CLINICAL STUDY PROTOCOL

A Multi-Center, Open-Label Pharmacokinetic and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months

Study Number: CPI-CL-022
ClinicalTrials.gov ID: NCT02583399

Protocol Version

Version Number: Original Protocol
Final: 01Jun2015

Amendment: Amendment 02
Revised Final: 30Sep2016

CONFIDENTIALITY STATEMENT

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws and regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential.

RESPONSIBLE PERSONNEL

Sponsor - Medically Responsible Person

[redacted]
Director, Medical Affairs

Cumberland Pharmaceuticals Inc.
2525 West End Avenue, Suite 950
Nashville, TN 37203
USA

Tel.: [redacted]
Fax.: [redacted]

Sponsor's Coordinating Office

[redacted]
Sr. Vice President & Chief Development Officer

Cumberland Pharmaceuticals Inc.
2525 West End Avenue, Suite 950
Nashville, TN 37203
USA

Tel.: [redacted]
Fax.: [redacted]
[redacted]

Sponsor's Clinical Operations

[redacted]
Sr. Manager, Clinical Operations
[redacted]

Cumberland Pharmaceuticals Inc.
2525 West End Avenue, Suite 950
Nashville, TN 37203
USA

Tel.: [redacted]
Fax.: [redacted]

1 INVESTIGATOR'S STATEMENT

I have read and agree to the Protocol CPI-CL-022, Amendment 02: "A Multi-Center, Open-Label Pharmacokinetic and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months." I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

Principal Investigator

Signature: _____ Date of Signature

Name:
Title:
Address:
Telephone:

Sponsor Signature

Signature: [redacted] [redacted]
Date of Signature
Director, Medical Affairs

Signature: [redacted] [redacted]
Date of Signature
Senior Vice President & Chief Development Officer

2 SYNOPSIS

Name of Sponsor: Cumberland Pharmaceuticals Inc.	**Finished Product:** CALDOLOR® (ibuprofen) injection	**Active Ingredient:** ibuprofen
Title of Study: A Multi-Center, Open-Label, Pharmacokinetic, and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months		
Study Centers (Planned): Approximately 5 centers in the United States		
Expected Study Duration: From Q3 2016 to Q3 2017		**Phase of Development:** IV

Objectives:

Primary Study Objective

- To determine the pharmacokinetic (PK) profile of intravenous ibuprofen administered over approximately 10 minutes in hospitalized pediatric subjects, aged birth (> 37 weeks gestational age) to < 6 months of age.

Secondary Study Objectives

- To determine the safety of single and repeated doses of intravenous ibuprofen administered in hospitalized pediatric subjects, aged birth (> 37 weeks gestational age) to < 6 months of age, with a clinical indication of pain and fever by assessing treatment–emergent adverse events (AE) and changes in vital signs (temperature, heart rate [HR], respiratory rate [RR], and systolic and diastolic blood pressures.

Methodology:

This is a multi-center, open-label, in-patient, single and/or multiple dose study in pediatric subject, aged birth (> 37 weeks gestational age) to < 6 months of age, with a clinical indication of pain and fever. Subjects who meet all of the inclusion and none of the exclusion criteria at the end of the Screening/Baseline Period are eligible to be enrolled into the study.

Assessments of vital signs and pain scores, if appropriate, will be conducted at baseline and at regular intervals when investigational medicinal product (IMP) dosing occurs. Pharmacokinetic blood samples will be done with the initial dose of IMP to determine plasma ibuprofen concentration in all subject's dosed with IMP. Blood samples for safety assessments including clinical chemistry, hematology, and coagulopathy, will be done at screening and on Study Days 1 and 2. Adverse event monitoring will occur throughout the study period. The study duration will be 72 hours.

Number of subjects (planned):

Twenty-four

Diagnosis and main criteria for inclusion:

A subject must have met the following inclusion criteria:

1. Be a hospitalized male or female subject between birth (> 37 weeks gestational age) and < six months of age.
2. Have a clinical indication of pain or fever.
3. Have written informed consent provided by legal parent, guardian, or authorized agent prior to participation in the study or performance of any study-only related procedures.

Name of Sponsor: Cumberland Pharmaceuticals Inc.	**Finished Product:** CALDOLOR® (ibuprofen) injection	**Active Ingredient:** ibuprofen

Investigational Medicinal Product (IMP), dose and mode of administration, batch number:

- Intravenous ibuprofen, 10 mg/kg, intravenous.

Duration of treatment:
48 hours

Criteria for evaluation:
The primary objective of this study is to evaluate the PK profile of a single dose of intravenous ibuprofen administered over approximately 10 minutes.

The secondary objective of this study is to evaluate the safety of single and repeated doses of intravenous ibuprofen administered to hospitalized pediatric patients by assessing treatment-emergent adverse events, vital signs, and laboratory assessments

Statistical methods:
Continuous data will be summarized in tables listing the mean, standard deviation or standard error. All data will be listed by patient. Safety will be evaluated on the basis of vital signs and treatment-emergent AEs. AE data will be listed individually and summarized by body system organ class and preferred terms within system organ class (MedDRA). Serious and/or unexpected AEs will also be discussed on a case-by-case basis. On the basis of plasma ibuprofen concentration-time data, PK parameters will be estimated by using a non-compartmental model.

3 TABLE OF CONTENTS

List of Tables

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event/Experience
AUC	Area Under the Curve
C	Celsius
CABG	Coronary Artery Bypass Surgery
CHD	Congenital Heart Disease
CM	Clinical Monitor
CRF	Case Report Form
C_{max}	Maximum concentration
Ct	Last Measurable Ibuprofen Concentration
DCF	Data Clarification Form
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
HR	Heart rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
λ	Terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
N	Number of Subjects
NS	Normal Saline
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over the Counter
PRN	pro re nata (as necessary)
PK	Pharmacokinetics
RR	Respiratory rate
SAE	Serious Adverse Event/Experience

Abbreviation	Definition
$T_{1/2}$	Half-life
T_{max}	Time to maximum concentration
US	United States

5 INTRODUCTION

This study is to be performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) E6.

5.1 Background Information

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that was first approved for marketing as a prescription drug in the United States (US) in 1974. Oral ibuprofen is currently approved for use as oral treatment for minimal to moderate pain from arthritis, surgery, sunburn, menstruation, and fever. Like aspirin and other drugs in the NSAID family, ibuprofen is believed to reduce the inflammatory response by inhibiting the formation of prostaglandins. Several studies have demonstrated the success of oral or rectal ibuprofen in the reduction of fever and the subjective symptoms associated with it (Schwartz 1999, Krishna 1995).

In 1989, the US Food and Drug Administration (FDA) approved ibuprofen for use in children. Approval for marketing pediatric ibuprofen as an over-the-counter product in the United States was granted in the mid-1990s, and today it is one of the most commonly used antipyretic and analgesic therapies in children. Oral ibuprofen is commonly used in hospitals to treat patients with pain and fever. However, hospitalized patients with endotracheal intubation, sedation, reduced gastric motility, nausea, recent surgery, or other factors are frequently unable to ingest, digest, absorb, or tolerate oral medications.

CALDOLOR® (ibuprofen) Injection was approved by the US Food and Drug Administration in June 2009 for adults and in May 2016 for pediatric patient greater than six months of age. CALDOLOR is indicated in adults and pediatric patients 6 months and older for the management of mild to moderate pain, management of moderate to severe pain as an adjunct to opioid analgesics and for the reduction of fever. This formulation of intravenous (IV) ibuprofen is now being studied for use in the pediatric population less than 6 months of age.

