CLINICAL REVIEW

Application Type	NDA
Submission Number	22-348
Submission Code	Supplement 5 (SD 65, 68, 69, 70, 71, 72, 73, 75, 80, 82, 83 and 86)
Letter Date	January 29, March 6, 11, 20, 26, and 27, April 3, May 1, August 6 and 10, September 3, October 28, and November 9, 2015
Stamp Date	Same as above
PDUFA Goal Date	November 29, 2015
Reviewer Name	Christina Fang, M.D., M.P.H.
Review Completion Date	November 9, 2015
Established Name	Ibuprofen IV injection
Trade Name	Caldolor® (ibuprofen) IV injection
Therapeutic Class	NSAID
Applicant	Cumberland Pharmaceuticals Inc.
Priority Designation	3P
Formulation	Solution for injection containing 100 mg/mL ibuprofen
Dosing Regimen	10 mg/kg q4 hours for fever and pain
Indication	Fever; pain (supplemental to morphine treatment)
Intended Population	Pediatric (≥6 months) hospitalized patients

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1 RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

A regulatory action of approval is recommended for use of IV ibuprofen injection in pediatric patients aged 6 months to 17 years for the proposed indications.

The recommendation for approval is based on an acceptable benefit/risk ratio according to my review of clinical efficacy and safety data submitted in the Supplement 5 of the NDA 22-348.

1.2 Risk Benefit Analysis

The benefits of treating fever with IV ibuprofen 10 mg/kg in hospitalized pediatric patients have been shown in terms of clinically meaningful fever reduction and temperature normalization within the first dosing interval after the initial infusion.

In comparison to the relatively low dose of acetaminophen at 10 mg/kg in the key efficacy Study 012, IV ibuprofen treatment was associated with a statistically significant treatment difference in the primary endpoint AUC_{0-2}, 0.2 to 0.6°C more temperature reduction in the first dosing interval, 0.4 hours shorter median time to reach a temperature reduction to <37.5ºC (99.5 ºF), and 17% more becoming afebrile by the end of the first dosing interval.

The risks associated with the use of ibuprofen in general are well known. Based on limited pediatric exposure to IV ibuprofen in the three clinical trials of 144 patients exposed to a single dose and 45 exposed to at least two doses, IV ibuprofen is reasonably well tolerated. The most commonly reported (≥2%) adverse events (AEs) in IV ibuprofen treated patients were infusion site pain, vomiting, nausea, anemia and headache.

The use of IV ibuprofen in pediatric patients is considered reasonably safe based on the lack of new safety signals or unexpected events in pediatric studies, the known safety profile of the ibuprofen moiety, and the anticipated short-term use and close safety monitoring in a hospital setting. Therefore, the benefit/risk ratio is considered acceptable in my opinion.

1.3 Recommendations for Postmarketing Risk Management Activities

None.

1.4 Recommendation for other Postmarketing Study Commitments

The Applicant has fulfilled two of the postmarketing study requirements that were instituted with the original approval of Caldolor. The remaining PMR is listed below, and has yet to be completed.

- A deferred pharmacokinetic (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. [Final study report due: December 2018]

This supplement does not trigger additional PMRs.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

IV ibuprofen injection (IV Ibu) is an IV formulation containing 100 mg/mL ibuprofen packaged in 800 mg/8 mL 10 mL vials to be diluted in 5% dextrose or 0.9 % sodium chloride solution prior to administration for the management of fever and pain.

The established name of the product is ibuprofen IV injection and the registered trade name was Caldolor. The active ingredient of the product, ibuprofen, is a propionic acid derivative and a member of the non-steroidal anti-inflammatory drug (NSAID) class.

The original NDA for ibuprofen IV was approved on June 11, 2009, for adult indications of management of mild-to-moderate pain or moderate-to-severe pain as an adjunct to opioid analgesics and reduction of fever. The recommended dosage is 400 mg to 800 mg intravenously over 30 minutes every 6 hours as necessary for pain and 400 mg intravenously over 30 minutes, followed by 400 mg every 4 to 6 hours or 100-200 mg every 4 hours as necessary for fever.

2.2 Table(s) of Currently Available Treatment(s) for Proposed Indication(s)

Several drugs of the NSAID class are currently available for treating fever and mild-to-moderate pain. Acetaminophen IV formulation was approved for fever and pain indications in 2010.

2.3 Availability of Proposed Active Ingredient in the United States

There are many ibuprofen containing products currently available in the United States. The information on these products is summarized in the table below by the proprietary name, active ingredient, strength of formulation, NDA number, and application approval date based on 2015 version of the Orange Book.

Table 2-1 Products Containing Ibuprofen Approved for the U.S. market

Proprietary Name	Active Ingredient	Strength	NDA#	Approval date
Rx				
DUEXIS	FAMOTIDINE; IBUPROFEN	26.6MG; 800MG	022519	Apr 23, 2011
Neoprofen	Ibuprofen lysine	EQ 20mg base/2mL (EQ 10mg base/mL)	021903	Apr 13, 2006
Combunox	Ibuprofen; oxycodone hydrochloride	400mg;5mg	021378	Nov 26, 2004
Vicoprofen	Hydrocodone bitartrate; ibuprofen	7.5mg;200mg	020716	Sep 23, 1997
Generic	Ibuprofen suspension	100mg/5mL	Multiple	
Generic	Ibuprofen tablet	400mg, 600mg, 800mg	Multiple	
OTC				
Advil Allergy and Congestion Relief	Chlorpheniramine maleate; ibuprofen; phenylephrine hydrochloride	4mg; 200mg; 10mg	022113	Dec 21, 2011
Children's Advil Allergy Sinus	Chlorpheniramine maleate; ibuprofen; pseudoephedrine hydrochloride	1mg/5mL; 100mg/5mL; 15mg/5mL	021587	Feb 24, 2004
Advil Allergy Sinus	Chlorpheniramine maleate; ibuprofen; pseudoephedrine hydrochloride	2mg;200mg;30mg	021441	Dec 19, 2002
Advil PM	Diphenhydramine citrate; ibuprofen	38mg;200mg	021394	Dec 21, 2005
Advil PM	Diphenhydramine hydrochloride; ibuprofen capsule	25mg;EQ 200mg free acid and potassium salt	021393	Dec 21, 2005
Children's Elixsure	Ibuprofen suspension	100mg/5mL	021604	Jan 7, 2004
Children's Advil	Ibuprofen suspension	100mg/5mL	020589	Jun 27, 1996
Children's Motrin	Ibuprofen suspension	100mg/5mL	020516	Jun 16, 1995
Midol Liquid Gels	Ibuprofen capsule	Capsule 200MG	021472	Oct 18, 2002

Advil Migraine Liqui-Gels & Advil Liqui-Gels	Ibuprofen capsule	EQ 200mg free acid and potassium salt	020402	Apr 20, 1995
Children's & Junior Strength Advil	Ibuprofen chewable tablet	50mg, 100mg	020944	Dec 18, 1998
Children's & Junior Strength Motrin	Ibuprofen chewable tablet	50mg, 100mg	020601	Nov 15, 1996
Pediatric Advil	Ibuprofen suspension/drops	100mg/2.5mL	020812	Jan 30, 1998
Children's Motrin	Ibuprofen suspension/drops	40mg/mL	020603	Jun 10, 1996
Junior Strength Advil	Ibuprofen tablet	100mg	020267	Dec 13, 1996
Junior Strength Motrin	Ibuprofen tablet	100mg	020602	Jun 10, 1996
Motrin Migraine Pain	Ibuprofen tablet	200mg	019012	Dec 17, 1990
Advil	Ibuprofen tablet	200mg	018989	May 18, 1984
Advil	Ibuprofen sodium	EQ 200mg base	201803	Jun 12, 2012
Advil Congestion Relief	Ibuprofen; phenylephrine hydrochloride	200mg; 10mg	022565	May 27, 2010
Advil Cold and Sinus	Ibuprofen; pseudoephedrine hydrochloride	EQ 200mg free acid and potassium salt; 30mg capsule	021374	May 30, 2002
Children's Advil Cold	Ibuprofen; pseudoephedrine hydrochloride	100mg/5mL;15mg/5mL suspension	021373	Apr 18, 2002
Children's Motrin Cold	Ibuprofen; pseudoephedrine hydrochloride	100mg/5ml;15mg/5mL suspension	021128	Aug 1, 2000
Sine-Aid IB	Ibuprofen; pseudoephedrine hydrochloride	200mg;30mg tablet	019899	Dec 31, 1992
Advil Cold and Sinus	Ibuprofen; pseudoephedrine hydrochloride	200mg;30mg tablet	019771	Sep 19, 1989

Source: Orange Book, 2015 edition.

Major safety concerns with the use of ibuprofen, especially at higher doses for a prolonged exposure, are risks of cardiovascular, gastrointestinal, and renal toxicities, and major bleeding.

2.4 Important Issues with Consideration to Related Drugs

The most recent safety findings concerning the use of NSAID drugs are their cardiovascular toxicities, for which all NSAID drugs are now required to have box warnings in their labels.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

The Applicant had several communications with the Division in 2004 (dated February 3, 2004 and October 4, 2004 in DARRTS) with regard to pediatric study requirements and was advised of deferring pediatric study until adult data became available and could be used for selection of target dosage for the pediatric fever study. At the pre-NDA meeting held in May 2008 (dated May 29, 2008 and June 27, 2008 in DARRTS), the recommendations were to obtain pediatric PK data on the IV formulation to show comparable bioavailability to the listed drug for pediatric use, or alternatively, to provide a PK link between the adult and pediatric populations on the use of IV formulation to bridge adult relative PK data to the pediatric population. The Division pointed out that if an adequate PK link between adult and pediatric formulations could not be established, then a pediatric indication could not be granted, and reminded the Applicant that the adequacy of pediatric data in support of pediatric labeling would be a review issue.

A Pediatric Written Request (PWR) was issued originally on March 30, 2009. The PWR was later revised and reissued on July 16, 2010. Pediatric studies described in the revised PWR included a single-dose PK study in patients birth to 16 years of age "to obtain data to bridge IV ibuprofen plasma concentrations in pediatric patients to known, existing ibuprofen plasma concentrations from pediatric and adult patients with IV and oral ibuprofen administration," a multiple-dose efficacy study of fever in patients younger than six months of age "to provide useful information for the formulation of appropriate pediatric dosing," and a multiple-dose safety study of up to five days in at least 100 patients birth to 16 years of age with at least 50 younger than six months of age to characterize safety profile for different age groups. The maximum dosage specified in the dosing regimen was not to exceed 10 mg/kg or 400 mg per dose or 2400 mg per 70 kg total daily dose (normalized for pediatric patients of lower weight).

At the time of approval of the original NDA the Applicant was granted deferral of pediatric study under PREA (Pediatric Research Equity Act) for the treatment of reduction in fever and for the management of mild-to-moderate pain and management of moderate-to-severe pain as an adjunct to opioid analgesics in pediatric patients aged 0 to 16 years. Subsequently, the timeline for the deferral of fever study in pediatric population up to 16 years of age was extended due to difficulty in enrolling patients aged birth to less than 6 months (refer to the Medical Reviewer's Memo dated July 2, 2013, letter to the Sponsor sent on July 9, 2013, and Pediatric Review Committee, or PeRC meeting minutes dated August 29, 2013 in DARRTS).

In response to the Applicant's request for a waiver of study in the youngest age group birth to <6 months of age, Dr. Donna Snyder from Pediatric and Maternal Health Staff (PMHS) concluded in her consult review (refer to the memo dated March 17, 2014 in DARRTS) that: "PMHS does not agree that studies should be waived for pain in the pediatric population from 0 to 6 months of age. Data on non-opioid alternatives for pain in the pediatric patients under 6 months of age, and especially in neonates, is lacking and there is a public health need to obtain this information." She also concluded that: "there are no products labeled for pediatric patients less than 6 months of age for treatment of fever and data in this population is also needed."

Based on the PeRC's recommendations (refer to the meeting minutes dated September 29, 2014 in DARRTS) the list of required pediatric studies under PREA was updated to include PK, efficacy, and safety study of fever in patients aged 6 months to 16 years, which might be fulfilled with the final results of Study 012; PK and safety study of pain in patients aged 6 months to 16 years, which might also be fulfilled with the final results of Study 012; PK and safety study of fever and pain in patients aged birth to 6 months (refer to letter to the Applicant dated December 24, 2014). PeRC's recommendations were made of the consideration of the following factors: oral ibuprofen is approved for pain and fever indications for pediatric population 6 months of age and above and pediatric dosing is the same for the two indications; bioavailability is comparable between oral and IV formulations of ibuprofen in adults. Comparable bioavailability needs to be demonstrated between the age group of birth to 6 months and the age group of 6 months to 2 years and efficacy and safety need to be shown in sufficient number of patients in the age group of 6 months to 2 years in order to bridge information between the two age groups. Otherwise, a full efficacy study in patients aged birth to 6 months may be required.

2.6 Other Relevant Background Information

None

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The quality of the submission in terms of data organization, retrieval, and completeness was inadequate at the time of submission of the efficacy supplement as exemplified by the following: non-functional links to tables and figures and links to appendices in the body of study reports; inadequate information about subpopulation classified by age groups; lack of narratives on dropouts due to adverse events; improper classification and inclusion of protocol deviation cases; missing or poorly organized and presented baseline data and efficacy and safety data in Study 005; incomplete temperature data reported in fever studies; lack of analysis of temperature difference at baseline in Study 012. The reviewer made several information requests in order to be able to conduct an extensive review.

3.2 Compliance with Good Clinical Practices

The steps to ensure compliance with Good Clinical Practices (GCP) included approval of protocols, informed consent forms, and assent forms by the Institutional Review Boards (IRBs) before the initiation of the study; providing complete explanations to parent or legal guardian and age-appropriate explanations to pediatric patients, about the purpose and evaluation of the study before obtaining signed informed consent and assent prior to the participation in the study. Additional steps for assuring proper conduct of study with regards to protocol adherence and validity of data included pre-study review of protocol, Case Report Forms (CRF), Screening Logs, and Enrollment Forms with Clinical Center Coordinators; providing instructional materials for study procedures (such as temperature measurements and PK sampling) and CRF data entry; monitoring CRF data against source documents; double-checking CRF data by PharPoint Clinical Research personnel.

Rates of protocol violation/deviation were relatively high, about 70% in both treatment groups in Study 012 and the deviations were mostly related to safety data collection. In Study 005 protocol deviation accounted for about 30% in the ibuprofen group and about 70% in the acetaminophen group, mostly related to the timing of a procedure.

Clinical site inspection of the two largest clinical investigator (CI) sites (accounted for 46% of the study population) by the Office of Scientific Evaluations revealed no significant deficiencies with regards to study conduct, including the oversight of study conduct by the Sponsor and IRB. As stated in Dr. John Lee's Clinical Inspection Summary: "in verifying the data for the primary efficacy endpoint, the AUC_{0-2} values calculated on-site using actual temperature measurement times appeared to be acceptably consistent with those reported in the NDA derived by the Sponsor as outlined in the study statistical analysis plan". "All audited data were adequately verifiable among source records, CRFs, and NDA data listings. The data from the two CI sites appear reliable as reported in the NDA" (refer to the memo dated September 16, 2015 in DARRTS).

3.3 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).

4 SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

There have been no CMC changes (refer to the reviews of the original NDA for CMC details).

4.2 Clinical Microbiology (if applicable)

Refer to the reviews of the original NDA.

4.3 Preclinical Pharmacology/Toxicology

The efficacy supplement does not contain non-clinical data.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action for ibuprofen is not completely understood but may be related to regulation of prostaglandin synthesis via prostaglandin synthetase. The mechanism involves an inhibition of cyclooxygenase (COX-1 and COX-2) pathways.

4.4.2 Pharmacodynamics

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models.

4.4.3 Pharmacokinetics

Pharmacokinetic (PK) data in this submission were obtained from pediatric fever Study 012 (refer to the Review Section 5.3, the review of individual study protocol and results for detail). After the initial dose of ibuprofen 10 mg/kg 10-minute IV infusion, plasma samples were collected immediately post-dose and at 0.5, 1, 2, and 4 hours.

For the purpose of PK comparison across age groups within the pediatric population, between pediatric and adult use of the IV formulation, and between pediatric use of IV formulation and oral formulation in febrile patients, data from pediatric fever Study 012 and adult fever Study 004 (refer to the Clinical Review and PK Review of the original NDA for detail) are summarized along with pediatric PK information in the labeling of Motrin suspension as shown in the table below.

Table 4-1 PK from Febrile Patients, Pediatric Study 012 Adult Study 004, Motrin Suspension Label

	N	PK parameters							
		AUC_{inf} (µg•hr/mL)	**AUC_{0-t} (µg•hr/mL)**	**AUC_{0-4} (µg•hr/mL)**	**Cmax (µg/mL)**	**Tmax (hr)**	**T½ (hr)**	**Cl/WT (mL/hr/kg)**	**Vz/WT (mL/kg)**
Study 012 IV ibuprofen 10mg/kg over 10 minutes in pediatric febrile patients									
< 2 mo	1		51.18	69.14	49.83	0.17	1.18	129.16	219.53
6 mo to < 2 years	5		71.15	70.92	59.24	0.17 (0.17-0.5)	1.78	133.66	311.20
2 to < 6 years	12		79.19	80.25	64.18	0.2 (0.17-0.77)	1.48	130.064	227.23
6 to 16 years	25		80.67	85.73	61.89	0.17 (0.17-0.67)	1.55	109.22	226.824
Study 004 IV ibuprofen over 30 minutes in adult febrile patients									
100 mg	31			22.33	12.17	0.5	2.47		
200 mg	30			32.62	18.94	0.5	2.11		
400 mg	31			70.64	39.76	0.5	2.26		
Motrin 10 mg/kg oral suspension in pediatric febrile patients based on package insert									
	18	155			55	0.97		68.6	

Source: Table 2.7.2.1-5 on page 18 of section 2.7 of NDA Supplement 5; Table 2.7.2.2-1 on page 4 of section 2.7 of the original NDA; Table 1 on page 4 of Dr. David Lee's PK Review.

