AQ-99-02 N/A AQ-99-02 N/A 2-Apr-01 N Single-Blind, Randomized, Open-Label, Single Center, Three-Way Crossover Study

The combination of ibuprofen 200 mg and pseudoephedrine hydrochloride 30 mg has been available as a tablet formulation (Advil Cold & Sinus) since 1989 for use in adults 12 years of age (NDA 19-771). A suspension formulation containing ibuprofen 110 mg/pseudoephedrine hydrochloride 15 mg per 5 mL has been developed (Children’s Advil Cold & Sinus Suspension). The present study was designed to obtain pharmacokinetic data on ibuprofen and pseudoephedrine hydrochloride when administered as a suspension containing ibuprofen 110 mg and pseudoephedrine hydrochloride 15 mg per 5 mL in children aged 2 to <12 years to support an application for OTC labeling.

Inclusion criteria:
- Male or female, 2 to <12 year of age;
- Male or female minors (if applicable) provided written informed consent;
- Subjects were aged 2 to <12 years;
- Subjects were mentally competent, able to understand, and sign the informed consent form. Children provide the assent, as appropriate;
- Subjects were able to swallow the medication;
- The subject weighs <24 lbs. or >95 lbs.;
- A known hypersensitivity to aspirin, pseudoephedrine, ibuprofen, or any other nonsteroidal anti-inflammatory agents;
- A history of melena or any significant hepatic, renal, endocrine, cardiac, neurological, psychiatric, gastrointestinal, pulmonary, hemodynamic, or metabolic disorders;
- Any serious medical condition or history felt by the Investigator to place the subject at increased risk;
- Concurrent use of any other cough/cold medications within 12 hours prior to the first dose of study medication (concomitant use of antibiotics will be permitted);
- Use of a monoamine oxidase inhibitor or sympathomimetics or other stimulating drugs;
- Use of any medication (prescription or OTC) within 7 days of study drug administration;
- Use of any nonsteroidal anti-inflammatory drug within 2 weeks of study drug administration;

Exclusion criteria:
- Relatives of the Sponsor or other personnel involved with the study;
- Members of the study staff directly involved with the study or conducting the study;
- Had taken an investigational drug within 30 days prior to entering the study;
- A history of melena or any significant hepatic, renal, endocrine, cardiac, neurological, psychiatric, gastrointestinal, pulmonary, hematologic or metabolic disorders;
- A history of melena or any significant hepatic, renal, endocrine, cardiac, neurological, psychiatric, gastrointestinal, pulmonary, hematologic or metabolic disorders;
- A known hypersensitivity to aspirin, pseudoephedrine, ibuprofen, or any other nonsteroidal anti-inflammatory agents.

Subjects were eligible for inclusion in the study provided they met all of the following criteria:
- A. Unable to swallow the medication;
- B. A known hypersensitivity to aspirin, pseudoephedrine, ibuprofen, or any other nonsteroidal anti-inflammatory agent;
- C. A history of or currently had high blood pressure (blood pressure above age specific range);
- D. A history of melena or any significant hepatic, renal, endocrine, cardiac, neurological, psychiatric, gastrointestinal, pulmonary, hematologic or metabolic disorders;
- E. Any serious medical condition or history felt by the Investigator to place the subject at increased risk;
- F. Clinically significant abnormal laboratory test, as judged by the Investigator;
- G. Female subjects who had undergone menarche and had a positive urine pregnancy test;
- H. Use of a nonsteroidal anti-inflammatory agent, and or sympathomimetics or other stimulating drugs for the treatment of ABDH within 2 weeks of study drug administration;
- I. Use of any medication (prescription or OTC) within 7 days of study drug administration;
- J. Judged by the Investigator to be unable or unwilling to comply with the requirements of the protocol;
- K. Had taken an investigational drug within 30 days prior to entering the study;
- L. Members of the study staff directly involved with the study or relatives of the Sponsor or other personnel involved with the study.
The efficacy and safety of ibuprofen and pseudoephedrine have been demonstrated in controlled clinical trials and by extensive therapeutic use over many years. Ibuprofen as an OTC analgesic/fever reducer has been available for use in adults in the U.S. since 1984 (NDA 16-989). Pseudoephedrine suspension (NDA 20-589) became available for OTC use in children in 1996. Advil Cold and Sinus Tablets are not currently indicated for use in children under the age of 12 years, except under the advice and supervision of a physician. In children, there is only one published study describing the pharmacokinetic characteristics of pseudoephedrine.

