CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-604

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-604	Submission Dates: 7/22/2003; 8/1/2003; 10/1/2003
Brand Name	Children's ElixSure™ IB (Ibuprofen) Oral Suspension, 100 mg/5 mL
Generic Name	Ibuprofen
Reviewer	Lei Zhang, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III (HFD-880)
ORM division	DAAODP (HFD-550)
Sponsor	Taro Pharmaceuticals USA Inc.
Relevant IND	IND 62,832
Submission Type; Code	505 (b)(2); 3S
Reference Drug	Children's Motrin Oral Suspension, 100 mg/5 mL
Formulation; Strength(s)	Suspension; 100 mg/5 mL
Indication	OTC use for the reduction of fever and the temporary relief of minor aches and pains associated with a cold, flu, headache, sore throat, [redacted] toothache

Memo to File

Since the original submission (on Dec. 30, 2002) of NDA 21-604, the sponsor has submitted the following three submissions to address information requests from the agency that are related to Clinical Pharmacology and Biopharmaceutics during the review process:

1. Submission N-000 (BC) on July 22, 2003: Results from the dissolution time profile study performed on three lots of Children's ElixSure™ IB (ibuprofen) Oral Suspension, 100 mg/5 mL, with planned marketed formulation including the lot used in the bioequivalence and PK studies .
2. Submission N-000 (BP) on August 1, 2003: Additional PK data analysis for the PK and bioequivalence studies.
3. Submission N-000 (BC) (BB) on October 1, 2003: Revision of product dissolution specification to Q = [redacted] at 30 minutes.

Review of these submissions was incorporated into the final question-based review (QBR) and individual study reviews. Please refer to these reviews for details. They are linked to the original submission (on Dec 30, 2002) in DFS.

Lei Zhang, Ph.D._____
PK Reviewer, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Dennis Bashaw, Pharm.D._____
Team Leader, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

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/s/

Lei Zhang
10/28/03 11:34:13 AM
BIOPHARMACEUTICS

Dennis Bashaw
10/30/03 12:21:55 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-604	Submission Dates: 12/31/2002; 7/22/2003; 8/1/2003; 10/1/2003
Brand Name	Children's ElixSure™ IB
Generic Name	Ibuprofen
Reviewer	Lei Zhang, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III (HFD-880)
ORM division	DAAODP (HFD-550)
Sponsor	Taro Pharmaceuticals USA Inc.
Relevant IND	IND 62,832
Submission Type; Code	505 (b)(2); 3S
Reference Drug	Children's Motrin Oral Suspension, 100 mg/5 mL
Formulation; Strength(s)	Suspension; 100 mg/5 mL
Indication	OTC use for the reduction of fever and the temporary relief of minor aches and pains associated with a cold, flu, headache, sore throat, [redacted], toothache

1 Executive Summary

Ibuprofen is a propionic acid derivative that belongs to the nonsteroidal anti-inflammatory class of drugs (NSAIDs). It was approved in 1974 for prescription use and in 1984 for over-the-counter (OTC) use. Children's ibuprofen oral suspension for OTC use has been marketed since 1995. In this 505 (b)(2) NDA application, the sponsor is seeking approval for Children's ElixSure™ IB (Ibuprofen free acid) (100 mg/5 mL) oral suspension, a new dosage form of ibuprofen resulting from a novel spill resistant liquid delivery system. This drug product is intended to be marketed over-the-counter (OTC) as an analgesic and antipyretic for children. The listed reference compound is Children's Motrin oral suspension (100 mg /5 mL) manufactured by McNeil.

Safety and efficacy of the active ingredient, ibuprofen, in several dosage forms have been previously established. The applicant is relying on the literature review of the safety and efficacy of the approved products (including preclinical, toxicology and clinical data) to support the safety and clinical portion of this application.

The Labeling, Chemistry and Manufacturing Controls (CMC), and Human Pharmacokinetics and Bioavailability Sections of this application are based on the new formulation. A fluoroscopic esophageal transit study was conducted in healthy subjects to determine whether the ibuprofen dose in this "nonspill" formulation passed completely into the stomach. During the review period, the same study in patients with dysphagia was conducted to determine the possibility of aspiration. Both studies are reviewed by the Medical Officer. In terms of clinical pharmacology and biopharmaceutics aspects, this application is supported by three pharmacokinetic studies (IUE-P1-262, IUE-P2-134, and 02212) and data from dissolution profile studies.

Bioequivalence was demonstrated for the Children's ElixSure™ IB (100 mg/5 mL) and Children's Motrin Oral Suspension (100 mg/5 mL) in healthy adults under both fasting and fed conditions (Studies IUE-P1-262 and IUE-P2-134). In addition, Children's ElixSure™ IB (100 mg/5 mL) was bioequivalent to Children's Motrin chewable tablets (50 mg) under fasting conditions in healthy adults (Study IUE-P1-262). Food decreased the peak plasma concentration of ibuprofen by 38%, decreased rate of absorption (T_{max} decreased by about 1 hr, 1.89 ± 0.99 hr fast vs. 2.98 ± 1.47 hr fed), but the extent of absorption (AUC_∞) was not affected by food (Study IUE-P2-134). Similar results were found for the reference product (Study IUE-P2-134).

To understand the PK characteristics of Children's ElixSure™ IB (100 mg/5 mL) in children, the sponsor further conducted a bioavailability study to evaluate the pharmacokinetics of the test product in healthy children (3-12 yr) under fasting conditions (Study 02212). Compared to adult data, the test product has higher clearance and shorter T_{max} in children. Elimination half-life is similar between adult and children. This finding is consistent with other ibuprofen products. The PK parameters for the test product (e.g., CL/F, T_{max}, $T_{1/2}$) in children were within the range of those for the reference product (Study 02212) and other ibuprofen products (database search by the reviewer).

Given the comparable PK profile of the test product to the reference product and other ibuprofen products in children, and the finding of bioequivalence in adults, this product is considered meeting the OCPB requirements under 21CFR320.

1.1 Comments to the Sponsor

1. A specification on [redacted] (Q) at 30 min is recommended to ensure uniformity of dissolution performance of different lots of Children's ElixSure™ IB. (*Reviewer's Note: This comment has been conveyed to the sponsor and they accepted our recommendation.*)
2. In the future, please include subjects with both genders and representative ethnic groups in the study.
3. In the future, please study PK in targeted pediatric patient population, e.g., febrile children.
4. In the future, when evaluating food effects using 90% confidence intervals, please using data from fasting conditions as the reference and data from fed conditions as the test.

1.2 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the NDA 21-604 submitted on December 31, 2002. The Human Pharmacokinetics and Bioavailability

Section of this submission(s) for Children's ElixSure™ IB (100 mg/5 mL) has been found to be acceptable for meeting the OCPB requirements under 21CFR320.

Lei Zhang, Ph.D._____
PK Reviewer, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Dennis Bashaw, Pharm.D._____
Team Leader, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

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3 Summary of Clinical Pharmacology and Biopharmaceutis Findings

In terms of clinical pharmacology and biopharmaceutics aspects, this application is supported by three pharmacokinetic studies (IUE-P1-262, IUE-P2-134, and 02212) and data from dissolution profile studies. Individual study reviews are presented as appendices in Section 6 of this review.

1. Study IUE-P1-262: Single Dose Crossover Comparative Bioavailability Study of Ibuprofen 100 mg/5 mL Oral Suspension vs Ibuprofen Oral Suspension and Chewable Tablets in Healthy Male Volunteers Following a 200 mg Dose Administration – Fasting State

2. Study IUE-P2-134: Single Dose Crossover Comparative Bioavailability Study of Ibuprofen 100 mg/5 mL Oral Suspension in Healthy Male Volunteers Following a 200 mg Dose Administration – Fasting and Fed States

3. Study 02212: Randomized, 1-Way Parallel, Comparative Pharmacokinetics Study of Ibuprofen 10 mg/kg Suspension and Children's Motrin 10 mg/kg Suspension Administered as 1 X 10 mg/kg Suspension in Healthy Children Under Fasting Conditions

4. *In vitro* Dissolution Profiles Data

Study IUE-P1-262 evaluated the bioequivalence of the test product with that of Children's Motrin oral suspension (100 mg/5 mL) and Children's Motrin 50 mg chewable tablets in healthy adults under fasting conditions in healthy adults. The data demonstrated that the estimated 90% confidence intervals for log transformed C_{max} and AUC for the test product versus both reference products in the fasting state were within the acceptable limits (80-125%). Therefore, the test product is bioequivalent to both reference products in adults under fasting conditions. The test product appeared to have slower absorption rate than Children's Motrin oral suspension and faster absorption rate than Children's Motrin chewable tablets, probably due to its unique formulation ("nonspill" oral suspension). Because both reference products are approved products that are safe and effective, the differences in T_{max} (or absorption rate) are not considered clinically relevant.

Study IUE-P2-134 was an evaluation of the bioequivalence of the test product and Children's Motrin oral suspension (100 mg/5 mL) in healthy adults under both fasting and fed states. The data from this study demonstrated that the estimated 90% confidence intervals for log transformed C_{max} and AUC for the test product versus Children's Motrin in both the fasting and fed states were within the acceptable limits (80-125%). Therefore, Children's ElixSure™ IB (100 mg/5 mL) oral suspension is bioequivalent to Children's Motrin (100 mg/5 mL) in healthy adults under both fasting and fed conditions. Similar to results from Study IUE-P1-262, the test product appeared to have slower absorption rate than Children's Motrin oral suspension, probably due to its unique formulation ("nonspill" oral suspension). Food delayed the rate of absorption (to a similar extent) for both the test and the reference product, with a decrease in C_{max} and an increase in T_{max}. Overall extent of exposure, as indicated by AUC_{∞}, was bioequivalent between fasting and fed conditions.

Study 02212 evaluated the bioavailabilty of the test product in healthy children (3-12 yr) under fasting conditions. Compared to adult data, the test product has higher clearance and shorter T_{max} in children. Elimination half-life is similar between adult and children. This finding is consistent with other ibuprofen products. Compared to PK data from the reference and other ibuprofen products in children, the test product has comparable PK parameters (e.g., CL/F, T_{max}, $T_{1/2}$).

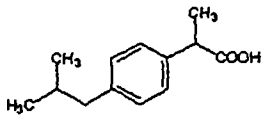
The dissolution method used by the sponsor was adopted directly from the USP monograph for ibuprofen oral suspension and validated as an in-house SOP [redacted] by the sponsor. Dissolution testing was conducted on Children's ElixSure™ IB Exhibit Batches (Formula Code [redacted], lot numbers S177-52967, S177-53137 and S177-53138. Lot S177-52967 was used in PK and bioequivalence studies. More than 90% of ibuprofen was dissolved at 15 min for all three batches. Therefore, a tighter specification of NLT [redacted] (Q) in 30 min instead of the proposed [redacted] (Q) in [redacted] (adopted from USP monograph), would be recommended for ensuring lot-to-lot uniformity of the drug product (see Comments to the Sponsor).

4 QBR

4.1 General Attributes

4.1.1 What are the highlights of the chemistry and physical-chemical properties of ibuprofen, and the formulation of the drug product?

Table 4.1.1.1. Physical-chemical Properties of Ibuprofen.

Drug Name	Ibuprofen
Chemical Name	(±)-2-(p-isobutylphenyl) propionic acid; Benzeneacetic acid
Structure	
Molecular Formula	$C_{13}H_{18}O_2$
Molecular Weight	206.28
pKa	5.2 (weak acid)
pH	Between 3.6 and 4.6
Appearance	Fine white to off-white crystalline powder.
Melting Point	75°C to 75.5°C
Polymorphism	There is no potential for polymorphism.
Solubility	Practically insoluble in water; very soluble in alcohol, methanol, acetone and chloroform; slightly soluble in ethyl acetate.

The sponsor has developed a novel spill resistant liquid delivery system. The resulting product (the subject of this application) pours like a thick syrup but resists spilling from a spoon. In addition, the physical properties of this delivery system maintain drug substance uniformity eliminating the need for product shaking.

Table 4.1.1.2 The Components and Composition of Children's ElixSure™ IB (Ibuprofen) Oral Suspension 100 mg/5 mL.

Ingredient	Concentration (%w/w)	Concentration per 5ml (mg)
Purified Water, USP		
FD&C Yellow#6, TARO		
Poloxamer 188, NF		
Ibuprofen, USP		
Sodium Hydroxide, NF		
Carbomer 934P,		
Sorbitol (Crystalline), NF		
Propylene Glycol, USP		
Butylparaben, USP		
Glycerin, USP		
Berry Flavour Natural & Artificial, TARO		
Total		

The liquid concentrate is an intensely sweet aqueous solution that contains at pH 4.4 and preserved with

4.1.2 What is ibuprofen's mechanism of action and therapeutic indication for Children's ElixSure™ IB?

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The exact mechanism of action of NSAIDs is not known, but anti-inflammatory effects are believed to be secondary to inhibition of synthesis and/or release of prostaglandins. Ibuprofen probably has a peripheral rather than central action as an analgesic. Antipyretic activity may be due to its action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation.

Children's ElixSure™ IB is indicated for the reduction of fever and temporary relief of minor aches and pains associated with a cold, flu, headache, sore throat, [redacted] and toothache.

4.1.3 What is the proposed dosage and route of administration?

The recommended doses are listed in the table below (these are standard ibuprofen doses for children). If needed, repeat dose every 6-8 hours, but do not use more than 4 times a day and do not exceed recommended dose. This product is specially designed for use only with the teaspoon provided by the manufacturer because of its unique "nonspill" formulation.

Table 4.1.3.1 Dose Recommended Based on Age and Weight.

Age (yr)	Weight (lbs)	Dose (tsp)
Under 2 years	Under 24	Ask a doctor
2-3	24-35	1
4-5	36-47	1 1/2
6-8	48-59	2
9-10	60-71	2 1/2
11	72-95	3

1 tsp = 5 mL

4.2 General Clinical Pharmacology

4.2.1 What is known about the PK characteristics of ibuprofen (background on ibuprofen in general)?

Ibuprofen is administered as a racemic mixture of S- and R-enantiomers; after systemic absorption, the inactive R-enantiomer is interconverted into the active S-form. Approximately 80% of ibuprofen is absorbed from the gastrointestinal tract after oral administration. When ibuprofen is administered with food, peak plasma concentrations are reduced by 30-50% and delayed by 30-60 minutes; however, total absorption is not affected. Approximately 90-99% of a dose is bound to plasma proteins; protein binding appears to be saturable, and at concentrations exceeding 20 μg/mL, the protein binding becomes non-linear. At an oral dose of 200 mg conventional tablet of ibuprofen in adults, C_{max} of 20 μg/mL is achieved at around 2 hr (T_{max}). The volume of distribution is about 0.12 L/kg and plasma half-life is about 2-4 hrs. Ibuprofen is metabolized via oxidation into 2 inactive metabolites. About 50-60% of an oral dose is excreted in urine as metabolites or their glucuronide conjugates within 24 hours (<10% of the drug is excreted in urine unchanged). The remainder of the drug is eliminated in feces, both as metabolites and unabsorbed drug.

4.2.2 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

The active moiety, ibuprofen (racemic mixture) was appropriately identified and measured. Please refer to the Bioanalytical Section (4.6).

4.2.3 What is PK of Children's ElixSure™ IB (100 mg/5 mL) in healthy adults? How does it compare to that of the RLD (Children's Motrin oral suspension, 100 mg/5 mL) under fasting and fed conditions in healthy adults?

