Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire
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20993-0002

Combined Clinical, Cross-Discipline Team Leader and Division Director Summary Review for Regulatory Action

Date	(Electronic stamp)
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NDA Number / Supplement	22348 / S24
Applicant	Cumberland Pharmaceuticals Inc.
Date of Submission	July 11,2022
PDUFA Goal Date	May 11, 2023
Established Name	Ibuprofen injection
Trade Name	Caldolor®
Dosage Forms / Strength	Solution for intravenous injection / 800 mg/8 mL (100 mg/mL), 800 mg/200 mL (4 mg/mL)
Proposed Indication	Management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics and reduction of fever
Action	Approval for use in patients aged 3 months and older

Material Reviewed/Consulted

Office of New Drugs (OND) Action Package, including:	
Clinical Review	Christina Fang, MD, MPH; Alla Bazini, MD
Clinical Pharmacology Review	David Lee, PhD; Yun Xu, PhD
Division of Pediatric and Maternal Health (DPMH) Consult Review	Carla Epps, MD, MPH; Shetarra Walker, MD, MSCR, FAAP; John Alexander, MD, MPH
Office of Prescription Drug Promotion (OPDP) Labeling Review	L. Sheneé Toombs, PharmD; Sam Skariah, PharmD
Office of Study Integrity and Surveillance (OSIS) Remote Regulatory Assessment	Monica Javidnia, PhD; Mei Ou, PhD; Seongeun Cho, PhD
Project Management Staff	Jaimin Patel, PharmD; Swati Patwardhan, MS, RAC

Note: Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP) Review, Pharmacology Toxicology Review, and Statistical Review were not required for this submission.

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Regulatory Action

This supplement proposes language for extending the pediatric use of IV ibuprofen injection to patients aged 3 months and older for the proposed pain and fever indications with the dosage for patients 3 to less than 6 months of age limited to a single dose not to exceed 10 mg/kg or 100 mg, whichever is less.

This supplement can be approved based on an acceptable benefit/risk ratio in using a single dose to treat pain and fever in patient aged 3 to less than 6 months.

Benefit-Risk Assessment

Assessment of benefit versus risk for pediatric use of ibuprofen injection in general was provided in the reviews of Supplement 5 at the approval of pediatric use of the product in patients 6 months to 17 years of age (refer to Clinical Review dated November 10, 2015) and will not be repeated here.

For patients aged 3 to less than 6 months pharmacokinetic (PD) comparison to the older age groups revealed similar total concentration (AUC), maximum concentration (Cmax), and time to maximum concentration (Tmax) after a single dose, despite possible age-related pharmacokinetic (PK) differences in infants younger than 6 months of age due to immature liver and renal functions. The demonstration of PK similarities to the older age groups provides PK bridge for establishing effectiveness of ibuprofen injection for treating fever and pain in patients 3 to less than 6 months of age. This will become the first non-opioid analgesic available for use in this age group to address both the individual and public health needs for non-opioid drugs in treating acute pain.

Safety concerns about potential adverse effects of ibuprofen on growth and development in infants younger than 6 months of age and possible increase in toxicities due to organ immaturities in comparison to older children can't be adequately addressed because of limitations on availability of multiple-dose safety data from clinical trials or safety information from literature and postmarketing surveillance due to very low drug utilization for off-label use of ibuprofen in treating fever and pain in patients less than 6 month of age. Nevertheless, a single-dose exposure in general is considered reasonably safe as shown in the current study, which did not report any adverse event (AE) known to be associated with NSAID use.

Therefore, the benefit/risk ratio is considered acceptable in using a single dose to treat pain and fever in patient aged 3 months to less than 6 months.

Background

Regulatory history on post-marketing requirements (PMRs)

At the time of the original NDA approval of Caldolor for pain and fever indications in adults in 2009, the post-marketing requirements (PMRs) of pediatric studies under the Pediatric Research Equity Act (PREA) included a study of fever (PMR 205-1) and a study of pain (PMR 205-2) in pediatric patients aged 0 to 16 years (refer to the Approval Letter dated June 11, 2009).

The two PMRs were later replaced by an efficacy, PK, and safety study of fever (PMR 205-3) and a PK and safety study of pain (PMR 205-4) in pediatric patients aged 6 months to 16 years and a PK and safety study of both fever and pain (PMR 205-5) in pediatric patients aged birth to 6 months (refer to the PMR/PMC Release and Acknowledge of New PMR/PMC Letter dated December 14, 2014).

