CLINICAL PHARMACOLOGY REVIEW

NDA: 22348	Submission Date: 1/30/15 Filing: 3/30/15
Submission Type; Code:	Prior Approval Supplement 005
Brand/Code Name:	Caldolor® Injection
Generic Name:	Ibuprofen intravenous injection
Clinical Pharmacology Primary Reviewer:	David Lee, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology 2
OND Division:	Division of Anesthesia, Analgesia, and Addiction Products
Sponsor:	Cumberland Pharmaceuticals
Relevant NDA(s)	-
Relevant IND(s):	62605
Formulation; Strength(s):	Injection 800 mg/mL
Proposed Indication:	For reduction of fever, and the management of mild to moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics
Proposed Dosage Regimen:	Pain: Recommended Dosing for Adults and Adolescents - Caldolor must be diluted prior to administration. Administer 400 mg to 800 mg intravenously every 6 hours as necessary. Infusion time must be no less than 30 minutes. Recommended Dosing for Children less than 12 years of age - Caldolor must be diluted prior to administration. Administer 10 mg/kg up to (b) (4) mg intravenously every 6 hours as necessary. Infusion time must be no less than 10 minutes. Fever: Recommended Dosing for Adults and Adolescents - Caldolor must be diluted prior to administration.

	Administer 400 mg intravenously, followed by 400 mg every 4 to 6 hours or 100-200 mg every 4 hours as necessary. Infusion time must be no less than 30 minutes. Recommended Dosing for Children less than 12 years of age - Caldolor must be diluted prior to administration. Administer 10 mg/kg up to 400 mg intravenously every 4 to 6 hours as necessary. Infusion time must be no less than 10 minutes.

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the NDA 22-349 submitted on 12/3/08. From OCP perspective, the information contained in the Application is acceptable provided that a satisfactory agreement can be reached with the Applicant regarding the Labeling. Only one subject was recruited from age group birth to < 2 months, and no subject was recruited from 2 months to 6 months. Therefore, additional subjects in these age groups need to be recruited to characterize efficacy, safety, and pharmacokinetics of the product.

1.2 Phase IV Commitments – Not applicable

1.3 Summary of CPB Findings

Cumberland Pharmaceuticals, Inc. has submitted a Prior Approval Supplement 005, to update the Caldolor®'s package insert. The Applicant is proposing the Change to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the package insert, to provide for antipyretic and analgesia use in the pediatric population, based on changes from post-marketing study results (the clinical safety and pediatric pharmacokinetic results). The changes also include information on the use in geriatric populations, and provide new dosage and administration recommendations. The updates to the following section are proposed: HIGHLIGHTS, Section 2 DOSAGE AND ADMINISTRATION, Section 6 ADVERSE REACTIONS (revised to include data obtained since the approval of Caldolor in 2009), Section 8 USE IN SPECIFIC POPULATIONS (the Pregnancy Section has been changed to reflect the new recommendations by the Agency according to the Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products Guidance for Industry issued December, 2014), Section 12 CLINICAL PHARMACOLOGY, Section 14 CLINICAL STUDIES, and Section 17 PATIENT COUNSELING INFORMATION.

The original Caldolor® NDA submission was submitted on 12/3/08 and approved on 6/11/09 with the following indication (the first intravenous product approved in the US for the treatment of fever): Caldolor is indicated in adults for the reduction of fever and for the management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics. The original NDA was reviewed under the Fast Track development program (designation granted on 7/15/08). References were made to three ibuprofen NDAs for this 505(b)(2) application: NDA 020-516, Children's Motrin (suspension; oral), NDA 020-402, Advil Liqui-Gels (capsule; oral), and NDA 017-463, Motrin (tablet; oral). Advil Liqui-Gel was used as a reference to obtain relative bioavailability information.

In the current submission, the Applicant submitted the results obtained from a clinical study, Study CPI-CL-012. The Study CIP-CL-012 was a Phase 4 efficacy, safety and pharmacokinetic (PK) study in pediatric patients with Caldolor. The PK information submitted in Study 012 was assessed in this current review.

Study 012 was a multi-center, randomized, open-label, parallel, active comparator, single or multiple-dose clinical study to assessed the efficacy, safety, and pharmacokinetics (PK) of ibuprofen administered intravenously to hospitalized febrile pediatric patients (temperatures of 101°F or greater) less than or equal to 16 years of age. Pediatric patients were randomized to intravenous ibuprofen at 10 mg/kg or acetaminophen at 10 mg/kg.
The pediatric patients were randomized to the following age groups: Birth to < 2 months, 2 months to < 6 months, 6 months to < 2 years, 2 years to < 6 years and 6 years to ≤ 16 years. The following mean pharmacokinetic parameters by age group (Table 1).

Table 1 Mean pharmacokinetic parameters by Age Group

Age Category	Birth to < 2 months	6 months to < 2 years	2 to < 6 years	6 to 16 years
N	1	5	12	25
AUC0-t (µg•hr/mL)	51.18	71.15	79.19	80.67
AUC0-4 (µg•hr/mL)	69.14	70.92	80.25	85.73
Cmax (µg/mL)	49.83	59.24	64.18	61.89
Tmax# (min)	10*	10 (10-30)	12 (10-46)	10 (10-40)
T½ (hr)	1.18	1.78	1.48	1.55
CL (mL/hr)	619.97	1172.5	1967.27	4878.47
Vz (mL)	1053.72	2805.73	3695.76	10314.21
CL/WT (mL/hr/kg)	129.16	133.66	130.064	109.22
Vz/WT (mL/kg)	219.53	311.2	227.23	226.824

AUC0-t: Area under the concentration-time curve from time zero to the last measurable concentration using linear-log trapezoidal rule.
AUC0-4: Area under the concentration-time curve from time zero to 4 hours.
Cmax: Maximum observed concentration.
Tmax#: Median (min-max)
*: Observed Tmax value (N=1).
T½ el: Elimination half-life, calculated as ln(2)/Kel
Cl: Total body clearance, calculated as Dose/AUC0-inf.
Vz: Volume of distribution, calculated as Dose/(Kel x AUC0-inf).
WT^: body weight (kg)
Study report CPI-CL-012

The mean AUC0-4 increased slightly with age. The mean T1/2 values were similar among age categories. The body weight normalized clearance (CL) and volume of distribution (Vz) values appear to be similar in all age groups. The elimination half-life ranged from 0.79 to 2.87 hours with a mean of 1.55 hours.

