CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-603/S-001, S-002, S-003

MEDICAL REVIEW

APR 14 1999

MEDICAL OFFICER REVIEW
Division of Over-The-Counter Drug Products

NDA #: 20-812, SE5-005
NAME: Pediatric Advil® (ibuprofen suspension) Drops100 mg/2.5 mL
SPONSOR: Whitehall-Robins
Five Giralda Farms
Madison, NJ 07940
Tel.:(973)660-5753
TYPE OF SUBMISSION: Commercial Pharmaceutical
DATE OF SUBMISSION: June 15, 1998 **CDER:** June 15, 1998
DATE OF REVIEW: March 22, 1999
REVIEWER: Rosemarie Neuner, MD, MPH
CSO: Mr. Kerry Rothschild, JD

Introduction

Ibuprofen is a propionic acid derivative that belongs to the nonsteroidal anti-inflammatory class of drugs (NSAIDs). A suspension formulation of ibuprofen has been available as a prescription drug for use in children since 1989. On January 30, 1998 Pediatric Advil® (ibuprofen suspension) Drops, 100 mg/2.5 mL was approved by the U.S. Food and Drug Administration for marketing as an over-the-counter (OTC) drug product for the temporary relief of fever and pain in children 2-3 years of age. In June 1998, the sponsor of this product, Whitehall-Robins, submitted a request to the agency for a pediatric exclusivity claim which was subsequently granted. The sponsor has now submitted this efficacy supplement for agency review in which they request the lowering of the currently approved group age range from two to three years of age down to six months of age for this product.

In support of this change in the product's dosing age range, the sponsor has re-submitted the data generated from 41,810 children who participated in the actual use drug safety trial, the Children's Analgesic Medicine Project (CAMP), which evaluated Children's Advil as an antipyretic and analgesic agent. [Note: This was the pivotal safety study that supported the approval for the sponsor's Pediatric Advil® (ibuprofen) Suspension 100 mg/5 mL (NDA 20-589) in 1995, and for the sponsor's Pediatric Advil® (ibuprofen) Drops100 mg/2.5 mL (NDA 20-812) in 1998.] The sponsor has included additional new safety information in this review regarding the occurrence of anaphylaxis, gastrointestinal (GI) bleeding, renal failure, and Reye syndrome in this study's population. In addition, the sponsor has submitted in support of this SNDA a published article from a peer reviewed journal which describes the results from the actual use Boston Fever Study in which the safety profile of pediatric ibuprofen was compared to that of acetaminophen in over 84,000 children with fever, and as well as the overheads used by Dr. Larry Lesko to present the new subcohort analysis of children $\leq$ 2 years of age from that study at the September 18,1998 NDAC. They have also included for review 1 article which describes a pharmacokinetic (PK) study in febrile children between the ages 3 months through 12 years, and resubmitted the

results of the PK Study AF-95-04 which demonstrated the bioequivalency of the sponsor's 2 pediatric formulations in adult volunteer's [Children's Advil® Suspension (NDA 20-289) to Pediatric Advil® Drops (NDA 20-812)]. Since the latter study was reviewed by the agency in support of the sponsor's bioequivalency claim, it will not be re-reviewed at this time, but the results from the published PK study are discussed in the PK section of this SNDA review by Dr. E. Dennis Bashaw, FDA Division of Pharmacokinetics (HFD-880).

Since prescription ibuprofen is currently approved for use in infants age 6 months and older, the major regulatory issue to be answered by this application is the safety of OTC ibuprofen for use in the pediatric age group between 6 months and 2 years of age, as the other doses proposed by the sponsor of this supplement have been previously approved for OTC use. This review will therefore concentrate on the drug's safety profile in this targeted age group since the sponsor did not submit any additional inform regarding ibuprofen's efficacy.

Safety

The focus of this review is to determine whether ibuprofen is safe to be used as an OTC agent in the sponsor's requested targeted pediatric age group of 6-months to 2-years. In support of this product's safety profile the sponsor has submitted for review the following safety data for children less than 2-years of age:

1. A new analysis of serious adverse events (i.e., $\geq$ 1%) as well as acute gastrointestinal bleeding, renal failure, and Reye syndrome that occurred during the Children's Analgesic Medicine Project (CAMP).
2. A copy of the original article from a peer-reviewed journal of the Boston University Fever Study.
3. The overheads used at the September 18,1998 NDAC presentation by Dr. Larry Lesko of the subgroup analysis of children less than 2-years of age from the Boston University Fever Study.

The sponsor did not submit any postmarketing adverse event information, overdose case reports, or other data from the worldwide literature as part of the global safety update for this product. The analysis of serious adverse events from the CAMP study will be discussed first followed by a brief discussion of the Boston University Fever Study, and the new subcohort analysis in children $\leq$ 2 years of age which was presented at the September 18, 1998 NDAC meeting.

1. Analysis of serious adverse events (i.e., death, anaphylaxis, gastrointestinal bleeding, renal failure, Reye syndrome, and any event with a frequency $\geq$ 1%) that occurred during the Children's Analgesic Medicine Project (CAMP).

(Note: This study has been reviewed and discussed in detail previously by agency reviewers in support of regulatory actions taken on NDA 20-589 and NDA 20-812. The

following is a brief overview of the study with a discussion of serious adverse events ≥ 1%, as well as any episodes of acute gastrointestinal bleeding, renal failure, and Reye syndrome that occurred in children < 2 years of age while participating in the trial.)

The Children's Analgesic Medicine Project (CAMP) study was a multi-center, multi-dose, open-label, nonrandomized, acetaminophen-controlled study conducted by [redacted], an affiliate of the University of Utah in an office-based pediatric population from the continental United States. The study's objective was to evaluate the actual clinical experience with Children's Advil® as compared to acetaminophen. Children who required treatment with either an antipyretic or analgesic were entered into the study by 424 health care providers from 69 pediatric centers during the time period from March 1993 through July 1995. A total of 41,810 children were entered, out of which 14,291 children < 2 years of age were treated with at least 1 dose of medicine and had follow-up information. Of these 14,291 children < 2 years of age, 7,381 children were treated with ibuprofen while the remaining 6,900 children were treated with acetaminophen. (Note: Treatment assignments of the study participants were made by their health care providers, and were to have reflected the latters usual therapeutic preferences.) Information regarding study drug exposure was collected at two time points during the trial: at the time of enrollment and at 1-2 weeks into the study via a telephone interview with the child's care giver.