Pediatric use of Caldolor for treating fever and pain in patients 6 months to less than 17 years of age was approved with PMRs 205-3 and 205-4 fulfilled in 2015 (refer to the Supplement Approval Letter for Supplement 5 dated November 20, 2015).

Regulatory history on establishing effectiveness in patients aged birth to 6 months

The original PMRs did not specify whether efficacy needs to be studied. (b) (4)

(b) (4) based on consideration of public health need for drug products to be available for treating pain and fever in the youngest age group as recommendations by Division of Pediatric and Maternal Health (DPMH) and Pediatric Review Committee (PeRC) (refer to DPMH review dated March17, 2014 and PeRC meeting minutes dated September 29, 2014). As recorded in the PeRC meeting minutes effectiveness data obtained from patients aged 6 months to 2 years "can be used to support the effectiveness for fever and pain for pediatric patients aged birth to 6 months based on bridging information (PK and efficacy) provided that a sufficient number of patients between 6 months and 2 years of age were studied in CPI-CL-012.

Study CPI-CL-012 submitted to the NDA Supplement 5 had limited exposure in patients aged 6 months to 2 years with only six patients exposed and five of them with PK data. PK results of the study demonstrated similarities between the three age groups of 6 months to <2 years, 2 to <6 years, and 6 to 16 years. Therefore, the review team determined that PK data from all three pediatric groups in the age range of 6 months to 16 years can serve as a PK bridge for establishing effectiveness of Caldolor for treating fever and pain in patients aged birth to <6 months.

Study CPI-CL-022 submitted in the current NDA was expected to provide PK data for comparison between the age group of younger than 6 months of age and older pediatric age groups for supporting the effectiveness of Caldolor for fever and pain for pediatric patients aged birth to 6 months.

Regulatory history on sample size requirement for study in patients aged birth to 6 months

(b) (4) .

(b) (4) the proposed sample size of 24 patients under 6 months of age to be studied in Study CPI-CL-022 was determined to be acceptable during the review of the original protocol (refer to the protocol review under IND 62605 dated June 7, 2016).

Product Quality

No new information submitted for review.

Nonclinical Pharmacology/Toxicology

No new information submitted for review.

Clinical Pharmacology

Study CPI-CL-022 was a multi-center, open-label, single-arm, multiple-dose, pharmacokinetic and safety study of Caldolor (IV ibuprofen) 10-minute infusion at 10 mg/kg in hospitalized pediatric patients with pain and/or fever who were in the age group of birth to less than six months of age.

PK findings in Study CPI-CL-022
The PK data collection and analyses and findings are described in detail in Dr. David Lee's review. Dr. Lee summarized PK results by age per month for the six age groups from birth to <6 months and noted that "There were no apparent trends observed with sex and body weight vs. ibuprofen Cmax and/or AUC values" (refer to Table 1 of Dr. Lee's Clinical Pharmacology Review dated April 11, 2023).

Only three patients aged less than 3 months, one in the age group of 1 to less than 2 months of age and two in 2 to less than 3 months of age received treatment and had PK data available. Because of insufficient PK data in the age groups of birth to less than 3 months of age, only PK data from patients aged 3 to less than 6 months were grouped together and used in comparison to older pediatric age groups as shown in the table below.

Table 1 PK Parameters by Age Group in Pediatric Patients Receiving 10 mg/kg IV Ibuprofen

Study	CPI-CL-022	CPI-CL-012 (NDA Supplement 5)		
Age	3 to < 6 months	6 months to <2 years	2 to <6 years	6 to 16 years
Number of Patients	20	5	12	25
PK parameters	Mean (SD)			
AUC (µg·h/mL)	69.63 (19.28)	71.1 (26.4)	79.2 (29.3)	80.7 (29.8)
C_{max} (µg/mL)	59.75 (12.85)	59.2 (20.6)	64.2 (22.1)	61.9 (16.5)
$T_{1/2}$ (h)	1.3	1.8 (0.5)	1.5 (0.6)	1.55 (0.41)
		Median (minimum-maximum)		
T_{max} (min)	10	10 (10-30)	12 (10-46)	10 (10-40)

Note: AUC=area under the curve; C_{max}=maximum concentration; T_{max}=time to reach maximum concentration; $T_{1/2}$= half-life; SD= standard deviation
Source: Dr. Lee's Clinical Pharmacology Reviews dated April 11, 2023, and October 21, 2015, and Caldolor labeling.