Only one subject was recruited from age group birth to < 2 months, and no subject was recruited from 2 months to 6 months. Therefore, additional subjects in these age groups need to be recruited to characterize efficacy, safety, and pharmacokinetics of the product.

Observed ibuprofen concentrations were compared between pediatric patients Study CPI-CL-012 (10 mg/kg 10-minute infusion) and adult patients Study CPI-CL-004 (400 mg 30-minute infusion) (submitted in the original NDA 12/3/08; review dated 5/4/09). For the comparison purpose, the first 4-h ibuprofen concentrations from the 400 mg dose will be used since the approved dose in adults are 400 mg administered over 30 minutes (the pain and fever indication in adults for Caldolor is 400 to 800 mg intravenous over 30 min Q6h as necessary and 400 mg intravenous over 30 min, followed by 400 mg Q4h to Q6h or 100-200 mg Q4h as necessary, respectively). The overall observation is that the general shapes of ibuprofen plasma profiles from the pediatric febrile groups are very similar to that of the

adult 400 mg febrile patients. In addition, the Cmax and AUC values are also comparable between the two groups. Detailed comparison can be found in section 2.3.2

2 QBR

2.1 General Attributes of the Drug

The reader is referred to Caldolor®'s original Clinical Pharmacology Review dated 5/11/09 (in DARRTS).

2.2 General Clinical Pharmacology

The reader is referred to Caldolor®'s original Clinical Pharmacology Review dated 5/11/09 (in DARRTS).

2.3 Intrinsic Factors

2.3.1 What is the ibuprofen exposure information in pediatric patients with Caldolor intravenous injection?

Study 012 was a multi-center, randomized, open-label, parallel, active comparator, single or multiple-dose clinical study to assessed the efficacy, safety, and pharmacokinetics (PK) of ibuprofen administered intravenously to hospitalized febrile pediatric patients (temperatures of 101°F or greater) less than or equal to 16 years of age. Pediatric patients were randomized to intravenous ibuprofen at 10 mg/kg or acetaminophen at 10 mg/kg.

The pediatric patients were randomized to the following age groups: Birth to < 2 months, 2 months to < 6 months, 6 months to < 2 years, 2 years to < 6 years and 6 years to ≤ 16 years. Blood samples were collected for ibuprofen concentration measurements as follows: 1) for subjects less than six months of age - samples were taken immediately after the first dose; then alternating subject had samples taken at 30 minutes and 2 hours or at 1 hour and 4 hours following the first ibuprofen dose; 2) for subjects of six months of age or older - samples were taken immediately after the first dose; then at 30 min., 1, 2, and 4 hours following the first ibuprofen dose. The following PK parameters were obtained if possible: AUC0-t, AUC0-4, Cmax, Tmax, T1/2, CL, and Vz using WinNonlin.

The following tables contain demographic information. Table 2 contains overall information. Tables 3 and 4 contain age and weight by age group, respectively.

Table 2 Overall demographic and baseline characteristics

	Intravenous ibuprofen (n=47)	**Acetaminophen** (n=53)	**Total** (n=100)

Age (years)			
Mean (SD)	7 (4.6)	6 (4.4)	7 (4.5)
Min, Max	<1, 16	<1, 15	<1, 16
Gender			
Male	27 (57%)	26 (49%)	53 53%)
Female	20 (43%)	27 (51%)	47 47%)
Race			
Caucasian	42 (89%)	42 (79%)	84 84%)
Black or African American	5 (11%)	8 (15%)	13 13%)
American Indian/Alaska Native	0	2 (4%)	2 (2%)
Other	0	1 (2%)	1 (1%)
Ethnicity			
Hispanic or Latino	29 (62%)	24 (45%)	53 53%)
Not Hispanic or Latino	18 (38%)	29 (55%)	47 47%)
Weight (kg)			
Mean (SD)	30.2 (19.50)	24.2 (15.18)	27.0 (17.52)
Min, Max	7.3, 80.1	7.2, 63.0	7.2, 80.1

Table 3 Age (months) vs groups:

Age group		< 6 months Months	6 months to < 2 years Months	2 to < 6 years Months	6 to 16 years Months
Overall	Mean	-	11.1	39.2	122.2
	SD	-	5.04	14	38.4
Males subject	Mean	1	11.4 (N=8)	39 (N=8)	125.3 (N=18)
	SD	-	5.7	15.4	38.2
	Range	-	6 - 11	24 - 60	72 - 156
Females subject	Mean	-	10 (N=2)	39.4 (N=7)	118.4 (N=15)
	SD	-	1.4	13.4	39.5
	Range		9 and 11	24 – 60	72 – 180

Table 4 Weight (kg) vs. groups:

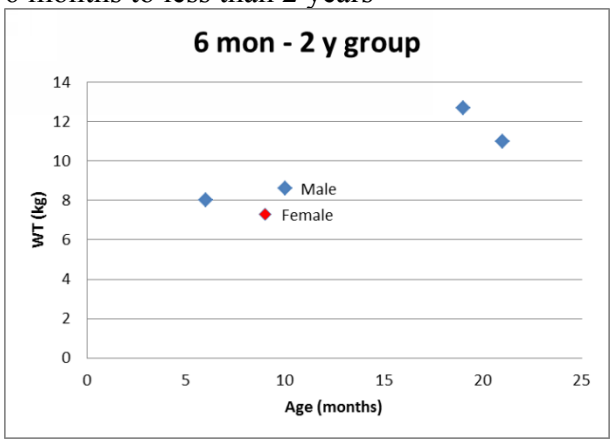
Age group		< 6 months kg	6 months to < 2 years kg	2 to < 6 years kg	6 to 16 years kg
Overall	Mean	-	10.3	16.4	39.3