The maximum concentration Cmax occurred at the end of infusion interval when a full dose was completed as expected in all the studies of the IV formulation and the levels were much higher in pediatric patients receiving 10-minute IV infusion than adults receiving 30-minute infusion of 400 mg ibuprofen. Cmax (50 to 64 µg/mL) associated with the initial 10-minute IV infusion in pediatric patients is roughly estimated to be equivalent to Cmax associated with a single-dose exposure to about 550 mg to 700 mg doses in adults based on the linear proportionality and previous findings of Cmax of 39 µg/mL at 400 mg dose level and Cmax of 73 µg/mL at 800 mg dose level from the single-dose PK Study 001 conducted in healthy volunteers (refer to Dr. Lee's PK Review of Study 001 in the original NDA). The data suggest that slowing down the infusion time might help to decrease the maximum exposure.

A comparison between PK data in febrile pediatric patients receiving IV and oral formulations at 10 mg/kg showed comparable Cmax for the two ibuprofen formulations.

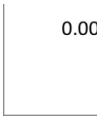
Half-life ($T_{1/2}$) seemed to be shorter with 10-minute infusion in pediatric patients than with 30-minute infusion in adults. The differences might be influenced by insufficient data points at the excretion phase used in calculation of $T_{1/2}$ as explained by Dr. Lee. According to Dr. Lee's summary of concentration per PK sampling time as shown in the table and graph below, drug concentration data from exposure to the initial dose were comparable between pediatric and adult populations in the time interval of 0.5 to 4 hours. Therefore, the difference in $T_{1/2}$ is not expected to affect single-dose duration. The potential impact of a shortened $T_{1/2}$ on multiple-dose duration could not be predicted due to lack of steady-state pediatric PK data and limitations in multiple-dose exposure and data collection in clinical studies.

Table 4-2 Mean Concentration by PK Sampling Time in Febrile Patients of Different Age Groups

Time (h)	**0.167**	**0.5**	**1**	**2**	**4**
10-minute IV infusion, Pediatric	Concentration (μg/mL): mean (SD)				
6 months – 2 years, n=5	59.22 (20.61)	**32.91** (14.31)	20.35 (7.91)	14.15 (5.88)	**7.05** (3.66)
2 – 6 years, n=12	62.62 (22.73)	**38.94** (17.90)	24.49 (9.54)	14.99 (8.64)	**10.58** (9.63)
6 – 16 years, n=25	61.81 (16.59)	**39.31** (12.45)	27.70 (9.71)	17.02 (7.55)	**9.03** (5.12)
30-min IV infusion 400mg in adults		**39.76** (17.75)	25.55 (11.77)	16.59 (7.77)	**9.79** (7.16)

Source: Table 6 on page 20 of Dr. David Lee's PK Review.

Figure 4-1 Mean Concentration by PK Sampling Time, Febrile Pediatric Patients versus Adults



Source: Figure 6 on page 19 of Dr. David Lee's PK Review.

5 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

5.1 Tables of Clinical Studies

Table 5-1 Clinical Study Inventory

Study # Dates, Phase	Study Design	Type	Treatments	N	Study Population Demographics	Use of Data	Review section
CPI-CL-005 1/06-7/07 2 US 3 foreign	Randomized, open-label, active-controlled, parallel group	Safety & efficacy	IV Ibu 10 mg/kg APAP 15 mg/kg oral or rectal q6 hours x 4 doses (24 hours)	14 16 T: 30	Hospitalized febrile pediatric 15 M/15 F Mean age 6.2 years (range 0.5-17- years)	Supportive efficacy data and multiple-dose safety	5.3 7.1-7.5
CPI-CL-012 9/10-4/13 14 US sites	Randomized, open-label, active-controlled, parallel group	PK, safety & efficacy	IV Ibu 10 mg/kg APAP 10 mg/kg q4 hours x24 hours then PRN for up to 5 days	48/47* 55/53 T: 103/100	Hospitalized febrile pediatric 55 M/48 F Mean age 6.1 years (range 0.1-15 years)	Pivotal efficacy data and multiple-dose safety	5.3 7.1-7.5
CPI-CL-014 8/11-7/12 6 US sites	Randomized, double-blind, placebo-controlled, parallel group	Safety & efficacy	IV Ibu 800 mg IV Placebo *Single dose*	82 79 T: 161	Pediatric post-tonsillectomy pain 62 M/99 F Mean age 9.5 years (range 6-17 years)	ISS: single-dose exposure	7.1-7.5

Note: 48/47 refers to 48 included in safety and 47 in efficacy analyses in the IV ibuprofen group and 55/53 refers to 55 included in safety and 53 in efficacy analyses in the acetaminophen group.

5.2 Review Strategy

The NDA supplement contains three pediatric studies: two fever studies and one analgesic study. Study CPI-CL-012 is the key fever study of superiority design and will be reviewed in detail. Study CPI-CL-005 is a small fever study of non- inferiority design. The study was exploratory in nature and had a very few efficacy endpoints. The results of Study 005 presented in this review are mostly based on post-hoc analyses by using a similar set of endpoints as in Study 012. Study CPI-CL-014 is a single-dose study of preemptive analgesia and will be included only in the safety review.

5.3 Discussion of Individual Studies

5.3.1 Fever Study 012

Protocol

Study CPI-CL-012 was planned as a multi-center, randomized, open-label, active-controlled, parallel group, multiple-dose, antipyretic study of IV ibuprofen 10 mg/kg 10-minute infusion in febrile pediatric patients.

Eligible subjects were to have been hospitalized or scheduled to be hospitalized pediatric patients between birth (28 weeks to <40 weeks gestational age) and 16 years of age with new onset (within last seven days) of fever, documented as temperature (by tympanic measurement) ≥101.0ºF (38.3ºC). (Refer to the eligibility criteria in Appendix for detail).

Eligible subjects were to have been randomized to one of the two treatment groups to receive either IV ibuprofen 10 mg/kg 10-minute infusion or acetaminophen 10 mg/kg oral solution or suppository to be dosed every four hours for the first 24 hours and then every four hours as needed during the 120-hour treatment

period. The planned maximum dosage was going to be 400 mg per dose or 2400 mg per day for ibuprofen and 650 mg per dose or 3900 mg per day for acetaminophen for up to 30 doses.

No other antipyretic treatments were to have been allowed as rescue two hours prior to the initial dose and during the 120-hour treatment period.

Body temperature (by tympanic route) was planned to be measured at 0, 15, 30, 45, 60, 75, 90, and 105 minutes and 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours with respect to the start of the initial infusion, and then every six hours through the PRN treatment period.

The planned primary efficacy endpoint was AUC_{0-2}, the area under the curve of temperature change from baseline over the first two hours post dose. The planned secondary efficacy endpoints included time-specific temperature change from baseline at 0.5, 1, and 4 hours after the start of the initial dose, summation of temperature change up to 4 hours (AUC_{0-4}) and up to 24 hours (AUC_{0-24}), the first time to reach a temperature reduction to <100.4ºF (38ºC), and the percentage of patients with temperature reduced to <100.4ºF (38ºC) at Hour 4.

Plasma samples for ibuprofen concentration were to have been collected at the end of infusion and then at 0.5, 1, 2, and 4 hours from the start of the initial infusion with sparse sampling to be assigned for patients <6 months of age.

Safety monitoring was planned to consist of frequent vital signs (heart rate, respiratory rate, and blood pressure) at 0, 1, 2, 4, 8, 12, 16, 20, and 24 hours after the initial dose and then every six hours through PRN treatment or daily; routine laboratory tests (clinical chemistry, hematology, and coagulation) at baseline, on Days 1, 2, 3, and 5, and at the end of study; continuous monitoring of adverse events (AEs) until Hour 144.

Statistical Analysis

Population for analysis

The planned intent-to-treat (ITT) population was to have included all pediatric patients 6 months to 16 years of age (age was added to the revised Statistical Analysis Plan) who received at least one partial dose of the study medication.

Efficacy analysis

The planned primary efficacy parameter, AUC_{0-2} was to have been analyzed using an ANCOVA model or the non-parametric method of Wilcoxon rank-sum test if endpoint is not normally distributed.

Missing data management

Missing data were to have been imputed using linear interpolation of adjacent values. If adjacent values were not available then the missing temperature value would have been missing for analysis.

Sample size

A sample size of 200 patients was planned to ensure 184 in the ITT population to provide 80% power for a two-sided t-test, at the significance level $\alpha = 0.05$, to detect a difference of 0.5°C in AUC_{0-2} between the two treatment groups.

The reviewer's brief summary of the major components of the protocol is presented in the table below.

Table 5-2 Reviewer's Summary of the Protocol

Study #	CPI-CL-012
Title	A Multi-Center, Randomized, Open-Label, Parallel, Active-Comparator, Multiple-Dose Trial to Determine the Efficacy, Safety, and Pharmacokinetics of Intravenous Ibuprofen in Pediatric Patients

Objectives	To study single-dose PK and multiple-dose efficacy and safety of IV ibuprofen in pediatric patients from birth to 16 years old with the primary objective as to determine superiority of a single dose of IV ibuprofen 10 mg/kg compared to acetaminophen 10 mg/kg for fever reduction during the first two hours of treatment
Design	Multiple-dose, randomized, open-label, active-controlled, parallel group, multi-center
Sample population	Hospitalized or scheduled to be hospitalized pediatric patients between birth (28 weeks to < 40 weeks gestational age) and 16 years of age with new (within last 7 days) onset of fever, documented as temperature (by tympanic measurement) ≥101.0ºF (38.3ºC). (Note: Emergency-Room treated patients became eligible for enrollment in Protocol Amendment 3)
Treatment	• IV ibuprofen 10.0 mg/kg 10-minute infusion (not to exceed 400 mg per dose or 2400 mg per day for up to 30 doses) or • Acetaminophen 10.0 mg/kg oral solution or suppository (not to exceed 650 mg per dose or 3900 mg per day) q4 hours for the first 24 hours and then q4 hours as needed during the 120-hour treatment period (dosing regimen was changed to q4 hours PRN during the entire study in Protocol Amendment 3)
Rescue & concomitant medication	No other antipyretic medication allowed two hours prior to the initial dose and during the 120-hour treatment period. (Procedures intended to reduce temperature such as ice packs, cooling blankets, fans, etc. were added to the exclusion list in Protocol Amendment 3)
Efficacy data	Temperature (tympanic) every 15 minutes until Hour 2, every 30 minutes until Hour 4, every 2 hours until Hour 24 (0, 15, 30, 45, 60, 75, 90, and 105 minutes, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours), and then every 6 hours through PRN treatment
Efficacy parameter	***Primary:*** AUC_{0-2}, the area under the change in temperature versus time curve from baseline to 2 hours after the start of the initial dose ***Secondary:*** • Change in temperature from baseline to 30 minutes after the start of the initial dose • Change in temperature from baseline to 60 minutes after the start of the initial dose • Change in temperature from baseline to 4 hours after the start of the initial dose • AUC_{0-4}, the area under the change in temperature versus time curve from baseline to 4 hours • AUC_{0-24}, the area under the change in temperature versus time curve from baseline to 24 hours • The first time when the patient becomes afebrile (temperature <100.4ºF [38ºC]) • The percentage of patients who are afebrile (temperature <100.4ºF [38ºC]) at 4 hours
Safety monitoring	• Vital signs (heart rate, respiratory rate, blood pressure) at Hours 0, 1, 2, 4, 8, 12, 16, 20, 24 and then every 6 hours through PRN treatment or daily • Routine laboratory tests (clinical chemistry, hematology, and coagulation) at baseline and on Days 1, 2, 3, and 5 and end of study • Continuous monitoring of treatment-emergent AEs (until Hour 144)
PK sampling	Plasma samples immediately post-dose and at 0.5, 1, 2, and 4 hours (sparse sampling to be assigned for patients <6 months of age)

Protocol Amendments

Amendment 1 (Dated September 27, 2009 and submitted on October 13, 2009)
Replacement of dropouts was amended to include also dropout patients who have not completed PK portion of the study within the first four hours. Antipyretic exclusion was changed from four hours to two hours prior to dosing. Time schedule for safety laboratory tests was clarified to include only Days 1 and 5 and end of study sample collections. Other changes were minor clarifications and additions of some references.

Amendment 2 (Dated February 25, 2010 and submitted on March 22, 2010, review dated June 1, 2010)
Pregnancy and nursing were added as exclusion criteria and urine pregnancy test was included as part of the Screening/Baseline Period Assessments.

Amendment 3 (Dated October 21, 2011 and submitted on December 7, 2011)
Pregnancy testing was clarified to allow either urine or serum pregnancy testing. Dosage was changed to allow flexible dosing regimen based need instead of fixed every 4-hour dosing. Sample size for age groups was

modified to six patients per treatment per age group in the age range of 6 months to 16 years instead of six patients for the entire age group. Replacement of dropout was simplified to allow replacement of only of those randomized and not treated with study mediation. Antipyretic exclusion was reclassified as not only antipyretic medication but also other procedures intended to reduce temperature, including, but not limited to ice packs, cooling blankets, fans, etc. Requirement of hospitalization was removed from inclusion criteria to allow patients treated by Emergency Room to be included in the study. Time schedule for temperature measurement was revised to pre-dose, 0.5, 1, 2, and 4 hours after each PRN dose. Time schedule for vital signs was revised to be less frequent during the first 24 hours and to be around PRN dosing as at pre-dose and four hours after each PRN dose.

The changes in dosing schedule and data collection schedule contained in all the amendments are summarized below for clarification purpose.

Table 5-3 Summary of Changes in Dosage and Data Collection Schedule

	Original protocol	**Amendment 1**	**Amendment 3**
Dosage	Every 4 hours for 24 hours, then PRN until Hour 120		PRN not sooner than four hours
Temperature measurements	0, 15, 30, 45, 60, 75, 90, and 105 minutes, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours after initial dose, then every 6 hours through PRN treatment		0, 15, 30, 45, 60, 75, 90, and 105 minutes, 2, 2.5, 3, 3.5, 4, and 6 hours after initial dose, then pre-dose, 0.5, 1, 2, and 4 hours after each PRN dose
Safety monitoring			
Vital signs	0, 1, 2, 4, 8, 12, 16, 20, 24 hours after initial dose then every 6 hours through PRN treatment or daily		0, 1, 2, 4, 8, and 24 hours after initial dose, then pre-dose and 4 hours after each PRN dose
Lab tests	Days 1, 2, 3, and 5	Days 1 and 5 or end of study	

The Study enrolled the first patient in September 2010 and the Protocol Amendment 3 was submitted in December 2011. The major changes in dosing regimen and efficacy data collection schedule for multiple-dose evaluation while study was ongoing would make data analyses and interpretation unusually complicated.

Results

Demographic and other baseline characteristics

The study sample population consisted of 103 pediatric patients exposed to study medication, with an age range of one month to 15 years and a mean about six years. Of the 103 patients, 83% were Caucasian and 15% were African American by race, 52% were Hispanic by ethnic origin, and 47% were females. The treatment groups were approximately balanced (no important differences) with regard to demographic characteristics such as age, gender, race, ethnicity, and weight.

Mean baseline temperature was 39.0°C (102.2°F) for the IV ibuprofen group and 38.8°C (101.84°F) for the acetaminophen group, leading to a group mean difference of 0.2°C or 0.36°F between the two treatment groups though the difference was not statistically significant.

The patients in the study population were mostly hospitalized for serious medical conditions such as sepsis, bowl perforation, appendicitis with abscess formation, different types of pneumonia, meningitis, cellulitis, urinary tract infection, severe burn, trauma with bone fracture, toxic shock syndrome, sickle cell anemia, febrile seizure, etc. Some were admitted to pediatric intensive care unit (PICU). Some had multiple medical conditions and were on a number of concomitant medications.

Table 5-4 Demographics and Baseline Characteristics

Study 012 Demographics and Baseline Characteristics	IV Ibu (N=48)	APAP (N=55)	Total (N=103)
Age (years)			
Mean (SD)	6.9 (4.68)	5.4 (4.45)	6.1 (4.60)
Min, Max	0.1, 15.0	0.3, 15.0	0.1, 15.0
Gender, N (%)			
Male	28 (58%)	27 (49%)	55 (53%)
Female	20 (42%)	28 (51%)	48 (47%)
Race, N (%)			
White or Caucasian	42 (88%)	43 (78%)	85 (83%)
Black or African American	6 (13%)	9 (16%)	15 (15%)
Other*	0	3 (5%)	3 (3%)
Ethnicity, N (%)**			
Hispanic or Latino	29 (60%)	25 (45%)	54 (52%)
Not Hispanic or Latino	19 (40%)	30 (55%)	49 (48%)
Weight (kg)			
Mean (SD)	29.7 (19.64)	23.5 (15.25)	26.4 (17.61)
Median	23.1	19.9	22.3
Min, Max	4.8, 80.1	6.8, 63.0	4.8, 80.1
Baseline Temperature (^{o}C)			
Mean (SD)	39.0 (0.68)	38.8 (0.48)	38.9 (0.59)

Note: * Other includes 2 American Indian or Alaska Native and 1 Hispanic or Latino.
** Ethnicity was collected separately from race for study CPI-CL-012
Source: Table 1.11.4-1 on page 15 of submission dated August 6, 2015 in response to the reviewer's information request and Tables 11-2 and 11-3 on pages 48-50 of the study report for Study 012 submitted May 1, 2015.

There were three patients less than 6 months of age. Efficacy data from this youngest age group were not included due to small sample size. Efficacy analysis population consisted of 100 pediatric patients, including 20 pediatric patients in the age group of 6 months to <2 years, 27 in the age group of 2 years to <6 years, 34 in the age group of 6 years to <12 years, and 19 in the age group of 12 years to <18 years. Gender distribution was about even in most treatment-by-age subgroups with exceptions of less females than males in the age group of 6 months to <2 years treated with ibuprofen and more females than males in the age group of 6 years to <12 years treated with acetaminophen. The mean, median and range of body weight for each age group are summarized in the table below.