The only demographic information that this study collected from patients enrolled into the trial was for the child's age and reason for enrollment (i.e., sick or well child visit). "Sick child" visits were for a variety of reasons. Some of the more frequently occurring reasons are listed as follows: otitis media, pharyngitis, viral illness, pain, upper respiratory tract infections, and bronchitis. "Well child" visits included prophylactic treatment following routine immunizations. Drug exposure ranged from a single dose (which occurred in approximately 7% of the total population entered) to more than 21 doses (which occurred in approximately 4% of the total population studied.)

The new safety analysis looked at the numbers of serious adverse events that occurred during the study which included: deaths, anaphylaxis, GI bleeding, renal failure, Reye syndrome, and any serious adverse event that occurred in ≥ 1% of the treated study population.

1.A. Deaths - Four (4) children < 2 years of age died while enrolled in the CAMP study. Two (2) of the 4 children were treated with ibuprofen, 1 received acetaminophen and 1 was assigned to take acetaminophen but never did take the study drug. The first case (Case Number 034141Y) involved a 1-year-old female evaluated for a viral syndrome associated with a fever of 104°. The child was assigned to treatment with 1 teaspoon of ibuprofen every 6 hours which was alternated with acetaminophen. (Note: Reason for administering both study medications was not stated.) She was treated with this regimen over a 3-day period of time following which she developed seizures, was hospitalized and placed on mechanical ventilation. She was diagnosed as having herpetic encephalitis and died 48 hours after admission to the hospital. An autopsy was not performed.

The second-death (Case Number 011410Y) occurred in a 11-month-old male patient evaluated earlier for otitis media associated with a fever. The patient was assigned to receive treatment with ibuprofen and an unknown antibiotic. Over the next 48-hour period of time, the child deteriorated and was admitted to the hospital with a diagnosis of bacterial *Strep. pneumoniae* meningitis. He recovered and was discharged home 10 days later, only to be readmitted approximately 10 days post discharge with septicemia due to the same organism. The child died 48 hours following the second admission and was found on autopsy to have congenital asplenia.

Of the remaining 2 deaths, one occurred (Case Number 032524) in a 23-month-old female seen for a viral illness associated with a headache. She was assigned to treatment with acetaminophen, but according to the information supplied by the sponsor, never received the study medication. A few months later she presented for follow-up with a history of constitutional complaints which included drowsiness and sluggishness. A CT scan of the patient's head demonstrated a large cerebellar medulloblastoma which hemorrhaged before resection could be performed. The child subsequently died due to complications from her brain tumor.

The fourth death occurred (Case Number 005035Y) in a 3-month-old male who was assigned to receive treatment with acetaminophen for prophylaxis following immunization. This patient received 7-10 doses over a 7-day period of time of the study medication. The child died 2 ½ weeks after finishing treatment with the study medication. The cause of death at autopsy was noted to be Sudden Infant Death Syndrome (SIDS).

B. Anaphylaxis - There were no cases of anaphylaxis reported to have occurred in children < 2 years of age in the CAMP Study.

C. Gastrointestinal (GI) Bleeding - There were no cases of GI bleeding reported to have occurred in children < 2 years of age in the CAMP Study.

D. Renal Failure - There were no cases of renal failure reported to have occurred in children < 2 years of age in the CAMP Study.

E. Reye syndrome - There were no cases of Reye syndrome reported to have occurred in children < 2 years of age in the CAMP Study.

F. Serious Adverse Experiences Occurring in ≥ 1% of Treated Subjects in the CAMP Study.

There were no serious adverse events reported to have occurred in ≥ 1% of treated patients enrolled in the CAMP Study. In Attachment I, at the end of this review, are tables prepared by the sponsor which summarize the number of serious adverse events as related to study treatment which occurred in children < 2 years of age who participated in this study. The most commonly reported serious adverse event in children < 2 years of age treated with ibuprofen were elective hospitalizations (0.46%) for the insertion of pressure equalizing tubes in the Eustachian tubes of some of the

children while being treated for otitis media.

Medical Reviewer's Comments: This limited post hoc analysis of serious adverse events in children between the ages of 6 months to 2 years enrolled in the CAMP study is plagued by a multitude of methodological flaws, thus raising questions regarding the validity of its findings. At best this reviewer can say that based on the paucity of drug related serious adverse events which occurred in this large pediatric study, ibuprofen suspension is safe to be used in an OTC pediatric population between the ages of 6 months to 2 years of age.

2. Lesko SL, Mitchell AA: An Assessment of the Safety of Pediatric Ibuprofen: A Practitioner-Based Randomized Clinical Trial. JAMA, 273(12):929-933, 1995.

In support of their request, the sponsor sent in a copy of the above article published in a peer-reviewed journal which describes the original Boston Fever Study. (Note: A full synopsis of this study by this medical reviewer can be found at the end of this review in Attachment II.) This was a 4-week, multi center, double-blind, randomized, acetaminophen-controlled antipyretic study in an office-based pediatric population from the continental United States. The study's objective was to assess the risk of hospitalization due to serious adverse events such as gastrointestinal bleeding, acute renal failure, anaphylaxis and Reye syndrome associated with the use of ibuprofen in febrile children. A total of 84,192 children between the ages of 6 months to 12 years were enrolled in the study, but data was available for final analysis on only 83,915 children who had been randomized into 1 of the 3 treatment groups as follows: 5 mg/kg ibuprofen (n=27,948), 10 mg/kg ibuprofen (n=27,837), and 12 mg/kg acetaminophen (n=28,130). Although all 3 treatment groups were similar for various demographic parameters, the article did not give the number of children < 2 years of age who participated in the study.

During the trial there were only 4 reported cases of GI bleeding, and no cases of acute renal failure, anaphylaxis, or Reye Syndrome. All 4 cases of GI bleeding occurred in children treated with ibuprofen (2 from the high-dose group and 2 from the low dose group). (Note: The article did not state the ages of these 4 children.) The observed risk for developing GI bleeding due to treatment with ibuprofen in this study was calculated to be 7.2 per 100,000 (95% confidence interval, 2 to 18 per 100,000). On comparison analysis, this risk was not found to be significantly different (p=0.31) from the risk for developing GI bleeding in the acetaminophen treated group (0 per 100,000; 95% confidence interval, 0 to 11 per 100,000). The observed risk for developing acute renal failure, anaphylaxis, or Reye's syndrome was calculated for all of the children (n=55,785) treated with ibuprofen in the study and was found to be 0 per 100,000 (95% confidence interval, 0 to 5.4 per 100,000 ibuprofen-treated children).

Based on these findings, the authors conclude that the short-term risk for hospitalization due to GI bleeding, acute renal failure, anaphylaxis and Reye's syndrome associated with the use of high and low dose ibuprofen in children in this trial was not any different from the risk in children treated with acetaminophen.