Dr. Lee concluded that "The mean ibuprofen concentrations across groups showed similar values."

Dr. Lee also described all the site inspection requests in his review and considered the responses obtained from the Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) acceptable for both the study site and analytical site selected for inspection.

Impact of age-related organ maturation on PK of ibuprofen for infants aged less than 6 months
Information from literature suggests that low CYP-dependent metabolic enzyme activity (such as CYP2C8 and CYP2C9 responsible for ibuprofen metabolism) and immature glomerular filtration, tubular secretion, and reabsorption in infants during the first 6 months of life may have potential impact on reduced drug metabolism, clearance, and renal secretion of ibuprofen. Certain physiologic differences between neonates and adults may result in a decreased volume of distribution of a hydrophobic drug like ibuprofen. There are reports of "higher interindividual variability in drug metabolism of infants compared with older children" (refer to Division of Pediatric and Maternal Health (DPMH) review by Dr. Carla Epps dated March 2, 2023).

Clinical Microbiology

Not applicable.

Clinical/Statistical – Efficacy

Efficacy study of the age group of birth to <6 months of age was not required. Effectiveness of Caldolor in treating fever and pain for the age group of birth to <6 months of age is established based on PK bridging.

Safety

Safety findings in Study CPI-CL-022
Exposure was limited to 24 patients with 21 of 24 aged 3 to <6 months and mostly single-dose exposure in 21 of 24 patients. Multiple-dose exposure was reported in four patients, including exposure to four doses in one patient in the 2 to <3 months age group and eight doses in three patients with one from each of the three age groups of 3 to <4, 4 to <5, and 5 to <6 months of age.

A total of 14 AEs were reported for eight patients and individual AEs were mostly reported in a single patient except constipation (n=2) and chylothorax (n=2). No dropouts due to AEs were reported. Three SAEs including pericardial effusion and chylothorax (two events) were reported for one patient and were considered unlikely to be related to the study drug. A few individual lab parameters had significant shifts from baseline values, and none of them was reported for more than one patient. The clinical safety database did not identify AEs known to be associated with the use of ibuprofen due to limitations of single-dose exposure in a very small study sample (refer to the Clinical Review of Study CPI-CL-022 included as the last section of this summary review for detail).

Impact of age-related organ maturation on safety of ibuprofen for infants aged less than 6 months
The information is very limited in assessing potential impact of age-related organ maturation on safety of ibuprofen for infants aged less than 6 months because most adverse reactions reported in literature and identified in multiple postmarketing surveillance safety databases are related to preterm infants treated for patent ductus arteriosus (PDA) (refer to the Applicant's submissions dated August 19, 2022, January 13, 2023, and Dr. Epps' review).

Dr. Epps identified two literature reports with the largest safety databases for analyses on ibuprofen use in young infants in her review. The first is a safety analysis by Walsh et al., (2018) based on "Medicaid pharmacy and medical claims data for 41,669 infants less than 6 months of age who were treated with

ibuprofen by prescription with most followed for 6 months." The authors concluded that "GI and renal AEs were not higher in infants younger than six months who were prescribed ibuprofen compared with those aged six to 12 months" and that "AEs were increased in infants younger than six months who were prescribed ibuprofen compared with infants who were prescribed acetaminophen alone."

The second is "a metanalysis of 19 randomized and non-randomized studies of 241,138 participants from seven countries comparing ibuprofen and acetaminophen safety in children less than 2 years of age" by Tan et al., (2020). The authors concluded that ibuprofen and acetaminophen had similar safety profiles in patients aged less than two years but were unable to analyze safety data for comparing safety between ibuprofen and acetaminophen in infants less than 6 months of age. Only two of the 19 randomized studies had patients younger than 6 months of age and "there were no extractable data for this prespecified subgroup analysis" as reported by the authors. Therefore, the authors were "cautious of extrapolation of evidence to this age group."