Table 5-5 Demographics and Baseline Characteristics by Age Group

Age group	< 0.5 years		0.5 to < 2 years		2 to < 6 years		6 to < 12 years		12 to < 18 years	
Treatment Group	**IV Ibu**	**APAP**	**IV Ibu**	**APAP**	**IV Ibu**	**APAP**	**IV Ibu**	**APAP**	**IV Ibu**	**APAP**
# Patients Exposed	1	2	6	14	13	14	15	19	13	6
Gender										
Male	1*	1*	5	8	7	8	8	7	7	3
Female	0	1*	1	6	6	6	7	12	6	3
Weight (kg)										
Mean (SD)	4.8	7.0 (0.21)	9.6 (2.03)	9.9 (1.52)	16.7 (4.76)	18.2 (8.46)	27.8 (8.49)	30.7 (9.70)	56.0 (14.57)	50.7 (13.48)
Median	4.8	7.0	9.3	10.2	16.0	15.7	26.1	30.0	52.2	55.0
Min, Max	4.8, 4.8	6.8, 7.1	7.3, 12.7	7.2, 12.0	11.3, 27.2	11.4, 42.2	16.3, 47.5	16.8, 55.5	38.9, 80.1	32.7, 63.0
Baseline Temperature (^{o}C)										
Mean (SD)	38.4	38.5 (0.08)	39.0 (0.49)	38.8 (0.54)	38.9 (0.79)	38.9 (0.37)	39.2 (0.72)	38.8 (0.56)	38.8 (0.59)	38.8 (0.42)

Note: For the age group of less than 6 months old the male patient in the IV ibuprofen group was 1-month old, the male patient in the acetaminophen group was 3-month old, and the female patient in the acetaminophen group was 5-month old.
Source: Table 1.11.4-2 on page 16 of submission dated August 6, 2015 in response to the reviewer's information request.

Patient disposition

Three quarters of 100 pediatric patients prematurely discontinued from the study. The dropout rates were similar between the treatments as shown in the table below. The reasons for dropouts were summarized in the table below. The most frequently reported cases in the IV ibuprofen group included fever no longer requiring treatment (n=9), discharge from hospital or ER (n=8), IV access inadequate or discontinued (n=5), withdrawn consent (n=3), and adverse event (n=3). The most frequent dropout cases in the acetaminophen group included discharge from hospital or ER (24 cases), fever no longer requiring treatment (five cases), and withdrawn consent (n=5).

Table 5-6 Patient Disposition, ITT

Study 012 **Patient Disposition**	**IV Ibu (N=47)** **N (%)**	**APAP (N=53)** **N (%)**	**Total (N=100)** **N (%)**
Completed study per protocol	12 (26%)	13 (25%)	25 (25%)
Prematurely discontinued study	35 (74%)	40 (75%)	75 (75%)
Reasons for withdrawal from study			
Fever no longer requiring treatment	9 (19%)	5 (9%)	14 (14%)
Discharge from hospital or ER	8 (17%)	24 (45%)	32 (32%)
IV access inadequate or discontinued	5 (11%)	0	5 (5%)
Withdrawn consent	3 (6%)	5 (9%)	8 (8%)
Adverse event	3 (6%)	1 (2%)	4 (4%)
Restricted medication violation	2 (4%)	0	2 (2%)
Treatment failure	1 (2%)	2 (4%)	3 (3%)
Other*	4 (9%)	3 (6%)	7 (7%)

Note: * Other includes 1 no research staff available, 1 no study staff available to continue overnight after initial dose, 1 patient could not tolerate study drug administration rectally secondary to severe abdominal pain, 1 patient going to surgery, 1 physician discretion (burn team), and 2 the study concluded on day 6.
Source: Table 1.11.4-3 on page 17 of submission dated August 6, 2015 in response to the reviewer's information request and Table 10-6 on page 46 of the study report for Study 012 submitted May 1, 2015.

Protocol violations

The proportion of patients with protocol deviations was about 70% and was similar in the two treatment groups. The most frequently reported deviations were related to safety data collection such as missing, incomplete, or miss-timed laboratory tests or vital signs, accounting for 58 of 85 (68%) counts in the IV ibuprofen group and 62 of 93 (67%) counts in the acetaminophen group. The less frequently reported deviations (<10 counts per treatment group in each category) were related to PK data sampling, timing and site of temperature measurements, dosing error (dose missing, incorrect amount, or miss-timed), as listed in the table below. The relatively low occurrence of these deviations was less likely to have a major impact on efficacy outcomes.

Table 5-7 Summary of Protocol Deviations/Violations, ITT

Study 012 **Protocol Deviations/Violations**	**IV Ibu** **(N=47)**	**APAP** **(N=53)**	**Overall** **(N=100)**
No. of Patients with ≥ 1 Deviation/Violation, N (%)	32 (68%)	39 (74%)	71 (71%)
Counts of Specific Deviation/Violation			
Missing or Incomplete Lab Tests	34	41	75
Missing or Incomplete Vital Signs	14	8	22
Miss-Timed Vital Signs	8	9	17
Missing or Miss-Timed PK Sampling	7	0	7
Incorrect Site of Temperature Measurement	6	4	10
Dose Missing or Incorrect Amount	5	9	14
Missing or miss-timed Temperature Measurement	3	6	9
Timing of Lab Sample Collection	2	4	6

Eligibility Criteria	2	3	5
Dosing Time Error	1	8	9
Taking Restricted Medication	1	1	2
Missing AE Assessment or Follow-Up	1	0	1
Other*	1	0	1
Total Counts	85	93	178

Note: Other refers to a case missing Day 6 follow-up.
Source: Table 1.11.4-4 on page 18 of submission dated August 6, 2015 in response to the reviewer's information request.

Exposure

The exposure information is summarized in the table below. About 50% of the IV ibuprofen group had cumulative exposure to at least four doses or had at least two days of exposure. Less than 50% of the acetaminophen group had cumulative exposure to at least two doses or had at least two days of exposure. More patients in the IV ibuprofen group received exactly two or exactly five doses in comparison to the acetaminophen group to make the cumulative exposure appear different in the range of ≥2 to ≥5 doses. The number of days of cumulative exposure was similar between the treatment groups.

Table 5-8 Exposure

Study 012 Exposure	**IV Ibu** (N=47)	**APAP** (N=53)	**Total** (N=100)		**IV Ibu** (N=47)	**APAP** (N=53)	**Total** (N=100)
Number of Doses				**Cumulative exposure**			
1 Dose	14 (30%)	28 (53%)	42 (42%)	**≥ 1 Dose**	47 (100%)	53 (100%)	100 (100%)
2 Doses	8 (17%)	3 (6%)	11 (11%)	**≥ 2 Doses**	33 (70%)	25 (47%)	58 (58%)
3 Doses	1 (2%)	2 (4%)	3 (3%)	**≥ 3 Doses**	25 (53%)	22 (42%)	47 (47%)
4 Doses	1 (2%)	1 (2%)	2 (2%)	**≥ 4 Doses**	24 (51%)	20 (38%)	44 (44%)
5 Doses	6 (13%)	1 (2%)	7 (7%)	**≥ 5 Doses**	23 (49%)	19 (36%)	42 (42%)
6 Doses	11 (23%)	9 (17%)	20 (20%)	**≥ 6 Doses**	17 (36%)	18 (34%)	35 (35%)
> 6 Doses	6 (13%)	9 (17%)	15 (15%)	**> 6 Doses**	6 (13%)	9 (17%)	15 (15%)
Number of Days							
1 Day	23 (49%)	30 (57%)	53 (53%)	**≥ 1 Day**	47 (100%)	53 (100%)	100 (100%)
2 Days	17 (36%)	17 (32%)	34 (34%)	**≥ 2 Days**	24 (51%)	23 (43%)	47 (47%)
3 Days	5 (11%)	2 (4%)	7 (7%)	**≥ 3 Days**	7 (15%)	6 (11%)	13 (13%)
4 Days	0	2 (4%)	2 (2%)	**≥ 4 Days**	2 (4%)	4 (8%)	6 (6%)
5 Days	0	2 (4%)	2 (2%)	**≥ 5 Days**	2 (4%)	2 (4%)	4 (4%)
> 5 Days	2 (4%)	0	2 (2%)	**> 5 Days**	2 (4%)	0	2 (2%)

Source: Table 1.11.4-5 on page 19 of submission dated August 6, 2015 in response to the reviewer's information request and Table 10-6 on page 46 of the report for Study 012 submitted May 1, 2015.

Efficacy results

Primary efficacy endpoint

Summed temperature reduction over the first two hours, AUC_{0-2}

The results of the analyses of AUC_{0-2} (the area under the curve of temperature change from baseline over the first two hours post-dose) are summarized in the table below. Mean AUC_{0-2} was 1.5 for the IV ibuprofen group and 0.9 for the acetaminophen group. The treatment difference of 0.6 in AUC_{0-2} was statistically significant.

Table 5-9 Temperature Reduction AUC_{0-2} by Treatment Group, ITT

Study 012 Primary endpoint	**IV Ibu** (N=47)	**APAP** (N=53)
N	46	50
AUC_{0-2} for T↓		

Mean (SD)	-1.5 (1.11)	-0.9 (0.89)
LS Means (SE)1	-1.5 (0.15)	-0.9 (0.14)
Median	-1.4	-0.9
Min, Max	-4.4, 0.1	-3.0, 0.7
Ibu>APAP	-0.6	
p-value	0.012	

Source: Table 1.11.3.1-1 on page 2 of submission dated September 3, 2015 in response to the reviewer's information request and Table 11-6 on pages 53 of the report for Study 012 submitted May 1, 2015.

Secondary efficacy endpoints

Time-specific response during the 24-hour treatment period in ITT population

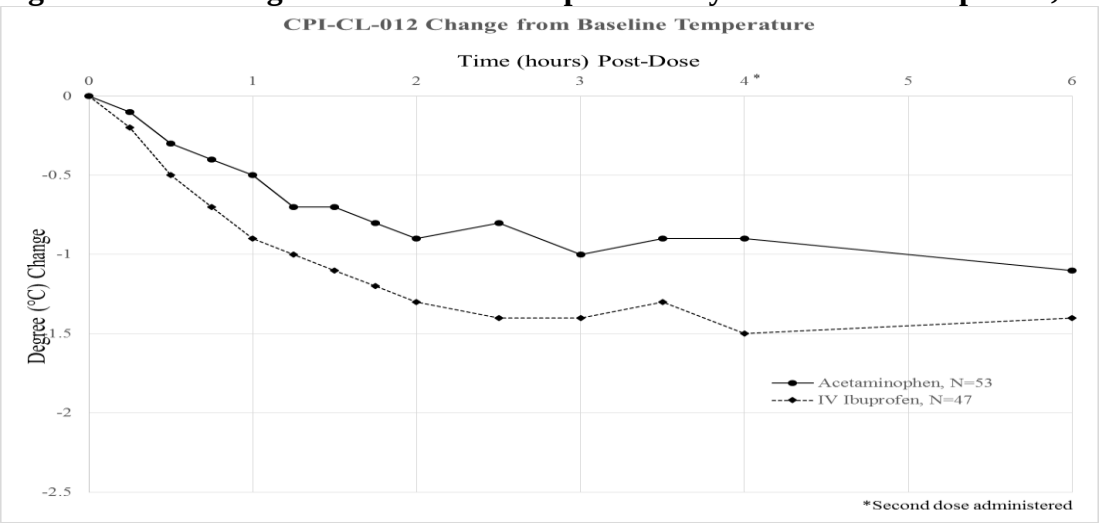
The mean temperatures and mean change of temperature from baseline over 24 hours for the ITT population are summarized in the table below. During the first dosing interval of four hours and up to Hour 6 the mean temperature reduction ranged from 0.5 to 1.5°C for the IV ibuprofen group and from 0.3 to 1.1°C for the acetaminophen group. The treatment differences were 0.2 to 0.6°C more temperature reduction in the IV ibuprofen group than that of the acetaminophen group, 0.3 to 0.4°C at most measurement time points and reached 0.6°C at Hours 2.5 and 4. The lack of data after Hour 6 could be partially attributable to the change of data collection schedule from fixed interval to around PRN dosing. Because of lack of data after Hour 6 the temperature curves in the figure below covered only for six hours.

Table 5-10 Time-Specific Temperature (°C) Reduction, ITT

Hour	0	0.25	0.5	0.75	1	1.25	1.5	1.75	2	2.5	3	3.5	4	6	8	12	18	24
IV Ibu																		
T mean	39.0	38.8	38.5	38.3	38.1	38.0	37.8	37.7	37.7	37.6	37.5	37.6	37.5	37.6	38.1	39.3	—	36.9
T SD	0.68	0.72	0.69	0.64	0.61	0.60	0.51	0.49	0.48	0.49	0.54	0.61	0.69	0.76	0.51	—	—	—
N	47	45	45	43	45	47	44	45	46	44	43	42	43	14	2	1	0	1
TΔ mean		-0.2	-0.5	-0.7	-0.9	-1.0	-1.1	-1.2	-1.3	-1.4	-1.4	-1.3	-1.5	-1.4	-1.4	0.3	—	-1.7
TΔ SD		0.41	0.50	0.64	0.69	0.72	0.76	0.82	0.76	0.80	0.84	0.75	0.92	0.86	0.40	—	—	—
APAP																		
T mean	38.8	38.7	38.5	38.4	38.3	38.1	38.1	38.1	38.0	38.0	37.8	37.9	37.9	37.7	—	—	38.1	37.6
T SD	0.48	0.63	0.73	0.72	0.70	0.79	0.76	0.73	0.77	0.75	0.79	0.88	0.92	0.97	—	—	—	1.06
N	53	51	53	52	53	52	50	51	51	41	42	40	37	15	0	0	1	2
TΔ mean		-0.1	-0.3	-0.4	-0.5	-0.7	-0.7	-0.8	-0.9	-0.8	-1.0	-0.9	-0.9	-1.1	—	—	-0.4	-1.1
TΔ SD		0.35	0.49	0.54	0.50	0.64	0.63	0.66	0.72	0.68	0.69	0.79	0.92	0.93	—	—	—	0.92
Ibu>APAP		-0.1	-0.2	-0.3	-0.4	-0.3	-0.4	-0.4	-0.4	-0.6	-0.4	-0.4	-0.6	-0.3	—	—	—	—

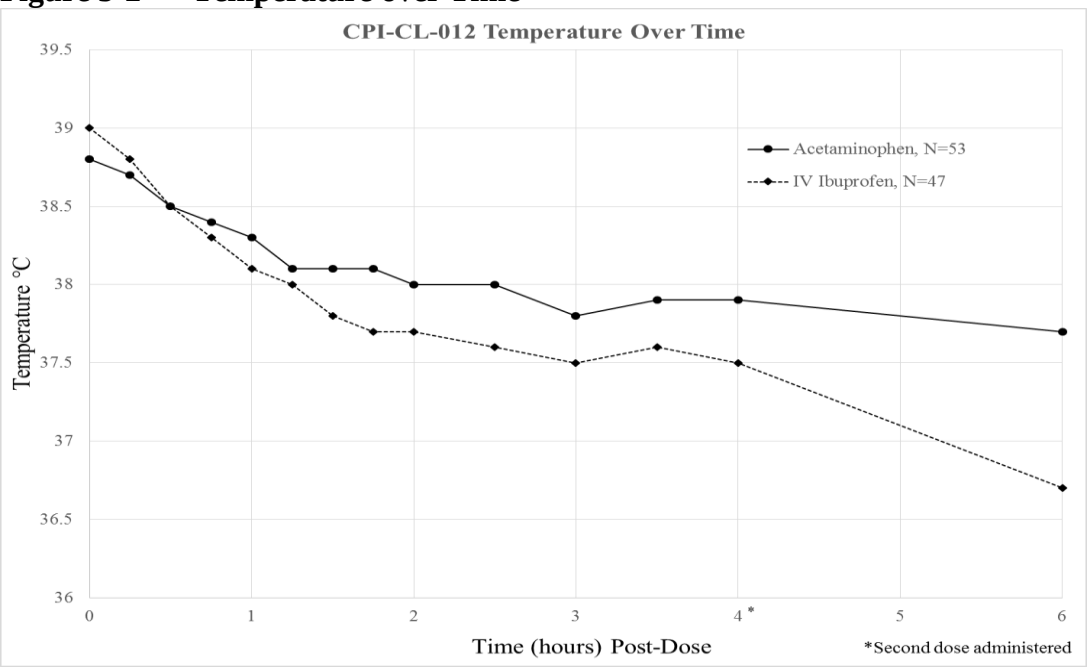
Source: Table 1.11.4-6 on page 20 of submission dated August 6, 2015 in response to the reviewer's information request and Table 11-8 on pages 55-56 of the report for Study 012 submitted May 1, 2015.

Figure 5-1 Change from Baseline Temperature by Treatment Group: ITT, CPI-CL-012



Source: Figure 11-2 on page 57 of the report for Study 012 in submission dated May 1, 2015.

Figure 5-2 Temperature over Time



Source: Figure 11-1 on page 57 of the report for Study 012 in submission dated May 1, 2015.

Secondary efficacy endpoints:

Summed temperature reduction over time AUC_{0-4} and AUC_{0-24}

The results of analyses for AUC_{0-4} and AUC_{0-24} are summarized in the table below. The treatment difference was 1.8 for AUC_{0-4} and 7.6 for AUC_{0-24}.

Table 5-11 Temperature Reduction AUC0-4 and AUC0-24 by Treatment Group, ITT

Study 012 Summed T reduction	**IV Ibu (N=47)**	**APAP (N=53)**
N	44	42
T↓AUC_{0-4}		
Mean (SD)	-4.4 (2.59)	-2.6 (2.02)
LS Means (SE)	-4.4 (0.35)	-2.6 (0.36)
Median	-4.4	-2.7
Min, Max	-12.0, 0.6	-7.4, 1.3

Ibu>APAP	-1.8	
p-value	<0.001	
N	29	24
T↓AUC$_{0-24}$		
Mean (SD)	-34.2 (17.97)	-26.6 (14.29)
LS Means (SE)	-34.2 (3.05)	-26.6 (3.35)
Median	-36.9	-25.0
Min, Max	-72.9, 1.3	-66.1, 1.7
Ibu>APAP	-7.6	
p-value	0.061	

Source: Table 1.11.3.1-2 on page 2 of submission dated September 3, 2015 in response to the reviewer's information request and Table 11-7 on pages 57 of the report for Study 012 submitted May 1, 2015.