Medical Reviewer's Comments: Unfortunately, this published pediatric study does not list the number of children < 2 years of age who participated in the trial. This information would have been very helpful since the sponsor has requested that their pediatric formulation be labeled for use in children 6 months of age and older. Thus, this study can provide only supportive evidence of the safety profile of ibuprofen in children < 2 years of age.

3. The overheads used at the September 18,1998 NDAC presentation by Dr. Larry Lesko of the subgroup analysis of children less than 2-years of age from the Boston University Fever Study.

Dr. Larry Lesko, the first author of the published article submitted by the sponsor which was reviewed and commented on in the preceding section of this review, presented a subcohort analysis of children < 2 years of age who participated in the Boston Fever Study at the September 18, 1998 NDAC meeting. (Refer to the above Safety Section 2 and the study synopsis in Attachment II found at the end of this review for further information regarding this study. Reproductions of these overheads can be found in Attachment III at the end of this review.)

This post hoc subcohort analysis revealed that there were 27,065 children < 2 years of age who participated in the Boston Fever Study, out of which 17,938 were treated with ibuprofen and 9,127 received acetaminophen. A total of 261 children out of the 17,938 children in the ibuprofen treatment group were hospitalized during the study [observed risk for hospitalization due to any cause: 1.5 per 100,000; 95% confidence interval (1.3 to 1.6 per 100,000)] as compared to 124 out of 9,127 from the acetaminophen group [observed risk for hospitalization due to any cause: 1.4 per 100,000; 95% confidence interval (1.1 to 1.6 per 100,000)]. The risk for hospitalization in children <2 years of age was not significantly greater when compared to the corresponding risk for hospitalization in children > 2 years of age (n=56,850) who participated in the study (observed risk: 2.6 per 100, 000; confidence interval not given).

There were 3 cases of GI bleeding reported to have occurred in the subcohort population < 2 years of age. (Note: The overheads do not provide any additional information regarding these 3 cases.) The observed risk for hospitalization due to GI bleeding in children < 2 years of age in the subcohort was found to be 17 per 100,000 with a 95% confidence interval (CI) of 3.5 to 49 per 100,000 as compared to an observed risk of 0 per 100,000 with 95% CI of 0 to 33 per 100,000 for children < 2 years of age treated with acetaminophen.

Although there were no cases reported of renal failure, anaphylaxis or Reye syndrome in children < 2 years of age who participated in this study, the observed risk for hospitalization due to any of these 3 other primary outcomes were calculated for both treatment groups and shown to be as follows: ibuprofen treatment group: [0 per 100,000 (95% CI: 0 to 17 cases per 100,000)]; acetaminophen treatment group: [0 per 100,000 (95% CI: 0 to 33 cases per 100,000)]. Due to additional safety concerns for hospitalizations due to asthma, bronchiolitis and vomiting/gastritis in this age group, Dr.

Lesko also presented the calculated observed risks for hospitalizations that occurred during the study due to these 3 illnesses which were similar for both treatment groups as shown in the following table, Table 1:

Table 1 - Risk for Hospitalization Due to Secondary Outcomes in Children < 2 Years of Age in the Boston Fever Study

Diagnosis	Ibuprofen	Acetaminophen
Total Number	17,938	9,127
Asthma, No. **Risk/100,000** **(95% CI)**	20 110 (68-172)	12 130 (70-230)
Bronchiolitis, No. **Risk/100,000** **(95% CI)**	21 120 (72-180)	12 130 (70-230)
Vomiting/Gastritis, No. **Risk/100,000** **(95% CI)**	7 39 (16-80)	2 22 (2.6-79)

Since there were no cases of acute renal failure reported to have occurred during this study, Dr. Lesko presented additional data from 112 children < 2 years of age who had serum creatinines drawn during study hospitalizations in an attempt to see if this surrogate marker for renal function would show any treatment associated nephrotoxicity in this subcohort age group. Table 2, shown below, shows the limited data presented at the NDAC meeting by the author regarding elevated serum creatinines in children < 2 years of age. (Note: No statistical analysis of the serum creatinine data was submitted for review by the presenter or the sponsor.)

Table 2 - Elevated Serum Creatinines in Hospitalized Children < 2 Years of Age in the Boston Fever Study

	Ibuprofen	Acetaminophen
Total Number	83	29
Serum creatinine, mg/dL **Mean** **(SEM)** **Range**	0.42 (0.023)	0.34 (0.025)
Serum creatine > 0.7mg/dL **No.** **(%)**	5 (6)	0 (0)

Based on the data that he presented, Dr. Lesko concluded that in the Boston Fever Study subcohort of children < 2 years of age (n=27,065), the use of ibuprofen suspension was not associated with an increased risk of hospitalization overall or for acute GI bleeding, acute renal failure, anaphylaxis or Reye syndrome compared to acetaminophen (n=9,127).

Medical Reviewer's Comments: The above subcohort analysis provides the safety data in children < 2 years of age which was missing from the original published article by Lesko et al, that was submitted by the sponsor and discussed and commented in the above Section 2 of this review. Since not all of the children who were hospitalized had serum creatinines drawn, this medical reviewer feels it would be inappropriate to comment on the significance of the serum creatinine data especially since no background information was provide regarding the 5 cases involved.

Recommendations: Based on the data contained in this submission generated from a major clinical pediatric study performed by the sponsor, as well as data from another published major pediatric study, Pediatric Advil® (ibuprofen suspension) Drops100 mg/2.5 mL appears to be safe to be used in an OTC pediatric population > 6 months of age. According to agency regulations regarding the contents of efficacy submissions, the sponsor has failed to submit complete safety data for this product which should include the following missing data: Whitehall-Robins adverse event monitoring system controlled clinical trial data on subjects ≤ 2 years of age enrolled in studies treated with ibuprofen since the completion of the CAMP study, reports of serious adverse events collected by Whitehall-Robins adverse event monitoring system which have occurred in children ≤ 2 years of age from the time of the sponsor's last submission for their pediatric ibuprofen products to the present, reports of serious adverse events collected by the FDA's Spontaneous Reporting System (SRS) for all ibuprofen products in children ≤ 2 years of age for the same time period, overdose data from the American Association of Poison Control Centers (AAPCC) for ibuprofen containing products in children ≤ 2 years of age, and information regarding foreign marketing of this product for the requested age-related indication. Thus, this medical officer can only recommend that this application be designated as approvable pending the sponsor submission and review of the missing required safety data.