Drug utilization in infants <3 months of age

An Information Request (IR) of 18-month drug utilization data to obtain information on number of doses and length of use by indication for each age group (categorized by month) of <3 months of age was sent to the Applicant as recommended by the Division of Pediatric and Maternal Health (DPMH). Based on the Applicant's response to the IR, there is very low drug utilization in the age group. Only eight patients in the age group of 0-1 month of age and five patients in the age group of 2-3 months of age were dispensed IV ibuprofen in comparison to more than 550 patients dispensed IV acetaminophen in each corresponding age group during the period of January 2020 to June 2021 (reference: STATinMED Research Report 40703 and 40704 on Ibuprofen IV & Acetaminophen IV Feasibility Study dated January 17, 2023, in the Applicant's submission dated January 30, 2023). Information on the number of doses or length of use by indication is not available.

Advisory Committee Meeting

No issues came up during the course of the review that warranted discussion at an Advisory Committee meeting**.**

Pediatrics

PMR 205-5 is copied below.

> "Deferred pharmacokinetics (PK) and safety study of Caldolor (ibuprofen) injection for reduction in fever, or management of mild-to-moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics, in pediatric patients aged birth to 6 months."

PMR 205-5 requirement was fulfilled based on data available from pediatric patients aged 3 to less than 6 months and a partial waiver is appropriate for patients aged birth to less than 3 months due to low drug utilization for fever and pain in this pediatric population.

The Agency may request the Sponsor to evaluate the use of IV ibuprofen for fever and pain in patients birth to less than 3 months of age if the Agency determines there is a need for data in this particular age group.

Other Relevant Regulatory Issues

None.

Labeling/OPDP Review

The following labeling sections will be revised to add labeling statement about inclusion of pediatric use of ibuprofen injection in patients aged 3 months to less than 6 months and statements related to the study findings from patients aged 3 months to less than 6 months (refer to the draft labeling with track changes for revision detail).

- Section 1 Indication and Usage
- Section 2.1 Important Dosage and Administration Instructions
- Section 2.3 Pediatric dosing recommendation
- Section 6.1 Clinical Trial Experience
- Section 8.4 Pediatric Use
- Section 12.3 Pharmacokinetics

The Office of Prescription Drug Promotion (OPDP) stated that they "do not have any comments at this time" after reviewing "the draft labeling emailed to OPDP on March 17, 2023."

Postmarketing Recommendations

None.

Clinical Review of Study CPI-CL-022

Protocol
According to the original protocol, Study CPI-CL-022 was planned as a multi-center, open-label, single-arm, single-dose and multiple-dose, pharmacokinetic, and safety study of Caldolor (IV ibuprofen) 10-minute infusion at 10 mg/kg for reduction of fever or management of pain in pediatric patients aged birth to less than six months.

Sample pediatric study population was planned to include hospitalized male and female patients from birth (greater than 37 weeks gestational age) to less than six months of age in need of pain and/or fever treatment who would not have any of the following: inadequate intravenous access; uncorrected ductus dependent congenital heart disease; any history of allergy or hypersensitivity to NSAIDs or aspirin; recent history of uncorrected hypovolemia or acute renal disease; recent current history of acute liver disease; treatment with NSAID, acetaminophen, or aspirin within four hours prior to dosing; treatment with another investigational drug within the past 30 days; be otherwise unsuitable for the study, in the opinion of the Investigator.

The planned treatment for eligible patients was IV ibuprofen 10-minute infusion at 10 mg/kg/dose every six to eight hours as needed at the Investigator's discretion, for up to eight deses during the 48-hour treatment period and not to exceed 40 mg/kg/day. The plan for concomitant medication was to restrict the

use of nonsteroidal anti-inflammatory drugs (NSAIDs other than the study drug) and acetaminophen during 4-hour time interval prior to the initial dose of IV ibuprofen and through 48-hour study period.

The Applicant did not plan to collect efficacy data in this study. The planned safety monitoring included the following: continuous monitoring of treatment-emergent adverse events (TEAEs); vital signs such as heart rate, respiratory rate, and blood pressure, to be measured immediately pre- and post-dose, at Hours 0.5, 1, 2, and 4 after each dose, and at Hours 24 and 48; routine laboratory tests such as clinical chemistry, hematology, and coagulation, to be conducted at baseline and Hours 24 (±6 hours) and 72 (±6 hours) or at discharge, whichever occurs first.

Scheduled pharmacokinetic sampling was planned as plasma samples of 1 mL each immediately after completion of the initial dose to be collected from all patients and then collected via sparse sampling at 0.5, 1, 2, and 4 hours.