Secondary and additional efficacy endpoints

Proportion becoming afebrile and time to reach afebrile status

The temperature define afebrile status was <38ºC (<100.4ºF) as proposed in the original protocol. The reviewer has requested similar data using <37.5ºC (<99.5 ºF) as a cut point. Median time to temperature reduction to <37.5ºC was 2.6 hours for the IV ibuprofen group and 3 hours for the acetaminophen group. The relative proportion of patients reaching temperature reduction to <37.5ºC (99.5 ºF) was 74% versus 57% by 4 hours (the end of the first dosing interval) and 91% versus 75% by 24 hours for the IV ibuprofen treatment in comparison to APAP. Treatment differences were 0.4 hours earlier to reach afebrile status and 16-17% more patients becoming afebrile in the IV ibuprofen group during the first dosing interval and by 24 hours. The effect sizes of such treatment differences are considered clinically meaningful.

Table 5-12 Temperature Reduction to <38ºC and to <37.5ºC, ITT

Study 012 **Temperature Reduction to <38ºC and <37.5ºC**	**IV Ibu (N=47)**	**APAP (N=53)**	**IV Ibu>APAP**
Number (%) with T↓ to <38ºC by end 1st dosing interval (4 hours)	43 (91%)	40 (75%)	16%
Number (%) with T↓ to <38ºC by 24 hours	45 (96%)	47 (89%)	7%
Number (%) with T↓ to <37.5ºC by end 1st dosing interval (4 hours)	**35 (74%)**	**30 (57%)**	**17%**
Number (%) with T↓ to <37.5ºC by 24 hours	**43 (91%)**	**40 (75%)**	**16%**
Median time in hours (CI) to T<38ºC	1.3 (1.0, 1.5)	1.5 (1.1, 1.5)	-0.2
Median time (hour) to T<37.5ºC	**2.6 (2.1, 3.5)**	**3.0 (2.1, NA)**	**-0.4**

Source: Table 1.11.4-7 on page 23 of submission dated August 6, 2015 in response to the reviewer's information request and Tables 11-10 and 11-11 on pages 59 of the report for Study 012 submitted May 1, 2015.

Additional efficacy endpoints

Time to remedication

The proportion of patients receiving repeated doses was 70% in the IV ibuprofen group versus 47% in the acetaminophen group. The effect size of treatment difference was 23% in favor of the low dose acetaminophen. Because the dosing regimen was changed while the study was ongoing, patients enrolled earlier were on a fixed dosing interval of every four hours and those enrolled later were on PRN dosing. Median time to remedication (time to the second dose) in the ITT population was no longer a valid measure of single-dose duration.

Data received as a response to the reviewer's information request revealed that 22 of 47 (47%) in the IV ibuprofen group and 20 of 53 (38%) in the acetaminophen group were on a fixed every 4-hour dosing regimen and the rest were on PRN dosing. Of the subpopulation that actually had a PRN dosing regimen, the mean and median time intervals between the adjacent doses were longer than six hours for the IV ibuprofen group.

Table 5-13 Time Interval between Adjacent Doses, Subpopulation on PRN Dosing

Study 012	IV Ibu (N=47)	APAP (N=53)	Dosing interval (hours)	IV Ibu			APAP		
				Mean	Median	Range	Mean	Median	Range
Received q4h dosing (original protocol)	N=22 47%	N=20 38%							
Received PRN dosing (Protocol Amendment 3)	N=25 53%	N=33 62%	Time to 2nd dose for entire subpopulation on PRN dosing	9.7	9.3		16.1	NE	
≥ 2 Doses	N=12	N=6	1st to 2nd dose	7.1	6.6	4.1-12.7	9.2	8.8	2.1-18.6
≥ 3 Doses	N=5	N=3	2nd to 3rd dose	8.2	7.4	4.2-12.4	12.3	9.6	7.3-20.0
≥ 4 Doses	N=4	N=1	3rd to 4th dose	9.0	9.3	6.0-11.4	6.4	6.4	6.4-6.4
≥ 5 Doses	N=4	N=1	4th to 5th dose	9.1	9.6	7.3-10.0	4.6	4.6	4.6-4.6
≥ 6 Doses	N=1	N=1	5th to 6th dose	7.9	7.9	7.9-7.9	4.4	4.4	4.4-4.4
> 6 Doses	N=1	N=1	6th to 7th dose	20.4	20.4	20.4-20.4	11.5	11.5	11.5-11.5

Source: Table 1.11.3-1 on page 1 of submission dated November 9, 2015 in response to the reviewer's information request.

Summary of Findings and Discussion

Study conduct

The two treatment groups IV ibuprofen and acetaminophen in Study 012 were approximately balanced (no important differences) with regard to demographic characteristics such as age, gender, race, ethnicity, and weight. In comparison of baseline temperature between the treatments there was a group mean difference of 0.2°C (0.36°F) higher in the IV ibuprofen group (39.0°C versus 38.8°C) than the acetaminophen group though the difference was not statistically significant.

About one quarter of patients completed the study as planned and dropout rates were about the same in the two treatment groups. The most frequently reported reasons for dropouts were 'fever no longer requiring treatment' and 'discharge from hospital or ER' in both treatment groups.

The rate of protocol deviation was about 70% and similar in the two treatment groups. Two thirds of reported deviations were related to safety data collection such as missing, incomplete, or miss-timed laboratory tests or vital signs in both treatment groups. Dosing error (dose missing, incorrect amount, or miss-timed) and missing or miss-timed temperature measurement were less frequently reported deviations and thus, not considered as having a major impact on efficacy outcomes.

A total of 51% of patients had a cumulative exposure to at least four doses or at least two days in the IV ibuprofen group. In the acetaminophen group 47% had a cumulative exposure to at least two doses and 43% had at least two days of exposure. Temperature data were mostly collected during the first six hours after the initial dose. After Hours 6 only one or two patients had temperature measurements reported at the scheduled time points. Multiple-dose efficacy was not evaluable due to lack of data.

Efficacy analyses and interpretation of results are complicated by the major changes in dosing regimen from a fixed dosing to PRN dosing and corresponding efficacy data collection schedule before the study was completed.

Efficacy

The magnitude of temperature reduction was 0.5 to 1.5°C for the IV ibuprofen group and 0.3 to 1.1°C for the acetaminophen group in the time interval of 0.5 to 6 hours after the initial dose. The majority of patients (74% of the IV ibuprofen group and 57% of the acetaminophen group) had temperature returned to the normal range of <37.5ºC (99.5 ºF) during the first dosing interval. Normalization of temperature occurred in most patients (91% of the IV ibuprofen group and 75% of the acetaminophen group) within 24 hours. Median time to reach

afebrile status was 2.6 hours for the IV ibuprofen group and 3 hours for the acetaminophen group. The proportion receiving repeated dose was 70% in the IV ibuprofen group versus 47% in the acetaminophen group.

Because of the lack of placebo control it is difficult to determine how long patients would need to receive repeated doses to maintain an afebrile status. In adult fever studies the proportion of placebo patients with temperature normalized in four hours was about 4% in Study 004 and about 35% in Study 006 (refer to the Clinical Review of the original NDA for detail).

In comparison to the low dose acetaminophen at 10 mg/kg, a statistically significant treatment difference of 0.6 in AUC_{0-2} was shown in favor of IV ibuprofen. Other treatment differences in favor of the IV ibuprofen group included 0.2 to 0.6°C more temperature reduction in the first dosing interval of 4 hours, 0.4 hours shorter median time to reach a temperature reduction to <37.5ºC, and 17% more becoming afebrile by the end of the first dosing interval. Treatment difference in favor of the lower dose acetaminophen group was shown in 23% less receiving repeated doses.

Dosing interval
Single-dose and multiple-dose duration are the parameters used in general to define dosing interval. Multiple-dose duration was not assessable due to of lack of efficacy measurements after Hours 6. The single-dose duration measured by median time to the second dose (and/or rescue) in the ITT population would provide a more accurate estimate if patients were all on PRN dosing from the beginning of the study. Because there were no patients receiving rescue and only a subpopulation was on PRN dosing, data from Study 012 were not sufficient even for determination of single-dose duration.

Conclusion

Ibuprofen 10 mg per kg was able to provide clinically meaningful temperature reduction and normalization in treating fever in hospitalized pediatric patients based on data demonstrating response to the initial dose of 10-minute infusion. Single-dose duration and multiple-dose effects were not assessable due to limitations in study design, conduct, and data collection.

Appendix

Eligibility Criteria for Study 012

Inclusion Criteria
To be considered eligible to participate in this study, a patient must have been meeting the following inclusion criteria:

1. Had written informed consent provided by legal parent, guardian, or authorized agent prior to participation in the study or study-only related procedures.
2. Was between birth (28 weeks to < 40 weeks gestational age) to ≤ 16 years of age.
3. Was hospitalized or have an admission scheduled and will soon become hospitalized.
4. Had new (not chronic, within last 7 days) onset of fever, documented by temperature greater than or equal to 101.0ºF (38.3ºC). (Temperature measurements will be performed utilizing the tympanic route).

Exclusion Criteria
To be eligible for entry into the study, the patient must not have been meeting any of the following exclusion criteria:

1. Had inadequate intravenous access
2. Had received antipyretic drug therapy within 2 hours before dosing
3. Had any history of allergy or hypersensitivity to NSAIDs or aspirin.
4. Had received another investigational drug within the past 30 days

5. Was otherwise unsuitable for the study, in the opinion of the Investigator
6. Had a fever due to hyperthermia

APPEARS THIS WAY ON ORIGINAL

5.3.2 Fever Study 005

Protocol

Study CPI-CL-005 was planned as a phase 2 exploratory study of IV ibuprofen 10mg/kg in comparison to acetaminophen 15 mg/kg dose in treating fever in hospitalized pediatric patients to be conducted at both domestic and foreign study sites.

The major components of the protocol are summarized briefly in the table below:

Table 5-14 Reviewer's Summary of the Protocol

Study #	CPI-CL-005
Title	A Single-Center, Randomized, Parallel, Open-Label, Active-Controlled Efficacy and Safety Study of Ibuprofen Injection in Hospitalized Febrile Pediatric Patients
Objectives	To study antipyretic effect of and tolerance to ibuprofen IV infusion in comparison to acetaminophen in pediatric population 6 months to 12 years of age
Design	Multiple-dose, randomized, open-label, parallel, active-controlled, single-center (changed to multi-center in Amendment 1)
Sample population	Hospitalized pediatric patients aged 6 months to 17 years with new (within last 7 days) onset of fever, documented by temperature >101.0ºF (38.3ºC) measured at 2 separate occasions at least 1 hour apart within 12 hours prior to study drug administration
Treatment	• Ibuprofen 10.0 mg/kg IV infusion over 30 minutes or • Acetaminophen 15.0 mg/kg oral (suppository was added in Amendment 3) (not to exceed 1000 mg per dose or 4000 mg per day) Q6 hours for 24 hours
Rescue & concomitant medication	No antipyretic medications such as aspirin, NSAIDs, and APAP within 4 hours before the initial dose; No aspirin and NSAIDs any time during the study; cooling procedures such as cold packs, cooling blankets, and alcohol baths and APAP available only as rescue for cases of treatment failures (see definition in the list of secondary endpoints below)
Efficacy data	Core temperature (consistent measurement route for each individual) at 0, 0.5, 1, 2, 3, 4, 6, 9, 12, 15, 18, 21, 24, 48, and 72 hours (after the oral dose or after the beginning of IV infusion)
Efficacy parameter	***Primary:*** AUC_{0-6}, the area under the temperature versus time curve over 6 hours post dose as compared to a target temperature of 98.6ºF (37.0ºC) ***Secondary:*** • AUC_{0-24} as compared to a target temperature of 98.6ºF (37.0ºC) • Number and % of treatment failures defined as T>104.0ºF (40.0ºC) by two consecutive measurements after at least 2 hours post dose
Safety monitoring	• Vital signs (heart rate, respiratory rate, blood pressure) at Hours 0, 2, 4, 6, 9, 12, 18, and 24 hours • Routine laboratory tests (clinical chemistry, hematology, and coagulation) at baseline and at 24, 48, and 72 hours • Continuous monitoring of treatment-emergent AEs (until Hour 72)

Table 5-15 Reviewer's Summary of the Protocol Amendments

Amendment	Date	
1	1-18-05	Change from single-center to multiple-center study; Add tympanic temperature measurement
2	2-2-05	Clarification on study period of 72 hours (last 48 hours of which as post treatment) and randomization statements
3	4-18-05	Addition of rectal route (suppository) of drug administration for APAP
4	7-29-05	Change method for calculation of creatinine clearance
5	1-20-06	Allow antipyretic medication up until 4 hours (instead of 8 hour) before the start of initial dose.
6	7-21-06	Age range of study subjects lowered to 1 month (instead of 6 months); 48-hour safety lab tests eliminated; Clarification of a couple of exclusion criteria

Results

Demographic and other baseline characteristics

The study sample population consisted of 30 pediatric patients exposed to study medication, with an age range of six months to 17 years and a mean about six years. Of the 30 patients, 50% were Hispanic (classified under race with no classification based on ethnic origin), 30% were Caucasian and 50% were females.

Mean baseline temperature was 39.0°C (102.2°F) for the ibuprofen group and 38.6°C (101.48°F) for the acetaminophen group, leading to a difference of 0.4°C or 0.72°F between the two treatment groups.

Table 5-16 Demographics and Baseline Characteristics

Study 005 Demographics and Baseline Characteristics	IV Ibu (N=14)	APAP (N=16)	Total (N=30)
Age (years)			
Mean (SD)	6.1 (3.28)	6.2 (4.10)	6.2 (3.68)
Min, Max	2.0, 13.0	0.5, 17.0	0.5, 17.0
Gender, N (%)			
Male	8 (57%)	7 (44%)	15 (50%)
Female	6 (43%)	9 (56%)	15 (50%)
Race, N (%)			
Hispanic	6 (43%)	9 (56%)	15 (50%)
White or Caucasian	5 (36%)	4 (25%)	9 (30%)
Black or African American	0	1 (6%)	1 (3%)
Asian	0	2 (13%)	2 (7%)
Other*	3 (21%)	0	3 (10%)
Weight (kg)			
Mean (SD)	26.0 (12.90)	24.0 (13.82)	25.0 (13.21)
Median	23.7	20.1	22.0
Min, Max	12.3, 60.0	7.7, 58.0	7.7, 60.0
Baseline Temperature (^{o}C)			
Mean (SD)	39.0 (0.80)	38.6 (0.49)	38.8 (0.67)

Note: * Other includes 2 American Indian or Alaska Native and 1 Hispanic or Latino.
Source: Table 1.11.4-8 on page 24 of submission dated August 6, 2015 in response to the reviewer's information request.

Most patients (27 of 30) were in the range of 2 to <12 years of age, 14 in the age group of 2 years to <6 years, 13 in the age group of 6 years to <12 years. There was only one patient in the age group of 6 months to <2 years and two patients in the age group of 12 years to <18 years. Gender distribution was about even in most treatment-by-age subgroups with an exception of more females than males in the age group of 6 to <12 years treated with acetaminophen. The mean, median and range of body weight for each age group are summarized in the table below.

Table 5-17 Demographics and Baseline Characteristics by Age Group

Age group	0.5 to < 2 years		2 to < 6 years		6 to < 12 years		12 to < 18 years	
Treatment Group	**IV Ibu**	**APAP**	**IV Ibu**	**APAP**	**IV Ibu**	**APAP**	**IV Ibu**	**APAP**
# Patients Exposed	0	1	6	8	7	6	1	1
Gender								
Male	0	0	3 (50%)	5 (63%)	4 (57%)	1 (17%)	1 (100%)	1 (100%)
Female	0	1 (100%)	3 (50%)	3 (38%)	3 (43%)	5 (83%)	0	0
Weight (kg)								
Mean (SD)	0	7.7	17.0 (4.50)	16.5 (4.87)	28.9 (7.75)	31.0 (10.38)	60.0	58.0
Median	0	7.7	15.9	16.5	26.0	27.8	60.0	58.0
Min, Max	0	7.7, 7.7	12.3, 24.0	9.7, 25.0	18.0, 38.5	20.1, 48.0	60.0, 60.0	58.0, 58.0

Baseline Temperature (^{o}C)								
Mean (SD)	0	38.4	38.9 (1.05)	38.8 (0.38)	39.2 (0.61)	38.5 (0.67)	38.5	38.7

Source: Table 1.11.4-9 on page 25 of submission dated August 6, 2015 in response to the reviewer's information request.

Patient disposition

Most (27 of 30 or 90%) patients received the required 4-dose treatment and completed the study. Only three dropped out for the reason of withdrawal of consent as shown in the table below.

Table 5-18 Patient Disposition, ITT

Study 005 Patient Disposition	**IV Ibu (N=14) N (%)**	**APAP (N=16) N (%)**	**Total (N=30) N (%)**
Completed study per protocol	12 (86%)	15 (94%)	27 (90%)
Prematurely discontinued study	2 (14%)	1 (6%)	3 (10%)
Reasons for withdrawal from study			
Withdrawn consent	2 (14%)	1 (6%)	3 (10%)

Source: Table 1.11.4-10 on page 26 of submission dated August 6, 2015 in response to the reviewer's information request.

Protocol violations

Protocol deviations included six counts reported in four ibuprofen treated patients versus 26 counts reported in 11 acetaminophen treated patients as shown in the table below. In terms of specific types of protocol deviations there were only one or two counts per specific deviation in the IV ibuprofen group. In the acetaminophen group the types of protocol deviation that had ≥3 counts in a specific category included missing or incomplete lab tests (n=5), dosing time error (n=4), miss-timed temperature measurement (n=4), and miss-timed vital signs (n=3). The miss-timed dosing and temperature measurements of four counts each were unlikely to have a major impact on efficacy outcomes.

Table 5-19 Summary of Protocol Deviations/Violations, ITT

Study 005 Protocol Deviations/Violations	**IV Ibu (N=14)**	**APAP (N=16)**	**Overall (N=30)**
No. of Patients with ≥ 1 Deviation/Violation, N (%)	4 (29%)	11 (69%)	15 (50%)
Counts of Specific Deviation/Violation			
Eligibility criteria	1	2	3
Dose missing or incorrect amount	1	0	1
Dosing time error	1	4	5
Missing temperature measurement	0	2	2
Miss-timed temperature measurement	0	4	4
Taking restricted medication	0	2	2
Missing or incomplete lab tests	0	5	5
Timing of lab sample collection	1	1	2
Missing or incomplete vital signs	0	2	2
Miss-timed vital signs	2	3	5
Other	0	1	1
Total Counts	6	26	32

Source: Table 1.11.4-11 on page 27 of submission dated August 6, 2015 in response to the reviewer's information request.