Males and females of any race were eligible for the study if:

- between 6 and <12 years of age
- within the 5th and 95th percentiles in physical growth as described by Hamill et al.15 between 6 and <12 years of age
- in normal physical health as judged by physical and laboratory examinations
- parents provided written informed consent and subjects provided their assent
- unable to swallow tablets
- known hypersensitivity to pseudoephedrine, any antihistamine, ibuprofen, aspirin, or any other non-steroidal anti-inflammatory agent
- history of melena or any significant hepatic, renal, endocrine (e.g., diabetes, thyroid disorder), cardiac, neurological, psychiatric, gastrointestinal, pulmonary (e.g., asthma, chronic bronchitis), hematologic or metabolic disorders; or attention deficit hyperactivity disorder (ADHD)
- any serious medical condition or history felt by the Investigator to place them at increased risk
- had a clinically significant laboratory result, as judged by the Investigator
### Interventions

| Children's Advil Cold & Sinus Suspension (ibuprofen 110 mg/pseudoephedrine hydrochloride 15 mg/5 mL) | Sensitivity (Children's Advil Cold & Sinus Suspension; Treatment A), a single ingredient product containing ibuprofen hydrochloride 15 mg/5 mL. (Children's Sudafed® Nasal Decongestant Liquid; Treatment B), or a single ingredient product containing pseudoephedrine hydrochloride 15 mg/5 mL (Children's Sudafed® Nasal Decongestant Liquid; Treatment B), or a single ingredient product containing pseudoephedrine hydrochloride 15 mg/5 mL (Children's Advil Cold & Sinus Suspension; Treatment C). | Log-transformed values of AUCL, AUCI, and Cmax were of primary interest with log-transformed AUCL being the primary pharmacokinetic parameter. | Log-transformed values of AUCL, AUCI, and Cmax were of primary interest with log-transformed AUCL being the primary pharmacokinetic parameter. | Treatment assignments were determined by a computer-generated randomization schedule provided by the Biostatistics Department of Whitehall-Robins Healthcare. All drugs were administered according to this randomization scheme by the Investigator or his/her designee. | None | N/A | N/A | N/A | All subjects received ibuprofen 110 mg/pseudoephedrine 15 mg/5 mL. Five-digit subject numbers were used with the leading digit identifying the study site: 10001, 10002, etc. for Study Site 1; 20001, 20002, etc. for Study Site 2. At each study site, treatment numbers were assigned in sequential order based on the subject's weight: from 1 to 100 for subjects weighing 24-47 pounds and from 101 to 200 for subjects weighing 48-95 pounds.

### Objective(s) of the trial

The objective of this study was to characterize the adverse experience profile of a suspension formulation of ibuprofen 110 mg/pseudoephedrine hydrochloride 15 mg per 5 mL, and to demonstrate its safety in the 2 to <12 year-old target population.

### Outcome measures _1 (Primary endpoint)

Efficacy: Efficacy was not subserved in this study. Below vital signs (blood pressure, pulse rate, respiratory rate, and temperature at baseline Visit 2 after 2 days dosing), and Visit 3 (at the end of study participation), with no experiences recorded by the parent/guardian in a daily diary.

### Outcome measures _2 (secondary endpoints)

Only subjects completing all three periods of the study were included in the respective pharmacokinetic and statistical analyses. Pharmacokinetic parameters AUCL, AUCI, and Cmax were analyzed. Pharmacokinetic parameters other than AUCL (the key pharmacokinetic parameter) were summarized. AUCL, AUCI, and Cmax (both log transformed and untransformed) were analyzed for differences between treatments using an analysis of variance with subject, study, subject (gender), period, treatment, and treatment-by-gender interaction. A 90% two-sided confidence interval for the relative bioavailability, relative to the reference, based on the least square means (equivalent to two one-sided t-tests) was calculated for AUCL, AUCI, and Cmax. For each of the above comparisons, bioequivalence was declared if the 90% two-sided confidence interval was between 0.8 and 1.25 for log transformed pharmacokinetic parameters or between 0.8 and 1.20 for untransformed
The objective of this study was to characterize the rate and extent of absorption, distribution, metabolism, and elimination of pseudoephedrine in children ages 6 to <12 years following a single dose administration of ibuprofen 200 mg plus pseudoephedrine 30 mg in a combination tablet or pseudoephedrine 30 mg alone in a tablet form.

