30	180	72.0	Small	Male	Caucasian
26	D B C A	19	165	58.5	Small	Male	Caucasian
27	C D A B	26	158	57.5	Medium	Female	Caucasian
28	A C B D	24	188	77.7	Medium	Male	Caucasian
29	B A D C	35	174	65.0	Medium	Male	Caucasian
30	B A D C	31	184	77.1	Small	Male	Caucasian
Mean		26.7	173.3	66.49			
± SD		5.88	9.84	9.428			
N		30	30	30			
CV%		22.0	5.7	14.2			

A = 10 mL Children's Advil-(r) (ibuprofen) 20 mg/mL suspension (fasting)
B = 2 x 100 mg Advil-(r) (ibuprofen) swallow tablets (fasting)
C = 2 x 100 mg Advil-(r) (ibuprofen) chewable tablets (fasting)
D = 2 x 100 mg Advil-(r) (ibuprofen) chewable tablets (fed)

* Subject did not complete the crossover.
ǂ Subject is 1.2 kg below the 10% ideal weight limit.
(r) denotes the registered trademark.

Subject ages are calculated as of Period 1 dosing.

▲ These represent height without shoes. In order to use the 1983 Metropolitan Height and Weight tables (Appendices 1 & 2), 2.5 cm were added to these heights.

2

Table 1

Whitehall-Robins Protocol No. AF-95-03
Summary of Results - Ibuprofen in Plasma
Pharmacokinetic Parameters

	ln AUC 0-t* (mcg·h/mL)	ln AUCinf* (mcg·h/mL)	ln Cmax* (mcg/mL)	tmax (h)	Half-life (h)	kel (1/h)	MRT (h)
(N = 25)							
Treatment A (A)							
Mean	64.898	65.546	22.65840	0.650	2.075	0.3476	2.996
CV	28.9	29.0	14.2	55.5	23.8	18.0	21.8
n	25	25	25	25	25	25	25
Treatment B (B)							
Mean	69.342	70.130	19.35068	1.490	2.188	0.3381	3.702
CV	27.4	28.1	22.1	49.7	34.1	21.1	29.7
n	25	25	25	25	25	25	25
Treatment C (C)							
Mean	67.589	68.289	19.39586	1.873	2.104	0.3465	3.867
CV	27.0	27.1	19.3	38.5	26.7	20.4	21.6
n	25	25	25	25	25	25	25
Treatment D (D)							
Mean	60.348	60.862	10.46111	3.280	2.676	0.2879	5.168
CV	29.8	30.3	28.2	66.7	35.7	31.2	20.5
n	25	24	25	25	24	24	24
Least-Squares Means							
Treatment A (A)	65.052	65.711	22.98907	0.661	2.030	0.3502	2.988
Treatment B (B)	69.027	69.854	19.37136	1.426	2.155	0.3408	3.648
Treatment C (C)	67.684	68.335	19.13619	1.953	2.166	0.3424	3.915
Treatment D (D)	60.395	61.204	10.43939	3.253	2.696	0.2866	5.184

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See Statistics Report for details on calculation of parameters.
AUCinf, t½, kel and MRT could not be estimated for Subject No. 27 Trt. D

PhAST STAB 2.3-000 DEFAULT

3

Table 1

Whitehall-Robins Protocol No. AF-95-03
Summary of Results - Ibuprofen in Plasma
Pharmacokinetic Parameters

	ln AUC 0-t* (mcg·h/mL)	ln AUCinf* (mcg·h/mL)	ln Cmax* (mcg/mL)	tmax (h)	Half-life (h)	kel (1/h)	MRT (h)
Ratio of Least-Squares Means							
(C/A)%	104.0	104.0	83.2	295.7	106.7	97.8	131.0
(C/B)%	98.1	97.8	98.8	137.0	100.5	100.5	107.3
(D/C)%	89.2	89.6	54.6	166.5	124.5	83.7	132.4
90% Confidence Intervals							
(C/A)%							
lower limit:	99.5%	99.5%	76.1%	203.4%	96.6%	92.2%	121.3%
upper limit:	108.8%	108.7%	91.1%	388.0%	116.7%	103.4%	140.8%
(C/B)%							
lower limit:	93.8%	93.6%	90.3%	94.3%	91.0%	96.7%	99.3%
upper limit:	102.5%	102.2%	108.1%	179.7%	109.9%	106.2%	115.3%
(D/C)%							
lower limit:	85.3%	85.6%	49.8%	135.1%	114.9%	77.9%	124.9%
upper limit:	93.3%	93.7%	59.7%	197.9%	134.0%	89.5%	140.0%
p-Value (ANOVA)							
C vs A	0.1395	0.1443	0.0012	0.0007	0.2727	0.5089	0.0001
C vs B	0.4614	0.4090	0.8217	0.1534	0.9337	0.8916	0.1310
D vs C	0.0001	0.0001	0.0001	0.0008	0.0001	0.0001	0.0001