Exposure

The exposure information is summarized in the table below. Most patients including 11 of 14 (79%) in the IV ibuprofen group and 15 of 16 (94%) in the acetaminophen group, had exposure to exactly four doses or had one day treatment.

Table 5-20 Exposure

Study 005 Exposure	IV Ibu (N=14)	APAP (N=16)	Total (N=30)
#Doses			
≤1 Dose	2 (14%)	1 (6%)	3 (10%)
4 Doses	11 (79%)	15 (94%)	26 (87%)
6 Doses	1 (14%)	0	1 (3%)

Source: Table 1.11.4-12 on page 28 of submission dated August 6, 2015 in response to the reviewer's information request.

Efficacy results

Primary efficacy endpoint

Summed temperature reduction over the first six hours, AUC_{0-6}

The results of the analyses of AUC_{0-6} (the area under the curve of temperature change from baseline over the first six hours post-dose) are summarized in the table below. Mean AUC_{0-6} was 2.0 over 6 hours for the IV ibuprofen group and 1.1 for the acetaminophen group.

Table 5-21 Temperature Reduction AUC_{0-6} by Treatment Group, ITT

Study 005 Primary endpoint	IV Ibu (N=14)	APAP (N=15)
N	13	15
AUC_{0-6} for T↓		
Mean (SD)	-2.0 (1.19)	-1.1 (1.26)
LS Means (SE)1	-2.0 (0.34)	-1.1 (0.32)
Median	-1.9	-1.3
Min, Max	-4.0, -0.2	-3.1, 1.6
Ibu>APAP	-0.83	
p-value	0.087	

Source: Table 1.11.3.1-2 on page 2 of submission dated September 3, 2015 in response to the reviewer's information request.

Secondary efficacy endpoint

Number and % of treatment failures defined as T>104.0ºF (40.0ºC) by two consecutive measurements after at least 2 hours post dose

No cases of treatment failure were identified.

Secondary and other efficacy endpoints:

Summed temperature reduction over time AUC_{0-4} (based on post-hoc analysis) and AUC_{0-24} (pre-defined secondary endpoint)

The results of analyses for AUC_{0-4} and AUC_{0-24} are summarized in the table below.

Table 5-22 Temperature Reduction AUC_{0-4} and AUC_{0-24} by Treatment Group, ITT

Study 005 Summed T reduction	IV Ibu (N=14)	APAP (N=153)
N	13	15
T↓AUC_{0-4}		
Mean (SD)	-5.2 (1.79)	-3.6 (3.45)
LS Means (SE)	-5.2 (0.78)	-3.6 (0.73)
Median	-5.3	-3.8
Min, Max	-8.5, -1.8	-9.0, 4.3
Ibu>APAP	-1.57	

p-value	0.123	
N	12	15
T↓AUC$_{0-24}$		
Mean (SD)	-41.3 (16.14)	-39.1 (23.95)
LS Means (SE)	-41.3 (6.03)	-39.1 (5.39)
Median	-37.6	-40.2
Min, Max	-79.4, -18.2	-81.1, 8.9
Ibu>APAP	-2.21	
p-value	0.922	

Source: Table 14.2.1.1.1 on pages 141-142 and Table 14.2.1.1.2 on pages 144-145, 147-148, and 150-151 of the report for Study 012 in submission dated March 20, 2015.

Additional efficacy endpoints (based on post-hoc analyses)

Time-specific response during the 24-hour treatment period in ITT population

The mean temperature and mean change of temperature from baseline over 24 hours, based on post-hoc analyses, are summarized in the table below and illustrated as 6-hour and 24-hour temperature curves in the figures below. Mean temperature reduction ranged from 0.6 to 1.7°C for the IV ibuprofen group and from 0.3 to 1.4°C for the acetaminophen group during the first dosing interval of 6 hours.

As shown in the Figure 5-3 the temperature curve for the IV ibuprofen group went down to 37.5°C at Hours 2 and 3 and came back to ≥38°C at Hours 4 and 6. This could be due either to variation in a very small sample where mean could be influenced by outliers, or it could suggest a need for redosing sooner than 6 hours. The temperature curve for the acetaminophen treatment stayed below 37.5°C from Hour 3 and beyond.

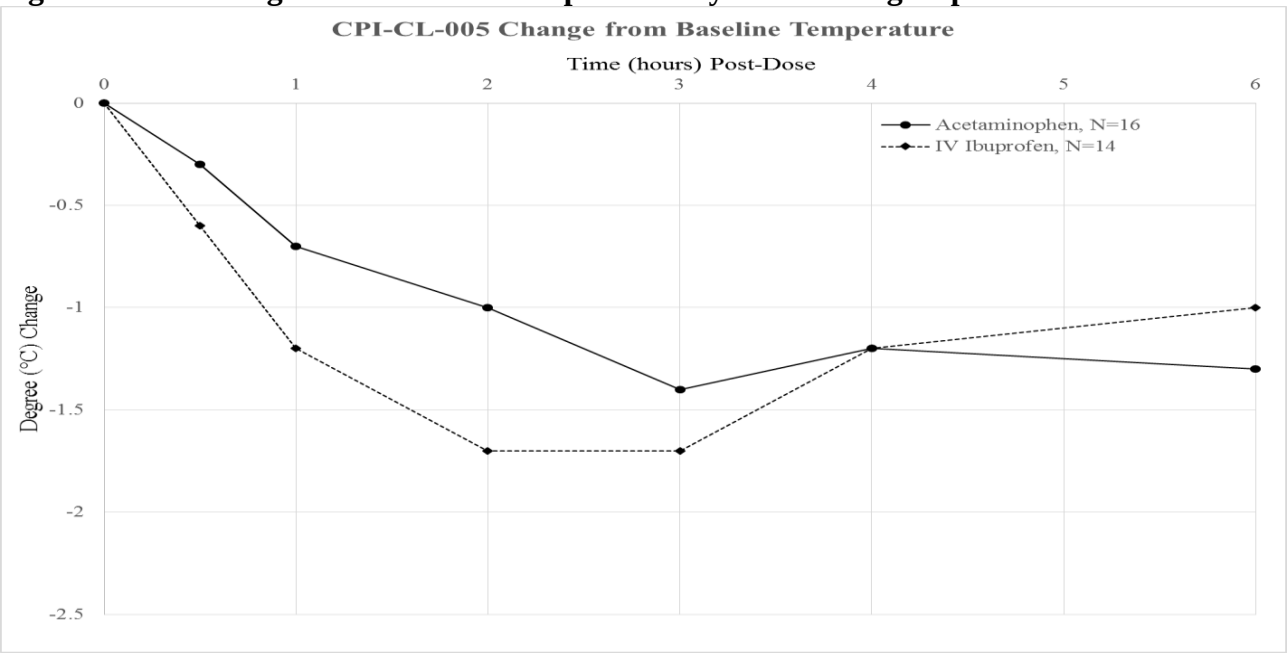
In the time interval from 8 to 24 hours mean temperature was basically ≤37.5°C for both treatment groups. Because patients were all receiving four doses of active treatments at a fixed dosing interval regardless if they still had fever and there was no placebo control, multiple-dose antipyretic effects could not be adequately assessed.

Table 5-23 Time-Specific Temperature (°C) Reduction, ITT

Hour	0	0.5	1	2	3	4	6	9	12	15	18	21	24
IV Ibu													
T mean	39.0	38.4	38.0	37.5	37.5	38.0	38.1	37.0	37.6	36.8	37.6	36.9	37.6
T SD	0.80	0.67	0.75	0.61	0.77	1.17	1.30	1.15	1.31	1.06	1.32	0.65	1.2
N	14	14	13	13	13	13	13	12	12	12	12	12	12
TΔ mean		-0.6	-1.2	-1.7	-1.7	-1.2	-1.0	-2.2	-1.6	-2.4	-1.5	-2.2	-1.6
TΔ SD		0.77	0.82	0.57	0.58	0.90	1.07	0.89	1.24	1.03	1.49	0.92	1.45
APAP													
T mean	38.7	38.3	38.0	37.6	37.3	37.5	37.3	36.7	36.8	36.7	37.1	36.7	36.5
T SD	0.51	0.69	0.68	0.77	0.93	1.15	1.54	1.37	0.86	0.96	0.91	0.59	1.34
N	15	14	14	15	15	15	15	14	15	15	15	15	15
TΔ mean		-0.3	-0.7	-1.0	-1.4	-1.2	-1.3	-1.9	-1.9	-2.0	-1.6	-1.9	-2.2
TΔ SD		0.54	0.82	0.97	1.18	1.38	1.70	1.47	1.10	1.14	1.27	0.85	1.52
Ibu>APAP		-0.3	-0.5	-0.7	-0.3	0	0.3	-0.3	0.3	-0.4	0.1	-0.3	0.6

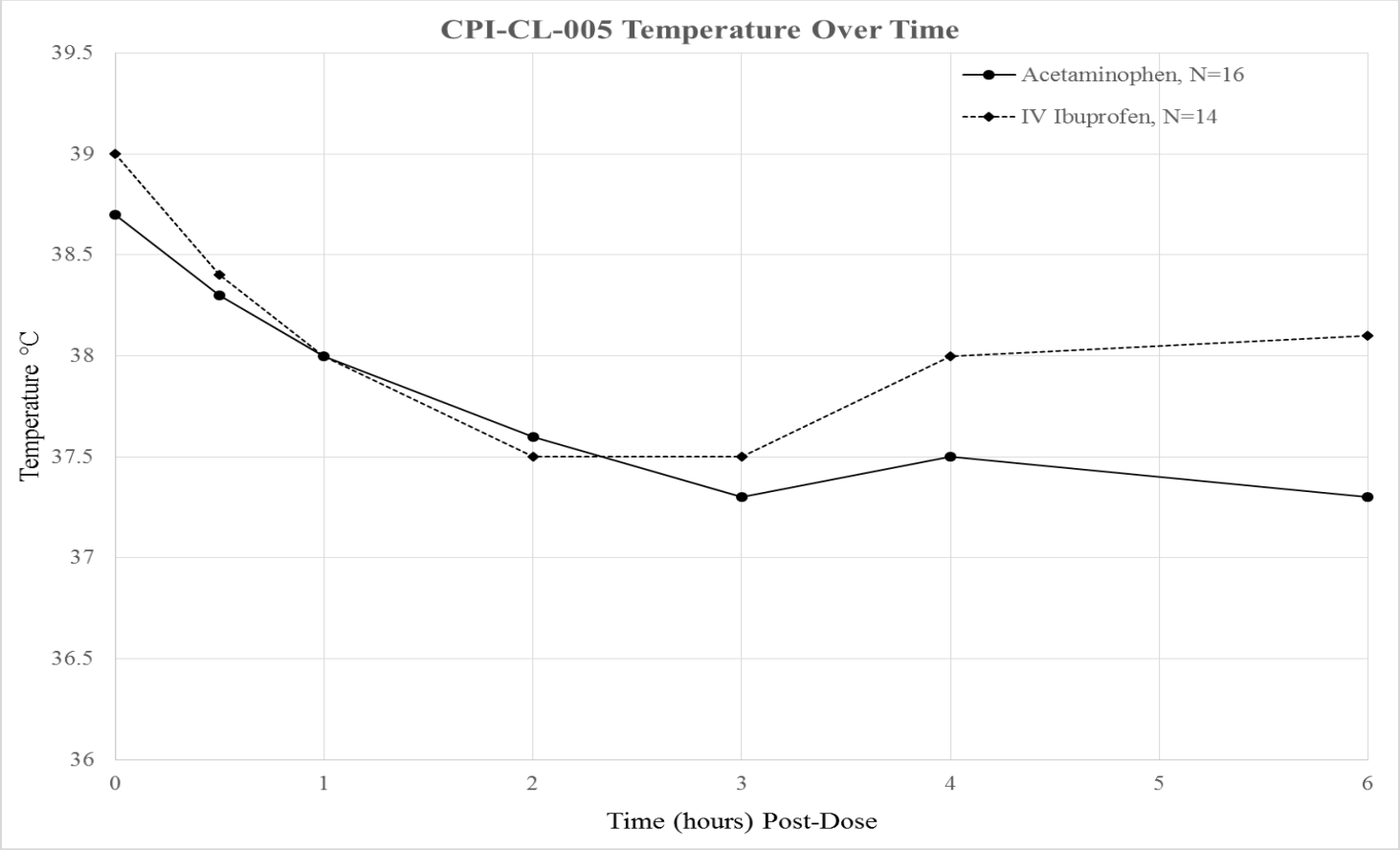
Source: Table 1.11.4-13 on page 29 of submission dated August 6, 2015 in response to the reviewer's information request.

Figure 5-3 Change from Baseline Temperature by Treatment group over 6 Hours: ITT



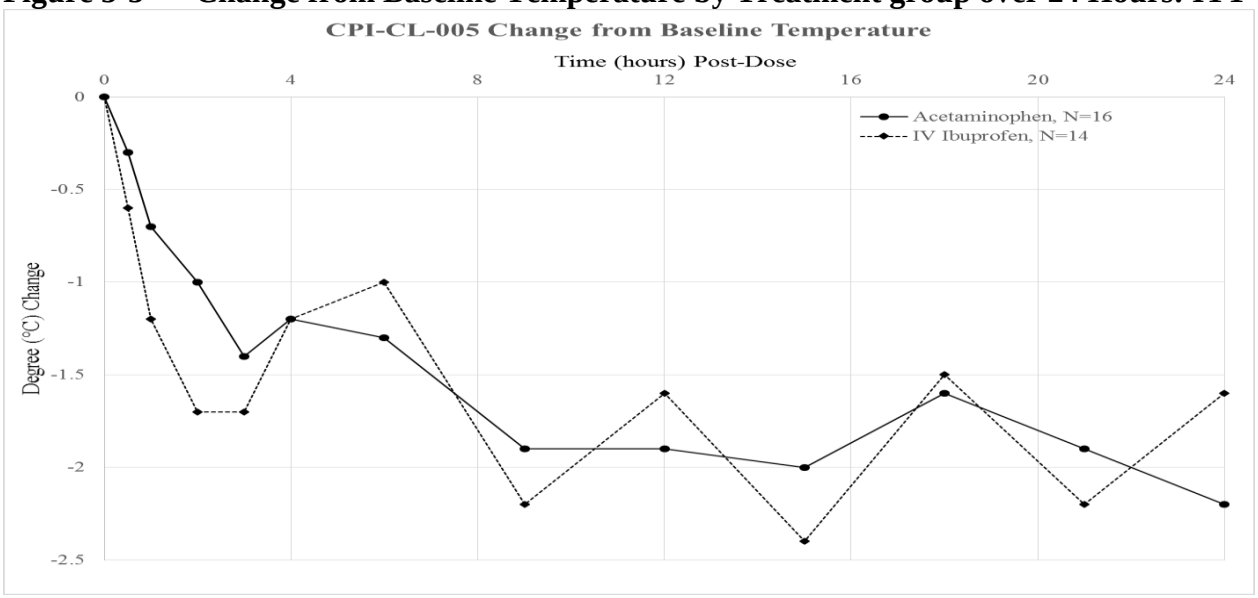
Source: Figure 1.11.4-5 on page 32 of submission dated August 6, 2015 in response to the reviewer's information request.

Figure 5-4 Temperature over Time by Treatment Group over 6 Hours: ITT



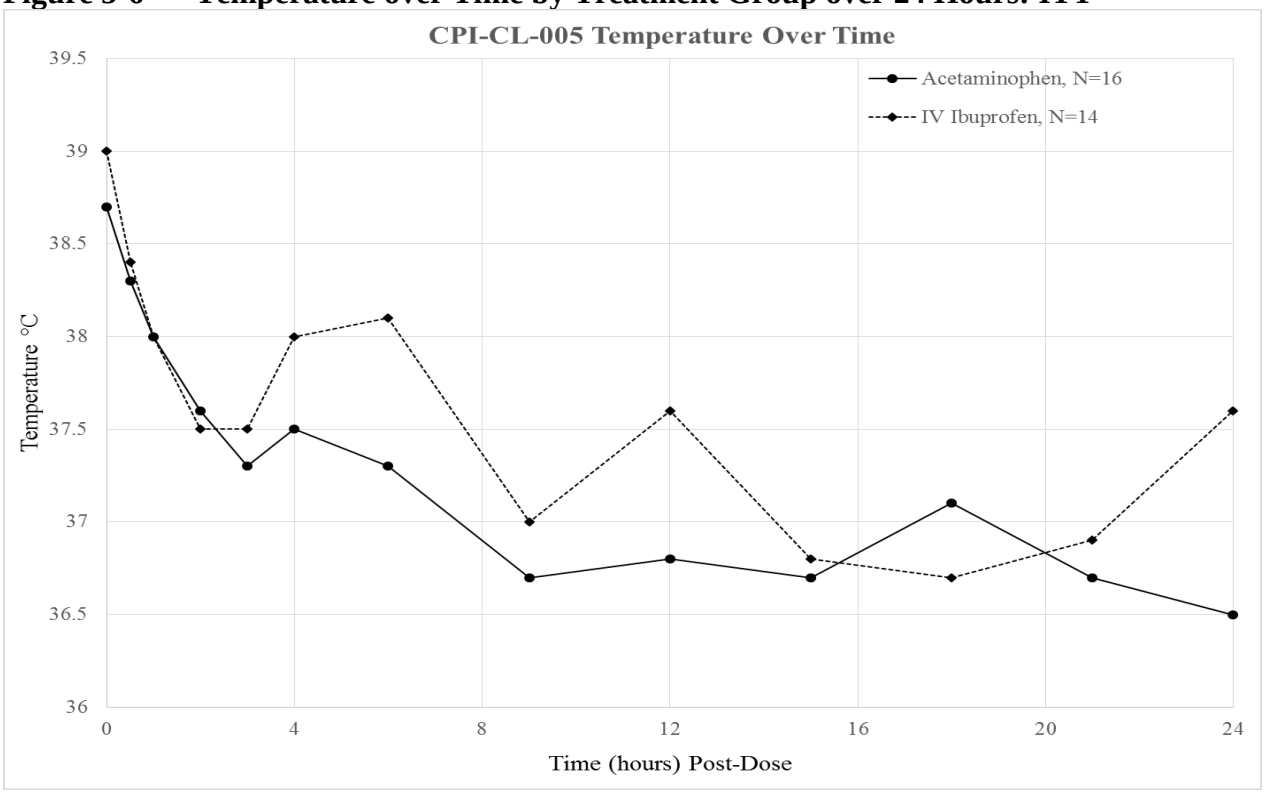
Source: Figure 1.11.4-3 on page 30 of submission dated August 6, 2015 in response to the reviewer's information request

Figure 5-5 Change from Baseline Temperature by Treatment group over 24 Hours: ITT



Source: Figure 1.11.4-6 on page 33 of submission dated August 6, 2015 in response to the reviewer's information request.