	SD	-	2.5	4.5	17.6
Males subject	Mean	4.8	10.6 (N=8)	16.3 (N=8)	39.8 (N=18)
	SD	-	2.6	3.8	16.3
	Range	-	7.1 – 14.5	11.3 – 21.1	20 – 80.1
Females subject	Mean	-	9.3 (N=2)	16.5 (N=7)	38.7 (N=15)
	SD	-	2.8	3.8	19.6
	Range	-	7.3 and 11.3	11.9 – 27.2	16.3 – 75.3

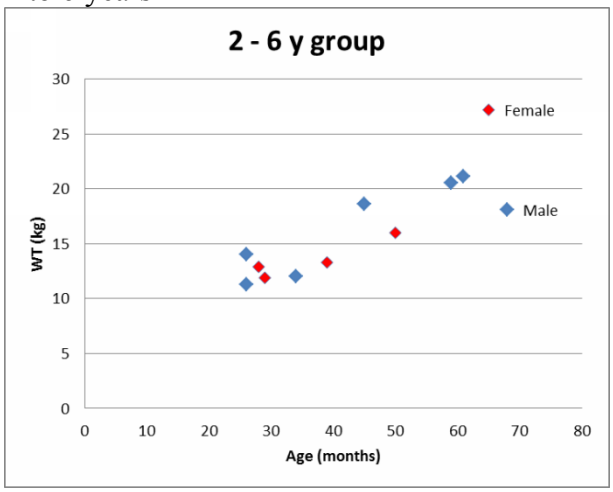
The Figures 1 a, b, and c contain individual body weight in terms of sex in 6 months to less than 2 years, 2 to 6 years, and 6 to 16 years, respectively.

Figure 1 a, b, and c: Individual body weight for 6 months to less than 2 years (a), 2 to 6 years (b), and 6 to 16 years (c)

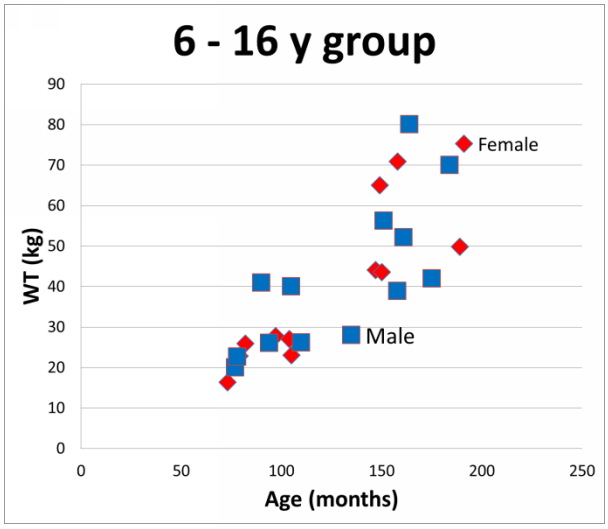
a) 6 months to less than 2 years



b) 2 to 6 years



c) 6 to 16 years

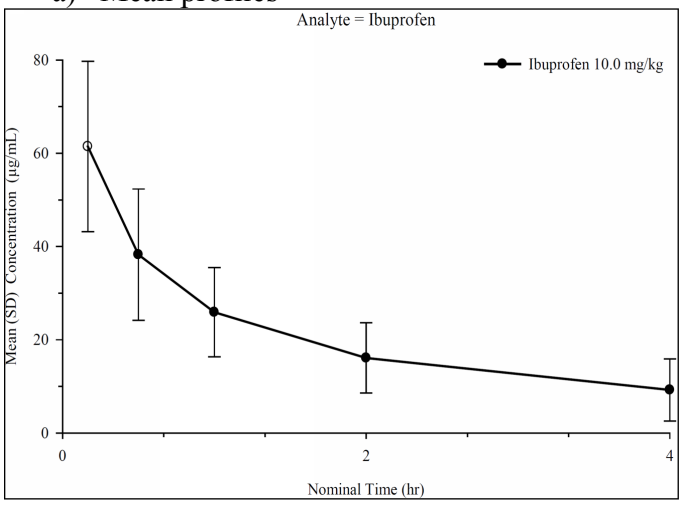


The Figures 2 a and b contain the ibuprofen mean and individual profiles, respectively, from all age groups.

The Figures 3 a, b and c contain the ibuprofen individual subject profiles by 6 months to less than 2 years, 2 to 6 years, and 6 to 16 years, respectively.

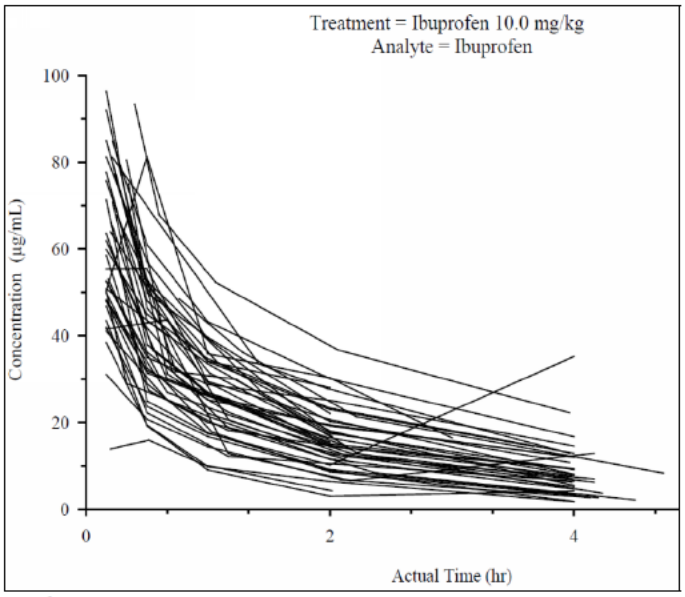
Figure 2 Mean Plasma Concentration-Time from all age groups.