Fasting conditions (Study IUE-P2-134):

The PK parameters (C_{max}, T_{max}, AUC_T and AUC_∞) for Test and Reference products under fasting conditions were summarized in Table 4.2.3.1.

Table 4.2.3.1. Summary of PK Parameters for Test and Children's Motrin Oral Suspension (Reference) Products under Fasting Conditions.

PARAMETER	TEST		REFERENCE		T-Value	P
	MEAN	C.V.	MEAN	C.V.		
C_{max} (µg/mL)	17.315	18.9	20.049	18.5	-3.91	<0.001
ln(C_{max}) (µg/mL)	2.8339	6.8	2.9807	6.5	-3.79	<0.001
T_{max} (hour)	2.00	52.3	0.75	82.1	5.60	<0.001
AUC_T (µg·h/mL)	63.514	20.0	64.315	20.0	-0.35	N.S.
ln(AUC_T) (µg·h/mL)	4.1330	4.7	4.1452	4.7	-0.40	N.S.
AUC_∞ (µg·h/mL)	66.790	20.9	69.114	29.8	-0.59	N.S.
ln(AUC_∞) (µg·h/mL)	4.1819	4.8	4.2032	5.9	-0.49	N.S.
$AUC_{T/\infty}$ (%)	95.29	3.4	94.62	6.7	0.46	N.S.
K_{el} ($hour^{-1}$)	0.3258	24.4	0.3096	27.7	0.78	N.S.
$T_{½el}$ (hour)	2.30	34.7	2.50	43.5	-0.79	N.S.

For Tmax, the median is presented.
For Tmax, the statistical analysis is based on ranks.
N.S.= Not Significant (P>0.01)

Under fasting conditions, the median T_{max} was 2.00 hr (range 0.75-5 hr, 1.89 ± 0.99 hr, N=28) and 0.75 hr (range 0.25-4 hr, 0.95 ± 0.78 hr, N=28) for the Test and Reference Product, respectively. Rates of absorption of ibuprofen Test and Reference products in adults under fasting conditions were estimated with parameters such as absorption rate constant (k_a) and mean absorption time (MAT) (listed in Table 4.2.3.2). The results suggest that absorption rate of the Test product appeared to be slower than that of the Reference product under fasting conditions.

Table 4.2.3.2. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant and Mean Absorption Time for Test and Reference Products in Healthy Adults under Fasting Conditions.

Parameter	Test (Fasting)		Reference (Fasting)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
k_a (h^{-1})	1.59 ± 1.64	103.3	2.49 ± 1.74	69.9
MAT (h)	0.71 ± 0.57	80.9	0.40 ± 0.37	91.8

Similar results were obtained in Study IUE-P1-126 (data not shown here). Please refer to Appendix 6.2.1 (individual study review) for details.

Fed conditions (Study IUE-P2-134):

The PK parameters (C_{max}, T_{max}, AUC_T and AUC_∞) for Test and Reference products under fed conditions were summarized in Table 4.2.3.3.

Table 4.2.3.3. Summary of PK Parameters for Test and Reference Products under Fed Conditions.

PARAMETER	TEST		REFERENCE		T-Value	P
	MEAN	C.V.	MEAN	C.V.		
C_{max} (µg/mL)	10.776	19.8	11.689	24.7	-1.52	N.S.
ln(C_{max}) (µg/mL)	2.3580	8.5	2.4311	9.7	-1.43	N.S.
T_{max} (hour)	3.00	49.3	1.50	65.5	4.15	<0.001
AUC_T (µg·h/mL)	56.639	17.4	57.879	20.9	-0.91	N.S.
ln(AUC_T) (µg·h/mL	4.0221	4.3	4.0378	5.1	-0.63	N.S.
AUC_∞ (µg·h/mL)	60.143	18.4	60.709	21.6	-0.39	N.S.
ln(AUC_∞) (µg·h/mL)	4.0805	4.5	4.0843	5.2	-0.15	N.S.
$AUC_{T/\infty}$ (%)	94.44	4.8	95.48	2.5	-1.43	N.S.
K_{el} ($hour^{-1}$)	0.3501	23.6	0.3787	21.9	-1.97	<0.10
$T½_{el}$ (hour)	2.15	37.9	1.93	25.6	1.41	N.S.

For Tmax, the median is presented.
For Tmax, the statistical analysis is based on ranks.
N.S.= Not Significant (P>0.05)

Under fed conditions, the median T_{max} was 3.00 hr (range 0.75-5 hr, 2.98 ± 1.47 hr, N=28) and 1.50 hr (range 0.5-5 hr, 1.81 ± 1.19 hr, N=28) for the Test and Reference Product, respectively. Rates of absorption of ibuprofen Test and Reference products in adults under fed conditions were estimated with parameters such as absorption rate constant (k_a) and mean absorption time (MAT) (listed in Table 4.2.3.4). The results suggest that absorption rate of the Test product appeared to be slower than that of the Reference product under fed conditions.

Table 4.2.3.4. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant and Mean Absorption Time for Test and Reference Products in Healthy Adults under Fed Conditions.

Parameter	Test (Fed)		Reference (Fed)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
k_a (h^{-1})	0.66 ± 0.52	78.7	1.66 ± 1.48	92.1
MAT (h)	1.56 ± 0.51	32.8	1.32 ± 0.52	39.5

4.2.4 How does PK of Children's ElixSure™ IB (100 mg/5 mL) compare to that of another formulation of ibuprofen (Reference 2), Children's Motrin chewable tablet (50 mg), under fasting conditions in healthy adults?

Because the new formulation is a thick syrup-like oral suspension, the physical properties are likely to be somewhere between oral suspension and chewable tablets. Therefore, the sponsor further characterized whether Children's ElixSure™ IB (100 mg/5 mL) was bioequivalent to another formulation of ibuprofen, Children's Motrin chewable tablet (50 mg) (Reference 2), under fasting conditions (Study IUE-P1-262). The PK parameters (C_{max}, T_{max}, AUC_T and AUC_∞) for Test and Children's Motrin tablet products under fasting condition were summarized in Table 4.2.4.1.

Table 4.2.4.1. Summary of PK Parameters for Test and Children's Motrin Tablet (Reference 2) Products under Fed Conditions.

PARAMETER	TEST		REFERENCE 2		T-Value	P
	MEAN	C.V.	MEAN	C.V.		
C_{max} (µg/mL)	18.189	23.8	15.969	22.8	3.56	<0.001
ln(C_{max}) (µg/mL)	2.8718	8.7	2.7465	8.1	3.65	<0.001
T_{max} (hours)	1.00	59.0	1.50	43.3	-3.18	<0.01
AUC_T (µg·h/mL)	57.582	22.0	62.888	25.4	-2.80	<0.01
ln(AUC_T) (µg·h/mL)	4.0295	5.6	4.1103	6.2	-2.65	<0.05
AUC_∞ (µg·h/mL)	59.723	21.6	65.005	25.0	-2.69	<0.01
ln(AUC_∞) (µg·h/mL)	4.0668	5.4	4.1445	6.1	-2.57	<0.05
$AUC_{T/\infty}$ (%)	96.34	0.9	96.65	0.9	-1.28	N.S.
K_{el} ($hours^{-1}$)	0.3501	17.0	0.3598	19.8	-0.76	N.S.
$T_{½el}$ (hours)	2.04	18.2	2.00	20.3	0.44	N.S.

For Tmax, the median is presented and the statistical analysis is based on ranks.

The median T_{max} was 1.00 hr for the Test (range 0.5-4 hr, 1.43 ± 0.84, mean ± SD, N=25) and 1.50 hr for Reference 2 (range 0.75-4 hr, 1.85 ± 0.80, mean ± SD, N=25) Product, respectively. Rates of absorption of ibuprofen Test and Children's Motrin tablet products in adults under

fasting conditions were estimated with parameters such as absorption rate constant (k_a) and mean absorption time (MAT) (listed in Table 4.2.4.2). The results suggest that absorption rate of the Test product appeared to be a little faster than that of the Children's Motrin chewable tablets under fasting conditions. The absorption rate for the Test product is somewhere between Children's Motrin oral suspension (Reference 1) and Children's Motrin chewable tablets (Reference 2) (Table 4.2.4.2), probably due to its unique formulation ("nonspill" oral suspension). Because both reference products are approved products that are safe and effective, the differences in T_{max} (or absorption rate) is not considered clinically relevant.

Table 4.2.4.2. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant and Mean Absorption Time for Test and Children's Motrin Chewable Tablet Products in Healthy Adults under Fasting Conditions.

Parameter	Reference 1 (Fasting) Mean ± SD CV (%)	Test (Fasting) Mean ± SD CV (%)	Reference 2 (Fasting) Mean ± SD CV (%)
k_a (h^{-1})	1.74 ± 1.30 74.6	1.32 ± 1.05 79.5	0.81 ± 0.46 57.2
MAT (h)	0.27 ± 0.36 136	0.46 ± 0.42 91	0.75 ± 0.51 69

Reference 1: Children's Motrin oral suspension
Reference 2: Children's Motrin chewable tablet

4.2.5 What is PK of Children's ElixSure™ IB (100 mg/5 mL) in children under fasting conditions? How does it compare to PK of Children's Motrin oral suspension in children?

The PK parameters (C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, and etc.) for Test and Reference (Children's Motrin oral suspension) products under fasting condition were summarized in Table 4.2.5.1. No significant group by treatment interaction was found for all the parameters, indicating that subjects of the different age groups behaved similarly in regard to the treatment effect.

Table 4.2.5.1. Summary of PK Parameters for Test and Children's Motrin Oral Suspension (Reference) Products under Fasting Condition (N=19 for each treatment).

Parameters		Test (Ibuprofen (A)) Mean	±	SD	CV (%)	Reference (Children's Motrin (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	163692.67	±	47500.67	29.02	146677.06	±	23633.08	16.11
AUC_{0-inf}	(ng·h/mL)	167290.01	±	51395.98	30.72	149517.74	±	23502.24	15.72
C_{max}	(ng/mL)	52000.12	±	8557.11	16.46	60515.40	±	6099.93	10.08
T_{max}	(h)	0.986	±	0.336	34.07	0.737	±	0.418	56.76
K_{el}	(h^{-1})	0.4057	±	0.1007	24.82	0.4667	±	0.0730	15.65
$T_{½ el}$	(h)	1.82	±	0.50	27.64	1.52	±	0.26	17.27
AUC_{0-4} (ng·h/mL)		126841.23 ± 23915.61			18.85	120061.04 ± 14938.24			12.44

The median T_{max} was 1.00 hr for the Test (range 0.5-1.5 hr, 0.986 ± 0.336, mean ± SD, N=19) and 0.5 hr for the Reference (range 0.367-1.93 hr, 0.737 ± 0.418, mean ± SD, N=19) Products, respectively. Rates of absorption of ibuprofen Test and Reference products in children were estimated with parameters such as absorption half-life and mean absorption time (listed in Table 4.2.5.2). The estimation of these parameters could be affected by limited number of sampling in

children. The results suggest that absorption rates of the Test and Reference products are comparable.

Table 4.2.5.2. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant and Mean Absorption Time for Test and Reference Products under Fasting Conditions in Children.

Parameter	Test (Fasting)		Reference (Fasting)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
k_a (h^{-1})	0.78 ± 0.35	44.79	0.81 ± 0.23	27.84
MAT (h)	0.14 ± 0.35	239.94	0.21 ± 0.23	110.75

4.2.6 How dose PK of Children's ElixSure™ IB (100 mg/5 mL) compare to PK of other ibuprofen products in children?

Literature and database search to compare PK of the Test product to other ibuprofen products in children was conducted by the reviewer. The PK profile of the Test product is comparable to the Reference product and other ibuprofen products in children (mean data were less than 25% of difference) (Table 4.2.6.1).

Table 4.2.6.1. Comparison of PK Parameters (Mean ± SD) of the Test Product to Other Ibuprofen Products in Children.

	Test (healthy children) N=19	Reference (healthy children) N=19	Ibuprofen Suspension (febrile children) N=18	Ibuprofen Chewable Tablets (febrile children) N=22
Dose (mg/kg)	10	10	6	10
C_{max} (µg/mL)	52 ± 8.6	61 ± 6.1	31 ± 12	59 ± 13
CL/F (mL/h/kg)	64 ± 15	68 ± 11	70.5 ± 21	68 ± 13
T_{max} (hr)	0.99 ± 0.34	0.74 ± 0.42	0.87 ± 0.42	0.99 ± 0.53
$T_{1/2el}$ (hr)	1.8 ± 0.5	1.5 ± 0.3	1.9 ± 1.0	2.1 ± 1.3

4.3 Intrinsic Factors

Age:

4.3.1 What are PK results of Children's ElixSure™ IB and Children's Motrin oral suspension (100 mg/5 mL) by age group under fasting conditions?

PK results by different age groups (2-6 yrs, 7-9 yrs, and 10-12 yrs) in children of both the Test product (Children's ElixSure™ IB) and the Reference product (Children's Motrin oral suspension) are listed in Table 4.3.1.1. No trend in effect of age (3-12 yrs) on PK of ibuprofen was observed for both the Test and Reference products. This result is consistent with previous findings in the literature.[1]

[1] Nahata MC, *et. al.*, Pharmacokinetics of ibuprofen in febrile children. *Eur J Clin Pharmacol* 40:427-428, 1991.

Table 4.3.1.1. Summary of PK Results by Age Group.

SUMMARY OF RESULTS
IBUPROFEN
Pharmacokinetic Parameters by Age Group

2 - 6 years old
(N = 4 for each treatment)

Parameters		Test (Ibuprofen (A)) Mean	±	SD	CV (%)	Reference (Children's Motrin (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	161005.25	±	22571.59	14.02	131205.43	±	21421.86	16.33
AUC_{0-inf}	(ng·h/mL)	163782.29	±	23537.58	14.37	135349.58	±	21414.29	15.82
C_{max}	(ng/mL)	48166.33	±	3841.83	7.98	57966.68	±	3748.44	6.47
T_{max}	(h)	0.809	±	0.215	26.59	0.517	±	0.235	45.49
K_{el}	(h^{-1})	0.4331	±	0.0933	21.55	0.4836	±	0.0726	15.01
$T_{½el}$	(h)	1.66	±	0.35	20.91	1.46	±	0.25	17.08

7 - 9 years old
(N = 7 for Treatment A, N = 6 for Treatment B)

Parameters		Test (Ibuprofen (A)) Mean	±	SD	CV (%)	Reference (Children's Motrin (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	171073.09	±	64566.61	37.74	139115.95	±	13084.87	9.41
AUC_{0-inf}	(ng·h/mL)	175352.63	±	70666.21	40.30	141699.77	±	13732.92	9.69
C_{max}	(ng/mL)	56652.66	±	8707.45	15.37	63772.66	±	6811.58	10.68
T_{max}	(h)	1.00	±	0.29	28.87	0.583	±	0.204	34.99
K_{el}	(h^{-1})	0.4442	±	0.1146	25.79	0.4978	±	0.0810	16.28
$T_{½el}$	(h)	1.69	±	0.59	35.03	1.43	±	0.25	17.25

10 - 12 years old
(N = 8 for Treatment A, N = 9 for Treatment B)

Parameters		Test (Ibuprofen (A)) Mean	±	SD	CV (%)	Reference (Children's Motrin (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	158578.52	±	43838.53	27.64	158594.09	±	25597.86	16.14
AUC_{0-inf}	(ng·h/mL)	161989.07	±	46590.09	28.76	161026.67	±	25646.49	15.93
C_{max}	(ng/mL)	49846.04	±	9034.87	18.13	59476.66	±	6085.55	10.23
T_{max}	(h)	1.06	±	0.42	39.27	0.937	±	0.510	54.42
K_{el}	(h^{-1})	0.3583	±	0.0813	22.69	0.4384	±	0.0644	14.69
$T_{½el}$	(h)	2.03	±	0.47	23.18	1.62	±	0.28	17.03

4.3.2 How does PK of Children's ElixSure™ IB (100 mg/5 mL) in children compare to that in adults under fasting conditions?