The log-transformed parameters were of primary interest (i.e., AUCL, AUCI, and Cmax) with the log-transformed AUCL being the primary pharmacokinetic parameter.

Assignments of treatment sequence were determined by a randomization schedule generated by the Biostatistics Department of Whitehall-Robins Healthcare. The randomization schedule can be found in the protocol (Appendix). Twenty-five children (12 males and 13 females) were enrolled to ensure that a minimum of 22 completed the study.

Individuals performing the analysis of plasma samples were blinded to treatments. AUCL was considered the primary PK parameter. The other PK parameters are summarized. AUCL, AUCI, and Cmax, (both log transformed and untransformed) were analyzed for differences between treatments using an analysis of variance with effects for gender, subject (gender), period, treatment, and treatment-by-gender interaction.

90% two-sided confidence interval for the bioavailability, relative to the reference, based on the least square means (equivalent to two one-sided t-tests) was calculated for AUCL, AUCI, and Cmax. Bioequivalence was declared if the 90% two-sided confidence interval for the ratio was between 0.80 and 1.25 for log transformed PK parameters or between 0.80 and 1.20 for untransformed PK parameters. The log-transformed analyses were considered primary.
A total of 106 children entered the study at two study sites. Of these 106 subjects, 78 were deemed to be “enrolled” (i.e., subject completed the baseline physical examination, took a minimum of four doses of study drug over the first two days of dosing, returned to the clinic for monitoring of vital signs at Visit 2, and returned to the clinic at the end of the study at Visit 3 and completed a pharmacokinetic monitoring and monitoring of vital signs and population, a representative sample of subjects 106 were evaluated (i.e., any subject who completed the baseline physical examination and took at least one dose of active age and gender was enrolled. study drug over the 7-day dosing period).

The following conditions were adhered to throughout the conduct of the clinical study:

- Only subjects who met all entry criteria, whose parent/guardian determined participation was appropriate based on the product's proposed labeling and provided written informed consent, and who provided their assent, if appropriate, were enrolled. A total of approximately 30 healthy children (classified as “Other”) was Caucasian (96%), followed by “other” (12.5%), Hispanic (10.4%), and Black (2.9%). The average age was 8.6 years, ranging from: 6-11 years. Twelve subjects (51%) were aged six to <12 years. Twenty-eight subjects (27%) were two-to-three years of age.
- Thirty-one subjects entered the study. Two subjects were discontinued prior to dosing for protocol violations. One subject (Subject No. 009) was a protocol violator during Period II of the study, was discontinued, and was excluded from the pharmacokinetic analyses, but was included in the safety analysis as specified in the protocol. The remaining 28 subjects randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome should be stated.
- A total of approximately 30 healthy children (classified as “Other”) was Caucasian (96%), followed by “other” (12.5%), Hispanic (10.4%), and Black (2.9%). The average age was 8.6 years, ranging from: 6-11 years. Twelve subjects (51%) were aged six to <12 years. Twenty-eight subjects (27%) were two-to-three years of age.

**Participant Flow**

<table>
<thead>
<tr>
<th>Recruitment</th>
<th>Baseline data</th>
<th>Trial interruption (Y/N)</th>
<th>Reasons for trial interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximately 109 subjects were to be enrolled</td>
<td>An approximately equal number of males (47.1%) and females (52.9%) participated in the study. The mean age of the subjects was 8.6 years. The majority of subjects were Caucasian (74.6%), followed by “other” (12.2%), Hispanic (10.4%), and Black (2.9%). The weight and height of the subjects was 47.8 pounds (range: 24.6-60 pounds) and 52.5 inches (range: 35-60 inches), respectively. Subjects were enrolled across all ages: 51 subjects (49%) were less than six years-old and 53 subjects (51%) were age six to &lt;12 years. Twenty-eight subjects (27%) were two-to-three years of age.</td>
<td>N</td>
<td>N/A</td>
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</table>

**Subject Accounting**

Thirty-one subjects entered the study. Two subjects were discontinued prior to dosing for protocol violations. One subject (Subject No. 009) was a protocol violator during Period II of the study, was discontinued, and was excluded from the pharmacokinetic analyses, but was included in the safety analysis as specified in the protocol. The remaining 28 subjects were enrolled. A minimum of 24 children (approximately 5 males and 15 females) were enrolled. A minimum of 24 children were required to complete the study.