Figure 5-6 Temperature over Time by Treatment Group over 24 Hours: ITT



Source: Figure 1.11.4-4 on page 31 of submission dated August 6, 2015 in response to the reviewer's information request**.**

Additional efficacy endpoints (based on post-hoc analyses)

Proportion becoming afebrile and time to reach afebrile status

Median time to temperature reduction to <37.5ºC (99.5 ºF) was 2 hours for both treatment groups. The proportions of patients reaching temperature reduction to <37.5ºC (99.5 ºF) were about two thirds of both treatment groups by the end of the first dosing interval and 100% of the IV ibuprofen group and 93% of the acetaminophen group by 24 hours as shown in the table below.

Table 5-24 Temperature Reduction to <38ºC and to <37.5ºC, ITT

Study 005 Temperature Reduction to <38ºC and <37.5ºC	**IV Ibu** (N=14)	**APAP** (N=15)	**IV Ibu>APAP**
Number (%) with T↓ to <38ºC by end of 1st dosing interval (6 hours)	12 (86%)	13 (87%)	-1%
Number (%) with T↓ to <38ºC by 24 hours	14 (100%)	15 (100%)	0
Number (%) with T↓ to <37.5ºC by 4 hours	9 (64%)	10 (67%)	-3%
Number (%) with T↓ to <37.5ºC by 6 hours	9 (64%)	10 (67%)	-3%
Number (%) with T↓ to <37.5ºC by 24 hours	14 (100%)	14 (93%)	7%
Median time in hours (CI) to T<38ºC	1.5 (0.5, 2.0)	2.0 (1.0, 3.0)	-0.5
Median time in hours (CI) to T<37.5ºC	2.0 (2.0, 14.6)	2.0 (1.0, 10.3)	0

Source: Table 1.11.4-14 on page 34 of submission dated August 6, 2015 in response to the reviewer's information request.

Summary of Findings and Discussion

Study conduct

Study 005 was a small study consisted of only 30 patients mostly in the range of 2 to <12 years of age. Half of the study population was female and half was Hispanic. Mean baseline temperature was higher in the ibuprofen group than the acetaminophen group: 39.0°C (102.2°F) versus 38.6°C (101.48°F), or a difference of 0.4°C (0.72°F).

Only a few patients, 3 of 30 (10%), dropped out for the reason of withdrawal of consent, two from the IV ibuprofen group and one from the acetaminophen group. Most patients received the four required doses regardless of their need for continued antipyretic treatments as planned in the protocol.

Few patients (4/14) in the IV ibuprofen group had protocol deviations. The reports of two counts of dosing error in the IV ibuprofen group and four counts of dosing time error and four counts of miss-timed temperature measurement in the acetaminophen group were not expected to have a major impact on efficacy outcomes.

Most patients (26 of 30) had exposure to four doses of study medication or one day treatment as planned.

Efficacy

Because of the non-inferiority design in a very small sample and confounding effect of a relatively large difference in baseline temperature between the treatment groups, any statistical comparison would be considered invalid.

Additional (post-hoc) analyses revealed that the magnitude of temperature reduction was 0.6 to 1.7°C for the IV ibuprofen group and 0.3 to 1.4°C for the acetaminophen group during the first dosing interval of 6 hours. Normalization of temperature (<37.5ºC or 99.5 ºF) occurred in about two thirds of the study population (64% of the IV ibuprofen group and 67% of the acetaminophen group) during the first dosing interval of six hours and in 100% of the IV ibuprofen group and 93% of the acetaminophen group within 24 hours. Median time to reach afebrile status was 2.0 hours in both groups. The findings were similar between the two treatment groups.

Dosing interval
Single-dose duration and multiple-dose effects could not be evaluated for multiple reasons. Median time to the second dose or between any adjacent doses based on need was not assessable because of the fixed dosing regimen. There were no data on median time to rescue or proportions taking rescue because there were no cases of treatment failure or dropouts due to use of rescue. Placebo control was not available for determination of the need and duration of multiple-dose treatment.

Conclusion
The results of this small study are similar to the findings from Study 012 in terms of temperature reduction and normalization in response to the initial dose of 10-minute IV infusion of Caldolor for treating fever in hospitalized pediatric patients. Single-dose duration and multiple-dose effects were not assessable due to limitations in study design.

Appendix

Eligibility Criteria
Inclusion Criteria
To be considered eligible to participate in the study, a patient must have been meeting the following inclusion criteria:

1. Was hospitalized
2. Was between 6 months and 17 years of age, inclusive
3. Was able to take medication orally
4. Had new (not chronic, within last 7 days) onset of fever, documented by temperature greater than or equal to 101.0ºF (38.3ºC) (The preferred method of temperature measurement is core. If a non-core route is used, temperature measurement should be verified by an additional route of measurement; the route of temperature measurement used immediately before randomization should be used immediately before dosing and for all temperature measurements during the Treatment Period.)
5. Had written informed consent provided by legal parent, guardian, or authorized agent, and have same agree to abide by the study restrictions and to return for the required assessments (Where appropriate, participants of appropriate intellectual maturity should personally provide written informed assent; age of assent may be determined by Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) or be consistent with local legal requirements.)

Exclusion Criteria

1. Had inadequate intravenous access
2. Had received antipyretic drug therapy within 8 hours before dosing
3. Was pregnant or nursing
4. Had any history of allergy or hypersensitivity to NSAIDs, aspirin, APAP, or any component of IV Ibu or APAP.
5. Had a history of severe head trauma that required the current hospitalization, had intracranial surgery or stroke within the previous 30 days, or have any history of intracerebral arteriovenous malformation, cerebral aneurysm, or central nervous system mass lesions
6. Had a history of febrile convulsion or have a sibling with a history of febrile convulsion
7. Had a history of congenital bleeding diatheses (e.g., hemophilia) or any active clinically significant bleeding, or have underlying platelet dysfunction, including (but not limited to) idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, or congenital platelet dysfunction
8. Had gastrointestinal bleeding that has required medical intervention within previous 6 weeks, unless definitive surgery has been performed
9. Had platelet count less than 30,000/mm3
10. Was receiving full dose anticoagulation therapy (Prophylaxis with subcutaneous heparin is acceptable.)

11. Had fever secondary to blood or drug reaction
12. Had an expected life span of less than 14 days because of imminent withdrawal of life support or severity of illness
13. Was receiving ongoing or imminent treatment with corticosteroids
14. Had neurogenic fever
15. Was on dialysis, have oliguria or calculated creatinine clearance of less than 70 mL/min (calculated using the Cockcroft and Gault formula), have impaired renal function, be receiving nephrotoxic drugs, or be expected to be unable to tolerate the extra fluid required for administration of CTM
16. Had had major surgery within the past 12 hours, unless adequate hemostasis has been achieved
17. Had received another investigational drug within the past 30 days
18. Was otherwise unsuitable for the study, in the opinion of the Investigator

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6 INTEGRATED REVIEW OF EFFICACY

6.1 Summary of Efficacy Results and Conclusions

The two efficacy studies were both randomized, open-label, active-controlled, multiple-dose studies of IV ibuprofen 10 mg/kg in comparison to acetaminophen in treating fever in hospitalized pediatric patients. Study 012 was the key efficacy study of a superiority design, in which IV ibuprofen was dosed every four hours on an as needed basis and was compared to a low dose of acetaminophen 10 mg/kg. Study 005 was an exploratory small study of fixed dosing of IV ibuprofen with four doses given every six hours regardless of febrile status, and used 15 mg/kg acetaminophen as the control group.

A change of dosing regimen from every4-hour dosing to PRN dosing accompanied by corresponding change of time schedule for efficacy data collection in the middle of the ongoing trial was noticed during the review process. Such changes lead to complications in data analyses and interpretation.

The treatment groups were approximately balanced (no important differences) with regard to demographic characteristics such as age, gender, race, ethnicity, and weight. The efficacy population consisted of 100 pediatric patients aged 6 month to 18 years in Study 012 and 29 pediatric patients mostly in the age range of 6 to 12 years in Study 005. The study population consisted of sick patients hospitalized mostly for serious medical conditions with mean baseline temperatures around 39.0°C (102.2°F).

The dropout rate was high (75%) in Study 012 mostly for the reasons of fever no longer requiring treatment, discharge from hospital or ER, and IV access inadequate or discontinued, and was low (10%), all due to withdrawn consent, in Study 005 because of required completion of four doses in 24 hours.

The counts of protocol deviations in the categories of dosing errors and errors in temperature measurements were relatively low and thus, not considered as having a major impact on efficacy outcomes.

IV ibuprofen treated patients had temperature reduction in a range of 0.5-1.5°C during the first dosing interval (0.5-4 hours) in Study 012 and similar degree of temperature reduction in Study 005. The proportions of IV ibuprofen treated patients achieving afebrile status (temperature <37.5ºC, or 99.5 ºF) were about three quarters during the first dosing interval in Study 012 and about two thirds in the first dosing interval in Study 005. Median time to reach afebrile status was 2.6 hours in Study 012 and 2 hours in Study 005. The extents of temperature reduction and normalization reported in Study 012 were similar to the findings based on post-hoc analyses in Study 005, taking into the consideration of the objective nature of temperature measurements.

In comparison to low dose of acetaminophen at 10 mg/kg in Study 012, IV ibuprofen treated patients had statistically significant better performance in AUC_{0-2} and AUC_{0-4} and 0.2 to 0.6°C more temperature reduction in the first dosing interval. IV ibuprofen treated patients had also 0.4 hours shorter median time to reach a temperature reduction to <37.5ºC and 17% more becoming afebrile by the end of the first dosing interval. The effect sizes of these treatment differences were considered clinically meaningful. The treatment difference in favor of the low dose acetaminophen was 23% less receiving more than one dose of treatment.

The effective fever reduction and temperature normalization associated with a single dose of 10-minute IV infusion of ibuprofen given at 10 mg per kg are substantial evidence in support of the use of IV ibuprofen in treating fever in hospitalized pediatric patients. Multiple-dose effects could not be evaluated due to lack of placebo control in determining whether additional doses are needed to keep the temperature in the normal range. Single-dose and multiple-dose durations could not be measured because of limitations in study design, conduct, and data collection.

6.2 Proposed Indication

The proposed indications for ibuprofen IV injection are the following:

- Management of mild to moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics
- Reduction of fever

6.3 Methods/Study Design

Studies 012 and 005 were randomized, open-label, active-controlled, parallel group, multiple-dose studies of fever in pediatric patients who were either hospitalized or received emergency treatment in a hospital. Study 012 was the key efficacy study of a superiority design conducted in the U.S. Study 005 was a small study with a design of non-inferiority conducted at a couple of US and foreign sites.

The two studies had different dosing regimens. Study 012 had IV ibuprofen dosed every 4 hours as needed using the low dose acetaminophen 10 mg/kg as a comparator, whereas Study 005 had IV ibuprofen dosed at fixed dosing interval of every six hours for 24 hours regardless of the need for fever treatment and had higher dose acetaminophen 15 mg/kg as a comparator. Efficacy assessments and efficacy endpoints were also different between the two studies (refer to the Review Section 5.3 for detail).

The focus of the efficacy review is to evaluate antipyretic effects of ibuprofen IV in terms of fever reduction and temperature normalization and duration of antipyretic effects associated with 10-minute infusion. There were a number of post-hoc analyses requested by the reviewer taking into consideration that the temperature measurements are objective. The results from the two studies are summarized side by side. The findings from Study 012 will serve as key evidence and data from Study 005 as supportive.

6.4 Demographics

Demographic and baseline characteristics of the sample population in each study are tabulated and described in detail in the individual study reviews in Section 5.3. Both fever studies had about 50% females. Study 012 had more than 80% Caucasian by race and about 50% Hispanic by ethnic origin. Study 005 did not classify study population by ethnic origin and had 50% Hispanic and 30% Caucasian.

The age distribution of efficacy population is summarized in the table below. Study 012 had two smaller subgroups with only 6 patients in each of them: 6 months to <2 years of age treated by IV ibuprofen and 12 to 18 years of age treated by acetaminophen. Study 005 had patients mainly in the age range of 2 to <12 years.

Table 6-1 Age Distribution of Efficacy Population

Efficacy samples	Study 012		Study 005		Total per treatment		Total per age group
Age group	IV Ibu	APAP	IV Ibu	APAP	IV Ibu	APAP	
0.5 to < 2 years	6	14	0	1	6	15	21
2 to < 6 years	13	14	6	8	19	22	41
6 to < 12 years	15	19	7	6	22	25	47
12 to < 18 years	13	6	1	1	14	7	21

The mean baseline temperature was higher in the IV ibuprofen group than the acetaminophen group in both studies, by 0.2°C or 0.36°F (the difference was not statistically significant) in Study 012 and by 0.4°C or 0.72°F in Study 005.

The study population consisted of mainly sick pediatric patients hospitalized for serious medical conditions such as sepsis, bowl perforation, appendicitis with abscess formation, different types of pneumonia, meningitis, cellulitis, urinary tract infection, severe burn, trauma with bone fracture, toxic shock syndrome, sickle cell anemia, febrile seizure, etc. Some had multiple medical conditions, were on multiple concomitant medications, and were admitted to PICU.

6.5 Patient Disposition

Patient disposition in each study is presented and discussed in details in the Review Section 5.3. Dropouts of 75% in Study 012 were mainly due to the reasons of fever no longer requiring treatment, discharge from hospital or ER, and IV access inadequate or discontinued. A small dropout rate of 10% in Study 005 was attributable to the requirement of completion of 4-dose treatment.

Protocol deviations

The type and occurrence of protocol deviations are discussed in detail in the Review Section 5.3. The relatively low counts of dosing errors and errors in temperature measurements were considered unlikely to have a major impact on efficacy outcomes.

6.6 Analysis of the Primary Endpoint(s)

The results of primary analyses are briefly summarized in the table below (refer to the Review Section 5.3 for detail). Treatment difference between IV ibuprofen 10 mg/kg and the low dose of acetaminophen 10 mg/kg was statistically significant in terms of temperature reduction AUC_{0-2} in Study 012. Because the non-inferiority design in Study 005 was not acceptable statistical comparisons between the treatment groups will not be discussed here.

Table 6-2 Summary of Efficacy Findings by Primary Endpoint

	Study 012			**Study 005**		
	IV Ibu (N=47)	**APAP 10* (N=53)**	**Ibu>APAP**	**IV Ibu (N=14)**	**APAP 15** (N=15)**	**Ibu>APAP**
Primary endpoint	**Temperature reduction AUC_{0-2}**			**Temperature reduction AUC_{0-6}**		
N	46	50		13	15	
Mean (SD)	-1.5 (1.11)	-0.9 (0.89)	-0.59	-2.0 (1.19)	-1.1 (1.26)	-0.83
LS Means (SE)	-1.5 (0.15)	-0.9 (0.14)	(p=0.012)	-2.0 (0.34)	-1.1 (0.32)	(p=0.087)

6.7 Secondary and Additional Endpoint(s)

The results of secondary and additional analyses are briefly summarized in the table below (refer to the Review Section 5.3 for detail). In terms of time-specific temperature reduction during the first dosing interval the results of Study 012 were similar to the findings in Study 005.

The majority of patients had temperature normalization during the first four hours in the two treatment groups in both studies. In comparison to low dose acetaminophen at 10 mg/kg in Study 012, IV ibuprofen treatment at 10mg/kg was associated with 17% more patients becoming afebrile in the first four hours and 0.4 hours earlier to reach afebrile status. In comparison of IV ibuprofen treatment to high dose acetaminophen at 15 mg/kg in Study 005, both treatment groups had about two thirds of patients with temperature normalized in the first four hours and median time of two hours to becoming afebrile.

The proportion receiving repeated doses was 23% more (70% versus 47%) in the ibuprofen group in comparison to the low dose acetaminophen group in Study 012. Time to the second dose based on the ITT

population was not assessable because different dosing regimens were used in different parts of the study that only a subpopulation was on PRN dosing. Neither study had patients who were given an antipyretic rescue. Single-dose duration could not be measured due to limitations in study design and conduct. Multiple-dose effects could not be adequately evaluated either for similar reasons.

Table 6-3 Summary of Efficacy Findings by Secondary and Additional Endpoints

	Study 012			**Study 005**		
	IV Ibu (N=47)	**APAP 10* (N=53)**	**Ibu>APAP**	**IV Ibu (N=14)**	**APAP 15** (N=15)**	**Ibu>APAP**
Baseline temperature	*39°C*	*38.8°C*	*0.2°C*	*39°C*	*38.6°C*	*0.4°C*
Temperature reduction (0.5-6 hours)	0.5-1.5°C	0.3-1.1°C	0.2-0.6°C	0.6-1.7°C	0.3-1.4°C	0.3-0.7°C (0.5-3 hours)
Temperature reduction AUC_{0-4}	-4.4	-2.6	-1.8	-5.2	-3.6	-1.6
Temperature reduction AUC_{0-24}	-34.2	-26.6	-7.6	-41.3	-39.1	-2.2
% with T↓ to <37.5ºC by 4 hours	74%	57%	17%	64%	67%	-3%
% with T↓ to <37.5ºC by 6 hours				64%	67%	-3%
% with T↓ to <37.5ºC by 24 hours	91%	75%	16%	100%	93%	7%
Median time to T<37.5ºC, hours	2.6	3.0	-0.4	2	2	0
Proportion having ≥2 Doses	70%	47%	23%			
Median time to the 2nd dose in patients receiving PRN dosing, hours						

Note: Acetaminophen 10 mg/kg was given in Study 012 and 15 mg/kg was given in Study 005.