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See Statistics Report for details on calculation of parameters.
AUCinf, t½, kel and MRT could not be estimated for Subject No. 27 Trt. D
PhAST STAB 2.3-000

DEFAULT

27-08-1996 Table 05 11:14

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Treatment A (A)

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	Half-life (h)
[redacted]							
Arithmetic Mean		67.99	68.69	99.01	22.8761	0.650	2.075
± SD		26.503	26.927	0.336	3.25261	0.3608	0.4939
CV%		39.0	39.2	0.3	14.2	55.5	23.8
n		25	25	25	25	25	25

4-2

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Treatment A (A)

Subject ID	Period	kel (1/h)	kel Start (h)	kel Stop (h)	MRT (h)
Arithmetic Mean		0.3476			2.996
± SD		0.06253			0.6529
CV%		18.0			21.8
n		25			25

27-08-1996 Table 06 11:14

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Treatment B (B)

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	Half-life (h)
Arithmetic Mean		72.42	73.44	98.88	19.7830	1.490	2.188
± SD		28.075	29.783	0.818	4.14182	0.7412	0.7472
CV%		38.8	40.6	0.8	20.9	49.7	34.1
n		25	25	25	25	25	25

27-08-1996 Table 06 13:34

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Treatment B (B)

Subject ID	Period	kel (1/h)	kel Start (h)	kel Stop (h)	MRT (h)
Arithmetic Mean		0.3381			3.702
± SD		0.07149			1.0980
CV%		21.1			29.7
n		25			25

27-08-1996 Table 87 11:14

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Treatment C (C)

Subject ID Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	Half-life (h)
Arithmetic Mean	70.23	71.00	98.98	19.7423	1.873	2.104
± SD	23.428	24.027	0.502	3.86503	0.7208	0.5618
CV%	33.4	33.8	0.5	19.6	38.5	26.7
n	25	25	25	25	25	25

PhAST PTAB 2.3-000 DEFAULT

Whitehall-Robins Protocol No. AT-93-03
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Treatment C (C)

Subject ID	Period	kel (1/h)	kel Start (h)	kel Stop (h)	MRT (h)
Arithmetic Mean		0.3465			3.867
± SD		0.07062			0.8366
CV%		20.4			21.6
n		25			25

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Treatment D (D)

Subject ID Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	Half-life (h)
[redacted]						
Arithmetic Mean	63.24	63.91	98.26	10.8718	3.280	2.878
± SD	23.366	24.460	0.831	3.26803	2.1870	0.9559
CV%	37.0	38.3	0.8	30.1	66.7	35.7
n	25	24	24	25	25	24

27-08-1996 Table 98 13:34

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Treatment D (D)

Subject ID	Period	kel (1/h)	kel Start (h)	kel Stop (h)	MRT (h)
Arithmetic Mean		0.2879			5.168
± SD		0.08970			1.0616
CV%		31.2			20.5
n		24			24

kel could not be estimated for Subject No. 27, Trt. D

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Treatment A (A)

Subject ID	Period	0	0.25	0.5	0.75	1	1.25	1.5	2	2.5

Arithmetic Mean	0.0000	15.6495	22.0304	20.0332	17.7289	16.0932	15.0167	12.5868	10.2392
± SD	0.00000	5.26694	3.75228	3.74178	3.47027	3.32739	3.40930	4.34017	3.63013
CV%	0.0	33.7	17.0	18.7	19.6	20.7	22.7	34.5	35.5
n	25	25	25	25	25	25	25	25	25

T -Time adjusted based on late or early blood draw BLQ -Below Limit of Quantitation

BLQ values set to zero for statistics and pharmacokinetics

PhAST CTAB 2.3-000 DEFAULT

Whitehall-Robins Protocol No. AF-95-05
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Treatment A (A)