Effect of age (children vs. adults) on PK of ibuprofen was observed for both Test (Table 4.3.2.1) and Reference products (data not listed). This result is consistent with previous findings for

other ibuprofen products. In general, ibuprofen has higher apparent clearance in children than in adults. Higher variability in the children's values is apparent and overall, several of them fall within the range for adults. The recommended dose in children is usually 6-10 mg/kg and in adults is usually 200 mg (~3 mg/kg) for the OTC indication of ibuprofen.

Table 4.3.2.1. Comparison of PK Parameters of the Test Product in Healthy Children and Adults.

	Children (2-12 year) (N=19)	Adult (N=25)
Dose (mg/kg)	10	~2.6
$AUC_{0\text{-}inf}$ (µg·h/mL)	167 ± 51	60 ± 13
CL/F (mL/h/kg)	64 ± 15	46 ± 9.6
T_{max} (hr)	0.99 ± 0.34	1.43 ± 0.84
$T_{1/2el}$ (hr)	1.8 ± 0.5	2.0 ± 0.37

Children data: from Study 02212.
Adult data: from Study IEU-P1-262.

4.4 Extrinsic Factors

Not applicable to this application.

4.5 General Biopharmaceutics

4.5.1 Is Children's ElixSure™ IB (100 mg/5 mL) bioequivalent to the RLD (Children's Motrin oral suspension, 100 mg/5 mL) under fasting and fed conditions in healthy adults?

In Study IUE-P2-134, the relative bioavailability of the Test product was determined under both fasting and fed conditions relative to the Reference product (Children's Motrin oral suspension) in a 4-period, 2-sequence, crossover study in 30 healthy male subjects. The study demonstrated that the Test product is bioequivalent to the Reference product in both fasting (Table 4.5.1.1) and fed (Table 4.5.1.2) conditions.

Table 4.5.1.1. Comparison of Geometric Means of C_{max}, AUC_T, AUC_∞ and $AUC_{0\text{-}4}$ for Test and Reference Products under Fasting Conditions.

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	17.06	19.70	86.59	81.16	92.39
AUC_T	62.38	63.03	98.97	94.66	103.48
AUC_∞	65.46	66.66	98.20	92.15	104.65
$AUC_{0\text{-}4}$	40.68	44.26	91.91	86.21	97.98

Table 4.5.1.2. Comparison of Geometric Means of C_{max}, AUC_T, AUC_∞, and AUC_{0-4} for Test and Reference Products under Fed Conditions.

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	10.56	11.36	92.95	85.20	101.42
AUC_T	56.18	57.07	98.44	94.37	102.69
AUC_∞	59.56	59.79	99.62	95.48	103.93
AUC_{0-4}	28.37	32.65	86.88	82.29	91.71

4.5.2 Is Children's ElixSure™ IB (100 mg/5 mL) bioequivalent to another formulation of ibuprofen, Children's Motrin chewable tablet (50 mg), under fasting conditions in healthy adults?

In Study IUE-P1-262, the relative bioavailability of the Test product was determined under both fasting and fed conditions relative to the 2 Reference products (Children's Motrin oral suspension and chewable tablets) in a 3-period, 3-sequence, crossover study in 27 healthy male subjects. The study demonstrated that the Test product is bioequivalent to both Reference products under fasting conditions. Data for comparison to Reference 2 product (Children's Motrin chewable tablet) are listed in Table 4.5.2.1.

Table 4.5.2.1. Comparison of Geometric Means of C_{max}, AUC_T, AUC_∞, and AUC_{0-4} for Test and Reference 2 Products under Fasting Conditions.

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST	REFERENCE 2		LOWER	UPPER
C_{max}	17.879	15.513	115.25	107.96	123.03
AUC_T	56.359	60.901	92.54	88.11	97.20
AUC_∞	58.504	63.027	92.82	88.41	97.45
AUC_{0-4}	40.26	40.99	98.20	93.12	103.57

4.5.3 Is there a food-effect on the PK of Children's ElixSure™ IB (100 mg/5 mL) in healthy adults?

Results from Study IUE-P2-134 suggested that food decreased the peak plasma concentration by 38%, decreased rate of absorption (T_{max} decreased by about 1 hr, 1.89 ± 0.99 hr fast vs. 2.98 ± 1.47 hr fed), but the extent of absorption (AUC_∞) was not affected by food (Table 4.5.3.1). Similar results were found for the Reference product (and other ibuprofen products) (data not shown).

Table 4.5.3.1.* Comparison of Geometric Means of C_{max}, AUC_T, AUC_∞, and AUC_{0-4} for the Test Product under Fasting and Fed Conditions.

Parameter	Geometric LS Means		Ratio	90% Confidence Limit	
	Test-Fed	Test-Fast		Lower	Upper
C_{max} (ng/mL)	10.56	17.06	61.90	56.91	67.34
AUC_{0-t} (ng·h/mL)	56.18	62.38	90.06	85.90	94.43
AUC_{0-inf} (ng·h/mL)	59.56	65.46	90.99	86.02	96.23
AUC_{0-4} (ng·h/mL)	28.37	40.68	69.74	64.78	75.05

** Reviewer's Note: Data were recalculated in this table using data from fasting conditions as the reference and data from fed conditions as the test (the sponsor did the opposite way). Ratio and 90% confidence interval data were generated from conversion of data submitted by the sponsor as follows: new data=100/original data that calculated by the sponsor using data from fed conditions as the reference and data from fasting conditions as the test.*

4.5.4 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The dissolution method used was adopted directly from the USP monograph for ibuprofen oral suspension and validated as an in-house SOP [redacted] by the sponsor (see Table below). Dissolution testing was conducted with Children's ElixSure™ IB (also called Ibuprofen NonSpil Gel Suspension in this study report) Exhibit Batches (Formula Code [redacted], lot numbers S177-52967, S177-53137 and S177-53138. Lot S177-52967 was used in PK and bioequivalence studies.

Apparatus	USP Apparatus 2 Type- Paddle
Speed	[redacted]
Number of units	6
Sampling times (minutes)	5, 15, 25, 45 and 60
Media	900 mL 0.05 M phosphate buffer, pH 7.2
Temperature	37°C
Analytical Method	HPLC using variable wavelength detector set at [redacted]
Proposed Specification	Not less than [redacted] (Q) is dissolved in [redacted] (adopted from USP monograph)

Dissolution Results (Lot S177-52967) at pH 7.2:

Ibuprofen NonSpil™ Gel Suspension Exhibit Batch Lot S177-52967
Reference RD281 p. 53

Vessel	Sampling Time (min)
1	[redacted]
2	
3	
4	
5	
6	
Average	
RSD	

Table 1. Dissolution Profiles of Ibuprofen NonSpil™ Gel Suspension Exhibit Batch Lot S177-52967 in Phosphate Buffer at pH = 7.2

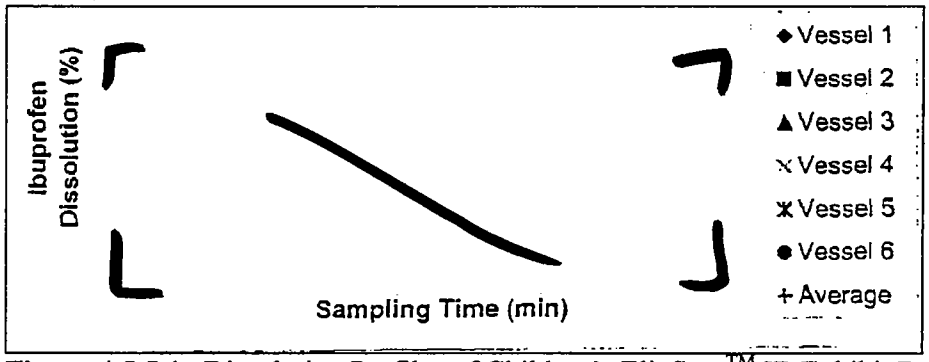


Figure 4.5.5.1. Dissolution Profiles of Children's ElixSure™ IB Exhibit Batch Lot S177-52967 in Phosphate Buffer at pH 7.2.

Dissolution results from other two lots were similar. Please refer to the individual study report (Appendix 6.2.4) for detail.

On average, more than [redacted] of ibuprofen was dissolved at [redacted] and about [redacted] at [redacted] for all three batches. A specification of [redacted] (Q) at 30 min is recommended to ensure uniformity of dissolution performance of different lots of Children's ElixSure™ IB.

4.6 Analytical

4.6.1 What moiety was measured in human plasma? Is free, bound or total measured?

Ibuprofen was isolated from human plasma by liquid-liquid extraction. Total concentrations of ibuprofen in plasma were determined.

4.6.2 What analytical methods were used to determine ibuprofen plasma concentrations?

Studies IUE-P1-262 and IUE-P2-134:
Ibuprofen concentrations were determined using [redacted] method [redacted] with UV detection [redacted] developed and validated in the laboratory of the Analytical Facility of [redacted] The details of analytical method and its validation are included in separate reports of the submission (Volumes 8 and 9 and Volumes 13 and 14).

Study 02212:
Analysis of ibuprofen was performed by the bioanalytical division of [redacted] using the analytical [redacted] The details of analytical method and its validation are included in separate reports of the submission (Volume 18).

The following table summarizes the analytical methods and their validation results:

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 143

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✓ § 552(b)(4) Draft Labeling

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Withheld Track Number: Clin Pharm/Bio- 243

6.2 Individual Study Reviews

6.2.1 Study IUE-P1-262: Single Dose Crossover Comparative Bioavailability Study of Ibuprofen 100 mg/5 mL Oral Suspension vs Ibuprofen Oral Suspension and Chewable Tablets in Healthy Male Volunteers Following a 200 mg Dose Administration – Fasting State (Volume 10, Appendix B)

Study Period: November 19, 2001 to December 4, 2001
Period 1: November 19 to November 20, 2001
Period 2: November 26 to November 27, 2001
Period 3: December 3 to December 4, 2001

Sample Analysis Period: December 13, 2001 to January 2, 2002
Analytical Re-assay: December 28, 2002 to January 4, 2002

Investigator: [redacted]

Study Center: [redacted]

Objectives: To evaluate and compare bioavailability and bioequivalence of three formulations of ibuprofen after a single oral dose administration under fasting conditions in healthy adults.

Subjects: A total of 27 male subjects (age 23 to 49 (38 ± 8, mean ± SD)) were enrolled to receive drug (Tables 1 and 2). All were Caucasians. 25 subjects completed the crossover design and were considered in the statistical and pharmacokinetic analyses. Subjects #8 and 21 withdrew their consent from the study before dosing of Periods 3 and 2, respectively. 14 subjects were smokers. The use of tobacco should not affect the bioequivalence assessment.

Table 1. Baseline Demographic Characteristics

	N	%
Age (y)		
23-49	27	100
Race		
Caucasian	27	100
Sex		
Male	27	100

Table 2. Summary Statistics For Age, Height, and Weight (All Subjects, N=27)

	Mean	Std	Min	Max
Age (y)	38	8	23	49
Height (cm)	175.6	6.4	164	192.5
Weight (kg)	77.2	11.6	60.9	101.0

Study Design: The study was a randomized, laboratory-blinded, single dose, 3-period, 3-sequence, crossover study in healthy male volunteers (Table 3). In each study period, a single 200 mg dose was orally administered in the morning; 10 mL of oral suspension (100 mg/5 mL) with 230 mL of water or four 50 mg chewable tablets with 240 mL of water. The subjects were randomized to receive the study medications. In each study period, subjects were fasted overnight for at least 10 hours before dosing until at least 4 hours after dose. For all periods, subjects were housed for at least 10 hours prior to drug administration until 16 hours post-dose. Each study period was separated by a 7-day washout period.

Table 3. Study design.

	Period 1	Period 2	Period 3
Sequence 1 (n=9)	Test	Reference 1	Reference 2
Sequence 2 (n=9)	Reference 1	Reference 2	Test
Sequence 3 (n=9)	Reference 2	Test	Reference 1

Dosage and Administration:

Test (A): Ibuprofen Nonspil™ (a.k.a. Children's ElixSure™ IB) 100 mg/5 mL, oral suspension
Taro Pharmaceuticals Inc.
Lot # S177-52967 Exp. N/AV

Reference 1 (C): Children's Motrin® 100 mg/5 mL, oral suspension
McNeil Consumer Healthcare (McNeil-PPC, Inc.)
Lot # DFM014 Exp. 06/03

Reference 2 (B): Children's Motrin® 50 mg chewable tablets
McNeil Consumer Healthcare (McNeil-PPC, Inc.)
Lot # EDM139 Exp. 05/03

A single 200 mg (10 mL of 100 mg/5 mL of oral suspension or four 50 mg chewable tablets) oral dose was administered under fasting conditions according to Table 3.

Sample Collection and Handling:
Timepoints: predose (in two tubes of 7 mL), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 16 hours post dose in one tube

7 mL blood samples were collected using EDTA as anticoagulant. Samples were stored at –70°C prior to shipping.

Sample Analysis: Ibuprofen concentrations were determined using a HPLC method [redacted] with UV detection [redacted] developed and validated in the laboratory of the Analytical Facility of [redacted]. The lower limit of quantitation (LOQ) was [redacted]. Quantitation was performed by peak height ratio using a weighted [redacted] linear regression (y = mx + b). The standard ibuprofen (reference standard No. RS-0096-C) and

internal standard ([redacted] (reference standard No. [redacted]) were supplied by [redacted] Whenever possible, all samples from a given subject (e.g., all sampling times and periods) were analyzed within a single analytical batch. Typically, the first aliquot was used for initial sample analysis, and the second aliquot was used for sample re-assay is necessary. The details of analytical method and its validation are included in separate reports (Volumes 13 and 14).

Pharmacokinetic and Statistical Analysis: Statistical and pharmacokinetic analyses were generated using [redacted] an application developed at [redacted] and SAS® version 8.2 (MIXED procedure). 25 subjects completed the crossover design and were considered in the statistical and pharmacokinetic analyses.

Pharmacokinetic parameters were analyzed by an Analysis of Variance (ANOVA) in which treatment, sequence, period as well as the left-over interaction terms between the three factors were modeled as fixed effects and the subjects (nested with sequence) was modeled with a random component. The parameter T_{max} was ranked transformed for all of the statistical analysis. Statistical significance was assessed at the 10% level. The 90% confidence interval of the relative geometric mean of C_{max}, AUC_T and AUC_∞ of the Test to the Reference product were calculated.

Pharmacokinetic Results:

Overall Profile

Figure 1 demonstrated the plasma concentration-time profile (mean ± SD, linear scale) for Test (Children's ElixSure™ IB, 100 mg/5 mL) and Reference 1 (Children's Motrin oral suspension, 100 mg/5 mL) and Reference 2 (Children's Motrin chewable tablets, 50 mg) products under fasting conditions.