6.8 Subpopulations

Subpopulation analyses of efficacy are not applicable because of very small subpopulation size of the study groups divided by age, gender or race.

6.9 Analysis of Clinical Information Relevant to Dosing Recommendations

In terms of dose levels 10 mg/kg was the only dose studied in the three pediatric trials. Single-dose efficacy demonstrated at this dose level supports its use in treating fever in hospitalized pediatric patients. It would be more informative to include also 5 mg/kg in the studies to evaluation dose response.

In terms of dosing interval neither single-dose duration nor multiple-dose duration could be adequately assessed due to limitations in study design, conduct, and data collection as discussed above.

Recommendations on pediatric dosing interval for IV ibuprofen should be largely based on dosing intervals approved for adult use of IV ibuprofen as well as the ones approved for pediatric use of oral formulations of ibuprofen in this reviewer's opinion.

6.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance effects in treating fever in pediatric population could not be adequately assessed because of the rapid temperature reduction and normalization in the first dosing interval and lack of placebo control in determination of the need for repeated dosing.

6.11 Additional Efficacy Issues/Analyses

None.

7 INTEGRATED REVIEW OF SAFETY

7.1 Summary of Safety Results and Conclusions

The safety database contains safety data from the three pediatric studies involving a total of 144 patients exposed to IV ibuprofen 10 mg/kg given by 10-minute infusion. The type of exposure to IV ibuprofen included single-dose in 82 patients in Study 014, four doses given on a fixed dosing interval within 24 hours in 14 patients in Study 005, and multiple-dose intermittently based on need in 48 patients in Study 012. Multiple-dose experiences in the two fever studies were limited to 45 patients exposed to at least two doses, 36 patients exposed to at least four doses, and 18 patients exposed to at least six doses. The majority of exposure was in the age group of 6 to <12 years (81 of 144 patients, or 56%). The exposure to IV ibuprofen in the age group of 6 months to <2 years involved only six patients, less than expected.

The pediatric study population consisted of mostly Caucasian patients (79%) and had slightly more females than males. The mean and median body weights of the study population were close to the mid-range weight listed for the corresponding age groups in the Motrin dosing chart. The study population included very sick pediatric patients hospitalized for serious medical conditions such as sepsis, bowl perforation, appendicitis with abscess formation, different types of pneumonia, meningitis, cellulitis, urinary tract infection, severe burn, trauma with bone fracture, toxic shock syndrome, sickle cell anemia, febrile seizure, etc. Some had multiple medical conditions, were on multiple concomitant medications, and were admitted to PICU.

There were no reports of deaths and seven reports of nonfatal serious adverse events (SAEs) in five pediatric patients, three of whom were treated with IV ibuprofen. Based on the review of narratives for all SAEs, the relationship of AE to ibuprofen could not be ruled out in case of the post tonsillectomy hemorrhage at the surgical site. The relationship of AEs to ibuprofen could not be completely ruled out in cases of transaminitis and pancreatitis due to concurrent illness and multiple concomitant medications known for drug-induced liver enzyme elevation and pancreatitis. The cases of cardiopulmonary arrest and left pleural pneumothorax were unlikely to be related to ibuprofen treatment because of patient's serious medical conditions involving septic shock and associated respiratory failure and other unstable conditions.

Of the five cases of AE-related dropouts four occurred in the IV ibuprofen group for the reasons of thrombocytopenia, hypothermia/bradycardia, headache, and urticarial, respectively. The case of urticarial was likely related to the ibuprofen treatment as the event commenced seven minutes after the start of the ibuprofen infusion.

In pediatric patients treated by IV ibuprofen the commonly reported individual AEs (≥2%) were infusion site pain, vomiting, nausea, anemia, and headache. For the surgical patients treated with a single dose of ibuprofen the common AEs were infusion site pain, nausea, vomiting, and urticaria. The commonly reported AEs in hospitalized febrile pediatric patients were gastrointestinal (GI) symptoms and laboratory test abnormalities in both active treatment groups.

Findings of laboratory (lab) test abnormalities in the two fever studies were similar for the two active treatment groups in general and are hard to interpret due to concurrent serious medical conditions, concomitant medications, lack of placebo control, and age-dependent as well as institution-related variations in defining normal range for the individual lab tests.

Time dependency of AEs could not be adequately assessed due to limited exposure, to a single dose in Study 014 and up to a few doses in the two fever studies.

Subpopulation safety analyses for drug-demographic interactions were not applicable due to limited sample sizes of subpopulations by age, gender, and race.

Based on the review of pediatric safety data there were no new safety signals or major issues identified. Short-term use of IV ibuprofen 10-minute infusion at 10 mg/kg in pediatric patients closely monitored at a hospital setting appears to be reasonably safe. Patients should be well hydrated before receiving IV ibuprofen to minimize the risks for acute renal toxicities. Minimum effective dosage in terms of dose level and dosing interval based on need should be targeted based on the individual response for better tolerance and safety.

7.2 Method

Safety data from individual study reports and Integrated Safety Summary (ISS) submitted on March 20, 2015 are used in the review. Safety review will focus on the review of individual cases of Serious Adverse Events (SAEs) and summary of commonly occurring AEs across studies and for different pediatric populations: patients undergoing tonsillectomy who had single-dose exposure in Study 014 and patients hospitalized for more serious medical conditions who had multiple-dose exposure in Studies 005 and 012. Most of the hospitalized pediatric patients had symptoms/signs and laboratory test abnormalities associated with serious medical conditions and multiple concomitant medications. With such small sample sizes, short exposure, and lack of placebo control, it is a challenge in interpreting the safety findings.

7.2.1 Discussion of Clinical Studies Used to Evaluate Safety

Studies 012 and 005 are the two active-controlled, multiple-dose fever studies conducted in hospitalized pediatric patients as discussed in detail in the Review Section 5. Study 014 is a placebo-controlled study of pre-emptive analgesic effect on post-operative pain in patients who received a single dose of study medication before tonsillectomy. Safety data from all three studies are used to evaluate safety.

7.2.2 Adequacy of Data

Data for safety analyses in terms of exposure, narratives of SAEs and of AE-related dropouts, adverse events, vital signs, and laboratory test results were either contained in the individual study reports, ISS, or available upon request and thus, considered acceptable in general.

7.2.3 Pooling Data across Studies to Estimate and Compare Incidence

Data on age-related exposure and demographic characteristics are pooled across all three studies. Data on common AEs are pooled across studies and also summarized for different study populations in terms of common AEs in hospitalized febrile pediatric patients in Studies 012 and 005 and common AEs in surgical patients in Study 014.

7.3 Adequacy of Safety Assessments

Safety data collection included exposure information and data from AE monitoring during the study in all three clinical trials and frequent vital signs measurements during treatments and routing laboratory tests before and after treatment period in the two studies conducted in hospitalized febrile pediatric patients and are considered adequate.

7.3.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As summarized in the table below the overall exposure to at least one dose of ibuprofen IV injection was reported in 144 pediatric patients. Exposure to IV ibuprofen by age group included one in the age group of <6 months, six in the age group of 6 months to <2 years, 19 in the age group of 2 years to <6 years, 81 in the age

group of 6 years to <12 years (the largest age group with more patients than the total of all other age groups), and 37 in the age group of 12 years to <18 years. The youngest two age groups had fewer patients due to difficulty in study enrollment. Exposure by indication (fever versus pain) included multiple-dose exposure in 62 hospitalized (or emergency room treated) pediatric patients with fever (Studies 012 and 005) and single-dose exposure in 82 pediatric patients with post-operative pain associated with tonsillectomy. Exposure by number of doses of IV ibuprofen included 45 pediatric patients exposed to at least two doses, 36 to at least four doses, and 18 to at least six doses of IV ibuprofen. Exposure by dosing regimen included 33 patients with intermittent multiple-dose exposure on PRN dosing in Study 012 and 12 patients with continuous multiple-dose exposure for four doses given at a fixed dosing interval of every six hours in Study 005. Exposure by duration of IV ibuprofen treatment included 36 treated for at least two days and seven for at least three days.

Table 7-1 Exposure by Number of Doses and Number of Days

	<6 months		6 mo to <2 yr		2 to <6 years		6 to <12 years			12 to < 18 years			All Age Groups		
	IV Ibu	APAP	IV Ibu	APAP	IV Ibu	APAP	IV Ibu	APAP	Pla	IV Ibu	APAP	Pla	IV Ibu	APAP	Pla
	N=1	N=2	N=6	N=15	N=19	N=22	N=81	N=25	N=62	N=37	N=7	N=17	N=144	N=71	N=79
#Doses															
1 Dose	1	2	2	8	6	7	65	12	62	25	2	17	99 (69%)	31 (44%)	79 (100%)
2 Doses	0	0	1	0	1	0	2	3	0	4	0	0	8 (6%)	3 (4%)	0
3 Doses	0	0	0	0	0	1	1	1	0	0	0	0	1 (<1%)	2 (3%)	0
4 Doses	0	0	0	1	4	9	6	5	0	2	1	0	12 (8%)	16 (23%)	0
5 Doses	0	0	3	1	2	0	0	0	0	1	0	0	6 (4%)	1 (1%)	0
6 Doses	0	0	0	2	5	1	4	4	0	3	2	0	12 (8%)	9 (13%)	0
>6 Doses	0	0	0	3	1	4	3	0	0	2	2	0	6 (4%)	9 (13%)	0
Cumulative															
≥1 Dose	1	2	6	15	19	22	81	25	62	37	7	17	144 (100%)	71 (100%)	79 (100%)
≥2 Doses	0	0	4	7	13	15	16	13	0	12	5	0	45 (31%)	40 (56%)	0
≥3 Doses	0	0	3	7	12	15	14	10	0	8	5	0	37 (26%)	37 (52%)	0
≥4 Doses	0	0	3	7	12	14	13	9	0	8	5	0	36 (25%)	35 (49%)	0
≥5 Doses	0	0	3	6	8	5	7	4	0	6	4	0	24 (17%)	19 (27%)	0
≥6 Doses	0	0	0	5	6	5	7	4	0	5	4	0	18 (13%)	18 (25%)	0
#Days															
1 Day	1	2	3	8	7	7	67	14	62	30	2	17	108 (75%)	33 (46%)	79 (100%)
2 Days	0	0	2	6	10	12	12	11	0	5	3	0	29 (20%)	32 (45%)	0
3 Days	0	0	1	0	2	2	1	0	0	1	0	0	5 (3%)	2 (3%)	0
4 Days	0	0	0	1	0	1	0	0	0	0	0	0	0	2 (3%)	0
5 Days	0	0	0	0	0	0	0	0	0	0	2	0	0	2 (3%)	0
>5 Days	0	0	0	0	0	0	1	0	0	1	0	0	2 (1%)	0	0
Cumulative															
≥1 Day	1	2	6	15	19	22	81	25	62	37	7	17	144 (100%)	71 (100%)	79 (100%)
≥2 Days	0	0	3	7	12	15	14	11	0	7	5	0	36 (25%)	38 (54%)	0
≥3 Days	0	0	1	1	2	3	2	0	0	2	2	0	7 (5%)	6 (8%)	0
≥4 Days	0	0	0	1	0	1	1	0	0	1	2	0	2 (1%)	4 (6%)	0
≥5 Days	0	0	0	0	0	0	1	0	0	1	2	0	2 (1%)	2 (3%)	0

Source: Table 1.11.4-21 on page 41 of submission dated August 6, 2015 in response to the reviewer's information request.

Demographic characteristics of pediatric patients in Studies 005, 012 and 014 are summarized in the table below. Female patients accounted for slightly more than half of the safety population. Subpopulation consisted of 79% Caucasian and 12% African American based on race classification and consisted of 28% Hispanic based on ethnic origin (classification used in studies 012 and 014 only).

Table 7-2 Demographics in Pediatric Studies

Studies 005, 012 and 014	IV Ibu (N=144)	Placebo (N=79	APAP (N=71)	Total (N=294)
Age (years)				
Mean (SD)	8.3 (4.10)	9.4 (2.96)	5.6 (4.36)	8.0 (4.12)
Min, Max	0.1, 17.0	6.0, 17.0	0.3, 17.0	0.1, 17.0
Gender n (%)				
Male	67 (47%)	31 (39%)	34 (48%)	132 (45%)

Studies 005, 012 and 014	IV Ibu (N=144)	Placebo (N=79	APAP (N=71)	Total (N=294)
Female	77 (53%)	48 (61%)	37 (52%)	162 (55%)
Race				
White or Caucasian	116 (81%)	68 (86%)	47 (66%)	231 (79%)
Black or African American	14 (10%)	10 (13%)	10 (14%)	34 (12%)
Asian	3 (2%)	0	2 (3%)	5 (2%)
Hispanic	6 (4%)	0	9 (13%)	15 (5%)
Other*	5 (3%)	1 (1%)	3 (4%)	9 (3%)
Ethnicity				
Hispanic or Latino	43 (30%)	13 (16%)	25 (35%)	81 (28%)
Not Hispanic or Latino	87 (60%)	66 (84%)	30 (42%)	183 (62%)
Weight (kg)				
Mean (SD)	36.4 (20.16)	40.5 (19.25)	23.6 (14.84)	34.4 (19.74)
Median	29.5	33.1	20.0	28.2
Min, Max	4.8, 104.4	17.1, 100.2	6.8, 63.0	4.8, 104.4

Note: Other includes 2 American Indian or Alaska Native, 1 Caucasian/Black, 1 Hispanic or Latino, 2 Indian, 1 Indian and American Guyanese, 1 Indigenous, and 1 Mixed.
Source: Table 1.11.4-19 on page 39 of submission dated August 6, 2015 in response to the reviewer's information request.

Selected demographic data in terms of gender and weight distribution by age group are summarized in the table below. Less female than male in the age group of 6 months to <2 years and more female than male in the age group of 12 years to <18 years were treated by IV ibuprofen. The values of mean and median weights were similar within each age group. With respect to Motrin pediatric dosing chart patients in the study population had mean and median body weight close to the middle value of weight range listed in Motrin dosing chart and had maximum body weight about twice as the upper limit of weight range for the age groups of 2 to < 6 years and 6 to <12 years.

Table 7-3 Selected Demographics and Baseline Characteristics by Age Group, Safety Population

Age Group	<6 months		6 mo to <2 yr		2 to <6 years		6 to <12 years			12 to < 18 years		
Treatment	**IV Ibu**	**APAP**	**IV Ibu**	**APAP**	**IV Ibu**	**APAP**	**IV Ibu**	**APAP**	**Pla**	**IV Ibu**	**APAP**	**Pla**
No. Patients	N=1	N=2	N=6	N=15	N=19	N=22	N=81	N=25	N=62	N=37	N=7	N=17
Gender												
Male	1	1	5	8	10	13	38	8	26	13	4	5
Female	0	1	1	7	9	9	43	17	36	24	3	12
Weight (kg)												
Mean SD	4.8	7.0 (0.21)	9.6 (2.03)	9.7 (1.57)	16.8 (4.56)	17.6 (7.27)	31.8 (11.47)	30.8 (9.64)	35.0 (15.76)	61.7 (15.93)	51.8 (12.60)	60.3 (18.11)
Median	4.8	7.0	9.3	10.0	16.0	16.3	27.7	28.8	29.1	58.5	58.0	58.4
Min, Max	4.8, 4.8	6.8, 7.1	7.3, 12.7	7.2, 12.0	11.3, 27.2	9.7, 42.2	15.8, 68.0	16.8, 55.5	17.1, 96.0	38.9, 104.4	32.7, 63.0	37.2, 100.2

Source: Table 1.11.4-20 on page 40 of submission dated August 6, 2015 in response to the reviewer's information request.

Table 7-4 Weight Range Corresponding to Age Groups in Motrin Pediatric Dosing Chart

Motrin dosing chart	6 mo to <2 yr	2 to <6 years	6 to <12 years
Weight in lb.	12-23	24-47	48-95
Weight in kg	5.5-10.5	10.9-21.4	21.8-43.2

Source: http://www.motrin.com/children-infants/dosing-charts?icid=home|tout|1.

7.3.2 Explorations for Dose Response

Dosage recommendations for pediatric use of oral formulations of ibuprofen are 5 to 10 mg/kg based on the degree of fever every 6-8 hours not to exceed 40 mg/kg per day. There had been no plan in this NDA for

studying dose response of IV ibuprofen in treating pediatric fever. The selection of 10 mg/kg of IV ibuprofen given every four hours PRN in Study 012 was based on data from Study 005.

7.3.3 Special Animal and/or In Vitro Testing

Refer to the Pharmacology/Toxicology Review of the original NDA.

7.3.4 Routine Clinical Testing

Safety monitoring consisted of mainly AE reporting (three studies), vital signs, and routine laboratory tests (Studies 005 and 012) and is considered adequate in studying short term (a few days) use of IV ibuprofen in hospitalized pediatric population.

7.3.5 Metabolic, Clearance, and Interaction Workup

Refer to the ibuprofen labeling for adult use of the IV formulation and for use of oral formulations in pediatric population of ages 6 months and older.

7.3.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The potential AEs associated with the NSAID drug class were measured by monitoring of GI events, measurement of blood pressure and heart rates, and laboratory tests of liver and renal function.

7.4 Major Safety Results and Discussion

7.4.1 Deaths

No deaths occurred in any of the pediatric studies.

7.4.2 Nonfatal Serious Adverse Events

There were seven cases of serious adverse events (SAE) reported in five pediatric patients, three in patients on IV ibuprofen and two in patients on acetaminophen. The related information is summarized briefly in the table below.

In the case of a 12 year-old White female who was admitted to intensive care unit for septic shock and associated respiratory failure and other unstable conditions, it is unlikely that her cardiopulmonary arrest and left pleural pneumothorax were related to ibuprofen treatment.