Subsequent protocol amendments provided more details about safety monitoring. In Amendment 1 it was clarified that all treatment emergent adverse events would be followed until resolution or stabilization, regardless of the assessment of severity or relationship to the study drug (submission to IND 62605 dated August 11, 2016). In Amendment 2 temperature measurement was added to the list of vital signs and specific laboratory tests were added and listed under chemistry, hematology, and coagulation laboratory tests to be obtained at Screening/Baseline (submission to IND 62605 dated October 14, 2016). Clarifications of assessment time window to be within 15 minutes of scheduled time for vital sign measurements and within five minutes of scheduled time for PK sampling were also added in Amendment 2.

Table 2 Reviewer's Summary of the Protocol

Study #	CPI-CL-022
Title	Multi-Center (4-site), Open-Label, Pharmacokinetic, and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months
Objectives	To study single-dose PK and multiple-dose safety of IV ibuprofen in treating fever and pain in hospitalized pediatric patients from birth to less than 6 months of age
Design	Multi-center, in-patient, open-label, single-arm, single- and multiple-dose
Sample population	Hospitalized male or female subject between birth (> 37 weeks gestational age) and < six months of age with pain or fever who does not have any of the following • Inadequate intravenous access • Uncorrected ductus dependent congenital heart disease • Any history of allergy or hypersensitivity to NSAIDs or aspirin • Recent history of uncorrected hypovolemia or acute renal disease • Recent current history of acute liver disease • Treatment with NSAID, acetaminophen, or aspirin within four hours prior to dosing • Treatment with another investigational drug within the past 30 days • Be otherwise unsuitable for the study, in the opinion of the Investigator Planned sample size: 24 patients
Treatment	IV ibuprofen 10 mg/kg/dose 10-minute infusion q6-8 hours PRN at the Investigator's discretion for up to eight deses during the 48-hour treatment period and not to exceed 40 mg/kg/day
Concomitant medication	NSAIDs (other than study drug) and acetaminophen will be restricted four hours prior to the initial dose of IV ibuprofen through study hour 48
Safety monitoring	• Vital signs (heart rate, respiratory rate, blood pressure) immediately pre- and post-dose, at Hours 0.5, 1, 2, and 4 after each dose, and at Hours 24 and 48

	• Routine laboratory tests (clinical chemistry, hematology, and coagulation) at baseline and Hours 24 (±6 hours) and 72 (±6 hours) or at discharge, whichever occurs first • Continuous monitoring of treatment-emergent AEs
PK sampling	Plasma samples of 1 mL each immediately after completion of the initial dose to be collected from all patients and then collected via sparse sampling at 0.5, 1, 2, and 4 hours

Results

Demographic and other baseline characteristics

The sample pediatric population consisted of 24 pediatric patients exposed to study medication, with an age range of one month to 5.9 months, a mean of about 4.2 months and a median of about 4.3 months. Of the 24 patients, 17 (71%) were Caucasian and 3 (12%) were African American by race with 4 (17%) categorized as other race, 5 (21%) were Hispanic by ethnic origin, and 9 (38%) were females.

Table 3 Demographics and Baseline Characteristics

Study CPI-CL-022 Demographics and Baseline Characteristics	**IV Ibuprofen (N=24)**
Age (days/months)	
Mean	127.7 / 4.2
Median	132.0 / 4.3
SD	33.77 / 1.1
Min, Max	32, 179 / 1.0, 5.9
Sex, N (%)	
Male	15 (62.5%)
Female	9 (37.5%)
Race, N (%)	
White or Caucasian	17 (70.8%)
Black or African American	3 (12.5%)
Other	4 (16.7%)
Ethnicity, N (%)	
Hispanic or Latino	5 (20.8%)
Not Hispanic or Latino	19 (79.2%)
Weight (kg)	
Mean	6.0
Median	5.9
SD	1. 5
Min, Max	2.3, 8.8

Note: SD= standard deviation; Min= minimum; Max= maximum
Source: Table 11-1 on page 45 of the Study Report

Demographic characteristics are summarized for the age subgroups as shown in the table below. There were no patients in the age group of birth to <1 month, one patient in the age group of 1 to <2, two patients in the age group of 2 to <3 months, five patients each in the age groups of 3 to <4 months and 5 to <6 months, and 11 patients in the age group of 4 to <5 months. Most age groups had more male than female patients. The weight distribution mostly followed a trend associated with weight increase with increase of age except in the age group of 4 to <5 months, which had two low weight infants leading to the group mean and medium less than expected.