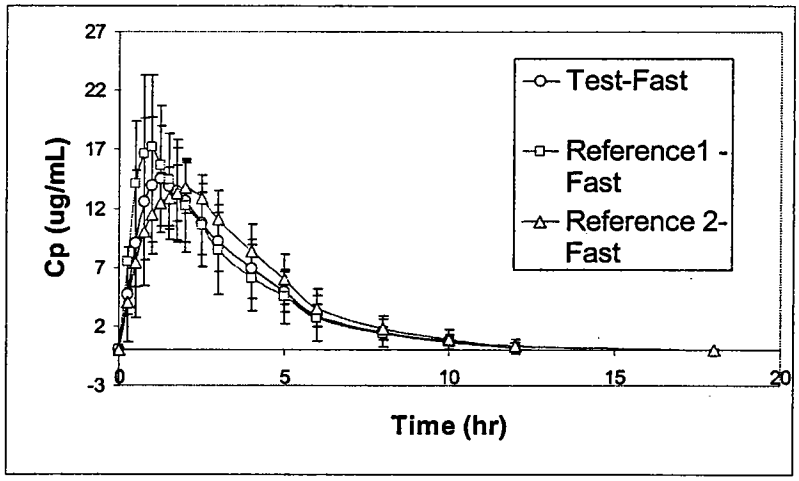

Figure 1. Plasma concentration-time profile (mean ± SD, N=27-28, linear scale) for Test (Children's ElixSure™ IB) and Reference 1 (Children's Motrin oral suspension) and Reference 2 (Children's Motrin chewable tablet) under fasting conditions.

Test vs Reference 1 under Fasting Conditions

The PK parameters (C_{max}, T_{max}, AUC_T and AUC_∞) for Test and Reference 1 products under fasting condition were summarized in Table 4. The parameters for which a statistically significant difference was observed between the Test and the Reference 1 product were C_{max}, ln (C_{max}), and T_{max}. No statistically significant differences were observed for other PK parameters listed.

Table 4. Summary of PK Parameters for Test and Reference 1 Products under Fasting Conditions.

PARAMETER	TEST		REFERENCE 1		T-Value	P
	MEAN	C.V.	MEAN	C.V.		
C_{max} (µg/mL)	18.189	23.8	20.589	21.9	-3.12	<0.01
ln(C_{max}) (µg/mL	2.8718	8.7	3.0008	7.6	-3.05	<0.01
T_{max} (hours)	1.00	59.0	1.00	55.1	3.02	<0.01
AUC_T (µg·h/mL)	57.582	22.0	59.381	25.1	-0.87	N.S.
ln(AUC_T) (µg·h/mL)	4.0295	5.6	4.0549	6.0	-0.76	N.S.
AUC_∞ (µg·h/mL	59.723	21.6	61.436	25.0	-0.79	N.S.
ln(AUC_∞) (µg·h/mL)	4.0668	5.4	4.0893	5.9	-0.66	N.S.
$AUC_{T/\infty}$ (%)	96.34	0.9	96.62	0.8	-1.19	N.S.
K_{el} (hours^{-1})	0.3501	17.0	0.3610	16.3	-0.96	N.S.
$T_{½el}$ (hours)	2.04	18.2	1.97	15.4	1.05	N.S.

For Tmax, the median is presented and the statistical analysis is based on ranks.

The 90% confidence interval of the relative geometric mean of the Test to the Reference 1 (Children's Motrin oral suspension) product for C_{max}, AUC_T, AUC_∞ and AUC_{0-4} were all within the acceptance range of 80-125% under the fasting conditions (Table 5).

Table 5. Comparison of Geometric Means of C_{max}, AUC_T, AUC_∞, and AUC_∞ for Test and Reference 1 Products under Fasting Conditions.

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST	REFERENCE 1		LOWER	UPPER
C_{max}	17.879	20.126	88.83	83.21	94.83
AUC_T	56.359	57.619	97.81	93.13	102.73
AUC_∞	58.504	59.643	98.09	93.43	102.98
AUC_{0-4}	40.26	43.09	93.42	88.58	98.52

The median T_{max} was 1.00 hr for the both Test (range 0.5-4 hr, 1.43 ± 0.84, mean ± SD, N=25) and Reference 1 (range 0.25-2.5 hr, 0.96 ± 0.53, mean ± SD, N=25) products, respectively. Stick

plot of the individual T_{max} values was shown in Figure 2. Distribution of individual T_{max} values was shown in Figure 3. T_{max} values were variable among subjects.

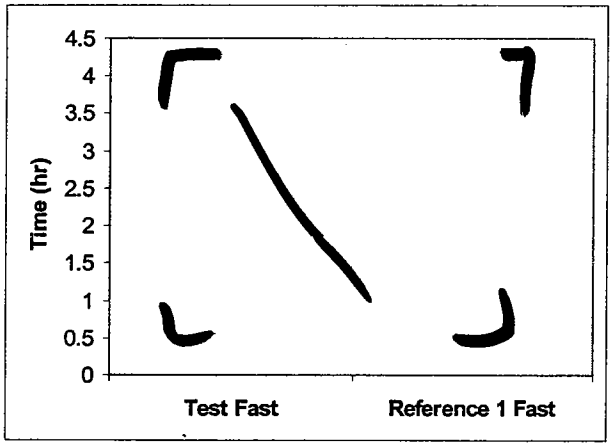

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Figure 2. Stick plot of the individual T_{max} values of Test and Reference 1 products under fasting conditions.

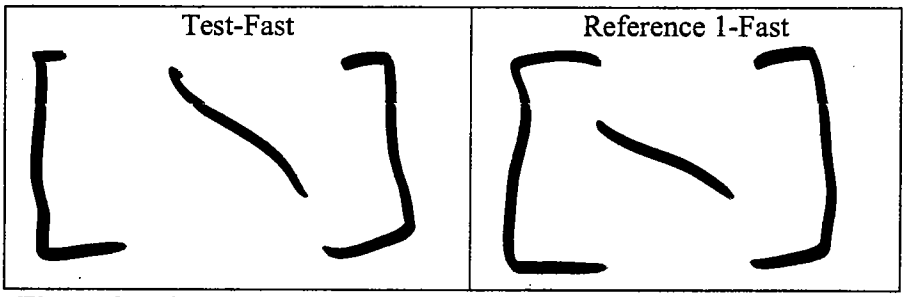

Figure 3. Distribution of individual T_{max} values of Test and Reference 1 products under fasting conditions.

Rates of absorption of ibuprofen Test and Reference 1 products in adults under fasting conditions were estimated with parameters such as absorption rate constant (k_a) and mean absorption time (MAT) (listed in Table 6). The results suggest that absorption rate of the Test product appeared to be a little slower than that of the Reference 1 product (Children's Motrin oral suspension) under fasting conditions.

Table 6. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant and Mean Absorption Time for Test and Reference 1 Products in Healthy Adults under Fasting Conditions.

Parameter	Test (Fasting)		Reference 1 (Fasting)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
k_a (h^{-1})	1.32 ± 1.05	79.5	1.74 ± 1.30	74.6
MAT (h)	0.46 ± 0.42	91	0.27 ± 0.36	136

Test vs Reference 2 under Fasting Condition

The PK parameters (C_{max}, T_{max}, AUC_T and AUC_∞) for Test and Reference 2 products under fasting condition were summarized in Table 7. The parameters for which a statistically significant difference was observed between the Test and the Reference 2 product were C_{max}, ln (C_{max}), AUC_T, ln (AUC_T), AUC_∞, ln (AUC_∞) and T_{max}. No statistically significant differences were observed for other PK parameters listed.

Table 7. Summary of PK Parameters for Test and Reference 2 Products under Fed Conditions.

PARAMETER	TEST		REFERENCE 2		T-Value	P
	MEAN	C.V.	MEAN	C.V.		
C_{max} (µg/mL)	18.189	23.8	15.969	22.8	3.56	<0.001
ln(C_{max}) (µg/mL)	2.8718	8.7	2.7465	8.1	3.65	<0.001
T_{max} (hours)	1.00	59.0	1.50	43.3	-3.18	<0.01
AUC_T (µg·h/mL)	57.582	22.0	62.888	25.4	-2.80	<0.01
ln(AUC_T) (µg·h/mL)	4.0295	5.6	4.1103	6.2	-2.65	<0.05
AUC_∞ (µg·h/mL)	59.723	21.6	65.005	25.0	-2.69	<0.01
ln(AUC_∞) (µg·h/mL)	4.0668	5.4	4.1445	6.1	-2.57	<0.05
$AUC_{T/\infty}$ (%)	96.34	0.9	96.65	0.9	-1.28	N.S.
K_{el} (hours^{-1})	0.3501	17.0	0.3598	19.8	-0.76	N.S.
$T½_{el}$ (hours)	2.04	18.2	2.00	20.3	0.44	N.S.

For Tmax, the median is presented and the statistical analysis is based on ranks.

The 90% confidence interval of the relative geometric mean of the Test to the Reference 2 (Children's Motrin chewable tablets) product for C_{max}, AUC_T, AUC_∞ and AUC_{0-4} were all within the acceptance range of 80-125% under the fasting conditions (Table 8).

Table 8. Comparison of Geometric Means of C_{max}, AUC_T, AUC_∞, and AUC_{0-4} for Test and Reference 2 Products under Fasting Conditions.

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST	REFERENCE 2		LOWER	UPPER
C_{max}	17.879	15.513	115.25	107.96	123.03
AUC_T	56.359	60.901	92.54	88.11	97.20
AUC_∞	58.504	63.027	92.82	88.41	97.45
AUC_{0-4}	40.26	40.99	98.20	93.12	103.57

The median T_{max} was 1.00 hr for the Test (range 0.5-4 hr, 1.43 ± 0.84, mean ± SD, N=25) and 1.50 hr for Reference 2 (range 0.75-4 hr, 1.85 ± 0.80, mean ± SD, N=25) product, respectively. Stick plot of the individual T_{max} values was shown in Figure 4. Distribution of individual T_{max} values was shown in Figure 5. T_{max} values were variable among subjects.

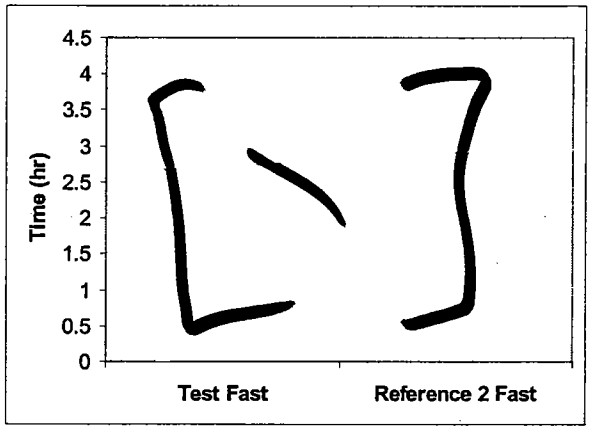

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Figure 4. Stick plot of the individual T_{max} values of Test and Reference 2 products under fasting conditions.

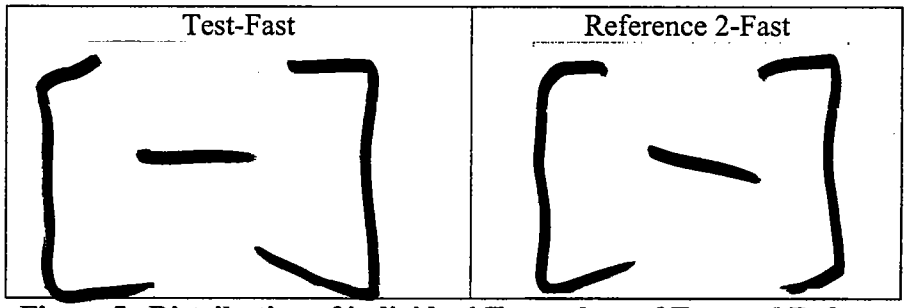

Figure 5. Distribution of individual T_{max} values of Test and Reference 2 products under fasting conditions.

Rates of absorption of ibuprofen Test and Reference 2 products in adults under fasting conditions were estimated with parameters such as absorption rate constant (k_a) and mean absorption time (MAT) (listed in Table 9). The results suggest that absorption rate of the Test product appeared to be a little faster than that of the Reference 2 product (Children's Motrin chewable tablets) under fasting conditions.

Table 9. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant and Mean Absorption Time for Test and Reference 2 Products in Healthy Adults under Fasting Conditions.

Parameter	Test (Fasting)		Reference 2 (Fasting)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
k_a (h^{-1})	1.32 ± 1.05	79.5	0.81 ± 0.46	57.2
MAT (h)	0.46 ± 0.42	91	0.75 ± 0.51	69

Conclusions: The 90% confidence interval of the relative geometric mean of the Test to the Reference 1 (Children's Motrin oral suspension) and Reference 2 (Children's Motrin chewable tablets) products for C_{max}, AUC_T, AUC_∞ and AUC_{0-4} were all within the acceptance range of 80-125% under the fasting conditions. Therefore, the test product is bioequivalent to both reference products. The Test product appeared to have slower absorption rate than the Reference 1 product and faster absorption rate than the Reference 2 product, probably due to its unique formulation ("nonspill" oral suspension). Because both reference products are approved products that are safe and effective, the differences in T_{max} (or absorption rate) is not considered clinically relevant.

Comments: In this study, only Caucasian male subjects were enrolled. It is recommended to enroll subjects with representative ethnic groups and both genders in future studies.

Appendix. Demographic Data (Study IUE-P1-262).

Subject	Initials	Age (years)	Height (cm)	Weight (kg)
01		37	171.0	78.8
02		46	174.0	64.5
03		48	168.5	83.0
04		45	167.0	65.9
05		49	167.5	70.1
06		49	174.0	85.4
07		48	178.0	82.7
08		41	176.0	78.1
09		27	177.0	87.1
10		37	176.0	60.5
11		47	183.0	73.4
12		39	177.0	77.1
13		25	192.5	96.6
14		38	168.0	62.5
15		38	177.0	80.0
16		32	176.0	71.2
17		31	184.0	101.0
18		47	177.0	86.2
19		40	178.0	66.3
20		38	178.0	76.5
21		33	185.5	100.7
22		37	180.0	76.5
23		45	172.0	58.9
24		30	167.5	77.1
25		31	172.0	60.9
26		23	180.0	84.2
27		38	164.0	79.0
	MEAN	38	175.6	77.2
	S.D.	8	6.4	11.6
	C.V.	19.8	3.7	15.0

6.2.2 Study IUE-P2-134: Single Dose Crossover Comparative Bioavailability Study of Ibuprofen 100 mg/5 mL Oral Suspension in Healthy Male Volunteers Following a 200 mg Dose Administration – Fasting and Fed States (Volume 4, Appendix A)

Study Period: July 7, 2002 to July 29, 2002
Period 1: July 7 to July 8, 2002
Period 2: July 14 to July 15, 2002
Period 3: July 21 to July 22, 2002
Period 4: July 28 to July 29, 2002

Sample Analysis Period: August 6, 2002 to September 4, 2002
Analytical and Pharmacokinetic re-assay: August 29, 2002 to September 11, 2002

Investigator: [redacted]

Study Center: [redacted]

Objective: To evaluate the effect of food on the bioavailability of two formulations of ibuprofen after a single oral dose administration under both fasting and fed conditions in healthy adults. *(Reviewer's Note: The main objective of this study is to determine whether there is food effect for the test product. Establishment of bioequivalence between the test and reference product under fasting conditions has been fulfilled in another study, IUE-P1-262 (Appendix 6.2.1 of the QBR review). In this study, the sponsor generated additional data to compare bioequivalence of the test product to the reference product under both fasting and fed conditions.)*

Subjects: A total of 30 male subjects (age 20 to 50 (37 ± 9, mean ± SD)) were enrolled to receive drug (Tables 1 and 2 and Appendix). 25 of them were Caucasian, 4 were African American and 1 was Asian. Statistical and pharmacokinetic analyses were performed on data from 28 subjects (Subject# 1-10, 12-24 and 26-30) for the fasting state and on data from 28 subjects (Subject # 1-10, 12-20 and 22-30) for the fed state.