**Demographics**

Of the 28 completed subjects, 11 (40%) were male and 17 (60%) were female. All but one (classified as “Other”) was Caucasian (96%). The average age was 8.6 years, ranging from: 6-11 years. Twelve subjects (43%) were aged six to 8 years. The average weight and height were 48.8 pounds (ranging from 47-113 pounds) and 52.5 inches (ranging from 46-59 inches), respectively.

**Protocol Deviations**

One subject (Subject No. 009) missed two consecutive blood samples and was discontinued from the study after Period II as a protocol violator. This subject was excluded from the pharmacokinetic analyses, but was included in the analysis of safety.

With the exception of only five subjects each missing one blood sample, all completed subjects provided all protocol administered study drug as required. At the conclusion of Treatment Periods I and II, subjects were scheduled to return to the study site approximately 7 days later for the next treatment period. At the end of Treatment Period III, subjects were discharged from the study following a post-treatment physical examination and drawing of blood for a complete blood count with differential.

**Flow of participants through each stage (diagram, if appropriate).** For each group the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome should be stated. This should include the number of participants in each group excluded in each analysis and whether the analysis was by “intention-to-treat” or “per protocol”. Protocol deviations from the study as planned, together with reasons should be stated.
Twenty-five subjects were enrolled in the study and completed both study periods. All 25 subjects were included in the analysis of pharmacokinetic parameters. Subjects underwent baseline screening which consisted of a medical history, physical examination, and fasting laboratory studies (hematology, biochemistry and urinalysis). Females who experienced menarche were required to have a negative urine pregnancy test at the start of each treatment period. Subjects were domiciled at the study site from approximately 8:00 PM on the evening prior to dosing until 24 hours following dosing. The physical examination and a CBC with differential were repeated at the conclusion of the study.

The baseline physical examination data are summarized as follows. Twelve percent of the subjects had abnormal baseline extremity findings; 12% had abnormal head/eyes/ears/nose findings; 4% had findings classified as other. These findings were considered not clinically meaningful.
### Outcomes and estimation

| Vital sign data (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) obtained at baseline, Visit 2 and at the end of the study (Visit 3) for all 104 subjects evaluated. There were no clinically significant changes in vital signs while subjects were taking study medication. Six of the 104 evaluable subjects (6%) had a fever (oral temperature 100°F) at baseline. In five of the subjects with fever, oral temperature had returned to normal (99°F) at Visit 2. In one subject, oral temperature was reduced from 101.1°F at baseline to 99.9°F at Visit 2, and returned to normal, 96.9°F, at Visit 3. | N/A | A total of 38 adverse experiences were reported by 29 of the 104 evaluable subjects (28%). Adverse experiences were most frequently associated with the nervous system (n=13). The most frequently reported adverse experience was somnolence (n=7) followed by vomiting (n=5). Each of the following symptoms had an incidence of two occurrences: asthma, fever, abdominal pain, nausea, tremor, and otitis media. The remaining adverse experiences were single occurrences: back pain, common cold, headache, pain, diarrhea, dyspepsia, lymphadenopathy, lymphocytosis, hyperkinesia, nervousness, rhinitis, pruritus, rash, conjunctivitis, ear disorder, and ear pain. Of the 38 occurrences of adverse experiences, 28 were rated as "mild," 16 were rated as "moderate," and two were rated as "severe." The "severe" adverse experiences were single occurrences of somnolence and ear pain. Only 12 of the 38 adverse experience occurrences were considered by the Investigator to have a relationship to the study medication: somnolence (n=3), tremor (n=2), and single occurrences of asthma, headache, vomiting, nausea, abdominal pain, hyperkinesia, and nervous system. | N/A | N/A | The results of this study demonstrate that a suspension formulation of ibuprofen 110 mg/pseudoephedrine hydrochloride 15 mg/5 mL is safe for use in children aged 2 to <12 years for the treatment of symptoms of the common cold, sinusitis or flu, including headache, fever, nasal congestion, body aches and pains. Adverse experiences reported were generally mild and unrelated to study medication. Additionally, ibuprofen 110 mg/pseudoephedrine hydrochloride 15 mg/5 mL combination suspension had no clinically significant effect on vital signs.