Table 4 Age, Sex and Weight Distribution by Age Group in Study 022

Age group by months	Birth to <1	1 to <2	2 to <3	3 to <4	4 to <5	5 to <6
	N=0	N=1	N=2	N=5	N=11	N=5
Age, months						
Mean		1.07	2.25	3.75	4.5	5.39
Median		1.07	2.25	3.82	4.36	5.13
Min, Max		1.07	2.16, 2.33	3.46, 3.98	4.13, 4.95	5.00, 5.89
Sex, N (%)						
Male		0	2	4	7	3
Female		1	0	1	4	2
Weight (kg)						
Mean		4.3	5.2	6.3	5.7	7.2
Median		4.3	5.2	6.1	5.9	6.7
Min, Max		4.3, 4.3	4.8, 5.5	5.8, 7.4	2.3, 7.6	5.4, 8.8

Source: Table 2.7.4.1–2 on pages 11-12 of Section 2.7.4, Summary of Clinical Safety

Patient disposition

Seven of 24 (23%) pediatric patients prematurely discontinued from the study. The reasons for dropouts were early discharge with no specific explanations provided in four patients and switching analgesics in three patients, including replacement by acetaminophen in two patients and by acetaminophen/hydrocodone combination in one patient as summarized in the table below.

Table 5 Patient Disposition

Study 022 **Patient Disposition**	**IV Ibu (N=47)** **N (%)**
Completed study per protocol	17 (56.7%)
Prematurely discontinued study	7 (23.4%)
Reasons for withdrawal from study	
Early discharge with no reasons specified	4 (16.79%)
Switching analgesics	3 (12.5%)
to acetaminophen with no future labs planned	1 (14.3%)
to acetaminophen with IMP discontinued	1 (14.3%)
to acetaminophen-hydrocodone	1 (14.3%)

Source: Table 10-1 on pages 43-44 of the Study Report

Protocol violations

There was a high proportion of patients, 20 of 24 or 83%, with protocol deviations. The most frequently reported deviations were related to pharmacokinetic (PK) sampling and safety data collection, especially the timing error in PK sampling and incomplete, missing, or mistimed vital sign measurement and lab test collection. PK sampling not following the scheduled time may not have a major impact on PK conclusion because individual concentration versus time profiles were included in the additional PK analysis conducted by Dr. Lee. Missing and incomplete lab test collections are not expected to affect the safety conclusion in this case because of limited usefulness of lab in detecting major safety signals after a single-dose exposure at the dose level studied.

Table 6 Summary of Protocol Deviations/Violations

Study 022 **Protocol Deviations/Violations**			
No. of patients with ≥ 1 deviation/violation, N (%)	20 (83%)		
Counts of specific deviation/violation	88		
Type of specific deviation/violation	**Counts**		
Dosing time error (PRN dosing outside q6 to 8-hour window	2		
Restricted medication given prior to complete of treatment period	8		
Data collection	Missing	Miss-timed	Incomplete
Pharmacokinetic sampling	1	19	0
Vital Sign measurement	5	14	12
Lab test collection	9	3	13

Source: Table 2.7.4.1–3 on page 12 of Section 2.7.4, Summary of Clinical Safety

Safety Findings

Exposure

Information on exposure per age group is summarized in the table below. Most pediatric patients in the age group of <6 months (21 of 24) exposed to the study medication were in the range of 3 to <6 months of age. Only three patients were aged <3 months, including two patients in the group of 2 to <3 months of age and one patient in the group of 1 to <2 months of age. Multiple-dose exposure was limited to four patients, one from each of the age groups of 2 to <3, 3 to <4, 4 to <5, and 5 to <6 months and included exposure to four doses in one patient and eight doses each in the other three patients.

Table 7 Exposure per Age Group in Study 022

Age group (month)	Birth to <1	1 to <2	2 to <3	3 to <4	4 to <5	5 to <6
Any dose	N=0	N=1	N=2	N=5	N=11	N=5
Multiple dose		N=0	N=1 (4 doses)	N=1 (8 doses)	N=1 (8 doses)	N=1 (8 doses)
PK data available	*N=0*	*N=1*	*N=2*	*N=5*	*N=10*	*N=5*

Deaths

No deaths occurred during the study.