Table 1. Baseline Demographic Characteristics

	N	%
Age (y)		
20-50	30	100
Race		
Caucasian	25	83.3
African American	4	13.3
Asian	1	3.3
Sex		
Male	30	100

Table 2. Summary Statistics For Age, Height, and Weight (All Subjects, N=30)

	Mean	Std	Min	Max
Age (y)	37	9	20	50
Height (cm)	172.9	6.1	163	188
Weight (kg)	76	7.7	62.5	99.8

Study Design: The study was a randomized, laboratory-blinded, single dose, 4-period, 2-sequence, crossover study in healthy male volunteers (Table 3). In the first two periods, a single 200 mg dose was orally administered with 230 mL of water in the morning. The subjects were randomized to receive the study medications. In these two study periods, subjects were fasted overnight for at least 10 hours before dosing until approximately 5 hours after dose. In the last two periods, a single 200 mg dose was dosed orally with 230 mL of water in the morning, thirty minutes after a high fat breakfast.

For all periods, subjects were housed for at least 10 hours prior to drug administration until 12 hours post-dose. Each study period was separated by a 7-day washout period.

Table 3. Study design.

	Period 1	Period 2	Period 3	Period 4
Sequence 1 (n=15)	Test (fasting)	Reference (fasting)	Test (food)	Reference (food)
Sequence 2 (n=15)	Reference (fasting)	Test (fasting)	Reference (food)	Test (food)

Dosage and Administration:

Test: Ibuprofen Nonspil™ (a.k.a. Children's ElixSure™ IB) 100 mg/5 mL, oral suspension
Taro Pharmaceuticals Inc.
Lot # S177-52967 EKB-103 Exp. N/AV
Measured Content: 99.1 mg/5 mL

Reference: Children's Motrin 100 mg/5 mL, oral suspension
McNeil Consumer Products
Lot # FCM 137 Exp. 04/05
Measured Content: 98.7 mg/5 mL

A single 200 mg (10 mL of 100 mg/5 mL of oral suspension) oral dose was administered either under fasting or fed conditions according to Table 3.

Sample Collection and Handling:
Timepoints: predose (in two tubes of 7 mL), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post dose

7 mL blood samples were collected using EDTA as anticoagulant. Samples were stored at –70°C prior to shipping.

Sample Analysis: Ibuprofen concentrations were determined using a HPLC method [redacted] with UV detection [redacted] developed and validated in the laboratory of the

Analytical Facility of [redacted] The lower limit of quantitation (LOQ) was [redacted] Quantitation was performed by peak height ratio using a weighted [redacted] linear regression (y = mx + b). The standard ibuprofen (reference standard No. [redacted], Lot No. 079H0939) and internal standard [redacted] (reference standard No. [redacted] were supplied by [redacted] The details of analytical method and its validation are included in separate reports (Volumes 8 and 9).

Pharmacokinetic and Statistical Analysis: Statistical and pharmacokinetic analyses were generated using [redacted] an application developed at [redacted] and SAS® version 8.2 (MIXED procedure). Statistical and pharmacokinetic analyses were performed on data from 28 subjects (Subject# 1-10, 12-24 and 26-30) for the fasting state and on data from 28 subjects (Subject # 1-10, 12-20 and 22-30) for the fed state. Subject# 11 was excluded from all analysis because of sample assay problems. Subject# 21 was excluded from fed data because several samples at Periods 3 and 4 were reported NR for analytical reasons. Subject# 25 had diarrhea at 1 hr before dosing in Period 2 and lasting for almost 4 hours, therefore all data under fasting conditions for this subject were excluded.

The 90% confidence interval of the relative geometric mean of C_{max}, AUC_T, AUC_∞, and AUC_{0-4} of the Test to the Reference product (within each diet) were calculated. In addition, the 90% confidence interval of relative geometric mean of C_{max}, AUC_T, AUC_∞, and AUC_{0-4} of the fast to the fed diet (within each formulation) were calculated.

Pharmacokinetic Results:

Overall Profile

Figure 1 demonstrated the plasma concentration-time profile (mean ± SD, linear scale) for the Test (Children's ElixSure™ IB, 100 mg/5 mL) and the Reference (Children's Motrin oral suspension, 100 mg/5 mL) product under fasting and fed conditions.

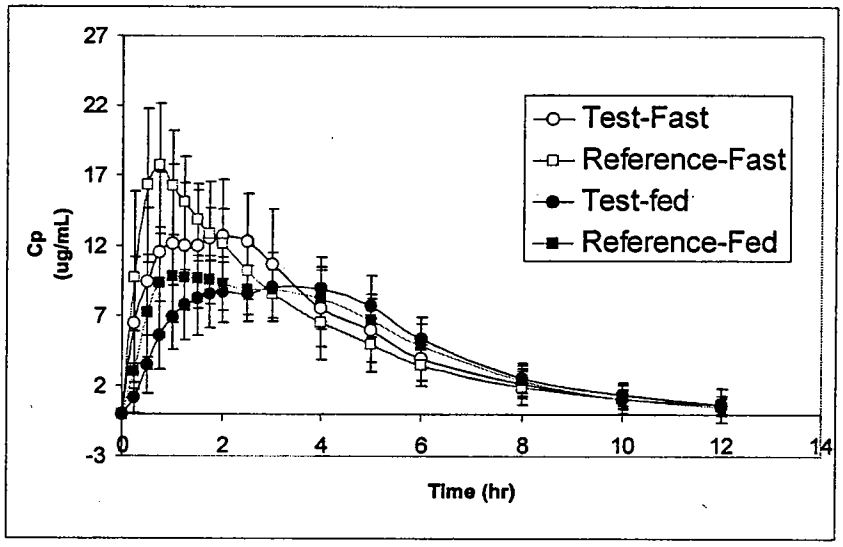

Figure 1. Plasma concentration-time profile (mean ± SD, N=27-28, linear scale) for Test (Children's ElixSure™ IB) and Reference (Children's Motrin) products under fasting and fed conditions.

Test vs Reference Under Fasting Conditions

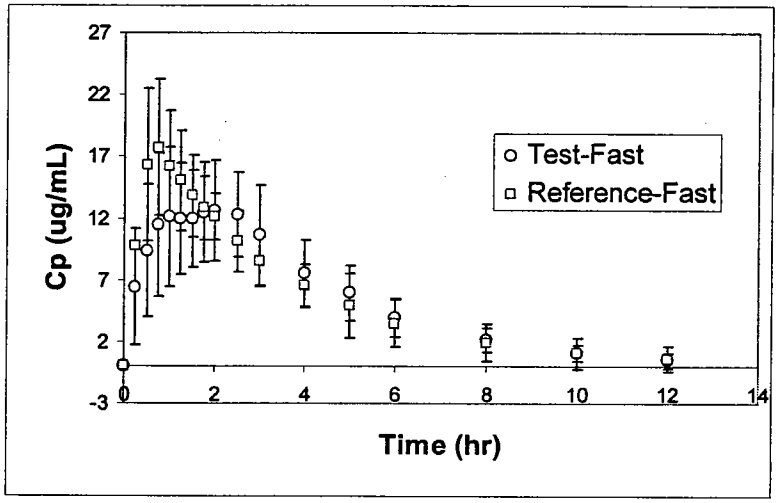

Figure 2. Plasma concentration-time profile (mean ± SD, linear scale) for Test (Children's ElixSure™ IB) and Reference (Children's Motrin) under fasting conditions.

The PK parameters (C_{max}, T_{max}, AUC_T and AUC_∞) for Test and Reference products under fasting conditions were summarized in Table 4. The parameters for which a statistically significant difference was observed between the Test and the Reference product were C_{max}, ln (C_{max}), and T_{max}. No statistically significant differences were observed for other PK parameters listed.

Table 4. Summary of PK Parameters for Test and Reference Products under Fasting Conditions.

PARAMETER	TEST		REFERENCE		T-Value	P
	MEAN	C.V.	MEAN	C.V.		
C_{max} (µg/mL)	17.315	18.9	20.049	18.5	-3.91	<0.001
ln(C_{max}) (µg/mL)	2.8339	6.8	2.9807	6.5	-3.79	<0.001
T_{max} (hour)	2.00	52.3	0.75	82.1	5.60	<0.001
AUC_T (µg·h/mL)	63.514	20.0	64.315	20.0	-0.35	N.S.
ln(AUC_T) (µg·h/mL)	4.1330	4.7	4.1452	4.7	-0.40	N.S.
AUC_∞ (µg·h/mL)	66.790	20.9	69.114	29.8	-0.59	N.S.
ln(AUC_∞) (µg·h/mL)	4.1819	4.8	4.2032	5.9	-0.49	N.S.
$AUC_{T/\infty}$ (%)	95.29	3.4	94.62	6.7	0.46	N.S.
K_{el} (hour^{-1})	0.3258	24.4	0.3096	27.7	0.78	N.S.
$T_{½el}$ (hour)	2.30	34.7	2.50	43.5	-0.79	N.S.

For Tmax, the median is presented.
For Tmax, the statistical analysis is based on ranks.
N.S.= Not Significant (P>0.01)

The 90% confidence interval of the relative geometric mean of the Test to the Reference (Children's Motrin oral suspension) product for C_{max}, AUC_T, AUC_∞ and AUC_{0-4} were all within the acceptance range of 80-125% under the fasting conditions (Table 5).

Table 5. Comparison of Geometric Means of C_{max}, AUC_T, AUC_∞ and AUC_{0-4} for Test and Reference Products under Fasting Conditions.

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	17.06	19.70	86.59	81.16	92.39
AUC_T	62.38	63.03	98.97	94.66	103.48
AUC_∞	65.46	66.66	98.20	92.15	104.65
AUC_{0-4}	40.68	44.26	91.91	86.21	97.98

The median T_{max} was 2.00 hr (range 0.75-5 hr, 1.89 ± 0.99 hr, N=28) and 0.75 hr (range 0.25-4 hr, 0.95 ± 0.78 hr, N=28) for the Test and Reference Product, respectively. It may indicate a slower onset of effect with the Test product. Stick plot of the individual T_{max} values was shown in Figure 3. Distribution of individual T_{max} values was shown in Figure 4. T_{max} values were variable among subjects.

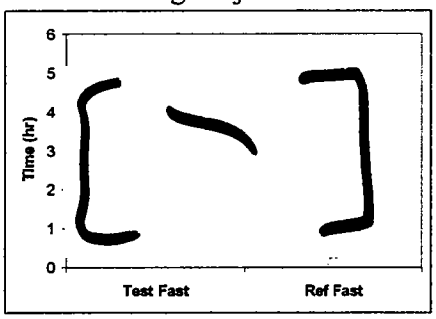

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Figure 3. Stick plot of the individual T_{max} values of Test and Reference products under fasting conditions.

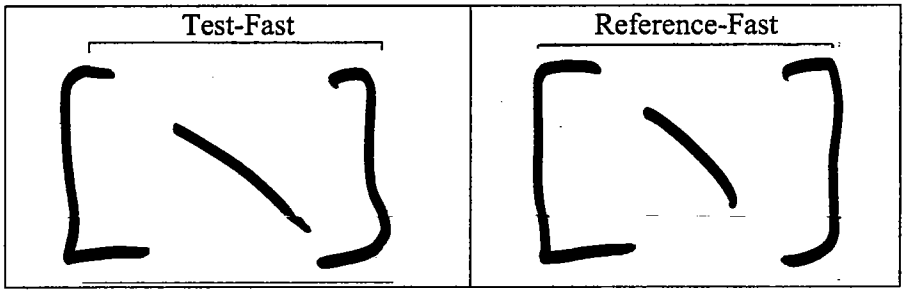

Figure 4. Distribution of individual T_{max} values of Test and Reference products under fasting conditions.

Rates of absorption of ibuprofen Test and Reference products in adults under fasting conditions were estimated with parameters such as absorption rate constant (k_a) and mean absorption time (MAT) (listed in Table 6). The results suggest that absorption rate of the Test product appeared to be slower than that of the Reference product under fasting conditions.

Table 6. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant and Mean Absorption Time for Test and Reference Products in Healthy Adults under Fasting Conditions.

Parameter	Test (Fasting)		Reference (Fasting)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
k_a (h^{-1})	1.59 ± 1.64	103.3	2.49 ± 1.74	69.9
MAT (h)	0.71 ± 0.57	80.9	0.40 ± 0.37	91.8

Test vs Reference under Fed Conditions

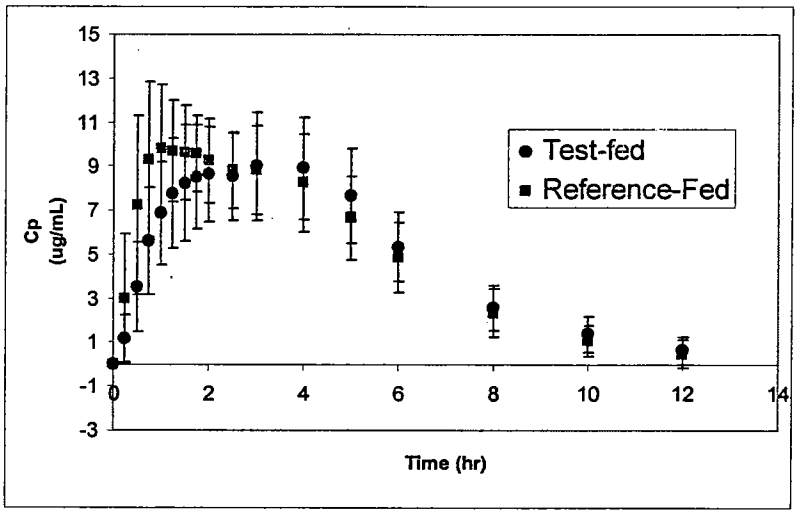

Figure 5. Plasma concentration-time profile (mean ± SD, linear scale) for Test (Children's ElixSure™ IB) and Reference (Children's Motrin) under fed conditions.

The PK parameters (C_{max}, T_{max}, AUC_T and AUC_∞) for Test and Reference products under fed conditions were summarized in Table 7. The parameters for which a statistically significant difference was observed between the Test and the Reference product were T_{max} and K_{el}. No statistically significant differences were observed for other PK parameters listed.

Table 7. Summary of PK Parameters for Test and Reference Products under Fed Conditions.