a) Mean profiles



Study report CPI-CL-012

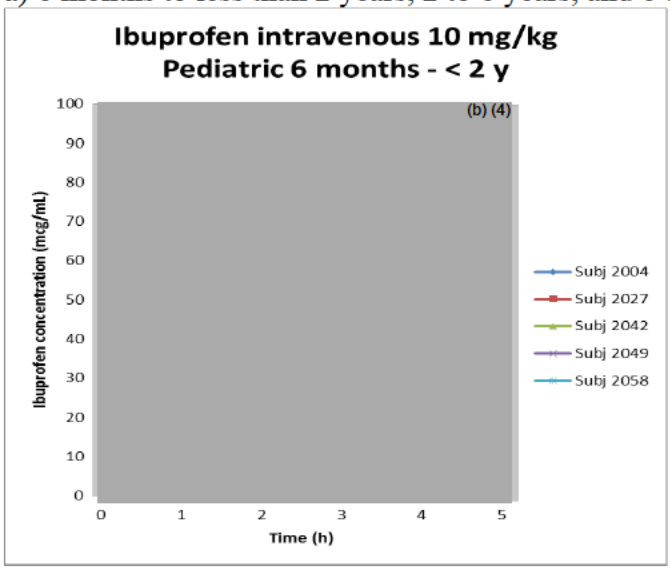
b) Individual profiles



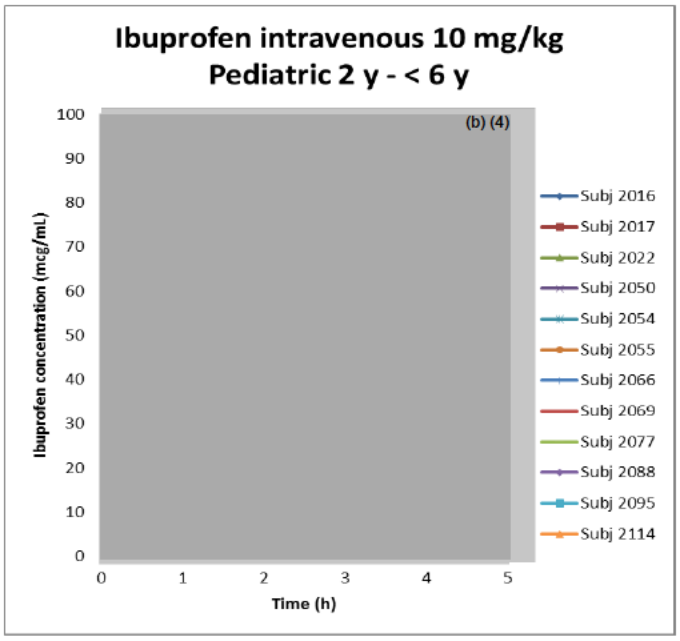
Study report CPI-CL-012

Figure 3 a, b and c: ibuprofen individual subject profiles by 6 months to less than 2 years, 2 to 6 years, and 6 to 16 years.

a) 6 months to less than 2 years, 2 to 6 years, and 6 to 16 years



b) 2 to 6 years



c) 6 to 16 years

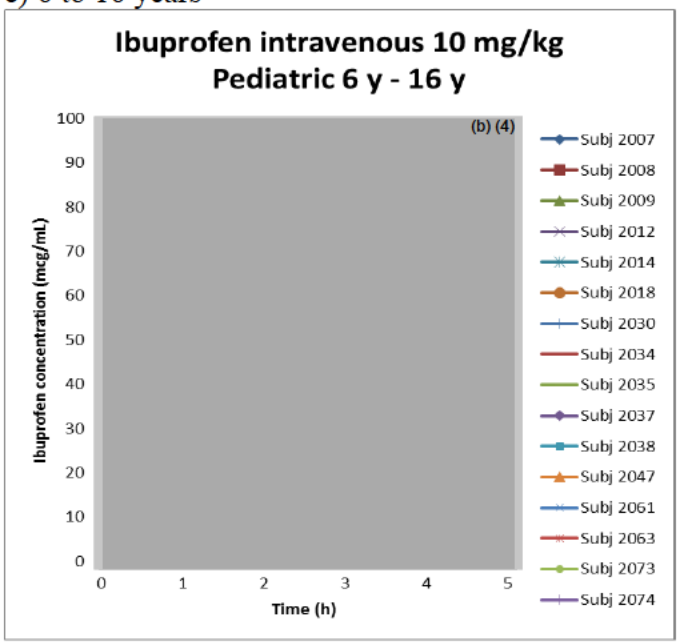


Table 5 contains mean pharmacokinetic parameters by age group.

Table 5 Mean pharmacokinetic parameters by Age Group

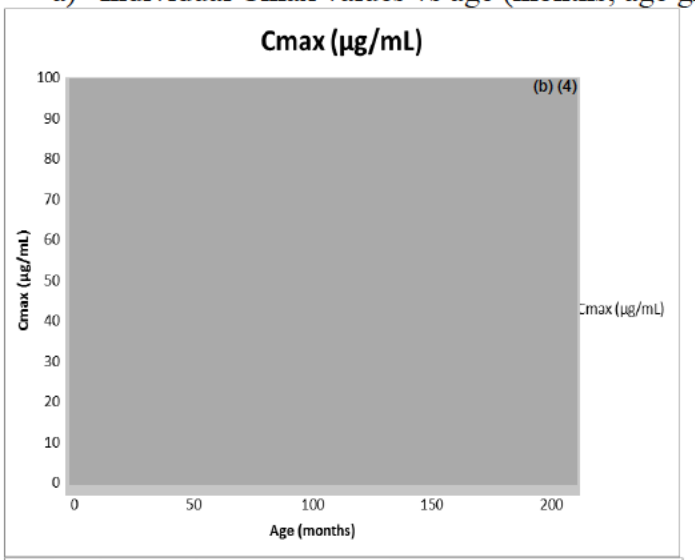
Age Category	Birth to < 2 months	6 months to < 2 years	2 to < 6 years	6 to 16 years
N	1	5	12	25
AUC0-t (µg•hr/mL)	51.18	71.15	79.19	80.67
AUC0-4 (µg•hr/mL)	69.14	70.92	80.25	85.73
Cmax (µg/mL)	49.83	59.24	64.18	61.89
Tmax# (min)	10*	10 (10-30)	12 (10-46)	10 (10-40)
T½ (hr)	1.18	1.78	1.48	1.55
Cl (mL/hr)	619.97	1172.5	1967.27	4878.47
Vz (mL)	1053.72	2805.73	3695.76	10314.21
Cl/WT (mL/hr/kg)	129.16	133.66	130.064	109.22
Vz/WT (mL/kg)	219.53	311.2	227.23	226.824