In the case of a 12 year-old Hispanic female with a very complicated medical history and multi-drug treatments who was hospitalized for abdominal pain and sweating, an association between ibuprofen (two doses) and increases of liver enzyme (3-4 times) and lipase (~300U/L) could not be completely ruled out. However, three of the listed medication, ertapenem, felbamate, and topiramate were on the list of drug-induced pancreatitis (http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=&s=PL&pt=2&fpt=2&dd=290403&AspxAutoDetectCookieSupport=1) and seven (ertapenem, felbamate, topiramate, albuterol, clonazepam, famotidine, and heparin) were reported to be associated with elevation of liver enzymes (http://livertox.nlm.nih.gov).

In the case of a 4 year-old female who was admitted to intensive care unit for septic shock and associated respiratory infection and respiratory failure, the development of pleural effusion would be unlikely to be associated with acetaminophen treatment.

In the case of a 15 year-old female who developed intra-abdominal abscess several days after being discharged from a surgical unit post appendectomy the complication was unlikely to be attributable to one dose of acetaminophen.

In the case of a 9-year old White female who had a single dose of IV ibuprofen before surgery and tonsillar hemorrhage at the surgical site two days post tonsillectomy the relationship between the bleeding event and IV ibuprofen could not be ruled out.

Table 7-5 Nonfatal Serious Adverse Events (SAEs)

Study 12	**Patient**	**Doses**	**Nonfatal SAE**	**Brief description**	**Outcome**
IV Ibu 10 mg/kg	09-2014 12y/W/F	7 doses	Cardiopulmonary arrest	Admitted to intensive care for septic shock with respiratory failure and multiple unstable conditions and lab abnormalities before ibuprofen treatment	Resolved with sequel
			Left pleural pneumothorax	Occurred 3 days after stop ibuprofen while being treated for Acute Respiratory Distress Syndrome	Resolved
	21-2106 12y/H/F	2 doses	Transaminitis	Admitted for abdominal pain and sweating; list of 15 significant medical problems involving multiple organ systems including several GI problems, one of which was transaminitis; On >10 concomitant medication for other conditions; AST/ALT↑ of 3-4X and high level of lipase (293 U/L) by lab tests 3 days after taking 2 doses of ibuprofen	Resolved
			Pancreatitis		Resolved
APAP 10 mg/kg	09-2021 4y/F	8 doses	Pleural effusion	Admitted to intensive care for septic shock; had multiple medical problems including respiratory infection and respiratory failure; chest X-ray findings of infiltrates changing to pleural effusion during treatment with acetaminophen	Resolved
	08-2123 15y/F	1 dose	Intra-abdominal abscess	Had 1 dose of acetaminophen post appendectomy and discharged 3 days afterwards; developed symptoms/signs consistent with intra-abdominal abscess after discharge; abscess confirmed by ultrasound	Resolved
Study 14					Resolved
IV Ibu 10 mg/kg	03-015 9y/W/F	1 dose	Tonsillar hemorrhage	Had 1 dose of ibuprofen before tonsillectomy and bleeding at the surgical site 2 days afterwards	Resolved

Source: Sections 1.11.4.1.1 and 1.11.4.1.2 on pages 3-12 of submission dated August 6, 2015 in response to the reviewer's information request.

7.4.3 Dropouts and/or Discontinuations

Five cases of dropouts due to AEs were reported including four on IV ibuprofen treatment and one on acetaminophen treatment. The AEs were listed as thrombocytopenia (moderate), hypothermia and bradycardia (both graded as mild), headache (mild), and urticaria in the ibuprofen group and body temperature increased (mild) in the acetaminophen group as described in the table below. The case of urticarial was likely related to the ibuprofen as the event commenced seven minutes after the start of the ibuprofen infusion. Dropouts due to AEs accounted for 4% in the multiple-dose Study 012, 0% in Study 005, and 0.6% in the single-dose Study 014.

Table 7-6 Dropouts Due to Adverse Events

Study 12	**Patient**	**Doses**	**Adverse events**	**Brief description**	**Outcome**
IV Ibu 10 mg/kg	21-2104 6.5y/W/F	3 doses	Thrombocytopenia (moderate)	Concurrent illness involving multiple organ systems and infections; many lab abnormalities including anemia and neutropenia before receiving ibuprofen for fever; on vancomycin	Not mentioned in the report

	03-2042 10m/B/M	5 doses	Hypothermia, bradycardia (both graded as mild)	Burn injury involving 1/3 of total body surface; Blood positive for gram negative rods; on several concomitant medication	Resolved
	05-2074 12y/W/M	1 dose	Headache (mild)		Resolved
APAP 10 mg/kg	10-2075 1.5y/B/M	1 dose	Body temperature increased (mild)		Not mentioned
Study 14					
IV Ibu 10 mg/kg	01-038 17y/H/F	1 dose	Urticaria	Urticaria noticed 7 minutes after the start of ibuprofen infusion.	

Source: Attachment A. on pages 418-422 of the updated study report for Study 012 submitted on May 1, 2015 and Section 1.11.4.1.3 on page 13 of submission dated August 6, 2015 in response to the reviewer's information requests.

7.4.4 Significant Adverse Events

No significant AEs other than known ibuprofen treatment-related AEs, have been identified in the safety database.

7.4.5 Submission Specific Primary Safety Concerns (optional)

None.

7.5 Supportive Safety Results and Discussion

7.5.1 Common Adverse Events

The adverse events (AEs) reported in ≥2 pediatric patients in any active treatment group across the three pediatric studies are summarized in the table below. The most common AEs in the IV ibuprofen group were infusion site pain (n=8), vomiting (n=6), nausea (n=5), anemia (n=4), headache (n=3), pruritus (n=2), hypokalemia (n=2), and aspartate aminotransferase increased (n=2). The most common AEs in the acetaminophen group were mainly gastrointestinal (GI) symptoms such as diarrhea (n=4), vomiting (n=3), and nausea (n=2), and lab abnormalities such as hypokalemia (n=5), eosinophilia (n=3), basophilia (n=3), blood lactate dehydrogenase increased (n=3), aspartate aminotransferase increased (n=2), lymphocyte count decreased (n=2), anemia (n=2), and hypomagnesemia (n=2). In addition, two cases of pruritus and two cases of pleural effusion were reported in the acetaminophen group.

Table 7-7 Treatment Emergent AEs in ≥2 Pediatric Patients in Any Active Treatment Group

	System Organ Class Preferred Term	IV Ibu (N=144)	APAP (N=71)	Placebo (N=79)	Overall (N=294)
Any Treatment-Emergent AE		51 (35%)	35 (49%)	16 (20%)	102 (35%)
Mild		30 (21%)	25 (35%)	10 (13%)	65 (22%)
Moderate		18 (13%)	10 (14%)	5 (6%)	33 (11%)
Severe		3 (2%)	0	1 (1%)	4 (1%)
Gastrointestinal disorders	Vomiting	6 (4%)	3 (4%)	2 (3%)	11 (4%)
	Nausea	5 (3%)	2 (3%)	1 (1%)	8 (3%)
	Diarrhea	1 (<1%)	4 (6%)	0	5 (2%)
Investigations	Aspartate aminotransferase increased	2 (1%)	2 (3%)	0	4 (1%)
	Blood lactate dehydrogenase increased	1 (<1%)	3 (4%)	0	4 (1%)
	Lymphocyte count decreased	0	2 (3%)	0	2 (<1%)
General disorders and administration site conditions	Infusion site pain	8 (6%)*	0	0	5 (2%)
Blood and lymphatic system disorders	Anemia	4 (3%)	2 (3%)	0	6 (2%)
	Eosinophilia	1 (<1%)	3 (4%)	0	4 (1%)
	Basophilia	0	3 (4%)	0	3 (1%)

Metabolism & nutrition disorders	Hypokalemia	2 (1%)	5 (7%)	0	7 (2%)
	Hypomagnesaemia	0	2 (3%)	0	2 (<1%)
Nervous system disorders	Headache	3 (2%)	1 (1%)	1 (1%)	5 (2%)
Skin and subcutaneous tissue disorders	Pruritus	2 (1%)	2 (3%)	0	4 (1%)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	0	2 (3%)	0	2 (<1%)

Source: Table 2.7.4.2-2 on pages 18-21 of ISS submitted on March 20, 2015.

Because of the differences in study population, exposure, control group, and safety assessment, common AEs are grouped also under two categories: AEs reported in relatively healthy pediatric subjects undergoing tonsillectomy treated with a single dose of IV ibuprofen pre-surgery in comparison to placebo in Study 014 and AEs reported in hospitalized (or emergency room treated) patients with more serious medical conditions including critically ill patients who had multiple-dose treatment with IV ibuprofen in comparison to acetaminophen in Studies 012 and 005.

In Study 014 single-dose exposure in pediatric surgical population was associated with fewer AE reports: 17% reported any AE in the IV ibuprofen group and 20% in the placebo group. The most commonly reported individual AEs included infusion site pain (n=3), vomiting (n=3), nausea (n=2), and urticarial (n=2) in the IV ibuprofen group and agitation (n=3), restlessness (n=2), vomiting (n=2), erythematous rash (n=2), and bronchospasm (n=2) in the placebo group.

Table 7-8 Common AEs: ≥2 Patients Per Treatment Group, Study 014

Study 014	**System Organ Class Preferred Term**	**IV Ibu (N=82)**	**Placebo (N=79)**	**Overall (N=161)**
Any Treatment-Emergent AE		14 (17%)	16 (20%)	30 (19%)
Mild		7 (9%)	10 (13%)	17 (11%)
Moderate		7 (9%)	5 (6%)	12 (7%)
Severe		0	1 (1%)	1 (<1%)
Gastrointestinal disorders	Vomiting	3 (4%)	2 (3%)	5 (3%)
	Nausea	2 (2%)	1 (1%)	3 (2%)
General disorders & administration site conditions	Infusion site pain	3 (4%)	0	3 (2%)
Nervous system disorders	Agitation	1 (1%)	3 (4%)	4 (2%)
	Restlessness	0	2 (3%)	2 (1%)
Skin and subcutaneous tissue disorders	Rash Erythematous	0	2 (3%)	2 (1%)
	Urticaria	2 (2%)	0	2 (1%)
Immune system disorders	Bronchospasm	0	2 (3%)	2 (1%)

Source: Table 14.3.1.1 on pages 139-144 of the study report for Study 014 in the original submission of Supplement 5.

Pediatric febrile patients hospitalized or treated in the emergency room for serous medical conditions in Studies 005 and 012 had more AE reports: 60% reported any AE in the IV ibuprofen group and 49% reported any AE in the acetaminophen group. The most commonly reported individual AEs in the IV ibuprofen group included infusion site pain (n=5), anemia (n=4), vomiting (n=3), nausea (n=3), headache (n=3), pruritus (n=2) and some laboratory test abnormalities such as aspartate aminotransferase increased (n=2) and hypokalemia (2 cases). The most commonly reported individual AEs in the acetaminophen group were diarrhea (n=4), vomiting (3 cases), nausea (n=2), pruritus (n=2), pleural effusion (n=2), and laboratory test abnormalities including five cases of hypokalemia, three cases of each of the following: blood lactate dehydrogenase increased, eosinophilia, and basophilia, and two cases of each of the following: aspartate aminotransferase increased, lymphocyte count decreased, anemia, and hypomagnesemia. The most commonly reported individual AEs in both treatment groups were GI symptoms and laboratory test abnormalities.

Table 7-9 Common AEs: ≥2 Patients Per Treatment Group, Studies 012 and 005 (Pooled Data)

Study 012 and 005	System Organ Class Preferred Term	IV Ibu (N=62)	APAP (N=71)	Overall (N=133)
Any Treatment-Emergent AE		37 (60%)	35 (49%)	72 (54%)
Mild		23 (37%)	25 (35%)	48 (36%)
Moderate		11 (18%)	10 (14%)	21 (16%)
Severe		3 (5%)	0	3 (2%)
Gastrointestinal disorders	Vomiting	3 (5%)	3 (4%)	6 (5%)
	Nausea	3 (5%)	2 (3%)	5 (4%)
	Diarrhea	1 (2%)	4 (6%)	5 (4%)
Investigations	Aspartate aminotransferase increased	2 (3%)	2 (3%)	4 (3%)
	Blood lactate dehydrogenase increased	1 (2%)	3 (4%)	4 (3%)
	Lymphocyte count decreased	0	2 (3%)	2 (2%)
General disorders and administration site conditions	Infusion site pain	5 (8%)	0	5 (4%)
Blood and lymphatic system disorders	Anemia	4 (7%)	2 (3%)	6 (5%)
	Eosinophilia	1 (2%)	3 (4%)	4 (3%)
	Basophilia	0	3 (4%)	3 (2%)
Metabolism & nutrition disorders	Hypokalemia	2 (3%)	5 (7%)	7 (5%)
	Hypomagnesaemia	0	2 (3%)	2 (2%)
Nervous system disorders	Headache	3 (5%)	1 (1%)	4 (3%)
Skin and subcutaneous tissue disorders	Pruritus	2 (3%)	2 (3%)	4 (3%)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	0	2 (3%)	2 (2%)

Source: Table 1.11.3-2 on page 3 of the submission dated October 28, 2015 in response to the reviewer's information requests.

7.5.2 Laboratory Findings

Two fever Studies 012 and 005 had laboratory (lab) tests before and after the study. Almost all pediatric patients (100% of the IV ibuprofen group and 98% of the acetaminophen group) in the study population had abnormal lab tests since they were hospitalized for serious medical conditions and were mostly on concomitant medications. The lab abnormalities could not be reported in a standardized manner due to age dependent variation in defining normal ranges and variation in normal ranges among institutions performing sample analyses. Neither listing individual lab test abnormality nor summarizing mean values for the treatment groups are considered useful due to lack of placebo control and the limitations mentioned above. Therefore, general trends in terms of reporting rates on selected lab tests with 'clinically notable abnormalities' (refer to pages 67-69 of the Integrated Summary of Safety, ISS submitted March 20, 2015) are discussed briefly here.

Most of the markedly abnormal values in hematology were decreased hematocrit and hemoglobin and the reporting rates were higher, by 13% (79% versus 66%) in decrease of hematocrit and by 11% (60% versus 49%) in decrease of hemoglobin in the IV ibuprofen group than the acetaminophen group. Increases in liver enzymes occurred in approximately 30% pediatric patients and were similar for the two treatment groups and increase in bilirubin occurred more frequently in the acetaminophen group than the IV ibuprofen group (10% versus 2%). Decreased in BUN and creatinine were observed in both groups and there was not a clear pattern of changes to suggest abnormal renal function. Electrolyte imbalances indicated by chloride, potassium and sodium levels, occurred in approximately equal rates in the two treatment groups.

7.5.3 Vital Signs

The summary data on the mean changes of vital signs per treatment group are not useful because of the concurrent serious medical conditions, concomitant medications and widely varied normal ranges by age. Nevertheless, there were no clear patterns to suggest treatment differences between the two groups.

7.6 Other Safety Explorations

7.6.1 Dose Dependency for Adverse Findings

Weight-based dose of 10 mg/kg was given by 10-minute IV infusion to all pediatric patients in the three studies. Dose dependency of AEs could not be assessed based on pediatric data in the current submission. However, ibuprofen-related drug toxicities had been shown to be dose dependent in the studies of oral formulations (refer to the professional drug labeling for ibuprofen oral formulation).

7.6.2 Time Dependency for Adverse Findings

Time dependency for adverse findings could not be adequately assessed because the exposure in pediatric study population was limited to a single dose in Study 014 and up to a few doses in the two fever studies. Safety profile on long-term exposure to oral formulation of ibuprofen had been established (refer to the professional drug labeling for ibuprofen oral formulation).

7.6.3 Drug-Demographic Interactions (gender, race)

Analyses of drug-demographic interactions are not applicable because of the limited subpopulation sizes of the treatment groups divided by age, gender, and race.

7.6.4 Drug Disease Interactions

Refer to the professional drug labeling for ibuprofen.

7.6.5 Drug-Drug Interactions

Refer to the professional drug labeling for ibuprofen.

7.7 Additional Safety Evaluations

7.7.1 Human Carcinogenicity

Refer to the professional drug labeling for ibuprofen.

7.7.2 Human Reproduction and Pregnancy Data

Refer to the professional drug labeling for ibuprofen.

7.7.3 Pediatric Assessment and/or Effects on Growth

The main purpose of this review is to assess efficacy and safety of pediatric use of IV ibuprofen to inform product labeling. Effects on growth could not be assessed based on limited drug exposure in treating acute conditions.

7.7.4 Overdose, Drug Abuse Potential/ Withdrawal and Rebound

There were no reports of drug overdose in the pediatric studies of IV ibuprofen. Ibuprofen is not known to have abuse potential and problems with withdrawal or rebound.

7.8 Additional Submission

There were 12 additional submissions dated from March 6 to November 9, 2015, mostly about responses to information requests by the NDA reviewers and updated versions of labeling.

8 POSTMARKETING EXPERIENCE

Postmarketing experience for use of IV ibuprofen in adult population during the period of 2009 to 2013 was summarized and jointly reviewed by reviewers from this Division and from the Division of Pharmacovigilance II (refer to the FDAAA Section 915 review dated September 3, 2013 in DARRTS). The 915 review did not contain pediatric information.

9 APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

According to the ISS there were eleven literature reports of serious AEs from pediatric use of IV ibuprofen (some were assumed as IV because of uncertainty about the route of drug administration). The reported AEs from literature included metabolic acidosis (n=2), hypoxia (n=2), bronchopulmonary dysplasia, decreased glomerular filtration rate (GFR), pulmonary hypertension, anuria, refractory hypotension, renal failure, circulatory collapse, oliguria, and neonatal respiratory acidosis in six preterm infants being treated for patent ductus arteriosus (PDA). For newborns not treated for PDA there was one report of gastrointestinal bleeding in a newborn and one report of hyperbilibilirubinemia in a preterm infant. In addition, one case of major bleeding, one case described as methemoglobinemia, and one case of streptococcal toxic shock syndrome were reported in children 6 to 10 years of age.

9.2 Labeling Recommendations

Labeling will be reviewed separately.

9.3 Advisory Committee Meeting

There is no Advisory Committee Meeting planned for use of IV ibuprofen in pediatric patients.

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/s/

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