PARAMETER	TEST		REFERENCE		T-Value	P
	MEAN	C.V.	MEAN	C.V.		
C_{max} (µg/mL)	10.776	19.8	11.689	24.7	-1.52	N.S.
ln(C_{max}) (µg/mL)	2.3580	8.5	2.4311	9.7	-1.43	N.S.
T_{max} (hour)	3.00	49.3	1.50	65.5	4.15	<0.001
AUC_T (µg·h/mL)	56.639	17.4	57.879	20.9	-0.91	N.S.
ln(AUC_T) (µg·h/mL	4.0221	4.3	4.0378	5.1	-0.63	N.S.
AUC_∞ (µg·h/mL)	60.143	18.4	60.709	21.6	-0.39	N.S.
ln(AUC_∞) (µg·h/mL)	4.0805	4.5	4.0843	5.2	-0.15	N.S.
$AUC_{T/\infty}$ (%)	94.44	4.8	95.48	2.5	-1.43	N.S.
K_{el} (hour^{-1})	0.3501	23.6	0.3787	21.9	-1.97	<0.10
$T½_{el}$ (hour)	2.15	37.9	1.93	25.6	1.41	N.S.

For Tmax, the median is presented.
For Tmax, the statistical analysis is based on ranks.
N.S.= Not Significant (P>0.0*)

The 90% confidence interval of the relative geometric mean of the Test to the Reference (Children's Motrin oral suspension) product for C_{max}, AUC_T, AUC_∞ and AUC_{0-4} were all within the acceptance range of 80-125% under the fed conditions (Table 8).

Table 8. Comparison of Geometric Means of C_{max}, AUC_T, AUC_∞, and AUC_{0-4} for Test and Reference Products under Fed Conditions.

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	10.56	11.36	92.95	85.20	101.42
AUC_T	56.18	57.07	98.44	94.37	102.69
AUC_∞	59.56	59.79	99.62	95.48	103.93
AUC_{0-4}	28.37	32.65	86.88	82.29	91.71

The median T_{max} was 3.00 hr (range 0.75-5 hr, 2.98 ± 1.47 hr, N=28) and 1.50 hr (range 0.5-5 hr, 1.81 ± 1.19 hr, N=28) for the Test and Reference Product, respectively. It may indicate a slower onset of effect with the Test product. Stick plot of the individual T_{max} values was shown in Figure 5. Distribution of individual T_{max} values was shown in Figure 6. T_{max} values were variable among subjects for both Test and Reference products.

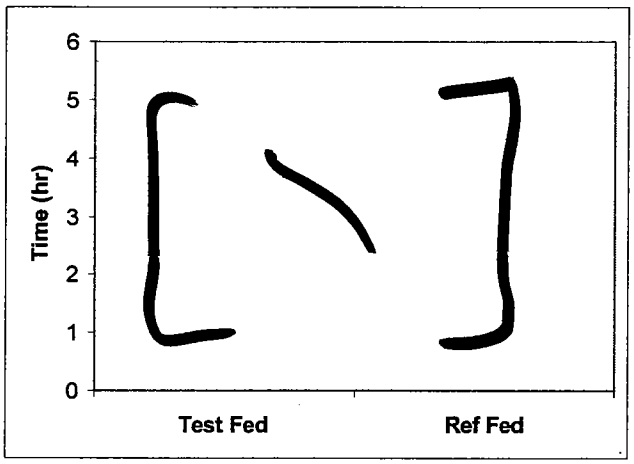

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Figure 5. Stick plot of the individual T_{max} values of Test and Reference products under fed conditions.

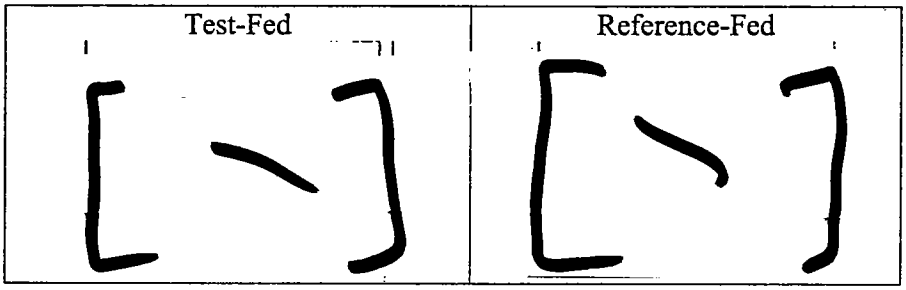

Figure 6. Distribution of individual T_{max} values of Test and Reference products under fed conditions.

Rates of absorption of ibuprofen Test and Reference products in adults under fed conditions were estimated with parameters such as absorption rate constant (k_a) and mean absorption time (MAT) (listed in Table 9). The results suggest that absorption rate of the Test product appeared to be slower than that of the Reference product under fed conditions.

Table 9. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant and Mean Absorption Time for Test and Reference Products in Healthy Adults under Fed Conditions.

Parameter	Test (Fed)		Reference (Fed)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
k_a (h^{-1})	0.66 ± 0.52	78.7	1.66 ± 1.48	92.1
MAT (h)	1.56 ± 0.51	32.8	1.32 ± 0.52	39.5

Food effect for the Test product **(Main Objective of the Study)**

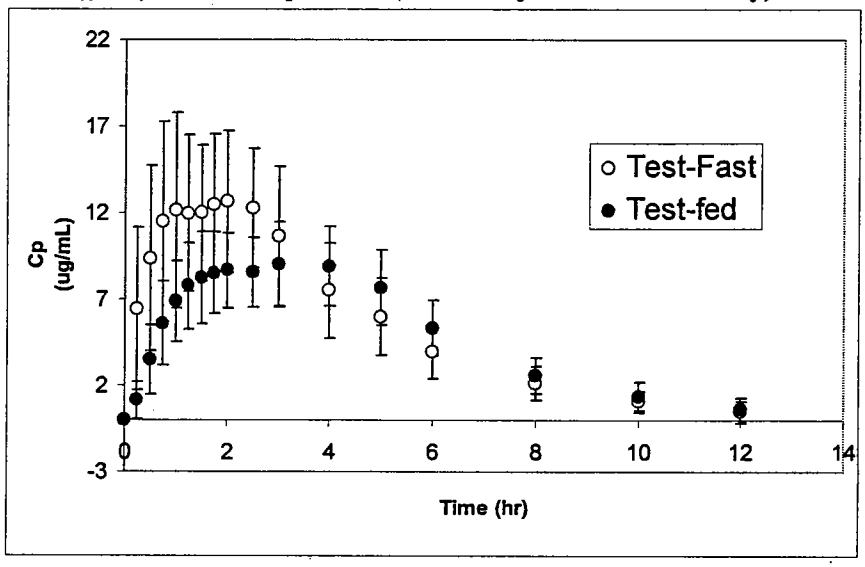

Figure 7. Plasma concentration-time profile (mean ± SD, linear scale) for the Test (Children's ElixSure™ IB) product under fasting and fed conditions.

The PK parameters (C_{max}, T_{max}, AUC_T and AUC_∞) for the Test product under fasting and fed conditions were summarized in Table 10. The parameters for which a statistically significant difference was observed between the Test and the Reference product were C_{max}, $\ln(C_{max})$, T_{max}, AUC_T, $\ln(AUC_T)$, AUC_∞ and $\ln(AUC_\infty)$. No statistically significant differences were observed for other PK parameters listed.

Table 10. Summary of PK Parameters for Test Product under Fasting and Fed Conditions.

PARAMETER	Test (fast)		Test (food)		T-Value	P
	MEAN	C.V.	MEAN	C.V.		
C_{max} (µg/mL)	17.315	18.9	10.776	19.8	8.69	<0.001
$\ln(C_{max})$ (µg/mL)	2.8339	6.8	2.3580	8.5	9.52	<0.001
T_{max} (hour)	2.00	52.3	3.00	49.3	-2.73	<0.01
AUC_T (µg·h/mL)	63.514	20.0	56.639	17.4	3.74	<0.001
$\ln(AUC_T)$ (µg·h/mL)	4.1330	4.7	4.0221	4.3	3.70	<0.001
AUC_∞ (µg·h/mL)	66.790	20.9	60.143	18.4	2.37	<0.05
$\ln(AUC_\infty)$ (µg·h/mL)	4.1819	4.8	4.0805	4.5	2.82	<0.01
$AUC_{T/\infty}$ (%)	95.29	3.4	94.44	4.8	0.90	N.S.
K_{el} (hour^{-1})	0.3258	24.4	0.3501	23.6	-1.32	N.S.
$T_{1/2el}$ (hour)	2.30	34.7	2.15	37.9	0.76	N.S.

For Tmax, the median is presented.
For Tmax, the statistical analysis is based on ranks.
N.S.= Not Significant (P>0.05)

The 90% confidence interval of the relative geometric mean (fasting vs. fed) of the Test product for AUC_T and AUC_∞ were within the acceptance range of 80-125% (Table 11).

For C_{max}, the 90% confidence interval of the relative geometric mean (fasting vs. fed) of the Test product was outside the specified range of 80-125% for bioequivalence (Table 11). The results showed that food decreased the peak plasma concentration by 38%.

Similarly, for AUC_{0-4}, the 90% confidence interval of the relative geometric mean (fasting vs. fed) of the Test product was outside the specified range of 80-125% for bioequivalence (Table 11), outside the specified range of 80-125% for bioequivalence. The results showed that food decreased the exposure of ibuprofen (Test product) at earlier timepoints.

Table 11. Comparison of Geometric Means of C_{max}, AUC_T, AUC_∞, and AUC_{0-4} for Test Product under Fasting and Fed Conditions (Sponsor's Table).

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST-FAST	TEST-FED		LOWER	UPPER
C_{max}	17.06	10.56	161.55	148.51	175.73
AUC_T	62.38	56.18	111.04	105.91	116.42
AUC_∞	65.46	59.56	109.91	103.92	116.25
AUC_{0-4}	40.68	28.37	143.42	133.25	154.36

(Reviewer's Note: Normally, we use data from fasting conditions as the reference and fed conditions as the test (the sponsor did the opposite way here). A comment will be conveyed to the sponsor regarding this. Ratio and 90% confidence limit data were recalculated by the reviewer. Please refer to the main review, P. 17, Table 4.5.3.1 for details.)

The median T_{max} was 2.00 hr (range 0.75-5 hr, 1.89 ± 0.99 hr, N=28) and 3.00 hr (range 0.75-5 hr, 2.98 ± 1.47 hr, N=28) for the Test product under fasting and fed conditions, respectively. Food appears to decrease absorption rate of the Test product in healthy adults (Table 12).

Table 12. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant and Mean Absorption Time for the Test Product in Healthy Adults under Fasting and Fed Conditions.

Parameter	Test (Fasting)		Test (Fed)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
k_a (h^{-1})	1.59 ± 1.64	103.3	0.66 ± 0.52	78.7
MAT (h)	0.71 ± 0.57	80.9	1.56 ± 0.51	32.8

Food effect for the Reference product

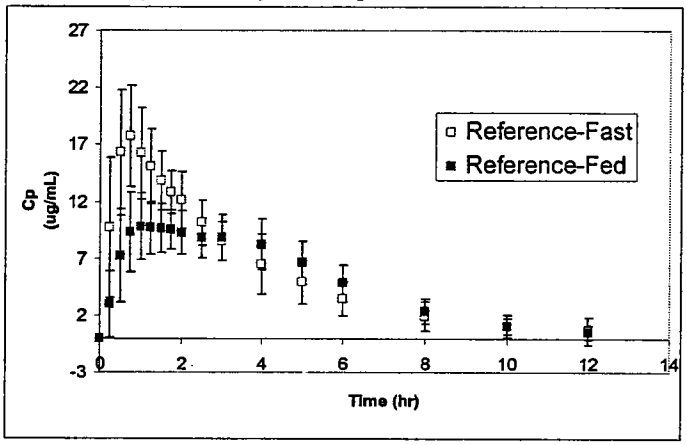

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Figure 8. Plasma concentration-time profile (mean ± SD, linear scale) for the Reference (Children's Motrin) product under fasting and fed conditions.

The PK parameters (C_{max}, T_{max}, AUC_T and AUC_∞) for the Reference product under fasting and fed conditions were summarized in Table 13. The parameters for which a statistically significant difference was observed between the fasting and fed conditions for the Reference product were C_{max}, $\ln(C_{max})$, T_{max}, AUC_T, $\ln(AUC_T)$, AUC_∞, $\ln(AUC_\infty)$, K_{el} and $T_{1/2el}$. No statistically significant differences were observed for $AUC_{T/\infty}$.

Table 13. Summary of PK Parameters for the Reference Product under Fasting and Fed Conditions.

PARAMETER	Reference (fast)		Reference (food)		T-Value	P
	MEAN	C.V.	MEAN	C.V.		
C_{max} (µg/mL)	20.049	18.5	11.689	24.7	11.03	<0.001
$\ln(C_{max})$ (µg/mL)	2.9807	6.5	2.4311	9.7	10.93	<0.001
T_{max} (hour)	0.75	82.1	1.50	65.5	-3.78	<0.001
AUC_T (µg·h/mL)	64.315	20.0	57.879	20.9	3.40	<0.01
$\ln(AUC_T)$ (µg·h/mL)	4.1452	4.7	4.0378	5.1	3.51	<0.001
AUC_∞ (µg·h/mL)	69.114	29.8	60.709	21.6	2.91	<0.01
$\ln(AUC_\infty)$ (µg·h/mL)	4.2032	5.9	4.0843	5.2	3.24	<0.01
$AUC_{T/\infty}$ (%)	94.62	6.7	95.48	2.5	-0.70	N.S.
K_{el} ($hour^{-1}$)	0.3096	27.7	0.3787	21.9	-3.81	<0.001
$T_{½el}$ (hour)	2.50	43.5	1.93	25.6	2.79	<0.01

For Tmax, the median is presented.
For Tmax, the statistical analysis is based on ranks.
N.S.= Not Significant (P>0.0·)

The 90% confidence interval of the relative geometric mean (fasting vs. fed) of the Reference product for AUC_T and AUC_∞ were within the acceptance range of 80-125% (Table 14).

For C_{max}, the 90% confidence interval of the relative geometric mean (fasting vs. fed) of the Reference product was outside the specified range of 80-125% for bioequivalence (Table 14). The results showed that food decreased the peak plasma concentration by 42%.

Similarly, for AUC_{0-4}, the 90% confidence interval of the relative geometric mean (fasting vs. fed) of the Reference product was outside the specified range of 80-125% for bioequivalence (Table 14). The results showed that food decreased the exposure of ibuprofen (Reference product) at earlier timepoints.

Table 14. Comparison of Geometric Means of C_{max}, AUC_T and AUC_∞ for the Reference Product under Fasting and Fed Conditions (Sponsor's Table).

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	REFERENCE-FAST	REFERENCE-FED		LOWER	UPPER
C_{max}	19.70	11.36	173.41	159.42	188.63
AUC_T	63.03	57.07	110.45	105.35	115.80
AUC_∞	66.66	59.79	111.50	105.42	117.93
AUC_{0-4}	44.26	32.65	135.56	125.95	145.91

(Reviewer's Note: Normally, we use data from fasting conditions as the reference and fed conditions as the test (the sponsor did the opposite way here). A comment will be conveyed to the sponsor regarding this. Data were not recalculated.)

The median T_{max} was 0.75 hr (range 0.25-4 hr, 0.95 ± 0.78 hr, N=28) and 1.50 hr (range 0.5-5 hr, 1.81 ± 1.19 hr, N=28) for the Reference product under fasting and fed conditions, respectively. Food appears to decrease absorption rate (Table 15).