If and when this application receives agency approval for the marketing of this indication, an overlap in dosing age ranges should be avoided for this product and its sister product, Children's Advil® (ibuprofen suspension)100 mg/5 mL because of the possible threat of dosing misadventures due to consumer confusion. Thus, the concentrated drops should be labeled for use in children ≤ 2 years of age, and the less concentrated solution should be labeled for use in children ≥ 2 years of age. To further help prevent these incidents from happening in the future, the sponsor needs to re-label this product as "concentrate" as follows: Pediatric Advil® (ibuprofen suspension) Concentrated Drops100 mg/2.5 mL

/S/

Rosemarie Neuner, MD, MPH
Medical Reviewer, HFD-560

/S/

Linda M. Katz, MD, MPH 4/14/99
Deputy Dir., HFD-560

CC: NDA 20-603 File
HFD-560 Div. File
HFD-550 Div. File
HFD-560 ActingDir/Bowen
HFD-560 Dep Dir/Katz
HFD-560 Team Leader/Lumpkins
HFD-550 Team Leader/Hyde
HFD-560 MO/Neuner
HFD-560 PM/KRothschild

Appendix I

DATA ON THE USE OF IBUPROFEN SUSPENSION AND ORAL DROPS IN CHILDREN AGES 6 MONTHS THROUGH 2 YEARS

Attachment B

Summary of Serious Adverse Experiences (AEs) by Relationship of AE to Study Medication

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Date: 05MAY98
Time: 15:04

Whitehall-Robins Healthcare
Protocol #: CAMP I
Investigator: Pooled

CAMP I Study

Table B.3a.1

Summary of Serious Adverse Experiences (AEs) by Relationship of AE to Study Medication

For All Children under 2 Years

Who Took at Least One Dose of Study Medication

(Took Ibuprofen or Acetaminophen Only)

Adverse Experience(AEs) (by Body System and Event Term)	Ibuprofen (n=7381)					Acetaminophen (n=6900)				
	No. of AEs(%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose	No. of AEs(%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose
Any Body System										
No. of AEs**	231	10	196	23	2	118	6	98	10	4
No. of subjects**	129 (1.75)	7	118	2	2	68 (0.99)	4	59	1	4
Body as a Whole										
SURGICAL PROCEDR	52 (0.70)	0	52	0	0	24 (0.35)	0	24	0	0
FEVER	7 (0.09)	0	7	0	0	2 (0.03)	0	2	0	0
SEPSIS	4 (0.05)	0	4	0	0	1 (0.01)	0	1	0	0
CELLULITIS	2 (0.03)	0	2	0	0	0 (0.00)	0	0	0	0
INFECT	2 (0.03)	0	2	0	0	2 (0.03)	0	2	0	0
OVERDOSE	2 (0.03)	0	0	0	2	3 (0.04)	0	0	0	3
PAIN	2 (0.03)	0	2	0	0	0 (0.00)	0	0	0	0
PAIN BACK	2 (0.03)	0	2	0	0	0 (0.00)	0	0	0	0
ABSCESS	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
DEATH	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
HEADACHE	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
HERNIA	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
INJURY ACCID	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
OVERDOSE ACCID	1 (0.01)	0	1	0	0	4 (0.06)	0	3	0	1
No. of AEs**	79	0	77	0	2	36	0	32	0	4
No. of subjects**	70 (0.95)	0	68	0	2	36 (0.52)	0	32	0	4
Cardiovascular										
CARDIAC SURGERY	0 (0.00)	0	0	0	0	1 (0.01)	0	1	0	0
No. of AEs**	0	0	0	0	0	1	0	1	0	0
No. of subjects**	0 (0.00)	0	0	0	0	1 (0.01)	0	1	0	0

See last page of the table for footnotes.

Whitehall-Robins Healthcare
Protocol #: CAMP I
Investigator: Pooled

CAMP I Study

Table B.3a.1 (Cont'd)

Summary of Serious Adverse Experiences (AEs) by Relationship of AE to Study Medication

For All Children under 2 Years

Who Took at Least One Dose of Study Medication

(Took Ibuprofen or Acetaminophen Only)

Adverse Experience(AEs) (by Body System and Event Term)	Ibuprofen (n=7381) No. of AEs(%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose	Acetaminophen (n=6900) No. of AEs(%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose
Digestive										
VOMIT	8 (0.11)	3	5	0	0	7 (0.10)	0	7	0	0
DIARRHEA	5 (0.07)	1	3	1	0	4 (0.06)	0	4	0	0
ANOREXIA	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
DIARRHEA BLOODY	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
STOMATITIS	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
CONSTIP	0 (0.00)	0	0	0	0	1 (0.01)	0	1	0	0
DYSPHAGIA	0 (0.00)	0	0	0	0	1 (0.01)	0	1	0	0
GASTROENTERITIS	0 (0.00)	0	0	0	0	1 (0.01)	0	1	0	0
PAIN ABDO	0 (0.00)	0	0	0	0	1 (0.01)	0	1	0	0
No. of AEs**	16	4	11	1	0	15	0	15	0	0
No. of subjects**	13 (0.18)	4	8	1	0	9 (0.13)	0	9	0	0
Hematic and Lymphatic										
CYANOSIS	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
No. of AEs**	1	0	1	0	0	0	0	0	0	0
No. of subjects**	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
Metabolic and Nutritional										
DEHYDRAT	28 (0.38)	2	24	2	0	6 (0.09)	1	5	0	0
No. of AEs**	28	2	24	2	0	6	1	5	0	0
No. of subjects**	28 (0.38)	2	24	2	0	6 (0.09)	1	5	0	0

See last page of the table for footnotes.

Whitehall-Robins Healthcare
Protocol #: CAMP I
Investigator: Pooled

CAMP I Study

Table B.3a.1 (Cont'd)

Summary of Serious Adverse Experiences (AEs) by Relationship of AE to Study Medication

For All Children under 2 Years

Who Took at Least One Dose of Study Medication

(Took Ibuprofen or Acetaminophen Only)

Adverse Experience(AEs) (by Body System and Event Term)	Ibuprofen (n=7381) No. of AEs(%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose	Acetaminophen (n=6900) No. of AEs(%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose
Musculoskeletal										
OSTEOMYELITIS	2 (0.03)	0	2	0	0	1 (0.01)	0	1	0	0
SYNOVITIS	0 (0.00)	0	0	0	0	1 (0.01)	0	1	0	0
No. of AEs**	2	0	2	0	0	2	0	2	0	0
No. of subjects**	2 (0.03)	0	2	0	0	2 (0.03)	0	2	0	0
Nervous System										
CONVULS	4 (0.05)	0	4	0	0	1 (0.01)	1	0	0	0
MENINGITIS	3 (0.04)	0	3	0	0	1 (0.01)	0	1	0	0
NERVOUSNESS	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
SOMNOLENCE	1 (0.01)	0	0	1	0	0 (0.00)	0	0	0	0
Unknown Event	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
No. of AEs**	10	0	9	1	0	2	1	1	0	0
No. of subjects**	9 (0.12)	0	9	0	0	2 (0.03)	1	1	0	0

See last page of the table for footnotes.