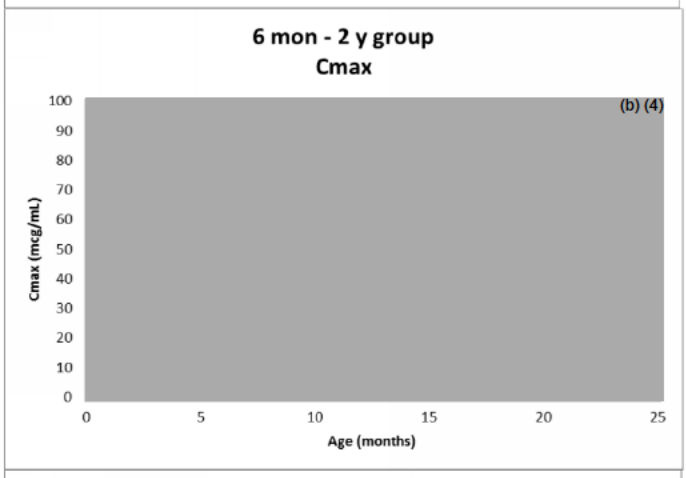
AUC0-t: Area under the concentration-time curve from time zero to the last measurable concentration using linear-log trapezoidal rule.
AUC0-4: Area under the concentration-time curve from time zero to 4 hours.
Cmax: Maximum observed concentration.
Tmax#: Median (min-max)
*: Observed Tmax value (N=1).
T½ el: Elimination half-life, calculated as ln(2)/Kel
Cl: Total body clearance, calculated as Dose/AUC0-inf.
Vz: Volume of distribution, calculated as Dose/(Kel x AUC0-inf).
WT^: body weight (kg)
Study report CPI-CL-012

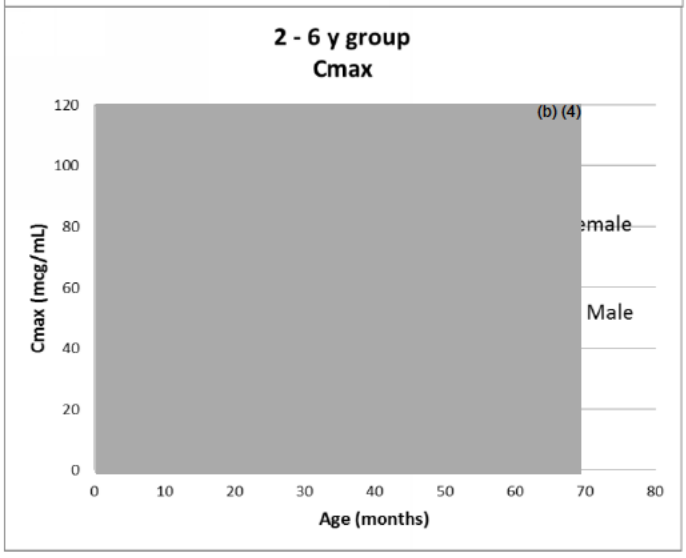
The Figures 4 a, b, c and d contain plots of individual Cmax, AUC0-4, Vz and CL values, respectively, vs age (months). The plots indicted that there were no obvious differences for Cmax and AUC0-4 values in age groups.

Figure 4 a, b, c and d: individual Cmax and AUC0-4, Vz (Vz/WT) and CL (CL/WT) values (sex as variable) vs age (months), respectively.

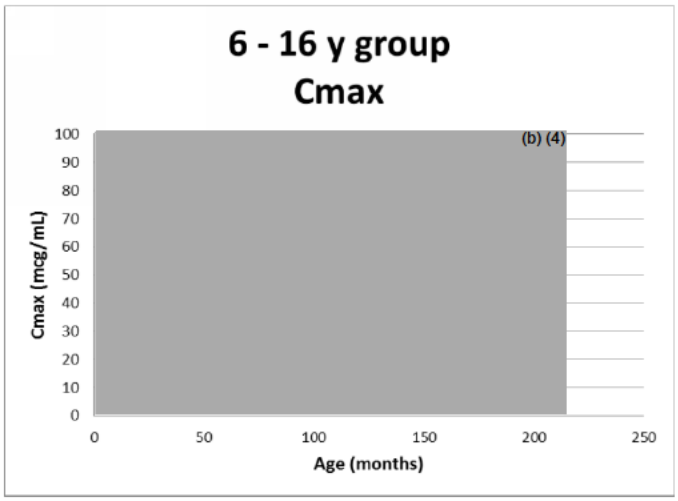
a) Individual Cmax values vs age (months; age groups).