5.2 Stage of Development

This is a phase 4 study to determine the pharmacokinetics (PK) and safety of single and/or multiple doses of intravenous ibuprofen administered over 10 minutes in children less than six months of age. This study will investigate the application of intravenous ibuprofen in the treatment of pain and/or fever.

To date, sixteen clinical studies have been conducted in adult and pediatric subjects with intravenous ibuprofen. Of the 16 completed studies (Number of Subjects [N] = 2107), three

provide PK data associated with various infusion times, three provide efficacy and safety data supporting use for temperature reduction in febrile adult patients, three provide efficacy and safety data supporting use for treatment of moderate to severe pain as an adjunct to opioid analgesics in adult patients undergoing elective abdominal and orthopedic surgeries, one study provides pilot data for temperature reduction in febrile pediatric patients, one study provides PK, safety, and efficacy data supporting use for temperature reduction in hospitalized febrile pediatric subjects, one study provides efficacy and safety data supporting use for pain as an adjunct to opioid analgesics in pediatric patients undergoing elective tonsillectomy surgery, two studies provide safety data supporting a shortened infusion time, and two studies assesses the analgesic efficacy of IV ibuprofen when administered at induction of anesthesia compared to IV ketorolac. Table 5-1 lists the completed intravenous ibuprofen studies.

Table 5–1 CALDOLOR® (ibuprofen) Injection Clinical Studies

Study Number	Title	N	Indication
CPI-CL-001	A Phase l, Open-Label, Randomized, Single-Dose, Crossover, Pharmacokinetic, and Safety Study with Intravenous and Oral Ibuprofen in Healthy Subjects	36	PK, Safety
CPI-CL-003	A Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Crossover Study of the Safety and Tolerability of Ibuprofen Injection in Healthy Adult Subjects	12	PK, Safety, Tolerability
CPI-CL-004	A Multicenter, Randomized, Double-blind, Parallel, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Ibuprofen Injection in Adult Febrile Patients	120	Fever
CPI-CL-005	A Multi-Center, Randomized, Parallel, Open-Label, Active-Controlled Efficacy and Safety Study of Ibuprofen Injection in Hospitalized Febrile Pediatric Patients	30	Fever
CPI-CL-006	A Single Center, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Ibuprofen Injection in Hospitalized Febrile Adult Patients	60	Fever
CPI-CL-008A	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Injection for Treatment of Pain in Post-Operative Adult Patients, Dose-Ranging	406	Pain
CPI-CP-008B	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Injection for Treatment of Pain in Post-Operative Adult Patients, Abdominal	319	Pain
CPI-CL-008C	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Injection for Treatment of Pain in Post-Operative Adult Patients, Orthopedic	185	Pain
CPI-CL-010	A Multicenter, Randomized, Double-blind Trial of Ibuprofen Injection (IVIb) for Treatment of Fever and Pain in Burn Patients	61	Fever, Pain
CPI-CL-011	A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Tolerability of Ibuprofen Injection in Healthy Adult Volunteers	11	PK, Safety, Tolerability
CPI-CL-012	A Multi-Center, Randomized, Open-Label, Parallel, Active-Comparator Trial to Determine the Efficacy, Safety, and Pharmacokinetics of Intravenous Ibuprofen in Pediatric Patients	103	Fever
CPI-CL-014	A Multi-Center, Randomized, Double-blind Placebo-Controlled, Single-Dose Trial of the Safety and Efficacy of Intravenous Ibuprofen for	161	Pain

Study Number	Title	N	Indication
	Treatment of Pain in Pediatric Patients Undergoing Tonsillectomy		
CPI-CL-015	A Multi-Center, Open-Label, Surveillance Trial to Evaluate the Safety and Efficacy of a Shortened Infusion Time of Intravenous Ibuprofen	150	Pain, Fever
CPI-CL-016	A Multi-Center, Open-Label, Surgical Surveillance Trial to Evaluate the Safety and Efficacy of a Shortened Infusion Time of Intravenous Ibuprofen	300	Pain
CPI-CL-017	A Pilot Study to Determine the Efficacy of Intravenous Ibuprofen for Pain Control Following Arthroscopic Knee Surgery	53	Pain
CPI-CL-020	A Multicenter, Prospective, Randomized, Double-blind Study to Determine the Efficacy of Intravenous Ibuprofen compared to Intravenous Ketorolac for Pain Control Following Arthroscopic Knee Surgery	100	Pain
IVIb = Ibuprofen Injection, N= Number of Subjects, PK = Pharmacokinetics			

Please refer to the Investigator's Brochure for additional detail surrounding these studies.

To date, three studies have been conducted utilizing intravenous ibuprofen in pediatric subjects. A pediatric fever trial (CPI-CL-005) was conducted in 30 subjects to assess the efficacy and safety of intravenous ibuprofen in pediatric subjects with fevers greater than or equal to 101.0ºF (Fahrenheit) (38.3ºCelsius [C]). The mean age for all patients was 6.19 (± 3.67) years. Age ranged from a minimum of 0.5 to a maximum of 17 years. The primary endpoint of the study was to determine the clinical equivalence of a single dose of intravenous ibuprofen compared to acetaminophen for the treatment of fever as measured by the area under the temperature versus time curve (AUC-Tº) within the first six hours of treatment (as compared to a target temperature of 98.6ºF [37.0ºC]). Both treatments demonstrated a statistically significant reduction in fever, with intravenous ibuprofen reducing fever more in the first two hours. While the two treatments were not shown to be equivalent with respect to the primary endpoint, the study was underpowered to demonstrate equivalence.

A pediatric fever trial (CPI-CL-012) was conducted in 103 subjects to assess the efficacy, safety, and PKs of intravenous ibuprofen in pediatric subjects less than or equal to sixteen years of age with fevers greater than or equal to 101.0ºF (38.3ºC). The mean age for all patients was 7 (± 4.5) years. The primary endpoint of the study was to determine the superiority of a single dose of intravenous ibuprofen compared to acetaminophen for the treatment of fever as measured by the area under the change in temperature versus time curve during the first 2 hours of treatment (AUC0-2). Compared to acetaminophen, patients receiving 10 milligram/kilogram (mg/kg) intravenous ibuprofen experienced a significant reduction in fever as measured by the area under the curve 0-2 hours and 0-4 hours).

A pediatric pain trial (CPI-CL-014) was conducted in 161 subjects to assess the efficacy and safety of intravenous ibuprofen in pediatric subjects undergoing tonsillectomy. The mean age for all patients was 9 (± 3.2) years. The primary endpoint of the study was to evaluate the efficacy of

a single preemptive dose on reducing the number of doses of fentanyl administered in the postoperative period to discharge. Compared to placebo there was a significant reduction in post-operative fentanyl use during the post-operative period. In addition to using less fentanyl, subjects experienced a significant reduction in the incidence of vomiting and emesis following discharge.

5.3 Patient Population

The population for this study will consist of hospitalized pediatric subjects from birth (> 37 weeks gestational age) to < 6 months of age with a clinical indication of pain and/or fever.