Whitehall-Robins Healthcare
Protocol #: CAMP I
Investigator: Pooled

CAMP I Study

Table B.3a.1 (Cont'd)

Summary of Serious Adverse Experiences (AEs) by Relationship of AE to Study Medication

For All Children under 2 Years

Who Took at Least One Dose of Study Medication

(Took Ibuprofen or Acetaminophen Only)

Adverse Experience(AEs) (by Body System and Event Term)	Ibuprofen (n=7381) No. of AEs(%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose	Acetaminophen (n=6900) No. of AEs(%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose
Respiratory										
PNEUMONIA	19 (0.26)	0	19	0	0	11 (0.16)	0	9	2	0
ASTHMA	8 (0.11)	1	7	0	0	12 (0.17)	1	10	1	0
BRONCHIOLITIS	7 (0.09)	1	6	0	0	4 (0.06)	0	4	0	0
LUNG DIS	7 (0.09)	0	7	0	0	5 (0.07)	0	5	0	0
DYSPNEA	6 (0.08)	1	5	0	0	4 (0.06)	0	4	0	0
LARYNGITIS	3 (0.04)	1	2	0	0	2 (0.03)	0	2	0	0
COUGH INC	2 (0.03)	0	2	0	0	2 (0.03)	0	2	0	0
BRONCHITIS	1 (0.01)	0	1	0	0	1 (0.01)	0	1	0	0
HYPOVENTIL	1 (0.01)	0	0	1	0	0 (0.00)	0	0	0	0
PHARYNGITIS	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
SINUSITIS	1 (0.01)	0	0	1	0	0 (0.00)	0	0	0	0
STRIDOR	1 (0.01)	0	1	0	0	1 (0.01)	0	0	1	0
ATELECTASIS	0 (0.00)	0	0	0	0	2 (0.03)	1	0	1	0
HYPERVENTIL	0 (0.00)	0	0	0	0	1 (0.01)	1	0	0	0
HYPOXIA	0 (0.00)	0	0	0	0	1 (0.01)	1	0	0	0
No. of AEs**	57	4	51	2	0	46	4	37	5	0
No. of subjects**	37 (0.50)	2	33	2	0	24 (0.35)	2	21	1	0
Skin										
RASH	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
No. of AEs**	1	0	1	0	0	0	0	0	0	0
No. of subjects**	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0

See last page of the table for footnotes.

Whitehall-Robins Healthcare
Protocol #: CAMP I
Investigator: Pooled

CAMP I Study

Table B.3a.1 (Cont'd)

Summary of Serious Adverse Experiences (AEs) by Relationship of AR to Study Medication

For All Children under 2 Years

Who Took at Least One Dose of Study Medication

(Took Ibuprofen or Acetaminophen Only)

Adverse Experience (AEs) (by Body System and Event Term)	Ibuprofen (n=7381) No. of AEs (%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose	Acetaminophen (n=6900) No. of AEs (%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose
Special Senses										
OTITIS MED	34 (0.46)	0	17	17	0	9 (0.13)	0	4	5	0
No. of AEs**	34	0	17	17	0	9	0	4	5	0
No. of subjects**	34 (0.46)	0	17	17	0	9 (0.13)	0	4	5	0
Uro-genital										
INFCT URIN TRACT	2 (0.03)	0	2	0	0	1 (0.01)	0	1	0	0
PYELONEPHRITIS	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
No. of AEs**	3	0	3	0	0	1	0	1	0	0
No. of subjects**	3 (0.04)	0	3	0	0	1 (0.01)	0	1	0	0

** A subject may have multiple AEs for each COSTART term. The number of AEs includes ALL Events. The number of subjects, however, counts a subject only ONCE within each body system. AEs are classified by the worst relationship to study medication.
+: Possibly, Probably, or Definitely.
Note: 'Not Related' includes AR-REMOTE, NO AE-PRI ILLNES, NO AE-CHILD ILL, NO AE-MED SURG, NO AE-SX>5 DAYS, NO AE-SX BEF TX, NO AE-MISCOMM, NO F-UP INFO, and NO AE-ANY REASON.

Whitehall-Robins Healthcare
Protocol #: CAMP I
Investigator: Pooled

CAMP I Study

Table B.3a.1 (Cont'd)

Summary of Serious Adverse Experiences (AEs) by Relationship of AE to Study Medication

For All Children under 2 Years

Who Took at Least One Dose of Study Medication

(Took Ibuprofen or Acetaminophen Only)

Adverse Experience(AEs) (by Body System and Event Term)	Ibuprofen (n=7381) No. of AEs(%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose	Acetaminophen (n=6900) No. of AEs(%)	RELATIONSHIP Drug Related +	Not Related	Missing	Overdose
Special Senses										
OTITIS MED	34 (0.46)	0	17	17	0	9 (0.13)	0	4	5	0
No. of AEs**	34	0	17	17	0	9	0	4	5	0
No. of subjects**	34 (0.46)	0	17	17	0	9 (0.13)	0	4	5	0
Uro-genital										
INFCT URIN TRACT	2 (0.03)	0	2	0	0	1 (0.01)	0	1	0	0
PYELONEPHRITIS	1 (0.01)	0	1	0	0	0 (0.00)	0	0	0	0
No. of AEs**	3	0	3	0	0	1	0	1	0	0
No. of subjects**	3 (0.04)	0	3	0	0	1 (0.01)	0	1	0	0

** A subject may have multiple AEs for each COSTART term. The number of AEs includes ALL Events. The number of subjects, however, counts a subject only ONCE within each body system. AEs are classified by the worst relationship to study medication.

+: Possibly, Probably, or Definitely.

Note: 'Not Related' includes AE-REMOTE, NO AE-PRI ILLNES, NO AE-CHILD ILL, NO AE-MED SURG, NO AE-SX>5 DAYS, NO AE-SX BEF TX, NO AE-MISCOMM, NO F-UP INFO, and NO AE-ANY REASON.

Appendix II

Lesko SL, Mitchell AA: An Assessment of the Safety of Pediatric Ibuprofen: A Practitioner-Based Randomized Clinical Trial. JAMA, 273(12):929-933, 1995.