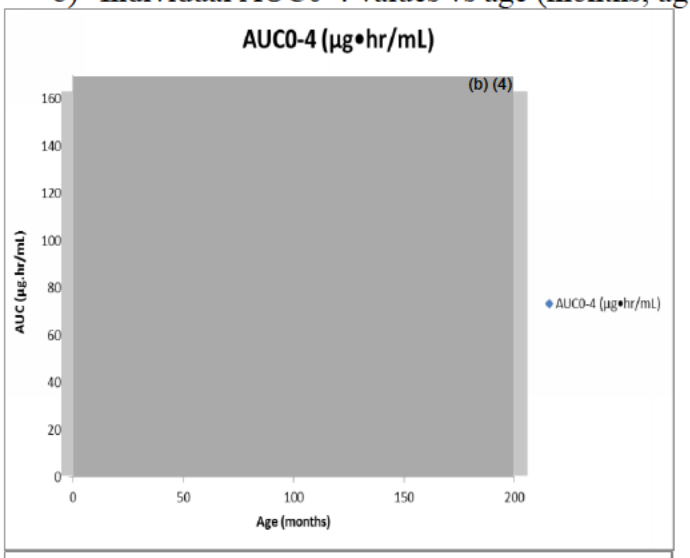


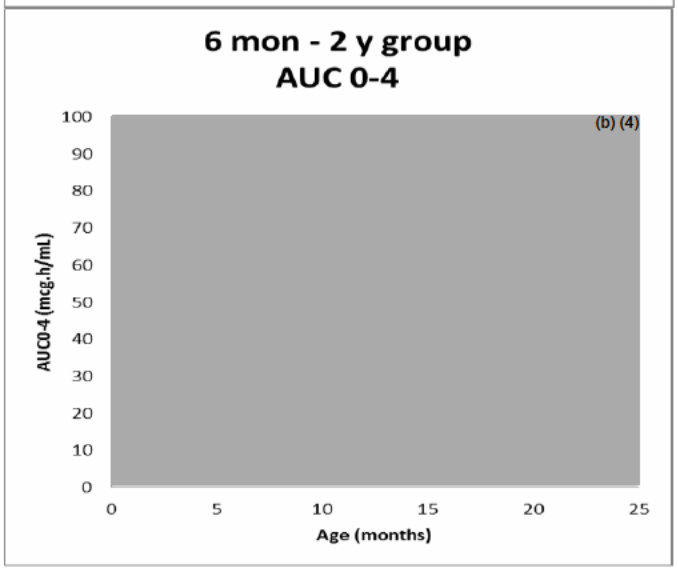


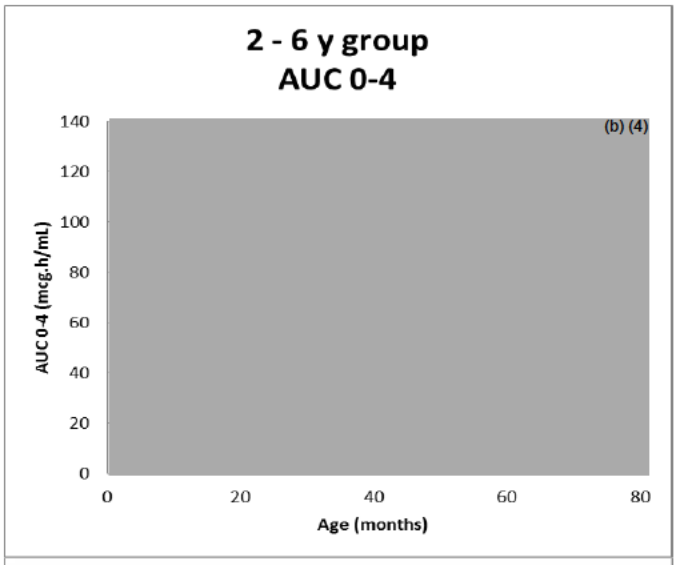
(b)
(4)



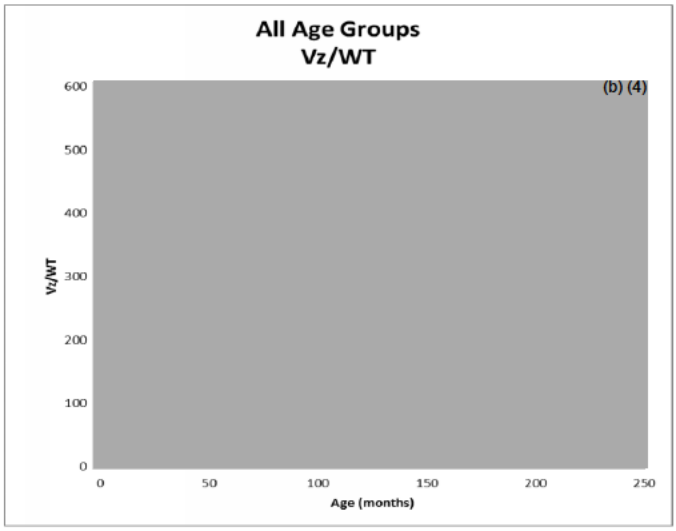
b) Individual AUC0-4 values vs age (months; age groups).