5.4 Trial Rationale

For the pediatric patient population, there are multiple oral over-the-counter (OTC) ibuprofen products available for the treatment of pain in children. Motrin® (McNeil Consumer Healthcare, Fort Washington, Pennsylvania) is one of the most commonly used oral ibuprofen products currently marketed. The recommended dose for Motrin for treatment of pain in children 6 months to 12 years of age is 10 mg/kg with the recommended maximum daily dose of 40 mg/kg. The recommended dosing for children 12 years of age and older is the same as that used for adults, 200 to 800 mg up to four times daily, with a maximum of 3200 mg per day.

Based on the approved dosing for the product in pediatric patients greater than 6 months, as well as published results from clinical studies, the dose selected for this study is 10.0 mg/kg of intravenous ibuprofen. The total daily dose should not exceed 40 mg/kg/day.

5.5 Risk-Benefit Assessment

5.5.1 Risk –Benefits Associated with Therapeutic Procedures

Risk-Benefits of Intravenous Ibuprofen Administration

The study is an open label design and therefore all subjects enrolled into the trial will receive ibuprofen. Ibuprofen is a widely prescribed medication in children greater than 6 months of age and in adults. It is commonly prescribed as a treatment for pain and fever. Inclusion into the trial is limited to subjects who have a clinical indication of pain and/or fever that would be treated with ibuprofen.

Intravenous ibuprofen is contraindicated in subjects with a known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to ibuprofen or other NSAIDs; in subjects who have experienced asthma, urticarial, or allergic-type reactions after taking aspirin or

NSAIDs; and for use during the peri-operative period in the setting of coronary artery bypass surgery (CABG).

Ibuprofen is contraindicated in newborn infants with uncorrected ductus dependent congenital heart disease (CHD) including ductus dependent systemic blood flow lesions (aortic stenosis/critical aortic stenosis, coarctation of aorta, interrupted aortic arch, and hypoplastic left heart syndrome) and ductus dependent pulmonary blood flow lesions (critical pulmonary stenosis, pulmonary atresia, pulmonary atresia with intact ventricular septum (hypoplastic right heart syndrome), tricuspid atresia with severe pulmonary stenosis, tetralogy of fallot with pulmonary atresia, Ebstein's anomaly, transposition of the great arteries with intact ventricular septum).

The most common adverse events, occurring in the pediatric clinical trials, experienced by 3% or more subjects were alanine aminotransferase increased, anemia, aspartate aminotransferase increased, blood lactate dehydrogenase increased, basophilia, diarrhea, eosinophilia, headache, hypokalemia, infusion site pain, neutropenia, pruritus, nausea, and vomiting.

Risk of Laboratory Assessments

The study involves both therapeutic and non-therapeutic blood draws. The laboratory assessments are therapeutic as the results may provide a direct benefit to the subject by providing health status information that may not have been otherwise obtained if the subject was not in the study. The risks of taking blood includes pain, bruising at the point where the blood is taken, redness and swelling of the vein, infection, and a rare risk of fainting. The risk associated with the blood draws can be decreased by utilizing standard of care laboratory results as opposed to study specific laboratory sample collection when possible; by the use of indwelling venous and/or arterial catheters to collect blood samples, when possible; by utilizing heel sticks if deemed appropriate by the investigator, and, by utilizing the smallest amount of blood necessary to complete the required procedures.

Risk-Benefits of other Therapeutic Procedures

To ensure the safety of the subject, vital signs will be monitored using the standard measurement devices located at each clinical center. Vital signs, especially blood pressure, should be performed utilizing clinical center standard of care age appropriate devices (i.e. automated blood pressure cuff measurements or indwelling blood pressure measurement devices are preferred to manual cuff measurements; unless personnel performing the manual blood pressure measurement is specifically training to perform the measurement in this age population). Laboratory testing will be monitored for changes in chemistry, hematologic, and coagulation measurements.

5.5.2 Risk–Benefits Associated with Non-Therapeutic Procedures

Risk of PK Assessments

The study involves both therapeutic and non-therapeutic blood draws. The laboratory assessments are therapeutic as the results provide a direct benefit to the subject by providing health status information that may not have been otherwise collected if the subject was not in the study. The PK sampling however would be considered non-therapeutic because they resultant data will not provide a direct benefit to the study subject; instead, these data will allow for the further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. The risks of both the therapeutic and non-therapeutic blood draws are similar. The risks of taking blood includes pain, bruising at the point where the blood is taken, redness and swelling of the vein, infection, and a rare risk of fainting. The risk associated with the blood draws can be decreased by utilizing standard of care laboratory results as opposed to study specific laboratory sample collection when possible; by the use of indwelling venous and/or arterial catheters to collect blood samples, when possible; by utilizing heel sticks if deemed appropriate by the investigator, and, by utilizing the smallest amount of blood necessary to complete the required procedures.

5.5.3 Risk to Confidentiality

The study has been designed to minimize the need to collect identifiable data by determining whether there is a legitimate reason to collect or maintain identifiable data. All sponsor maintained study records will identify the subject by their screening number if the subject is not enrolled and dosed with the Investigational Medicinal Product (IMP) in the trial and by the subject number if the subject is enrolled and dosed with IMP in the trial. Clinical Center Team Member are instructed to de-identify/redact any record that are provided to the sponsor and identify necessary documents by the subject's randomization number. In addition to minimizing data collection, each subject's parent or legal guardian will be asked to review and sign the Clinical Center's IRB approved consent and or independent Health Information Portability and Accountability Act (HIPAA) confidentiality agreement.

6 STUDY OBJECTIVES AND PURPOSE

The primary objective of this study is to evaluate the PK profile of a single dose of intravenous ibuprofen administered over approximately 10 minutes.

The secondary objectives of this study are:

- to evaluate the safety of single and repeated doses of intravenous ibuprofen administered to hospitalized pediatric patients by assessing treatment-emergent adverse events, vital signs, and laboratory assessments

7 STUDY ENDPOINTS

7.1 Primary Study Endpoints

To evaluate the primary objective of PKs, the following endpoint will be measured:

- Clearance
- Volume of distribution
- Elimination $T_{1/2}$
- $C_{max,}$
- $AUC_{(0-\infty,\ 0-t)}$

7.2 Safety Endpoints

To evaluate safety, the following endpoints will be measured:

- Treatment emergent adverse events
- Vital signs (temperature, heart rate, respiratory rate, blood pressure)
- Clinical chemistry, hematology, and coagulation assessments

8 STUDY DESCRIPTION

8.1 Study Design

This multi-center, open-label, single and/or multiple dose clinical study will assess the PKs (following a single dose) and safety during and after the administration of intravenous ibuprofen. A total of twenty-four subjects, between the ages of birth (> 37 weeks gestational age) to less than six months of age, will be enrolled at up to five clinical centers. The study duration will be up to 72 hours.

This 72 hour study will consist of a Screening/Baseline Period (up to 48 hours prior to the first dose of IMP), a Treatment Period (beginning with the first dose of IMP and continuing for 48 hours) and a Post-Treatment Period (beginning at the end of the Treatment Period and continuing for 24 hours).

The Screening/Baseline Period may begin up to 48 hours prior to Study Hour 0. During the Screening/Baseline Period an evaluation of the inclusion and exclusion criteria, a complete medical history, and a physical examination will be conducted. A review of the subject's pre-IMP vital signs, baseline signs and symptoms, including pain scores (if applicable), concomitant medications, and laboratory assessments will be also conducted to establish the subject's eligibility to participate in the study.