Subject ID	Period	3	4	6	8	10	12	16	24
Arithmetic Mean		8.5192	6.2314	2.8594	1.5263	0.8474	0.4859	0.1438	0.0190
± SD		3.35735	2.87391	1.91379	1.29991	0.91807	0.69274	0.33070	0.09480
CV%		39.4	46.1	66.9	85.2	108.3	142.6	229.9	500.0
n		25	25	25	25	25	25	25	25

† -Time adjusted based on late or early blood draw BLQ -Below Limit of Quantitation

BLQ values set to zero for statistics and pharmacokinetics

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Treatment B (B)

Subject ID	Period	0	0.25	0.5	0.75	1	1.25	1.5	2	2.5
Arithmetic Mean		0.0000	1.7260	8.7961	13.1414	14.5838	14.4316	14.4073	15.4908	13.9280
± SD		0.00000	2.30959	6.62081	7.62193	7.50598	6.06948	4.73381	3.85690	4.32330
CV%		0.0	133.8	75.3	58.0	51.5	42.1	32.9	24.9	31.0
n		25	25	25	25	25	25	25	25	25

T -Time adjusted based on late or early blood draw BLQ -Below Limit of Quantitation

BLQ values set to zero for statistics and pharmacokinetics

Table 9-2

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Treatment B (B)

Subject ID Period	3	4	6	8	10	12	16	24
Arithmetic Mean	12.0402	8.7534	3.8442	2.0005	1.1330	0.6476	0.2498	0.0544
± SD	4.26579	3.88897	2.45137	1.78835	1.38362	1.08224	0.65988	0.24893
CV%	35.4	44.4	63.8	89.4	122.1	167.1	264.2	457.2
n	25	25	25	25	25	25	25	25

BLQ -Below Limit of Quantitation

BLQ values set to zero for statistics and pharmacokinetics

PhAST CTAB 2.3-000

DEFAULT

Table 10-1

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Treatment C (C)

Subject ID	Period	0	0.25	0.5	0.75	1	1.25	1.5	2	2.5
Arithmetic Mean		0.0000	3.2656	5.6546	7.5155	9.4292	11.2622	13.4511	15.5861	14.5231
± SD		0.00000	1.85453	3.86136	5.35261	6.87969	6.68720	6.28042	5.36189	5.01110
CV%		0.0	56.8	68.3	71.2	73.0	59.4	46.7	34.4	34.5
n		25	25	25	25	25	25	25	25	25

† -Time adjusted based on late or early blood draw

BLQ -Below Limit of Quantitation

BLQ values set to zero for statistics and pharmacokinetics

DEFAULT

PhAST CTAB 2.3-000

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Treatment C (C)

Subject ID	Period	3	4	6	8	10	12	16	24
Arithmetic Mean		12.7357	9.4530	4.1119	2.0694	1.1230	0.6091	0.1946	0.0302
± SD		4.73943	3.75217	2.28079	1.57244	1.09305	0.71711	0.38772	0.13132
CV%		37.2	39.7	55.5	76.0	97.3	117.7	199.2	435.4
n		25	25	25	25	25	25	25	25

BLQ -Below Limit of Quantitation

BLQ values set to zero for statistics and pharmacokinetics

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Treatment D (D)

Subject ID	Period	0	0.25	0.5	0.75	1	1.25	1.5	2	2.5
Arithmetic Mean		0.0000	1.3318	3.0147	4.6880	6.3186	7.3430	8.2230	7.8380	7.8772
± SD		0.00000	0.63939	1.70489	2.22706	2.85238	3.06143	3.89396	2.54195	2.33719
CV%		0.0	48.0	56.6	47.5	45.1	41.7	47.4	32.4	29.7
n		25	25	25	25	25	25	25	25	25

BLQ -Below Limit of Quantitation

BLQ values set to zero for statistics and pharmacokinetics

Whitehall-Robins Protocol No. AF-95-03
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Treatment D (D)

Subject ID Period	3	4	6	8	10	12	16	24
Arithmetic Mean	8.2410	9.3536	5.6094	2.7667	1.8714	1.2137	0.4642	0.0642
± SD	2.27926	3.06274	2.30338	1.52102	1.49803	1.37614	0.57489	0.15487
CV%	27.7	32.7	41.1	55.0	80.1	113.4	123.8	241.2
n	25	25	25	25	25	25	25	25