This was a 4-week, multi center, double-blind, randomized, acetaminophen-controlled antipyretic study in an office-based pediatric population from the continental United States. The study's objective was to assess the risk of hospitalization due to serious adverse events such as gastrointestinal bleeding, acute renal failure, anaphylaxis and Reye syndrome associated with the use of ibuprofen in febrile children. A total of 84,192 children between the ages of 6 months to 12 years weighing 7-50 kg were recruited after presenting for a pediatric evaluation of an acute febrile illness to any one of the 1,735 pediatricians or family practitioners participating in the trial. In order to be eligible for study entry, the children had to be able to take the study medication by mouth, and have a parent/guardian administer the study medication while observing and caring for them. Children who were dehydrated, unable to take medication by mouth, or with histories of hypersensitivity to acetaminophen or NSAIDS, renal or hepatic diseases, bleeding disorders, anemia, neoplasia, endocrine or metabolic problems, or peptic ulcer disease were ineligible for study entry. Participants were randomized to receive 1 of the following 3 study treatments: 5 mg/kg ibuprofen, 10 mg/kg ibuprofen, or 12 mg/kg acetaminophen.

Results: Two hundred seventy-seven (277, 0.3%) of the 84,192 children enrolled in the study were lost to follow-up and were not included in the final data analysis. Of the 83,915 children in which there was data available for study analysis, 27,948 were treated with 5mg/kg ibuprofen, 27,837 were treated with 10mg/kg ibuprofen, and 28,130 were treated with acetaminophen. All 3 treatment groups were found to be demographically similar with respect to age, weight, sex, and race. The most frequently reported causes of the presenting fever for all 3 treatment groups are as follows: upper respiratory tract infection, otitis media, pharyngitis, lower respiratory tract and gastrointestinal tract infections. A total of 795 (1%) children were hospitalized during the study. The hospitalization rates were found to be similar for all 3 treatment groups as follows: 0.9% for the 5 mg/kg ibuprofen group, 1% for the 10 mg/kg ibuprofen group, and 1% for the 12 mg/kg acetaminophen group. During the study there were only 4 reported cases of GI bleeding, and no cases of acute renal failure, anaphylaxis, or Reye Syndrome. All 4 cases of GI bleeding occurred in children treated with ibuprofen (2 from the high-dose group and 2 from the low dose group). The observed risk for developing GI bleeding due to treatment with ibuprofen in this study was calculated to be 7.2 per 100,000 (95% confidence interval, 2 to 18 per 100,000). On comparison analysis, this risk was not found to be significantly different (p=0.31) from the risk in the acetaminophen treated group (0 per 100,000; 95% confidence interval, 0 to 11 per 100,000). The observed risk for developing acute renal failure, anaphylaxis, or Reye's syndrome was calculated for all of the children treated with ibuprofen (n=55,785) in the study and found to be 0 per 100,000 (95% confidence interval, 0 to 5.4 per 100,000 ibuprofen-treated children). The remaining 112 serious hospitalizations were for a variety of adverse events as follows: asthma (n=68), vomiting or gastritis (n=26),

neutropenia (n=9), erythema multiforme (n=4), abdominal pain (n=4), serum sickness (n=1). Of these 6 conditions, only the risk for developing neutropenia in the ibuprofen group (14 per 100,000; 95% confidence interval, 6.2 to 28 per 100,000) was found to be significantly different (p=0.4) from the risk in the acetaminophen treated group (0 per 100,000; 95% confidence interval, 0 to 11 per 100,000). The authors state that this unexpected association was noted after multiple comparisons and that they do not know what to make of it since pretreatment white blood cell counts were not obtained.

Conclusion: The short-term risk for hospitalization due to GI bleeding, acute renal failure, anaphylaxis and Reye's syndrome associated with the use of high and low dose ibuprofen in children in this trial was not shown to be any different from the risk in children treated with acetaminophen. Although children treated with ibuprofen in this study were shown to have an unexpected increased risk for hospitalization due to neutropenia as compared to children treated with acetaminophen, the significance of this finding is unclear since pretreatment white cell counts were not obtained for comparison.

APPEARS THIS WAY
ON ORIGINAL

16 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

MAR 2 9 1999

MEDICAL OFFICER REVIEW
Division of Over-The-Counter Drug Products

NDA #: 20-603, SE3-003
NAME: Children's MOTRIN® (ibuprofen oral suspension) Drops, 50 mg/1.25 mL
SPONSOR: McNeil Consumer Products Company
7050 Camp Hill Road
Fort Washington, PA 19034-2299
Tel.:(215)233-7000
TYPE OF SUBMISSION: Commercial Pharmaceutical
DATE OF SUBMISSION: June 15, 1998 **CDER:** June 15, 1998
DATE OF REVIEW: March 15, 1999
REVIEWER: Rosemarie Neuner, MD, MPH
CSO: Mr. Kerry Rothschild, JD

Introduction

Ibuprofen is a propionic acid derivative that belongs to the nonsteroidal anti-inflammatory class of drugs (NSAIDs). A suspension formulation of ibuprofen (100 mg/5 mL) has been marketed in the United States since 1989 by McNeil Consumer Products for use in children (age 6 months and older) as a prescription drug, under the trade names, Pedia-Profen and Children's MOTRIN® Suspension. On June 10, 1995 Children's MOTRIN® (ibuprofen oral suspension) Drops, 50 mg/1.25 mL was approved by the U.S. Food and Drug Administration for marketing as an over-the-counter (OTC) drug product for the temporary relief of fever and pain in children 2-3 years of age. In June 1998, the sponsor of this product, McNeil Consumer Products, submitted a request to the agency for a pediatric exclusivity claim which was subsequently granted. The sponsor has now submitted this efficacy supplement for agency review in which they request the lowering of the currently approved group age range from two to three years of age down to two months of age for this product.

In support of this change in the product's dosing age range, the sponsor has submitted the results of a new subgroup analysis of data generated from 27,000 children less than 2 years of age who participated in the actual use drug -safety trial, the Boston University Fever Study, which evaluated the safety profile of Children's MOTRIN® as an antipyretic agent. (Note: This was the pivotal safety study that supported the approval for the sponsor's NDA 20-516 Children's MOTRIN® Ibuprofen Oral Suspension 100 mg/5 mL in 1995. It also served as the supportive safety study in the approval of the sponsor's other NDA 20-603 Children's MOTRIN® Ibuprofen Drops 50 mg/1.25 mL in 1996.) In addition, the sponsor has included the results of 21 clinical trials where children 2 years old and younger participated as study subjects, in addition to 4 published pharmacokinetic (PK) studies involving children ages 2 months to 2 years. The results from these PK studies are discussed in the PK section of this SNDA review by Dr. E. Dennis Bashaw, FDA Division of Pharmacokinetics (HFD-880).

Since prescription ibuprofen is currently approved for use in infants age 6 months and older, the major regulatory issue to be answered by this application is it

safe for OTC ibuprofen to be used in the pediatric age group 2 months and older at the doses proposed by the sponsor of this supplement. This review will therefore concentrate on the drug's safety profile in this targeted age group.