The Treatment Period will begin at Hour 0 when an initial dose of investigational medicinal product will be administered over a 10 minute period. Subsequent doses of IMP will be administered, at the investigators discretion, every 6 to 8 hours, as needed, during the 48 hour treatment period. The total daily dose should not exceed 40 mg/kg/day. Pharmacokinetic sampling will be performed utilizing a sparse sampling technique following the initial dose of IMP. Vital signs, pain scores (if applicable), laboratory assessments and concomitant medications will be monitored during the treatment period and adverse events (AEs) will be monitored during the treatment and post-treatment periods. All treatment emergent adverse events will be followed until resolution or stabilization, regardless of the assessment of severity or relationship to the study drug.

The Schedule of Time and Events is provided in Table 8-1.

Table 8–1 Overall Schedule of Time and Events

Measurement/Evaluation	Study Period			
	Screening/ Baseline	Treatment		Post-Treatment
Time(s)	Hour - 48 to Hour 0	Hour 0 to Hour 24	Hour 24 to Hour 48	Hour 48 to Hour 72
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Medical History	X			
Physical Examination	X			
Demographic Data	X			
Baseline Signs & Symptoms	X			
Vital Signs	X	X	X	X♯
Laboratory Assessments	X*	Xˢ		X♯
Pharmacokinetic Assessments		Xᵠ		
Concomitant Medications	X+	X	X	
IMP Administration (Initial & PRN)		X	X	
Adverse Event Monitoring		X**	X**	X**

IMP = Investigational Medicinal Product

* Laboratory data collected within 48 hours prior to dosing may be used for Screening/Baseline Period laboratory assessments.

\+ Record concomitant medication actually administered to the subject in the 8 hours prior to the first dose of IMP.

ᵠ PK assessment must be taken immediately following the first dose of IMP then per the sparse sampling schedule.

ˢ Laboratory Assessment must be performed at Study Hour 24 (± 6 hours)

♯Laboratory Assessment and Vital Signs must be performed at Study Hour 72 (± 6 hours) or at the time of discharge, whichever occur first.

**All treatment adverse events will be followed until resolution or stabilization, regardless of the assessment of severity or relationship to the study drug.

8.1.1 Randomization

All subjects who meet all the inclusion and exclusion criteria during the Screening/Baseline Period will be enrolled into the study. Only eligible subjects will be assigned to receive intravenous ibuprofen, 10 mg/kg per dose.

There is no randomization; this study is open-label with respect to the treatment assignment.

8.1.2 Blinding Conditions and Methods

This study is open-label with respect to the treatment assignment. All study personnel, sponsor, research team, and subject's parent or legal guardian are unblinded to the treatment assignment.

8.1.3 Pharmacokinetics

Pharmacokinetic parameters, including clearance, volume of distribution, elimination $T_{1/2}$, C_{max}, and AUC, will be determined from analysis of collected blood samples (Section 13.5). One milliliter (mL) samples for PK analysis will be collected at specified times on all subjects. The PK profile of intravenous ibuprofen for the study will be completed utilizing sparse sampling techniques.

PK samples will be collected on all subjects immediately (± 5 minutes) following completion of the first dose of intravenous ibuprofen; then alternating subjects will have PK sampling performed at 30 minutes and 2 hours or at 1 hour and 4 hours following the first dose of intravenous ibuprofen (12 subjects will have samples collected immediately following the first dose, then at 30 minutes and 2 hours; and, 12 subjects will have samples collected immediately following the first dose, then at 1 hour and 4 hours).

Pharmacokinetic sampling will only be performed following the first dose of IMP regardless of the total number of doses of IMP administered. Sites will be notified by the sponsor of which PK samples to be collected.

8.2 Drugs and Dosages

8.2.1 Identification and Description of Test Agents

Intravenous ibuprofen is available for investigation use only in the pediatric population. Intravenous ibuprofen is packaged as a clear, colorless liquid in 10 mL glass vials, each containing 800 mg ibuprofen in a total of 8 mL (100 mg/mL). Each vial also contains approximately 78 mg/mL arginine.

Normal saline (NS), which will be supplied by each site, will be used as the diluent for intravenous ibuprofen in this study.

All investigational materials should be kept in a secured area inaccessible to unauthorized individuals. A Study Procedures Manual will be provided to the sites documenting the IMP storage and preparation procedures.

8.2.2 Dosing Instructions and Schedule

The dose in this study was selected using the results generated from three previous clinical studies in pediatric subjects conducted by Cumberland and by the current recommended available dosing information (Taketomo 2003).

Commercially available drug product will be provided to the site pharmacist in an unblinded fashion. The pharmacist will prepare each dose of the intravenous ibuprofen for the subject by adding weight appropriate amounts of ibuprofen to NS. The addition of the ibuprofen will be done directly to commercially available bags of NS. Each dose of intravenous ibuprofen will be prepared at a concentration of 4 mg/mL or less.

The vials of Intravenous ibuprofen will contain information on the label providing name of product, strength, and storage conditions:

- CALDOLOR® (Ibuprofen) injection
- 800 mg/8 mL (100 mg/mL)
- FOR INTRAVENOUS USE
- Store at controlled room temperature
- 20ºC -25ºC (68ºF-77ºF)
- Manufactured for: Cumberland Pharmaceutical Inc. Nashville, TN 37203

Labels for Intravenous ibuprofen infusion bags will include the information listed above as well as the patient identification number and protocol number.

An initial dose of 10 mg/kg intravenous ibuprofen administered intravenously over 10 minutes will be administered. Following the initial dose, subsequent doses of IMP may be administered every 6-8 hours as needed, at the investigator's discretion, during the 48 hour Treatment Period. The maximum daily dose of intravenous ibuprofen will not exceed 40 mg/kg/day. A total of up to eight doses of IMP may be administered during the 48 hour Treatment Period.

With each dose of IMP, the intravenous catheter should be flushed with NS before and after each infusion. The intravenous catheter can be used for other infusions during the Treatment Period if it is adequately flushed. If a central venous catheter is available, that route of administration is preferred; however, a peripheral intravenous line with good blood return is also acceptable. A dedicated line is not required.

The Study Procedures Manual will contain directions for the preparation of intravenous ibuprofen by the pharmacist.

8.2.3 Accountability Procedures for Investigational Medicinal Product

All IMP shipments should be inspected upon receipt. Any discrepancy, breakage or unacceptable temperature condition should be reported immediately to the sponsor. If the shipment is acceptable, the site pharmacist or their designee will sign and date the packing slip and file the original form in the pharmacy study binder. Receipt of IMP shipments must be documented on the appropriate Pharmacy Accountability Record.

IMP inventory and accountability records for the study drug will be kept by the investigator/pharmacist. IMP accountability throughout the study must be documented. The following guidelines are pertinent:

- The investigator agrees not to supply study drugs to any persons except the subjects in this study.
- The pharmacist will keep the study drug in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the pharmacist. The inventory will include details of material received and a clear record of when they were dispensed and to which subject. Intravenous ibuprofen vials should be saved for the duration of the study. Upon completion of IMP preparation, the pharmacist should tally and reconcile the number of vials used per patient with the Pharmacy Accountability Record. The used vials should be retained until the end of the study. It is not necessary to retain empty infusion bags.
- Upon conclusion of the study trial, all unused intravenous ibuprofen will be inventoried by the Clinical Monitor and packaged for return to the Sponsor or their designee. The Clinical Monitor will review all worksheets and Investigational Product inventory logs. Used vials of intravenous ibuprofen will be retained and provided to the Clinical Monitor to complete the accountability procedures. Following drug shipment and use accountability reconciliation the Clinical Monitor will instruct the Clinical Center regarding disposal of the IMP and pharmacy supplies at the site close-out visit. It must be possible to reconcile delivery records with those of used and returned medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.