Table 15. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant and Mean Absorption Time for the Reference Product in Healthy Adults under Fasting and Fed Conditions.

Parameter	Reference (Fasting)		Reference (Fed)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
k_a (h^{-1})	2.49 ± 1.74	69.9	1.66 ± 1.48	92.1
MAT (h)	0.40 ± 0.37	91.8	1.32 ± 0.52	39.5

Conclusions: The 90% confidence interval of the relative geometric mean of the Test to the Reference product for C_{max}, AUC_T, AUC_∞, and AUC_{0-4} were all within the acceptance range of 80-125% under both fasting and fed conditions. Therefore, these two products are considered bioequivalent in healthy adults. The Test product appeared to have slower absorption rate than the Reference product probably due to its unique formulation ("nonspill" oral suspension). In

Study IUE-P1-262, the test product was shown to have faster absorption rate than chewable tablet formulation.

Food delayed rate of absorption (to a similar extent) for both the Test and the Reference products, with a decrease in C_{max} and an increase in T_{max}. Overall extent of exposure, as indicated by AUC_{∞}, was bioequivalent between fasting and fed conditions for both products.

Comments: In this study, only male subjects were included. It is recommended to include both genders in future studies.

Appendix. Demographic Data (Study IUE-P2-134).

Subject	Initials	Age (years)	Height (cm)	Weight (kg)
01		46	188.0	77.7
02		50	168.0	77.0
03		36	173.0	78.0
04		35	163.0	81.0
05		45	169.0	71.5
06		45	177.0	79.2
07		39	176.0	81.0
08		34	170.0	82.7
09		36	162.0	82.5
10		49	178.0	89.5
11		24	173.0	68.4
12		39	176.0	76.7
13		35	177.0	85.5
14		30	178.0	80.0
15		24	167.5	71.4
16		49	170.5	72.5
17		50	167.0	74.0
18		46	176.0	69.5
19		43	171.0	76.7
20		45	173.0	70.3
21		37	179.5	99.8
22		26	165.0	74.0
23		38	172.0	68.3
24		36	178.5	69.7
25		38	169.0	67.5
26		20	171.0	62.5
27		25	167.0	67.2
28		24	185.0	81.5
29		24	178.0	76.8
30		42	168.0	68.0
	MEAN	37	172.9	76.0
	S.D.	9	6.1	7.7
	C.V.	24.3	3.5	10.1

6.2.3 Study 02212: Randomized, 1-Way Parallel, Comparative Pharmacokinetics Study of Ibuprofen 10 mg/kg Suspension and Children's Motrin 10 mg/kg Suspension Administered as 1 X 10 mg/kg Suspension in Healthy Children Under Fasting Conditions (Volume 15, Appendix C)

Study Period (Clinical Portion): September 29, 2002

Sample Analysis Period: October 3, 2002 to October 17, 2002

Principle Investigator: Jose M. Carpio, MD
Sub-Investigator: [redacted]

Study Center: SFBC International, 11190 Biscayne Blvd., Miami, FL 33181

Objectives: To compare the rate and extent of absorption of ibuprofen 10 mg/kg oral suspension (Children's ElixSure™ IB, Test) versus Children's Motrin oral suspension (Reference), administered as a 1 X 10 mg/kg dose under fasting conditions in healthy children.

Subjects: A total of 40 pediatric subjects (age 3 to 12 (9 ± 3, mean ± SD)) were enrolled to receive drug (Tables 1 and 2 and Appendix). All 40 subjects completed the study and 38 were included in the statistical and pharmacokinetic analyses. 2 subjects (Subject # 30 and 40) were excluded from the statistical analyses because they did not meet the inclusion criteria regarding NCHS Physical Growth Percentiles for stature and weight.

Table 1. Baseline Demographic Characteristics

	N	%
Age (y)		
3-6	10	25
7-9	13	32.5
10-12	17	42.5
Race		
Hispanic	34	85
African American	6	15
Sex		
Male	14	35
Female	26	65

Table 2. Summary Statistics For Age, Height, and Weight (All Subjects, N=40)

	Mean	Std	Min	Max
Age (y)	9	3	3	12
Height (cm)	136	18.9	94	167.6
Weight (kg)	33.9	12	14.1	54.5

Study Design: This was a single-center, open-label, single-dose, randomized, 1-period, parallel, comparative bioavailability study in healthy children. The distribution of subjects assigned to

the randomization sequences was proportional within age groups, but not age matched. Subjects were confined to the clinical site from at least 10 hours prior to drug administration, until after 12 hour post dose blood draw.

Dosage and Administration:

Test (A):	Children's ElixSure™ IB 100 mg/5 mL, oral suspension Taro Pharmaceuticals Inc. Lot # S177-52967 (EBK-103)	Exp. N/AV
Reference (B):	Children's Motrin® 100 m/5 mL, oral suspension McNeil Consumer Healthcare (McNeil-PPC, Inc.) Lot # FMC137	Exp. 04/05

On the study date, subjects were administered a single oral dose of either the test ibuprofen or reference ibuprofen, as a 1 X 10 mg/kg oral suspension (in a [redacted] syringe) after an overnight fast of at least 10 hours. The medication was swallowed and the syringe was rinsed 3 times with approximately 5 mL of water for each rinse; this water was swallowed. This procedure was completed within 2 minutes. An additional 15 mL of water was administered to each subject (total of 30 mL of potable water). Subjects fasted for at least 2 hours after drug administration.

Sample Collection and Handling:
Timepoints: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post dose

3 mL of blood samples were collected using EDTA as anticoagulant. Blood samples were [redacted] Two aliquots of at least 0.3 mL of plasma were dispended into polypropylene tubes as soon as possible before transferred to a -20°C freezer, pending transfer to the analytical facility.

Sample Analysis: Analysis of ibuprofen was performed by the bioanalytical division of [redacted] using the analytical [redacted] entitled "Determination of Ibuprofen in Human EDTA Plasma over a Concentration Range of [redacted] using High Performance Liquid Chromatographic Method with Tandem Mass Spectrometry Detection". Ibuprofen was extracted from an aliquot of human EDTA plasma using a [redacted] extraction procedure, then injected into a liquid chromatograph equipped with a tandem mass spectrometric detector (LC/MS/MS). Quantitation is by peak area ratio method. A weighted [redacted] linear regression is performed to determine the concentration of the drug. The lower limit of quantitation (LOQ) was [redacted]. Validated calibration curve range was [redacted] The standard ibuprofen (Lot # J) and internal standard fenoprofen (Lot # G-1) are official USP reference standards. The details of analytical method and its validation are included in separate reports (Volume 18).

Pharmacokinetic and Statistical Analysis: Statistical and pharmacokinetic analyses were generated using [redacted] and SAS® (release 6.12 for Windows). As noted previously, all 40 subjects completed the study and 38 were included in the statistical and pharmacokinetic analyses.

The pharmacokinetic parameters for this study were AUC_{0-t}, AUC_{0-inf}, AUC_{0-4}, C_{max}, T_{max}, K_{el} and $T_{1/2el}$. In addition, Absorption rate constant (k_a) was estimated using Modified Wagner-Nelson's method as implemented in [redacted] according to the following formula: $[C_t + (K_{el} \times AUC_{0-t})] \times 100/(K_{el} \times AUC_{0-inf})$. Absorption half-life ($T_{1/2abs}=0.693/k_a$) was calculated accordingly. Mean residence time and mean absorption time were calculated with equations: $MRT = AUMC_{0-inf}/AUC_{0-inf}$ and $MAT = MRT_{po} - 1/k_{po}$.

When the difference between the scheduled and actual sampling time exceed 3 min, the actual sampling times were used to calculate PK parameters, except for pre-dose samples. The samples recorded as below limit of quantitation were set to zero for PK and statistical analyses. Samples that were not available or unacceptable were recorded as NS (No sample) in concentration tables.

Analysis of Variance (ANOVA) was performed on ln-transformed AUC_{0-t}, AUC_{0-inf}, AUC_{0-4}, and C_{max}, and on untransformed T_{max}, K_{el} and $T_{1/2el}$. Ratio of means (Treatment A/Treatment B) and 90% geometric confidence interval for the ratio of the mean, based on least-squares means from the ANOVA of the ln-transformed data, were calculated for AUC_{0-t}, AUC_{0-inf}, AUC_{0-4}, and C_{max}.

Pharmacokinetic Results:

Test vs Reference under Fasting Conditions

Figure 1 demonstrated the plasma concentration-time profile (mean ± SD, linear scale) for Test (Children's ElixSure™ IB, 100 mg/5 mL) and Reference (Children's Motrin oral suspension, 100 mg/5 mL) products under fasting conditions.

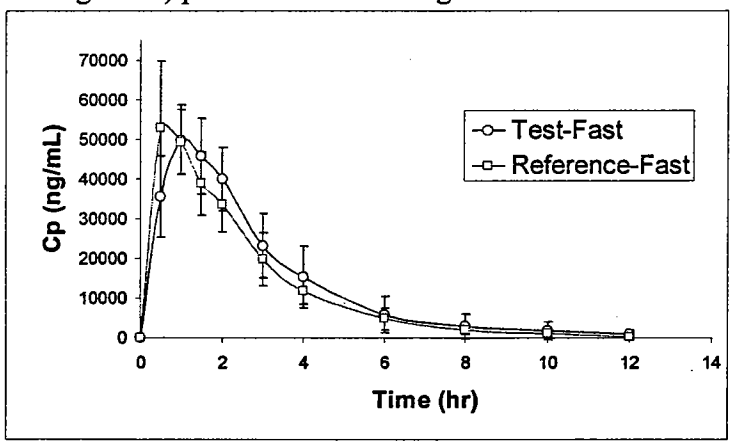

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Figure 1. Plasma concentration-time profile (mean ± SD, N=19, linear scale) for Test (Children's ElixSure™ IB) and Reference (Children's Motrin) products under fasting conditions.

The PK parameters (C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, AUC_{0-4}, and etc.) for Test and Reference products under fasting conditions were summarized in Table 3. The parameters for which a statistically significant difference was observed between the Test and the Reference product were ln-transformed C_{max}, T_{max}, K_{el} and $T_{1/2el}$ ($P<0.05$). No statistically significant differences were observed for ln-transformed AUC_{0-t}, AUC_{0-inf} and AUC_{0-4}. No significant group by treatment interaction was found for all the parameters, indicating that subjects of the different age groups behaved similarly in regard to the treatment effect.

Table 3. Summary of PK Parameters for Test and Reference Products under Fasting Condition (N=19 for each treatment).

Parameters		Test (Ibuprofen (A)) Mean	± SD	CV (%)	Reference (Children's Motrin (B)) Mean	± SD	CV (%)
AUC_{0-t}	(ng·h/mL)	163692.67	± 47500.67	29.02	146677.06	± 23633.08	16.11
AUC_{0-inf}	(ng·h/mL)	167290.01	± 51395.98	30.72	149517.74	± 23502.24	15.72
C_{max}	(ng/mL)	52000.12	± 8557.11	16.46	60515.40	± 6099.93	10.08
T_{max}	(h)	0.986	± 0.336	34.07	0.737	± 0.418	56.76
K_{el}	(h^{-1})	0.4057	± 0.1007	24.82	0.4667	± 0.0730	15.65
$T_{½ el}$	(h)	1.82	± 0.50	27.64	1.52	± 0.26	17.27
AUC_{0-4} (ng·h/mL)		126841.23 ± 23915.61		18.85	120061.04 ± 14938.24		12.44

T_{max} is one of indicators for rate of absorption but it is affected by the sampling time. The median T_{max} was 1.00 hr for the Test (range 0.5-1.5 hr, 0.986 ± 0.336, mean ± SD, N=19) and 0.5 hr for the Reference (range 0.367-1.93 hr, 0.737 ± 0.418, mean ± SD, N=19) products, respectively. Stick plot of the individual T_{max} values was shown in Figure 2. Distribution of individual T_{max} values was shown in Figure 3. T_{max} values were variable among subjects, especially for the Reference product.

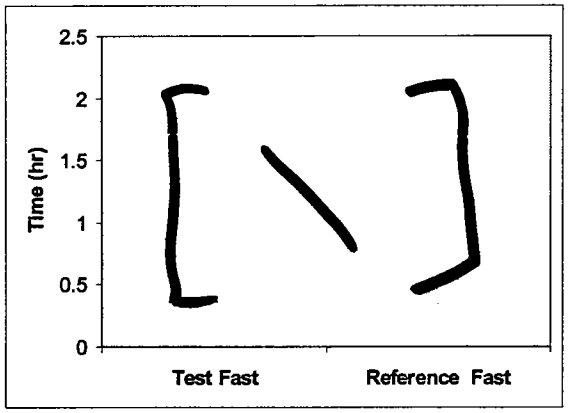

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Figure 2. Stick plot of the individual T_{max} values of Test and Reference products under fasting conditions.

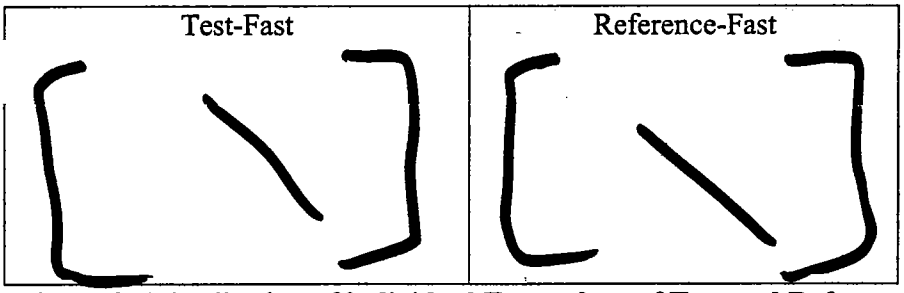

Figure 3. Distribution of individual T_{max} values of Test and Reference products under fasting conditions.

Rates of absorption of ibuprofen Test and Reference products in children were estimated with parameters such as absorption half-life and mean absorption time (listed in Table 4). The estimation of these parameters was also affected by limited number of sampling in children. The results suggested that absorption rates of the Test and Reference products were comparable in children.

Table 4. Arithmetic Means (± Standard Deviations) of Absorption Rate Constant, Absorption Half-life, Mean Residence Time and Mean Absorption Time for Test and Reference Products.

Parameter	Test (A)		Reference (B)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
k_a (h^{-1})	0.78 ± 0.35	44.79	0.81 ± 0.23	27.84
$T_{1/2abs}$ (h)	1.03 ± 0.39	37.49	0.92 ± 0.25	27.32
MRT (h)	2.77 ± 0.63	22.72	2.41 ± 0.41	17.03
MAT (h)	0.14 ± 0.35	239.94	0.21 ± 0.23	110.75

Comparison of PK of Test Product to Other Ibuprofen Products in Children

Literature and database search to compare PK of the Test product to other ibuprofen products in children was conducted by the reviewer. The PK profile of the Test product is comparable to the Reference product and other ibuprofen products in children (mean data were less than 25% of difference) (Table 5).

Table 5. Comparison of PK Parameters of the Test Product to Other Ibuprofen Products in Children.