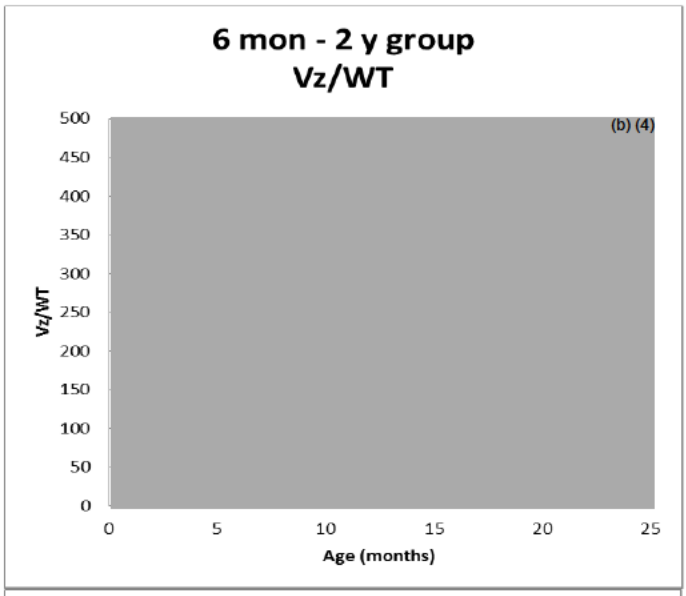


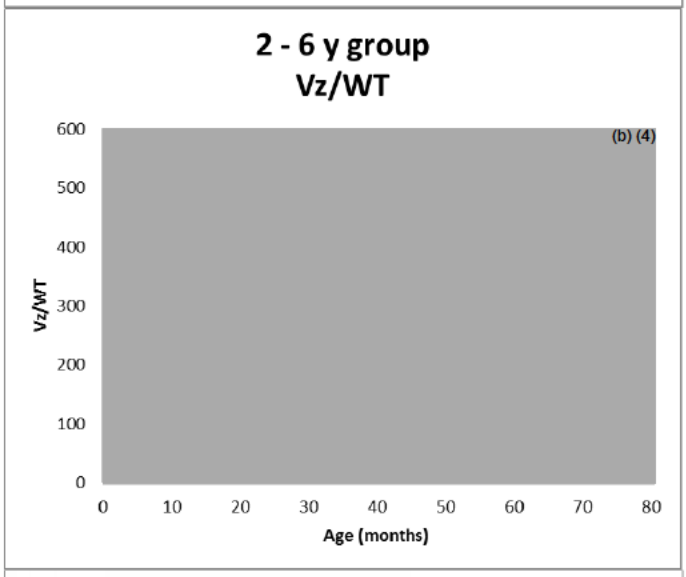


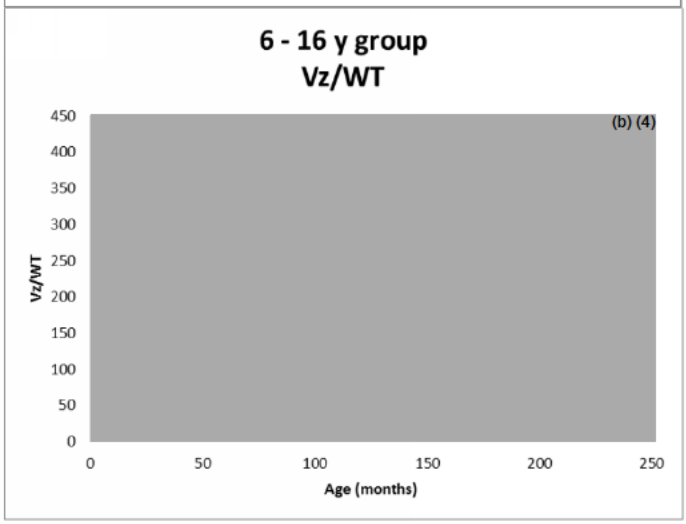


c) Vz and Vz/WT (kg) values vs age (months; age groups).

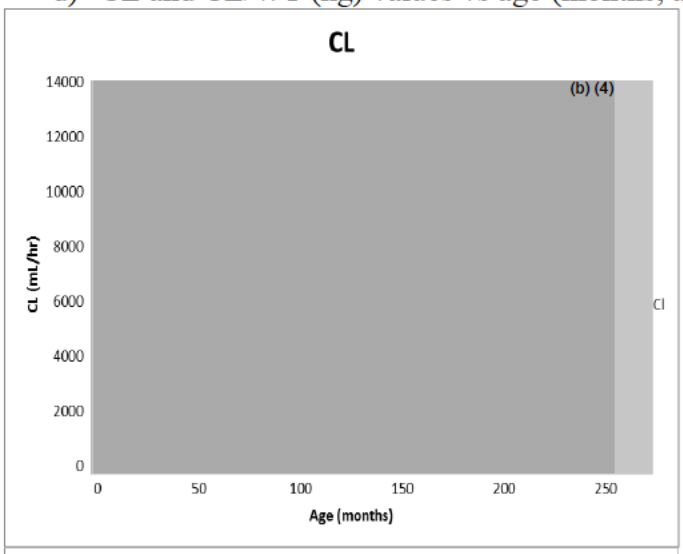


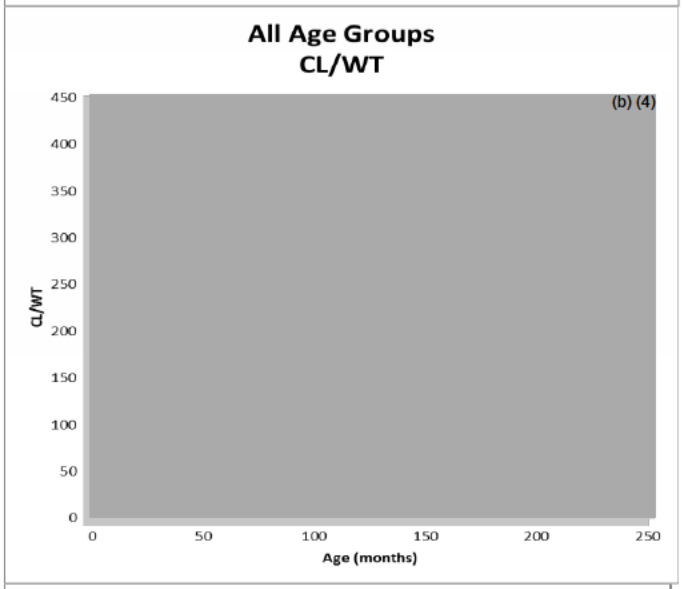

6 mon - 2 y group
Vz/WT
(b) (4)
Vz/WT
Age (months)