8.3 Selection of Study Population

Determination of study eligibility will be made by the Investigator on the basis of the inclusion and exclusion criteria listed below.

8.3.1 Inclusion Criteria

To be considered eligible to participate in this study, a patient must meet all of the following inclusion criteria:

- Be a hospitalized male or female subject between birth (> 37 weeks gestational age) and < six months of age.
- Have a clinical indication of pain or fever.
- Have written informed consent provided by legal parent, guardian, or authorized agent prior to participation in the study or performance of any study-only related procedures.

8.3.2 Exclusion Criteria

To be considered eligible to participate in this study, a patient must not meet any of the following exclusion criteria:

- Have inadequate intravenous access.
- Have an uncorrected ductus dependent congenital heart disease.
- Have any history of allergy or hypersensitivity to NSAIDs or aspirin.
- Have a current history of uncorrected hypovolemia or acute renal disease.
- Have a current history of acute liver disease.
- Have received NSAID, acetaminophen, or aspirin drug therapy within four hours prior to dosing. Have received another investigational drug within the past 30 days.
- Be otherwise unsuitable for the study, in the opinion of the Investigator.

8.4 Prior and Concomitant Therapy

Concomitant medication will be collected during the Screening/Baseline Period through Study Hour 48 or discharge, whichever occurs first. Intravenous concomitant medications may be administered through the same line if it is adequately flushed before and after administration of the IMP.

Ibuprofen is metabolized by the cytochrome P450 CYP2C9 and CYP2C8 enzymes. CYP2C9 activity is low immediately after birth, increasing to peak at a young age. Co-administration of medications that are primarily metabolized by, or are inducers or inhibitors of CYP2C9 are listed in Table 8-2 and should be closely monitored or avoided. The Investigator's Brochure should also be used as a reference for the co-administration of medications.

Table 8-2 Selected Inducers and Inhibitors of CYP2C9

Substrate	Inhibitors	Inducers
Ibuprofen	• Amiodarone • Efavirenz • Fluconazole • Fluvastatin • Ketoconazole • Sulfamethoxazole • Zafirlukast	• Carbamazepine • Phenobarbital • Phenytoin • Rifampin

8.4.1 Excluded Medications/Procedures/Therapy

The following medications will be restricted for the specified times prior to receiving the first dose of IMP through study hour 48:

- Any NSAID (excluding IMP) will be restricted 4 hours prior to receiving the first dose of IMP through study hour 48.
- Acetaminophen will be restricted 4 hours prior to receiving the first dose of IMP through study hour 48.

9 EXPERIMENTAL PROCEDURES

9.1 Overview – Schedule of Time and Events

This is a multi-center, open-label, in-patient, single and/or multiple dose study in pediatric subject, aged birth (> 37 weeks gestational age) to < 6 months of age, with a clinical indication of pain and fever. A total of twenty-four subjects, between the ages of birth (> 37 weeks gestational age) to less than six (6) months of age, will receive IMP.

This 72 hour study will consist of a Screening/Baseline Period (up to 48 hours prior to the first dose of IMP), a Treatment Period (beginning with the first dose of IMP and continuing for 48 hours) and a Post-Treatment Period (beginning at the end of the Treatment Period and continuing for 24 hours).

During the Screening/Baseline Period, an evaluation of the inclusion and exclusion criteria, a complete medical history, and a physical examination will be conducted. Participant's vital signs will be measured before the start of the IMP, at regular intervals following the initial dose of IMP, and before and after multiple (as needed, PRN) IMP doses. A review of baseline signs and symptoms, including pain scores, concomitant medications, and laboratory assessments will be also conducted.

During the Treatment Period, the initial dose of investigational medicinal product will be administered over a 10 minute period. Subsequent doses of IMP will be administered at the investigators discretion. Pharmacokinetic sampling will be performed utilizing a sparse sampling technique following the initial dose of IMP. Vital signs, pains scores, laboratory assessments will be monitored during the treatment period and AEs will be monitored during the treatment and post-treatment period. All treatment emergent adverse events will be followed until resolution or stabilization, regardless of the assessment of severity or relationship to the study drug.

9.2 Measurements and Evaluations

9.2.1 Screening/Baseline Period

During the Screening/Baseline Period, the following evaluations will be performed to determine the subject's eligibility for this study:

- Informed consent (by parent or legal guardian)
- Inclusion and exclusion criteria
- Complete medical history: The medical history should be recorded at Screening/Baseline and should include history of hepatic, renal, neurological, endocrine, cardiovascular, and pulmonary disease, operations, serious illnesses and any other condition the investigator feels is significant. Medical history should include information related to the duration, i.e. the number of months must be recorded in the case report form.
- Physical examination
- Demographic date (age, race, ethnicity, weight, sex)
- Baseline signs & symptoms: Any new signs and symptoms occurring since the screening medical history and physical exam, but prior to receiving the IMP should be recorded as part of the medical history.
- Vital signs (temperature, heart rate, respiratory rate, and blood pressure)

- Laboratory assessment: Samples for chemistry, hematology, and coagulation will be obtained at Screening/Baseline. If the panels were obtained within 48 hours of Study Hour 0 and at the same hospital/institution and no current history or physical exam findings suggest a clinically relevant change is likely, these labs do not need to be repeated during the screening period.

  Clinical chemistry includes:
  Sodium
  Potassium
  Chloride
  Total carbon dioxide
  Glucose
  Blood urea nitrogen
  Creatinine
  Total bilirubin
  Albumin
  Total protein
  Aspartate aminotransferase
  Alanine aminotransferase
  Lactate dehydrogenase

  Hematology and coagulation include:
  White blood cell count and differential
  Hematocrit
  Hemoglobin
  Platelets
  Prothrombin time
  Partial thromboplastin time

- Concomitant medications

9.2.2 Treatment Period (Study Hour 0 to Study Hour 48)

Study Hour 0 = initiation of administration of the initial dose of IMP.

The following assessments will be performed during the Treatment Period:

- Vital Signs: Immediately pre-dose and post-dose, 30 minutes, 60 minutes, 120 minutes, and 240 minutes following each dose of IMP, at Study Hour 24, and at Study Hour 48 (The vital sign assessments should be performed within 15 minutes of the specified nominal time to avoid any conflicts with the blood sampling time points).
- Laboratory assessments: Samples for chemistry, hematology, and coagulation will be obtained at Study Hour 24 (± 6 hours). If the samples are taken for standard of care

procedures and are within the allowable time window for data collection, these labs do not need to be repeated during the Treatment Period; however, any missing laboratory assessments must be obtained.