Nonfatal Serious Adverse Events

There were three serious adverse events (SAEs) reported as pericardial effusion (one event) and chylothorax (two events) in one patient.

The patient is a four-month-old Caucasian male with a body weight of 7.5 kg and a history of prenatal diagnosis of Tetralogy of Fallot (TOF), a combination of four congenital heart defects including a ventricular septal defect (VSD), pulmonary stenosis, a misplaced aorta and right ventricular hypertrophy, accompanied by low oxygen saturation and cyanosis.

The patient underwent a very complicated surgical repair procedure and was intubated, sedated, and admitted to the pediatric intensive care unit (PICU) after surgery. Medication on arrival to the PICU included cefazolin, famotidine, heparin lock flush, sodium bicarbonate dexmedetomidine infusion drip, dextrose 5% and 0.45% NaCl, epinephrine infusion drip, fentanyl, dextrose 5% with additives, sodium

chloride 0.9% with heparin 1000 units, arterial line fluid, milrinone 200 mcg/ml infusion drip, and rocuronium 10mg/ml.

The patient received a single dose of 75 mg IV ibuprofen on post-operative Day 1. ECHO on post-operative Day 2 revealed small residual structural defects, several functional abnormalities, and evidence suggesting pleural effusion and pericardial effusion with the results of pleural fluid analysis consistent with a chylothorax (accumulation of chyle in pleural cavity due to lymphatic fluid leakage). While the right sided chylothorax was improving with a few days of fluid drainage and standard care, a follow-up X-ray on post-operative Day 6 revealed a new left sided effusion, also chyle. The AEs of chylothorax lead to prolonged hospitalization and resolved with treatments without sequela.

The SAEs appeared more likely to be related to the surgical complications and unlikely to be related to a single dose of IV ibuprofen.

Dropouts and/or Discontinuations
There were no cases of dropouts due to AEs.

Common Adverse Events
A total of 14 adverse events (AEs) were reported in eight patients as summarized in the table below. The most common AEs were chylothorax (three events in two patients) and constipation (two events in two patients). AEs were rated as mild in eight cases and moderate in six cases, and all resolved before completion of the study. The types of AEs were more consistent with patients' medical conditions and commonly reported post-operative reactions to surgery, and none appeared to be known AEs related to the use of ibuprofen.

Table 8 Summary of Treatment Emergent AEs

System Organ Class	Preferred Term	Event	Patient
Cardia Disorders	Pericardial Effusion	1	1
Eye Disorder	Eye Discharge	1	1
Gastrointestinal Disorder	Abdominal distension	1	1
	Constipation	2	2
Injury, poisoning and procedural complications	Post procedural fever	1	1
Investigations	White Blood Cell count elevated	1	1
Metabolism and nutrition disorders	Hypokalemia	1	1
Respiratory, thoracic, and mediastinal disorders	Atelectasis	1	1
	Chylothorax	3	2
	Pleural Effusion	1	1
Vascular Disorder	Peripheral artery thrombosis	1	1
Total		14	8

Source: Table 12-1 on pages 54-55 of the Study Report.

Laboratory Findings
The individual lab tests were collected in some patients. The columns under 'lab test' in the table below summarized the number of patients providing individual lab test results at 24 hours and 72 hours, respectively. Abnormal shifts from baseline values reported in more than one patient included 11

individual lab parameters at 24 hours and four individual lab parameters at 72 hours. None of the clinically significant shifts from baseline values were reported in more than one patient.

Table 9 Summary of Laboratory Shifts from Baseline and Clinically Significant Shifts