Efficacy

In support of ibuprofen's efficacy in the targeted pediatric age group of 2 months to 2 years, the sponsor performed an extensive search of the worldwide literature. This search yielded 23 articles and 6 abstracts which described the results of 21 randomized, controlled antipyretic (16) and analgesia (5) trials which evaluated ibuprofen in children ages less than 2 years of age. A complete listing of these articles and abstracts, and their trial summaries written by the sponsor can be found in the following sponsor's tables, Tables 8-10 and 8-12, in Attachment I.

A total of 2,032 febrile children between the ages of 2 months to 13 years participated in the antipyretic studies. (See the following sponsor's table, Table 8-10, found in Appendix I.) Of these 16 studies, 2 were placebo-controlled trials. The other 14 studies compared ibuprofen to active controls such as acetaminophen or aspirin. Five (5) out of the 16 studies were single-dose studies while the remaining 11 trials were multi-dose studies of ibuprofen. These 16 trials tested doses of ibuprofen in the range of 0.5 mg/kg to 10 mg/kg. All 16 studies showed that ibuprofen at the doses tested, with the exception of the lowest dosing range, was an efficacious antipyretic agent in the populations tested. (Refer to Table 8-10 found in Attachment I at the end of this review.)

A total of 504 children between the ages of 6 months to 14 years participated in the 4 postoperative and 1 otitis media analgesic studies. (See the following sponsor's table, Table 8-12, located in Attachment I.) Two out of the 5 trials were placebo-controlled studies, 2 were placebo- and active- controlled studies, and 1 study evaluated ibuprofen as a single-agent with codeine used for rescue pain. Three of the 5 studies evaluated multi-doses while 2 were single-dose trials. The dose range of ibuprofen used in these analgesia studies ranged from 5 mg/kg to 13 mg/kg. All 5 studies showed that ibuprofen at the doses tested was comparable to acetaminophen or more efficacious than placebo in the control of pain in the patients studied.

The sponsor created the following 2 tables, Sponsor's Tables 1 and 2, below, to show how many studies in this collection included study subjects from the targeted pediatric age group. With the exception of one randomized, double-blind, actively controlled antipyretic trial which compared ibuprofen 7.5 mg/kg to acetaminophen 10 mg/kg in 154 children aged 6-months to 5-years, all of the remaining studies used descriptive statistics (i.e., mean, standard deviation, and range) in discussing the age of the subjects who participated in the studies. Thus, it is impossible to know how many children less than 2 years of age actually participated in these studies.

Sponsor's Table 1 - Age of the Youngest Patient Included in Published Efficacy Antipyretic Trials

Age	Number of Studies	Literature Reference [one study]
2-3 months	6	[8] [19,49] [20] [25] [26] [27]
4-11 months	9	[6] [7] [10,13] [11,17] [12] [15,22] [14,16,24] [18,21] [23]
12-23 months	1	[9]

Sponsor's Table 2 - Age of the Youngest Patient Included in Published Efficacy Analgesic Trials

Age	Number of Studies	Literature Reference [one study]
2-3 months	0	None
4-11 months	1	[30]
12-23 months	4	[28] [29,33] [31] [32]

Since these studies are not proprietary studies, and their actual case reports and data sets were not included in this submission for review, they can only be considered supportive of the already established efficacy profile of ibuprofen in children ≤ 2 years old. As previously discussed, ibuprofen as a prescription drug is considered to be efficacious in the sponsor's requested pediatric target age group for this submission. Thus, these studies are being included in this review at this time for completeness and reference.

Medical Reviewer's Comments: All 21 studies showed that ibuprofen was an efficacious agent for the indications studied when compared to placebo and other recognized antipyretic and analgesic agents. Thus, these studies can be used in support of ibuprofen's already recognized effectiveness as an antipyretic and analgesic agent in the sponsor's requested targeted age group.

Safety

As discussed in the preceding introduction, the focus of this review is to determine whether ibuprofen is safe to be used as an OTC agent in the sponsor's requested targeted pediatric age group of 2-months to 2-years. In support of this product's safety profile the sponsor has submitted for review the following safety data for children less than 2-years of age:

1. The Boston University Fever Study subgroup analysis of children less than 2-years of age.
2. McNeil CPC controlled clinical trial data on subjects ≤ 2-years of age enrolled on or after November 17, 1993 and treated with ibuprofen.
3. McNeil CPC Spontaneous Reporting System for McNeil CPC ibuprofen products in children ≤ 2-years of age for the time period November 17, 1993 through October 2, 1997, including serious reports in the published literature.
4. FDA Spontaneous Reporting System for all ibuprofen products in children ≤ 2-years of age for the time period November 1, 1993 through August 25, 1997. (Note: Adverse events reported through McNeil Spontaneous Reporting System are not included here.)
5. Published randomized controlled clinical trials and human pharmacokinetic studies of ibuprofen products for the years 1966 through October 1997 that reported including children ≤ 2-years of age.
6. AAPCC TESS ibuprofen data from the years 1994 through 1996 for children ≤ 2-years of age. (The 1997 report was not yet available.)

The sponsor has compiled the following summary table, Table 8-13, which outlines the total number of serious adverse events that have been reported to have occurred in children < 2-years of age since November 1993 from the above submitted safety data base. (See sponsor's table, Table 8-13, below.)

The cornerstone of this safety data base for children (see sponsor's table, Table 8-13, below) is generated from the actual use safety study, the Boston Fever Study. Although this study was reviewed by the agency in support of a regulatory action for NDA 20-516 Children's MOTRIN® Ibuprofen Oral Suspension 100 mg/5 mL in 1995, the sponsor has submitted for review a new subcohort analysis of the 27,065 children < 2 years of age who participated in this study which compares the incidence of adverse events that occurred during the trial in this group to that of subjects age ≥ 2 years. This study will be discussed first followed by reviews of the other safety data as listed above.