Clinical chemistry includes:

Sodium
Potassium
Chloride
Total carbon dioxide
Glucose
Blood urea nitrogen
Creatinine
Total bilirubin
Albumin
Total protein
Aspartate aminotransferase
Alanine aminotransferase
Lactate dehydrogenase

Hematology and coagulation include:

White blood cell count and differential
Hematocrit
Hemoglobin
Platelets
Prothrombin time
Partial thromboplastin time

- Pharmacokinetic assessments: Immediately following completion of the first dose of IMP for all subjects, then utilizing sparse sampling techniques for 30 minutes, 1 hour, 2 hour, and 4 hours following completion of the initial dose of IMP only. (The PK assessments should be performed within 5 minutes of the specified nominal time to avoid any conflicts with the vital signs time points).
- IMP administration: At Study Hour 0, then every 6-8 hours PRN at the investigator's discretion.
- Concomitant medications
- Adverse event monitoring: Adverse events will be assessed regularly during the Treatment Period. Adverse event collection will begin at the start of IMP administration and continue through Study Hour 48 or discharge, whichever comes first. Subjects do not need to remain hospitalized for the 48-hour Treatment Period. All treatment emergent adverse events will be monitored until resolution or stabilization, regardless of the assessment of severity or relationship to the study drug. All AEs, observed by,

documented in the subject's medical record, or reported to the research team must be recorded in both the subject's research record and the case report form.

9.2.3 Post-treatment Period (Study Hour 48 to Study Hour 72)

The following assessments will be performed during the Post-Treatment Period:

- Vitals Signs: must be performed at Study Hour 72 (± 6 hours) or at the time of discharge, whichever occur first.
- Laboratory assessments: Samples for chemistry, hematology, and coagulation will be obtained at Study Hour 72 (± 6 hours) or discharge, whichever occurs first. If the samples are taken for standard of care procedures and are within the allowable time window for data collection, these labs do not need to be repeated during the Treatment Period; however, any missing laboratory assessments must be obtained.

  Clinical chemistry includes:
  Sodium
  Potassium
  Chloride
  Total carbon dioxide
  Glucose
  Blood urea nitrogen
  Creatinine
  Total bilirubin
  Albumin
  Total protein
  Aspartate aminotransferase
  Alanine aminotransferase
  Lactate dehydrogenase

  Hematology and coagulation include:
  White blood cell count and differential
  Hematocrit
  Hemoglobin
  Platelets
  Prothrombin time
  Partial thromboplastin time

- Adverse event monitoring: Adverse events will be assessed during the Post-Treatment Period up to Study Hour 72. If the subject is discharged before Study Hour 72, a phone call must be made to assess for any AEs following discharge up to Study Hour 72 and must be recorded in both the subject's research record and the case report form. All

treatment emergent adverse events will be followed until resolution or stabilization, regardless of the assessment of severity or relationship to the study drug.

If the subject is discharged from the hospital before Study Hour 72, all post-treatment period assessments should be performed before hospital discharge. A member of the research team will contact the subject's parent or legal guardian by telephone to obtain a report of any adverse events occurring through Study Hour 72. All adverse events that occur before Study Hour 72 (in the hospital or after discharge) will be recorded in the subject's case report form (CRF).

10 SUBJECT DISCONTINUATION

10.1 Circumstances for Subject Discontinuation

Parents and/or legal guardians will be encouraged to allow the subject to complete the study; however, they may voluntarily withdraw their child from the study at any time and for any reason. The Investigator will describe in the CRF the reason for the subject's parent(s) and/or legal guardian(s) choice to discontinue. If a subject withdraws before completion, every effort should be made to complete the assessments scheduled during the final scheduled assessment.

A subject may be removed from the study for the following reasons; in each case, the decision to discontinue should be confirmed following consultation between the Investigator and Sponsor:

- **Adverse event:** If a subject experiences an AE for which continued study participation presents an unacceptable consequence or risk to the subject, the subject may be discontinued.
- **Subject non-compliance:** A subject's past, current, or anticipated inability to comply with study visits, clinical trial medication or other processes required by the protocol may lead to the decision to discontinue the subject from the study.
- **Enrollment violation:** If it is realized after the initiation of investigational treatment that a subject did not meet all eligibility requirements, the Sponsor and Investigator will discuss whether it is safe, ethical, and scientifically sound to keep the subject in the study or to discontinue the subject. The IRB may be consulted as appropriate.
- **Concurrent Treatment:** If a subject initiates a procedure or medication that may interfere with their study conduct or for which study involvement may pose a significant risk to the prescribed therapy, the subject may be discontinued. This also includes the use of therapies restricted by the protocol in Section 8.4.1.

10.2 Procedures for Subject Discontinuation

If the subject is withdrawn from the study data collected on the subject up to the time of withdrawal must remain in the trial database (FDA 2008).

If a decision is made to withdraw the subject from the study; the investigator should clarify with the subject's parent or legal guardian if the subject is to be withdrawn from all components of the study or if the subject is withdrawn from the primary interventional component but if the subject's parent or legal guardian would be willing to allow the investigator to continue other research activities as described below and in the informed consent:

- Medical course or laboratory results obtained through non-invasive chart review
- Vital signs, as outlined in the protocol
- Adverse event monitoring, as outlined in the protocol
- Post-Treatment follow-up

If the subject's parent and/or legal guardian permits continued follow-up of associated clinical outcome information as described in the previous bullets, the investigator must obtain the parent's or legal guardian consent for this limited participation in the study (FDA 2008). Reasonable efforts should be made to monitor the subject for AEs and to complete follow-up assessments following discontinuation.

The reason, level of continued follow-up, if appropriate, and documentation of limited participation consent, if appropriate, should be documented in the research record and the subject's CRF.

Subjects who are enrolled into the study but do not receive any IMP will be replaced. Subjects who withdraw from the study after receiving IMP but who do not complete the PK portion of the study within the first 4 hours will also be replaced.

11 Study or Site Termination

If conditions arise during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, Medical Monitor, and Study Monitor.

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- A study conducted at a single study site or a single study site in a multicenter study may also warrant termination under the following conditions:
    - Failure of the Investigator to enroll subjects into the study at an acceptable rate
    - Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
    - Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate regulatory authority
    - Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the ICH sixth efficacy publication (E6) on Good Clinical Practice, Section 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21.

12 ADVERSE EVENTS

Information about AEs, whether spontaneously reported by the subject, discovered by the Investigator by questioning/review of diary records or detected through physical examination, laboratory test or other means, will be collected and recorded on the adverse event form and followed until resolution or stabilization, regardless of your assessment of severity or relationship to the study drug. Information about serious adverse events (SAEs) should be reported to the Sponsor within 24 hours of obtaining knowledge of the event.

12.1 Definitions

Adverse event: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Treatment-emergent adverse event: Any adverse event not present prior to the initiation of IMP or any adverse event already present that worsens in either intensity or frequency following exposure to IMP.

Serious adverse event: An adverse event is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- death
- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject **and** may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-threatening adverse event: An adverse event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected adverse event: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Severity: The maximum severity of an AE should be assessed by the Investigator using the following definitions:

- **Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Moderate:** minimal, local or noninvasive intervention indicated; may interfere with daily activities
- **Severe:** severe or medically significant; events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment

Anticipated: Anticipated events include known consequences of the underlying disease or condition under investigation, events anticipated from any background regimen, events common in the study population, or re-emergence or worsening of a condition relative to pretreatment baseline.

12.2 Collection, Recording and Reporting of Adverse Events

It is the responsibility of the Investigator to perform periodic and special assessments for AEs. The Investigator and clinical staff will note all AEs observed in or offered by the subject during administration of IMP. All clinical complaints volunteered by or elicited from the patient or observed by clinical staff during the study will be recorded in the appropriate area of the CRF for the study period indicated.