Study 022		**24-hour N=24**			**72-hour N=24**		
Lab Test		**Number of patients with the following**					
Lab Test	**Shift**	**Lab test**	**Lab Shift**	**Sig shift**	**Lab test**	**Lab Shift**	**Sig shift**
Hematology/coagulation							
aPTT (Seconds, 25.5-35)	N → H	14	0	0	5	1	0
	H → L	14	1	0	5	0	0
INR (0.8-1.2)	N → H	14	1	1 *	5	0	0
PT (seconds, 9.9-12.7)	N → L	14	0	0	5	1	0
	N → H	14	0	0	5	1	0
Hemoglobin (g/dL, 10.5-13.5)	H → L	19	1	0	9	1	0
	N → L	19	4	0	9	0	0
Hematocrit (%, 29-41)	N → L	19	2	0	9	1	0
Leukocytes (%, 6.0-17.5 or 6.0-13.5)	N → H	19	3	0	8	0	0
Lymphocytes (%, 46-76)	N → L	16	3	0	8	0	0
Monocytes (%, 0-10)	N → H	16	1	0	8	0	0
Neutrophils (%, 16-48 or 15-35)	N → H	16	6	0	8	0	0
	L → H	16	1	0	8	0	0
Platelets (10^3/uL, 140-440)	N → L	18	2	1 **	9	3	0
	N → H	18	0	0	9	1	0
Chemistry							
Albumin (g/dL, 3.0-4.8)	N → L	16	3	1 ***	8	1	0
ALT (U/L, 13-69)	N → H	16	1	1 ***	8	1	1 ***
Bilirubin (mg/dL, 0.6-1.4)	N → L	16	2	0	8	2	0
BUN (mg/dL, 4-15 or 1-14)	N → L	16	2	0	8	0	0
	N → H	16	0	0	8	2	0
Chloride (mmol/L, 98-107)	N → L	16	0	0	8	1	0
	N → H	16	0	0	8	1	0
Creatinine (mg/dL, 0.3-0.5)	N → L	16	1	0	8	1	0
Glucose (mg/dL, 45-100 or 76-126)	N → H	16	2	0	8	1	0
Bicarbonate (mmol/L, 18-27)	N → H	16	1	0	8	3	0
LDH (U/L, 129-376)	N → H	16	1	0	8	0	0
Potassium (mmol/L, 3.5-5.1 or 3.5-6.0)	N → H	16	0	0	8	1	0
	N → L	16	2	0	8	0	0
Protein (g/dL, 5.4-7.0)	N → L	16	1	0	8	0	0

Note:
*A clinically meaningful change in INR is defined as a change of more than 0.3 above normal
**A clinically meaningful change in platelets is defined as a change of more than 1.5 x the Lower Limit Normal (LLN)
***A clinically meaningful change in chemistry was defined as a change of more than 1.5x ULN or 1.5x LLN
N → H means lab value shift from normal to high; N → L means lab value shift from normal to low; Sig shift means the shift is considered clinically significant (define what represents a clinically meaningful change for each lab parameter, e.g. liver enzyme increases of ≥ 3x Upper Limit Normal (ULN); aPTT=activated partial thromboplastin time; INR=International Normalized Ratio; PT=prothrombin time; ALT=alanine transaminase; BUN=blood urea nitrogen; LDH=lactate dehydrogenase; g/dL=grams per deciliter; %=percent; 10^3/uL=thousand per microliter; U/L=units per liter; mg/dL=milligrams per deciliter mmol/L=millimoles per liter;

Source: Table 11-2 on pages 22-24 of the Integrated Summary of Safety.

Summary

Study 022 enrolled 24 hospitalized pediatric patients in the age group of birth to <6 months of age who required IV treatment for pain (n=24) and/or fever (n=1). Of 24 patients treated 21 were in the age range of 3 to <6 months of age. PK data revealed that Cmax and AUC for the age group of 3 to <6 months are similar to those of the age group of 6 months to <2 years in Study 012. PK data in Study 022 were insufficient in the youngest three age groups of birth to <1 month (n=0), 1 to <2 months (n=1), and 2 to <3 months (n=2) to make adequate PK conclusions and comparisons.

Safety exposure was limited mostly to a single dose (n=20). Multiple-dose exposure was reported in four patients, including four doses in one patient in the 2 to <3 months age group and eight doses in three patients with one patient from each of the three age groups of 3 to <4, 4 to <5, and 5 to <6 months. A total of 14 AEs were reported in eight patients and individual AEs were mostly reported by a single patient except constipation (reported by two patients) and chylothorax (three events reported by two patients). No dropouts due to AEs were reported. Three SAEs including pericardial effusion and chylothorax (two events) leading to prolonged hospitalization were reported in one patient and were considered unlikely to be related to the study drug. A few individual lab parameters had significant shifts from baseline values, and none of them were reported in more than one patient.

Financial Disclosures

The financial disclosure form signed by the Applicant certified that no financial arrangement with the listed clinical investigators (a complete list of all clinical investigators involved in the two fever studies was attached to the form) had been made whereby study outcomes affected compensation as defined in 21 CFR 54.2(a); certified that each listed investigator was required to disclose to the Applicant whether the investigator with a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such interests; and certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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