### Ancillary analysis

The results of the present study demonstrate that the pharmacokinetic profiles of ibuprofen and pseudoephedrine hydrochloride when administered as a combination suspension were bioequivalent to the pharmacokinetic profiles of ibuprofen suspension and pseudoephedrine hydrochloride liquid when administered as single ingredients. These results demonstrate the following:

1. The rate and extent of absorption of ibuprofen and pseudoephedrine hydrochloride from the combination suspension are similar to that from Children's Advil Oral Suspension and Children's Sudafed Nasal Decongestant Liquid Medication, respectively, when both are administered as a combination.
2. The presence of pseudoephedrine hydrochloride does not affect the rate and extent of absorption of ibuprofen and the presence of ibuprofen does not affect the rate and extent of absorption of pseudoephedrine hydrochloride when both are administered as a combination.
3. These data are consistent with a pharmacokinetic study conducted previously in adults as well as a previous pharmacokinetic study comparing Advil Cold & Sinus Tablets and Sudafed Tablets in children aged 6 to <12 years old. All pharmacokinetic parameters are similar for adults and children.
4. The pharmacokinetic profiles of ibuprofen and pseudoephedrine hydrochloride were not influenced by sex, age, and body weight.

### Adverse events

The majority of adverse experiences (53%) were mild in nature and not thought by the Investigator to have a relationship to the treatment. No subject discontinued due to an adverse event. There were no clinically significant changes in laboratory parameters or vital signs.

| 1. The majority of adverse experiences (53%) were mild in nature and not thought by the Investigator to have a relationship to the treatment. | N/A | There was only one adverse event during the entire study. One subject reported dizziness of moderate severity while on Children’s Sudafed Nasal Decongestant Liquid Medication. The adverse event was deemed unrelated to the treatment as it occurred the night before dosing. No subject discontinued due to an adverse event. | N/A | N/A | The results of this study in children aged 6 to <12 years demonstrate that the pharmacokinetic properties of ibuprofen and pseudoephedrine hydrochloride when administered as a combination product (Children’s Advil Cold and Sinus Suspension) are bioequivalent to those of single ingredient ibuprofen (Children’s Advil Oral Suspension) and pseudoephedrine hydrochloride (Children’s Sudafed Nasal Decongestant Liquid Medication) demonstrating the absence of any pharmacokinetic interaction when the two drugs are administered as a combination product. Ibuprofen and pseudoephedrine hydrochloride were well tolerated by this population (children aged 6 to <12 years) whether taken alone or in combination.
Subject Disposition: Twenty-five subjects were enrolled in the study and completed both study periods. All 25 subjects were included in the analysis of pharmacokinetic parameters.

Demographics: The mean age of the study population was 8.0 ± 1.74 years (range: 6 - 11 years). Twelve (48%) were male and 13 (52%) were female. The mean height was 52.0 ± 4.6 inches (range: 45 - 60 inches) and the mean weight was 66.2 ± 16.04 pounds (range 46 - 109 pounds). 92% of the subjects were Caucasian, 4% were Black and 4% were Other.

Pharmacokinetics: Key pseudoephedrine PK parameters are summarized in the table above.

The results of this pediatric study demonstrate that the pharmacokinetic properties (rate and extent of absorption, distribution, and elimination) of pseudoephedrine when administered as a combination product (ibuprofen/pseudoephedrine) are bioequivalent to those of pseudoephedrine when administered alone. Hence, there was no interference caused by ibuprofen regarding the pharmacokinetics of pseudoephedrine in combination tablets. Pseudoephedrine was well tolerated by this population (children ages 6 to <12 years) whether taken alone or in combination with ibuprofen.
Discussion and interpretation of study results - by competent authority (if available)

N/A