T -Time adjusted based on late or early blood draw BLQ -Below Limit of Quantitation

BLQ values set to zero for statistics and pharmacokinetics

Figure 1

Project No. 951583 /AF-95-03

Mean Plasma Ibuprofen Concentrations

(Semi – Log Plot)

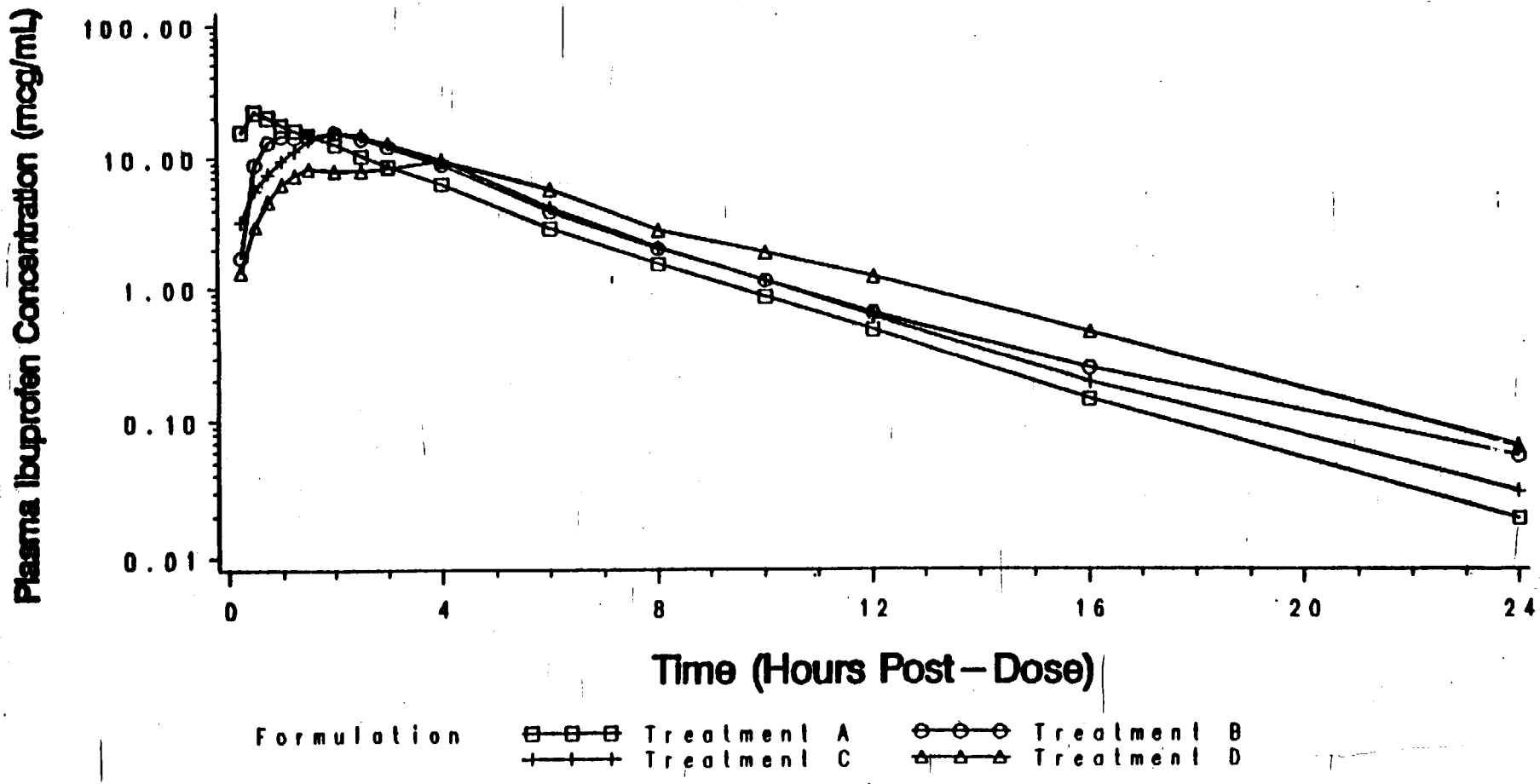


Figure 2

Project No. 951583/AF-95-03

Mean Plasma Ibuprofen Concentrations

(Linear Plot)