	Test (healthy children) N=19	Reference (healthy children) N=19	Ibuprofen Suspension (febrile children) N=18	Ibuprofen Chewable Tablets (febrile children) N=22
Dose (mg/kg)	10	10	6	10
C_{max} (µg/mL)	52 ± 8.6	61 ± 6.1	31 ± 12	59 ± 13
CL/F (mL/h/kg)	64 ± 15	68 ± 11	70.5 ± 21	68 ± 13
T_{max} (hr)	0.99 ± 0.34	0.74 ± 0.42	0.87 ± 0.42	0.99 ± 0.53
$T_{1/2el}$ (hr)	1.8 ± 0.5	1.5 ± 0.3	1.9 ± 1.0	2.1 ± 1.3

Summary of PK Results by Age Group

Summary of PK results by age group (3-6 yrs, 7-9 yrs, and 10-12 yrs) is listed in Table 6. No trend in effect of age (3-12 yrs) on PK of ibuprofen was observed for both Test and Reference products. This result is consistent with previous findings in the literature.[1]

[1] Nahata MC, *et. al.*, Pharmacokinetics of ibuprofen in febrile children. *Eur J Clin Pharmacol* 40:427-428, 1991

Table 6. Summary of PK Results by Age Group.

SUMMARY OF RESULTS
IBUPROFEN
Pharmacokinetic Parameters by Age Group

2 - 6 years old
(N = 4 for each treatment)

Parameters		Test (Ibuprofen (A)) Mean	±	SD	CV (%)	Reference (Children's Motrin (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	161005.25	±	22571.59	14.02	131205.43	±	21421.86	16.33
AUC_{0-inf}	(ng·h/mL)	163782.29	±	23537.58	14.37	135349.58	±	21414.29	15.82
C_{max}	(ng/mL)	48166.33	±	3841.83	7.98	57966.68	±	3748.44	6.47
T_{max}	(h)	0.809	±	0.215	26.59	0.517	±	0.235	45.49
K_{el}	(h^{-1})	0.4331	±	0.0933	21.55	0.4836	±	0.0726	15.01
$T_{½ el}$	(h)	1.66	±	0.35	20.91	1.46	±	0.25	17.08

7 - 9 years old
(N = 7 for Treatment A, N = 6 for Treatment B)

Parameters		Test (Ibuprofen (A)) Mean	±	SD	CV (%)	Reference (Children's Motrin (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	171073.09	±	64566.61	37.74	139115.95	±	13084.87	9.41
AUC_{0-inf}	(ng·h/mL)	175352.63	±	70666.21	40.30	141699.77	±	13732.92	9.69
C_{max}	(ng/mL)	56652.66	±	8707.45	15.37	63772.66	±	6811.58	10.68
T_{max}	(h)	1.00	±	0.29	28.87	0.583	±	0.204	34.99
K_{el}	(h^{-1})	0.4442	±	0.1146	25.79	0.4978	±	0.0810	16.28
$T_{½ el}$	(h)	1.69	±	0.59	35.03	1.43	±	0.25	17.25

10 - 12 years old
(N = 8 for Treatment A, N = 9 for Treatment B)

Parameters		Test (Ibuprofen (A)) Mean	±	SD	CV (%)	Reference (Children's Motrin (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	158578.52	±	43838.53	27.64	158594.09	±	25597.86	16.14
AUC_{0-inf}	(ng·h/mL)	161989.07	±	46590.09	28.76	161026.67	±	25646.49	15.93
C_{max}	(ng/mL)	49846.04	±	9034.87	18.13	59476.66	±	6085.55	10.23
T_{max}	(h)	1.06	±	0.42	39.27	0.937	±	0.510	54.42
K_{el}	(h^{-1})	0.3583	±	0.0813	22.69	0.4384	±	0.0644	14.69
$T_{½ el}$	(h)	2.03	±	0.47	23.18	1.62	±	0.28	17.03

Comparison of Children PK Data to Adult PK Data

Effect of age (children vs. adults) on PK of ibuprofen was observed for both Test (Table 7) and Reference products (data not listed). This result is consistent with previous findings for other ibuprofen products. In general, ibuprofen has higher apparent clearance (CL/F) in children than in adults. . Higher variability in the children's values is apparent and overall, several of them fall within the range for adults (historical data). Recommended dose in children is usually 6-10 mg/kg and in adults is usually 200 mg (~3 mg/kg) for the OTC indication of ibuprofen.

Table 7. Comparison of PK of Children's ElixSure™ IB (Test) in Healthy Children and Adults.

	Children (2-12 year) (N=19)	Adult (N=25)
Dose (mg/kg)	10	~2.6
$AUC_{0\text{-}inf}$ (μg·h/mL)	167 ± 51	60 ± 13
CL/F (mL/h/kg)	64 ± 15	46 ± 9.6
T_{max} (hr)	0.99 ± 0.34	1.43 ± 0.84
$T_{1/2el}$ (hr)	1.8 ± 0.5	2.0 ± 0.37

Children data: from Study 02212.
Adult data: from Study IEU-P1-262.

Demographic Comparison between Study Treatments

Table 8. Summary and Comparison of Demographic Parameters by Treatment.

Age (years)	Treatment A (N = 19)	Treatment B (N = 19)	Pr > |T|
Mean	8.63	8.79	0.8674
SD (±)	2.87	2.92	

Height (cm)	Treatment A (N = 19)	Treatment B (N = 19)	Pr > |T|
Mean	137.32	136.61	0.9102
SD (±)	17.83	20.38	

Weight (kg)	Treatment A (N = 19)	Treatment B (N = 19)	Pr > |T|
Mean	34.32	34.16	0.9690
SD (±)	12.29	12.57	

NCHS Growth Percentile	Treatment A (N = 19)	Treatment B (N = 19)	Pr > |T|
Mean	67.11	67.47	0.9653
SD (±)	25.68	26.21	

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Subjects receiving Treatment A or Treatment B did not differ significantly (P>0.05) in terms of age, height, weight and NCHS growth percentile.

"Bioequivalence" Analysis by the Sponsor

(Reviewer's Note: The sponsor performed a "bioequivalence" type of analysis (90% confidence interval for the ratio of least square means from log transformed data between test and reference products) even though bioequivalence determination in children is not needed for approval.)
The data are listed in Table 9.

Table 9. Comparison of Geometric Means of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ for Test and Reference Products under Fasting Condition.

Parameter	Geometric LS Means		Ratio	90% Confidence Limit	
	Test	Reference		Lower	Upper
C_{max} (ng/mL)	50970.38	60132.16	84.77	78.60	91.42
$AUC_{0\text{-}t}$ (ng·h/mL)	158783.99	141308.40	112.37	99.21	127.27
$AUC_{0\text{-}inf}$ (ng·h/mL)	161716.49	144408.30	111.99	98.53	127.29
$AUC_{0\text{-}4}$ (ng·h/mL)	124417.73	117747.76	105.66	95.38	117.05

Safety Results: No adverse events were reported in this study.

Summary: PK parameters of the Test product are comparable to the Reference product and other ibuprofen products (suspension and chewable tablets) in children. The Test and Reference products also have similar absorption rate in children.

Compared to adult data (e.g., data from Study IUE-P1-262), ibuprofen has larger clearance and shorter T_{max} in children. Elimination half-life is similar between adult and children. This finding is consistent with other ibuprofen products.

Comments: The sponsor did not conduct this BE study in the targeted patient population, e.g., febrile children, which made it difficult to know the exposure of the Test product in patient population. To utilize the data in this study, we must make the assumption that disease state would not affect PK of the Test product in children.

Appendix.

Demographic Data and Randomization Scheme (Study 02212).

Appendix. Demographic Data and Randomization Scheme (Study 02212).

Subj. No.*	Study Treatment	At Screening					Gender	Race
		Age (years)	Height (cm)	Weight (kg)	NCHS Growth Percentile†	Sexual Maturity*		
01	A	12	165.1	54.5	90	4	Female	Hispanic
02	B	12	154.9	33.9	10	3	Female	Hispanic
03	B	12	162.6	48.2	75	3	Male	Hispanic
04	A	12	154.9	51.4	75	4	Female	Hispanic
05	B	12	167.6	53.6	90	4	Male	Black
06	A	12	157.5	51.4	75	4	Female	Hispanic
07	A	12	152.4	50.9	80	4	Female	Hispanic
08	B	11	157.5	47.7	90	3	Male	Hispanic
09	A	11	149.9	45.4	75	4	Female	Black
10	B	11	152.4	50.5	90	4	Female	Hispanic
11	B	11	144.8	35.9	50	3	Female	Hispanic
12	A	11	132.0	27.3	25	2	Male	Black
13	B	11	147.3	50.8	92	3	Female	Hispanic
14	B	11	147.3	42.3	90	3	Male	Hispanic
15	A	10	147.3	34.5	50	2	Male	Hispanic
16	A	9	139.7	30.9	50	3	Male	Hispanic
17	A	9	139.7	34.5	75	2	Male	Hispanic
18	A	9	134.6	35.5	90	3	Female	Hispanic
19	B	8	132.0	26.8	50	2	Female	Black
20	B	8	132.0	30.0	75	2	Female	Hispanic
21	B	8	116.8	21.8	10	1	Female	Hispanic
22	A	8	124.5	27.3	60	1	Male	Hispanic
23	B	8	134.6	33.0	90	2	Male	Hispanic
24	A	8	134.6	30.5	75	3	Female	Hispanic
25	A	7	127.0	24.9	50	1	Female	Hispanic
26	B	7	134.6	27.7	80	1	Female	Black
27	B	7	124.5	24.1	50	1	Female	Hispanic
28	A	7	139.7	30.9	95	1	Female	Black
29	A	6	134.6	30.0	95	2	Female	Hispanic
30	B	6	121.9	28.2	97	1	Male	Hispanic
31	B	12	154.9	46.4	70	4	Female	Hispanic
32	A	3	99.6	14.1	25	1	Female	Hispanic
33	B	3	94.0	14.5	50	1	Male	Hispanic
34	B	4	106.7	18.2	75	1	Male	Hispanic
35	A	4	109.2	19.1	90	1	Male	Hispanic
36	A	4	109.2	15.4	10	1	Female	Hispanic
37	B	5	116.8	24.1	95	1	Female	Hispanic
38	A	10	157.5	43.6	90	3	Female	Hispanic
39	B	6	114.3	19.6	50	1	Female	Hispanic
40	A	4	114.3	26.4	98	1	Female	Hispanic

Abbreviation: Subj. No. = Subject Number

Range	3-12	91.0-167.6	14.1-54.5
Mean	9	136.0	33.9
SD	3	18.9	12.0

* All subjects were non-smokers

† NCHS Physical Growth Percentile for stature and weight.

* Sexual maturity was classified according to the Tanner Stage Classification. More details of this classification can be found in individual subject raw data, Section 16.2.

A=Taro Pharmaceuticals USA Inc., U.S.A., ibuprofen1 x 10 mg/kg oral suspension

B=McNeil Consumer Healthcare, U.S.A. (Children's Motrin), ibuprofen1 x 10 mg/kg oral suspension

Reviewer's Note: In the original submission, the sponsor only tested dissolution at one time point (60 min). While this meets the USP dissolution test for ibuprofen suspension, USP, it is insensitive as to the rate of release, being that it is a single point specification. The sponsors were asked to determine dissolution time profile for at least three lots of the planned marketed formulation including the lot used in bioequivalence and PK studies. The sponsor submitted new dissolution profile results on July 22, 2003. The following is the review from the newly submitted data.

Objective: To determine the rate of release of ibuprofen active drug substance from the suspension formulation.

Methods: The method was adopted directly from the USP monograph for ibuprofen oral suspension and validated as an in-house SOP [redacted] by the sponsor (see Table below). Dissolution testing was conducted on Children's ElixSure™ IB (also called Ibuprofen NonSpil Gel Suspension in this study report) Exhibit Batches (Formula Code [redacted]), lot numbers S177-52967, S177-53137 and S177-53138. Lot S177-52967 was used in PK and bioequivalence studies.

Apparatus	USP Apparatus 2 Type- Paddle
Speed	[redacted]
Number of units	6
Sampling times (minutes)	5, 15, 25, 45 and 60
Media	900 mL 0.05 M phosphate buffer, pH 7.2
Temperature	37°C
Analytical Method	HPLC using variable wavelength detector set at [redacted]
Proposed Specification	Not less than [redacted] (Q) is dissolved in [redacted] (adopted from USP monograph)

Results:

1. Dissolution Profiles at pH 7.2 (Lot S177-52967)

Ibuprofen NonSpil™ Gel Suspension Exhibit Batch Lot S177-52967
Reference RD281 p. 53

Vessel	Sampling Time (min)
1	[redacted]
2	
3	
4	
5	
6	
Average	
RSD	

Table 1. Dissolution Profiles of Ibuprofen NonSpil™ Gel Suspension Exhibit Batch Lot S177-52967 in Phosphate Buffer at pH = 7.2

Appears This Way On Original

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 343

6.3 Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-604	Brand Name	Children's Elixsure™ IB
OCPB Division (I, II, III)	DPE III (HFD-880)	Generic Name	Ibuprofen
Medical Division	DAAODP (HFD-550)	Drug Class	NSAID
OCPB Reviewer	Lei Zhang, Ph.D.	Indication(s)	For the reduction of fever and the temporary relief of minor aches and pains associated with a cold, flu, headache, sore throat, [redacted] toothache
OCPB Team Leader	Dennis Bashaw, Pharm. D.	Dosage Form	Suspension (100 mg/5 mL)
		Dosing Regimen	The recommended doses are based on age and weight of children (see table below). If needed, repeat dose every 6-8 hrs, but do not use more than 4 times a day and do not exceed recommended dose.
Date of Submission	12/31/2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	8/22/2003	Sponsor	Taro Pharmaceuticals USA Inc.
PDUFA Due Date	10/31/2003	Priority Classification	Standard (3-S)
Division Due Date	8/22/2003		

Age (yr)	Weigh t (lbs)	Dose (tsp)
Under 2 years	Under 24	Ask a doctor
2-3	24-35	1
4-5	36-47	1 1/2
6-8	48-59	2
9-10	60-71	2 1/2
11	72-95	3

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			Study No. IUE-P2-134, IUE-P1-262 and 02212
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			Study No. IUE-P2-134

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X			**Study No. 02212**
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			**Study No. IUE-P1-262, 2 reference formulations (oral suspension and chewable tablet) Study No. IUE-P2-134, 1 reference formulation Study No. 02212, 1 reference formulation**
Bioequivalence studies -				
traditional design; single / multi dose:	X			**Study No. IUE-P1-262, and IUE-P2-134**
replicate design; single / multi dose:				
Food-drug interaction studies:	X			**Study No. IUE-P2-134**
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**4**	**4**	

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	• **Is the new formulation of ibuprofen oral suspension bioequivalent to reference product Children's Motrin oral suspension under the fasting condition?** • **If there food effect with this new formulation of ibuprofen oral suspension?** • **What is PK profile of this new product of ibuprofen in children? And how is it compared to its PK in adult?** • **How does PK profile of this new product compare to PK profiles of other ibuprofen products in children?** • **What is the dissolution profile of the new formulation?**	
Other comments or information not included above		

Primary reviewer Signature and Date	Lei Zhang, Ph.D.
Secondary reviewer Signature and Date	Dennis Bashaw, Pharm.D.

CC: NDA 21-604, HFD-850 (P. Lee), HFD-860 (M. Mehta), HFD-550 (Dean), HFD-880 (L. Zhang, Bashaw, Lazor, Selen), CDR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lei Zhang
10/25/03 12:08:44 PM
BIOPHARMACEUTICS

Dennis Bashaw
10/27/03 09:51:12 AM
BIOPHARMACEUTICS