Table 8-13. Summary of Ibuprofen Safety Data For Children Less Than Two Years of Age (data since November 1993, except where noted otherwise)

Boston University Fever Study (children < two years of age)	(Total Patients)	27,065
Total Ibuprofen Exposures		17,938
Hospitalizations for events of primary interest		3
Other hospitalizations (excluding deaths)		258
Deaths		0
McNeil CPC Controlled Clinical Studies (children < two years of age)		
Antipyretic Study	(Total Patients)	1
Total Ibuprofen Exposures[1]		1
Reports of AEs with serious outcomes (excluding deaths)[2]		0
Deaths		0

[redacted]

Published Randomized Controlled Studies (inclusive of, but not limited to, children < two years of age[4]) (first study published in 1976)		
Antipyretic Studies	(Total Patients)	2032
Total Ibuprofen Exposures		974
Serious AEs (excluding deaths)[5]		0
Deaths		0
Analgesic Studies	(Total Patients)	504
Total Ibuprofen Exposures		213
Serious AEs (excluding deaths)[5]		0
Deaths		0
Pharmacokinetic/Pharmacodynamic Studies	(Total Patients)	340
Total Ibuprofen Exposures		194
Serious AEs (excluding deaths)[5]		0
Deaths		0

1 One child less than two years of age was unintentionally enrolled in a McNeil CPC controlled trial of ibuprofen for which enrollment was planned for children two to 11 years of age (Protocol No. 95-516).

2 A serious outcome is defined as an adverse event that is life threatening (immediate risk of death from the reaction), requires inpatient hospitalization, prolonged hospitalization, or is permanently or severely disabling. Outcomes of death, congenital anomaly, or cancer are also considered serious.

3 Generally, a moderate outcome involves a patient who exhibits signs or symptoms as a result of the exposure which are pronounced, prolonged, or of a systemic nature; usually some form of treatment is required. Symptoms are not life-threatening and the patient has no residual disability or disfigurement. A major outcome generally involves a patient who exhibits signs or symptoms as a result of the exposure which are life-threatening or result in significant residual disability or disfigurement.

4 While overall safety information was reported, such information for children less than two years of age was not specified.

5 Serious as defined by the investigator.

1. The Boston Fever Study Subcohort Analysis of Children Less Than 2 Years of Age.

This was a 4-week, multicenter, double-blind, randomized, acetaminophen-controlled antipyretic study conducted by the Slone Epidemiology Unit of Boston University in office-based pediatric population from the continental United States. The study's objective was to assess the risk of serious adverse events such as gastrointestinal bleeding, acute renal failure, anaphylaxis and Reye syndrome associated with the use of ibuprofen in febrile children. Children between 6 months to 12 years of age weighing between 7-50 kg were recruited after presenting for a pediatric evaluation of an acute febrile illness to any one of the 1,735 pediatricians or family practitioners who participated in the trial. In order to be eligible for study entry, the children had to be able to take the study medication by mouth, and have a parent/guardian able to administer the study medication while observing and caring for them. Children who were dehydrated, unable to take medication by mouth, or with histories of hypersensitivity to acetaminophen or NSAIDS, renal or hepatic diseases, bleeding disorders, anemia, neoplasia, endocrine or metabolic problems, or peptic ulcer disease were ineligible for study entry. A total of 84,192 patients were entered into the trial out of which 83,915 patients were randomized and received 1 of the following 3 treatments: 5 mg/kg ibuprofen, 10 mg/kg ibuprofen, or 12 mg/kg acetaminophen.

Out of the total of 83,915 children entered into the study, 27,065 were < 2 years and 56,850 were ≥ 2 years of age. Demographically, the 2 age groups on comparison as well as the 3 randomized treatment groups were very similar in make up as shown in the following 2 tables, Sponsor's Tables 3 and 4, below.

Sponsor's Table 3 - Demographic Characteristics of All Participants

Characteristic	Age	
	< 2 years (n =27,065)	≥ 2 years (n = 56,850)
Median Age (Months)	13	59
Median Weight (kg)	10	18
Sex, %Male **% Female**	54 46	50 50
Race, %White **% African-American** **%Hispanic**	81 7.2 7.2	82 7.3 6.6

Sponsor's Table 4 - Demographic Characteristics of 27,065 Participants ≤ 2 Years Old According to Treatment Group

Characteristic	Acetaminophen	Ibuprofen (5 mg/kg)	Ibuprofen (10 mg/kg)
Total Number	9,127	9,159	8,779
Median Age (Months)	14	13	13
Median Weight (kg)	10	10	10
Sex, % Male	54	54	55
Race, % White	82	81	80
% African-American	7.3	6.8	7.4
% Hispanic	6.7	7.2	7.7

Three-hundred nineteen (319) children (1.1%) ≤ 6 months of age were entered into the study despite an entry age requirement of being at least 6 months or older. Table 5 below lists the numbers of infants ≤ 6 months who participated in the study. (Note: In the official study report the sponsor states that because age was not routinely confirmed, children ≤ 6 months of age were only included in the analysis of the study data if their reported weight was between the 5th and 95th percentile for month of reported age.).

Table 5 - Age Distribution For 319 Children Younger than 6-Months of the 27,065 Participants ≤ 2 Years Old at Enrollment

Age in Months	Number	Percent
1	**4**	**0.015%**
2	**13**	**0.048%**
3	**27**	**0.010%**
4	**76**	**0.281%**
5	**199**	**0.735%**

The 2 age groups differed in the reported causes of their fevers as shown in Sponsor's Table 6. Although upper respiratory tract infection was the most commonly reported cause of fever for both age groups, in children < 2 years of age, otitis media was more common ($p<0.001$) as compared to children ≥ 2 years of age, who were more commonly afflicted with pharyngitis and lower respiratory tract infections ($p<0.001$ for

both comparisons).

Sponsor's Table 6 - Cause of Fever Among All Participants

Illness (%)	Age < 2 years (n =27,065)	Age ≥ 2 years (n = 56,850)
Upper Respiratory Infection	43	42
Otitis Media	48[1]	27
Pharyngitis	19	40[2]
Lower Respiratory Infection	6.3	8.8[3]
Gastrointestinal Infection	3.0	3.2

[1]Statistically significant difference at (p<0.001).
[2]Statistically significant difference at (p<0.001).
[3]Statistically significant difference at (p<0.001).

Sponsor's Table 7 shown immediately below demonstrates that there were no differences in the causes of fever in the 27,065 participants ≤ 2 years of age when examined by randomized antipyretic treatment group.

Sponsor's Table 7 - Cause of Fever Among 27,065 Participants ≤ 2 Years Old According to Treatment Group

Illness (%)	Acetaminophen	Ibuprofen (5 mg/kg)	Ibuprofen (10 mg/kg)
Upper Respiratory Infection	43	43	43
Otitis Media	48	48	48
Pharyngitis	20	19	20
Lower Respiratory Infection	6.5	6.2	6.2
Gastrointestinal Infection	3.0	3.3	2.8

The following 2 tables, Sponsor's Tables 8 and 9, show by age and randomized treatment group the numbers and percentages of children who were randomized, but did not receive study medications. The tables also show that the median number of doses and the median duration of treatment by those who did receive medications was very similar for the subcohort and the original cohort groups, as well as all 3 treatment groups ≤ 2 years of age.