If any AE occurs during or after dosing with IMP, the patient will receive appropriate treatment and medical supervision. In addition, the Investigator will record AE, whether or not judged to be IMP-related, on the appropriate page of the CRF and will provide all requested information (*e.g.,* date and time of occurrence, date and time of resolution [or information to indicate that it is still ongoing], severity, seriousness, relationship to IMP administration, causality of the event, IMP or other action taken in response to the event, and outcome of the AE). Definitions of seriousness, severity and anticipated are provided in Section 12.1. Definitions of causality, actions taken and outcome are provided in the CRF.

The investigator must report initial information on all SAEs events to the Sponsor within 24 hours of obtaining knowledge of the event. Furthermore, the investigator must complete the SAE forms within 72 hours of obtaining knowledge of the SAE.

The Investigator is responsible for informing their IRB in accordance with local requirements in force and the ICH guidelines for Good Clinical Practice (GCP) and the Food and Drug Administration (FDA) Title 21 Code of Federal Regulations, Part 312.64 & 312.66.

Necrotizing enterocolitis and gastrointestinal hemorrhage are adverse events of special interest. Any events occurring during the study will be followed until resolution or stabilization, regardless of the assessment of severity or relationship to the study drug.

12.3 Follow-up of Adverse Events

All treatment emergent adverse events will be followed until resolution or stabilization, regardless of severity or relationship to the study drug.

All serious adverse events should be followed until resolved.

13 STATISTICAL METHODS AND DATA ANALYSIS

There is no statistical analysis plan for this study. Results will be analyzed and reported descriptively.

13.1 General Overview

Formal sample size calculations were not performed. The intent is to enroll 24 subjects to provide descriptive safety data. Continuous data will be summarized in tables listing the mean, standard deviation or standard error. All data will be listed by patient. Safety will be evaluated on the basis of vital signs and treatment-emergent AEs. AE data will be listed individually and summarized by body system organ class and preferred terms within system organ class (MedDRA). Serious and/or unexpected AEs will also be discussed on a case-by-case basis. On the basis of plasma ibuprofen concentration-time data, PK parameters will be estimated by using a non-compartmental model.

13.2 Populations of Interest

The populations of interest for analysis are defined as below:

Safety Population: The safety analysis population consists of all participants who were enrolled and received at least part of the IMP; no treated participants will be excluded from the safety analysis population. Safety analysis will be conducted on an as treated basis.

Pharmacokinetic-evaluable Population: Participants who received the single dose of IMP over the 10 minute infusion period and have the primary PK assessments in the 48 hour study period will be eligible for inclusion in the pharmacokinetic-evaluable population (PEP).

13.3 Baseline Comparability

Descriptive statistics of demographic, background and baseline clinical variables will be provided for all subjects.

13.4 Safety Analysis

The participant population of interest for the safety analyses is the safety analysis population.

Safety will be evaluated on the basis of treatment emergent AEs (Section 7.2).

AE data will be listed individually and summarized by body system organ class and preferred terms within system organ class (MedDRA). Serious and/or unexpected AEs will also be discussed on a case by case basis. Each AE will be counted only once for a given participant. If

the same AE occurs on multiple occasions, the highest severity and least favorable relationship reported will be assumed. If two or more AEs are reported as a unit, the individual terms will be reported as separate experiences.

13.5 PK Analysis

On the basis of plasma ibuprofen concentration time data, the following PK parameters will be estimated by using a non-compartmental model:

- AUC_{0-t}, calculated by using the linear-log trapezoidal rule: linear trapezoidal rule up to time to maximum concentration, and then a log trapezoidal rule for the remainder of the curve, where t corresponds to the last measurable time point
- $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, where C_t is the last measurable ibuprofen concentration and λz is the terminal elimination rate constant calculated by using log linear regression of the terminal elimination phase of the plasma concentration versus time curve
- C_{max} of ibuprofen estimated by inspection of the ibuprofen concentration time curve
- T_{max} estimated by inspection of the ibuprofen concentration time curve
- Terminal $T_{1/2} = \ln(2)/\lambda_z$

13.6 Interim Analysis

No interim analysis is planned

13.7 Sample Size Determination

A total of 24 subjects will be enrolled in the study. No power calculations will be performed. If required, subjects will be replaced as described in Section 10.2 for a total of 24 PK-evaluable subjects.

14 STUDY MANAGEMENT AND DATA COLLECTION

14.1 Confidentiality

All information regarding the nature of the proposed investigation provided by the Sponsor or Study Monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject number on CRFs and other study documents submitted to the Study Monitor.

Documents that will not be submitted to the Study Monitor and that identify the subject (e.g., the signed informed consent document) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

14.2 Source Documents

Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. The Monitor, representatives of the Sponsor and the applicable regulatory authority will be allowed access to source documentation.

14.3 Case Report Forms

All required study information must be recorded on the appropriate CRF pages. CRFs are considered complete when all data fields have been completed. In addition, as the person ultimately responsible for the accuracy of all CRF data, the Investigator must sign the Investigator's Statement in each subject's CRF.

The Investigator must make study data accessible to the Clinical Monitor, to other authorized representatives of the sponsor, and to the appropriate regulatory authority inspectors. The original CRF for each subject will be checked against source documents at the study site by the Clinical Monitor. A copy of the final CRF will be placed in the Investigator's study file, and the original will be taken by the Clinical Monitor or sent by the site to the Clinical Monitor.

14.4 Study Files

Documentation concerning Investigator data, IRB data, and clinical laboratory data (when applicable) is required before shipment of IMP to the study site. Copies of these documents as well as supplemental information, such as the Investigator's Brochure and Responsibilities and Obligations of Investigators and Sponsors, will be kept on-site in a special study file. This file also will contain drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB correspondence, changes to the protocol, information regarding monitoring activities, subject exclusion records, biological samples records, and CRFs.

14.5 Records Retention

According to 21CFR312.62, all CRFs, as well as supporting documentation and administrative records, must be retained by the Investigator for a minimum of two years following notification that the appropriate regulatory authority has approved the product for the indication under study, notification that the entire clinical investigation will not be used in support of a marketing application, or notification that the marketing application was not approved. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed upon designee, such as the Study Monitor, another Investigator, or the institution where the study was conducted.

15 STUDY MONITORING, AUDITING, AND INSPECTING

15.1 Study Monitoring Plan

The progress of the study will be monitored by using the following methods:

- Periodic on-site visits
- Electronic and/or telephone communications between the Investigator, Clinical Monitor, and Medical Monitor
- Review of the CRF, clinical, and research records

Representatives of the sponsor may accompany the Clinical Monitor to the study site during scheduled visits. The completed, original CRFs will be submitted to the Clinical Monitor as described in Section 14.3.

15.2 Quality Control and Quality Assurance

To assure data completeness clinical centers will participate in a pre-study initiation meeting. This meeting will include representatives of the Sponsor and the Investigator and the research team from the clinical center. The meeting will include a thorough review of the protocol, the case report form, and associated study forms and logs.

The investigator or their designee will enter data collected from the subject's parent or legal guardian, from the subject's medical and/or research record into the subject's CRF. The investigator or their designee is responsible for ensuring that all data in the CRFs and Data Clarifications Forms (DCF) are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The Clinical Monitor will monitor the study in accordance with FDA guidelines by comparing the data in the CRFs with source documents and confirm that there are no inconsistencies between CRF and the subject's source documents. For screening failures, the minimum data collected should include all data used to evaluate the subject up to the point where screen failure is determined. This should include consent data and reason(s) for screening failure will be collected.

Laboratory tests will be performed at local laboratories and results will be verified by the Clinical Monitor. PK samples will be sent to the designated central laboratory for testing. Data will be transferred to Data Management at during the study.

16 ETHICAL CONSIDERATIONS

This study will be conducted according to the standards of ICH, GCP Guidelines, IRB regulations, any applicable government regulations and procedures. This protocol and any amendments will be submitted to a properly constituted IRB for approval of the study conduct.

16.1 Informed Consent

Written informed consent must be obtained from each subject (or the subject's legal guardian/representative) before performing any Screening/Baseline Period evaluations. The signed informed consent document will be retained by the Investigator, and a signed copy will be given to the subject or subject's legal guardian/representative. The informed consent document, which is prepared by the Investigator, must have been reviewed and approved by the Sponsor and the Investigator's IRB before the initiation of the study. The document must contain the 20 elements of informed consent described in 21CFR50.25 and ICH E6 4.8.

16.2 Protocol Compliance

Investigators must follow the IRB-approved protocol. If the Investigator intends to deviate from the protocol, the IRB and Sponsor should be informed prior to the deviation.

In cases where the Investigator decides to deviate from the protocol in order to avoid an apparent immediate risk to a specific subject, the Investigator may proceed with emergency and appropriate treatment at his discretion and the IRB and Sponsor will be notified as soon as possible afterward. In addition, the Investigator will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental

design, dosages, assessment variable(s), the number of subjects treated, or the subject selection criteria. Such changes must be prepared as a protocol amendment by the Sponsor. A protocol amendment must receive IRB approval before implementation.

In parallel with the IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the informed consent document, the revised informed consent document prepared by the Investigator must be approved by the Sponsor, Study Monitor, and the IRB.

17 REFERENCES

Schwartz JI, Chan C, Mukhopadhyay S, et al. 1999. Cyclooxygenase 2 inhibition by rofecoxib reverses naturally occurring fever in humans. *Clin Pharmacol Ther*. 65:653-60.

Krishna S, Pukrittayakamee S, Supanaranond W, et al. 1995. Fever in uncomplicated Plasmodium falciparum malaria: randomized double blind comparison of ibuprofen and paracetamol treatment. *Trans R Soc Trop Med Hyg*. 89:507-09.

Guidance for Sponsors, Clinical Investigators, and IRB's: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. October 2008.

Taketomo CK, Hodding JH, Kraus, DM, Lexi-Comp's Pediatric Dosing Handbook, 10th Edition.

18 APPENDICES

18.1 Responsibilities and Obligations of Investigators and Sponsors

18.1.1 Sponsor

The Sponsor will:

Conduct a pre-investigation Site Selection Visit and/or Study Initiation Visit to:

- Establish the acceptability of the facility and record the visit in a written report (i.e., memorandum or form).
- Discuss with the Investigator the proposed clinical trial and supply CRFs, the Investigator's Brochure, and the protocol for his review and approval.
- Discuss with the Investigator the regulatory requirements with respect to informed consent, IRB/IEC approval of the trial, the protocol, protocol amendments, and changes to the informed consent document.

- Discuss with the Investigator the timing of interim and final reports to the Study Monitor and the obligation to supply the Study Monitor with copies of all study-related documents (including IRB/IEC approval, IRB/IEC charter or equivalent, membership and qualifications, protocol amendments, informed consent documents, and consent changes), CRFs, CRF changes, and all pertinent correspondence to and from the IRB/IEC.

Conduct periodic on-site visit(s) to:

- Ensure adherence to the protocol.
- Review CRFs and source documentation for accuracy and completeness of information.
- Examine pharmacy or other IMP storage and dispensing records for documentation of quantity and date of receipt of IMP, dispensation and accountability data for product administration to each subject, loss of materials, contamination, and unused supplies.
- Record and report (summarize) observations on the progress of the trial and continued acceptability of the facilities, and prepare an on-site visit report.
- Review Investigator files for required documents, (e.g., protocols; protocol amendments; Investigator's Brochure; Study Procedures Manual; IRB/IEC approval of protocols, amendments, and informed consent documents; IRB/IEC charter and membership; and communications to and from the IRB/IEC and the Study Monitor.

18.1.2 Investigator

Institutional Review Board/Independent Ethics Committee

The Investigator must assure the Study Monitor in writing that the Institutional Review Board/Independent Ethics Committee (IRB/IEC):

- Meets FDA regulations as defined in 21CFR56: Institutional Review Board/Independent Ethics Committee.
- Has the authority delegated by the parent Institution and found in the IRB/IEC by-laws, operation guidelines, or charter to approve or disapprove clinical trials and protocols, including informed consent and other documents (e.g., protocol amendments and information to be supplied to subjects concerning informed consent).
- Complies with proper personnel make-up of the Board.
- Convenes meetings using acceptable rules of order for making decisions, recording such decisions, and implementing them.

- Maintains files that contain (a) documentation of its decisions, such as are found in IRB/IEC minutes and correspondence, (b) written guidelines or by-laws governing IRB/IEC functions, (c) protocol, (d) protocol amendments, (e) approved informed consent document and information to be supplied to the subject, and (f) correspondence between the IRB/IEC and Investigator (e.g., consent changes, protocol amendments).

Informed Consent of Human Subjects

The Investigator must assure the Study Monitor in writing that the informed consent document for a subject:

- Meets FDA regulations as defined in 21CFR50: Informed Consent of Trial Subjects.
- Has been approved by the IRB/IEC, including (when required) information to be given to the subject regarding the trial in which he is enrolled.
- Includes the basic elements and any additional elements of informed consent that are appropriate.
- Has been signed by both the subject and the Investigator or designee, and a copy has been given to the subject.
- May be provided to the subject in the "short form" informed consent document with written information as an alternative.

Storage and Dispensing of Product Supplies

The Investigator (or his Pharmacist) must assure the Study Monitor in writing that:

- Adequate and accurate written records show receipt and disposition of all product supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each subject.
- Purpose and reasons are given in written records for product disposal (e.g., the amount contaminated, broken, or lost) and the quantity that was returned to the Sponsor.

Case Report Forms

The Investigator must assure the Study Monitor in writing that:

- The completed CRF accurately reflects the source documentation for each subject.
- The CRFs and source documentation will be accessible to the Clinical Monitor during on-site visits.

Files and Records

The Investigator must assure the quality, integrity, and content of his/her files, which will be subject to audit by the Study Monitor and the appropriate regulatory authority inspectors. The files must contain, as minimum:

- Significant correspondence to/from the IRB/IEC and to/from the Clinical Monitor.
- Documents including the following:
  - IRB/IEC-approved protocols.
  - IRB/IEC-approved protocol amendments.
  - IRB/IEC-approved informed consent/assent documents and information to be supplied to the subject.
  - IRB/IEC-approved recruitment advertisement(s)
  - IRB/IEC charter, membership, and qualifications of each member.
- Clinical supplies records including the following:
  - Receipt, date and quantity, and batch or lot number.
  - Disposition dates and quantity administered to each subject.
  - Inventory records.