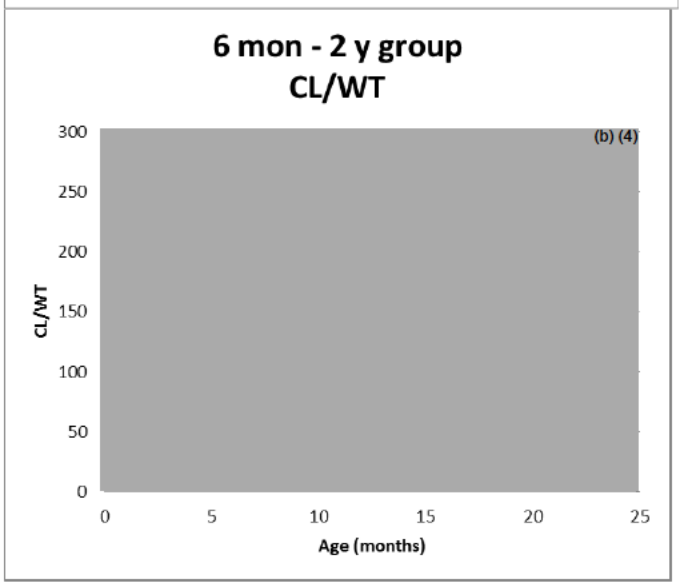

2 - 6 y group
Vz/WT
(b) (4)
Vz/WT
Age (months)

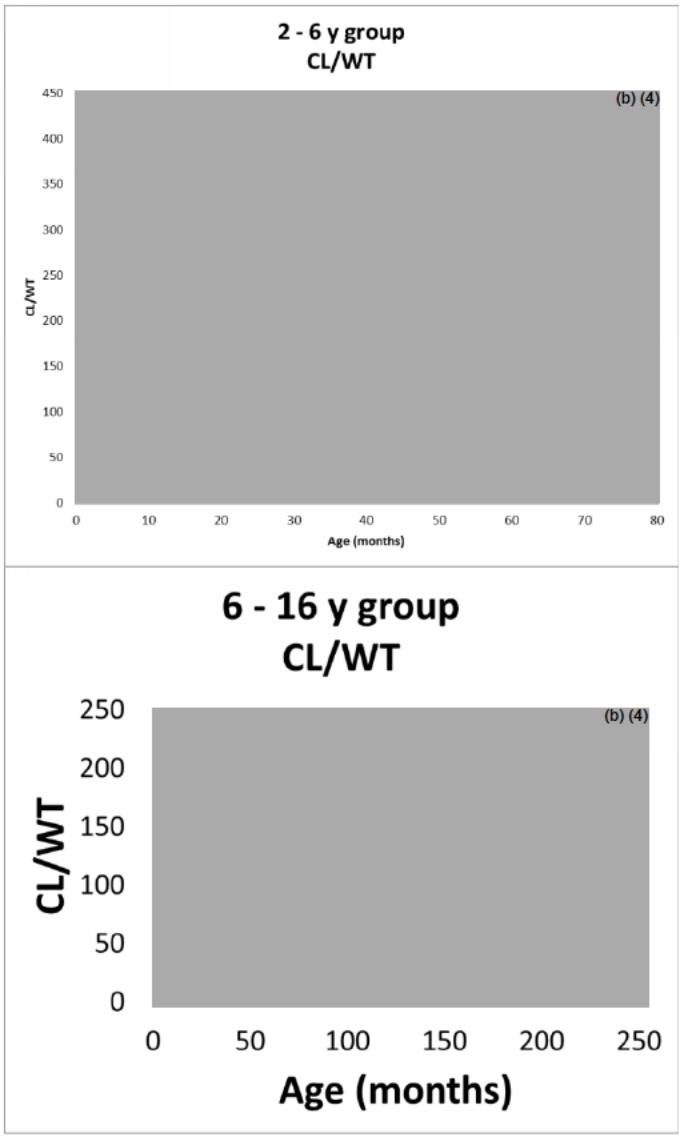

6 - 16 y group
Vz/WT
(b) (4)
Vz/WT
Age (months)

d) CL and CL/WT (kg) values vs age (months; age groups).









The extent (AUC0-4) and rate of absorption (Cmax) ranged respectively from 22.96 to 162.03 µg*hr/mL and 15.91 to 96.31 µg/mL. The AUC0-4 increased with age. The mean T1/2 values were similar among age categories. The body weight normalized clearance (CL) and volume of distribution (Vz) values appear to be similar in all age groups. The elimination half-life ranged from 0.79 to 2.87 hours with a mean of 1.55 hours.

2.3.2 What does ibuprofen exposure in pediatric patients look like when compared to adult patients after Caldolor intravenous injection?

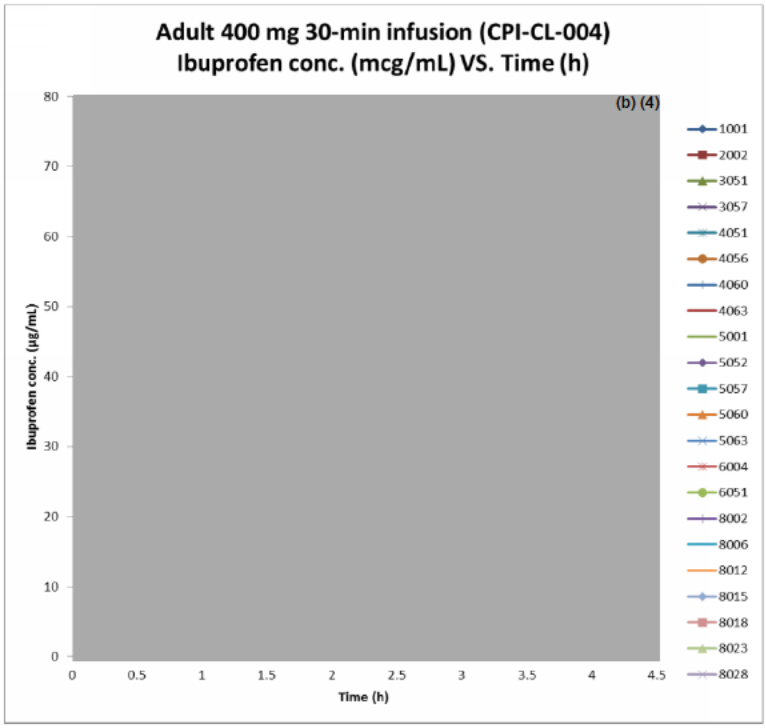
Observed ibuprofen concentrations were compared from pediatric patients Study CPI-CL-012 and adult patients Study CPI-CL-004 (submitted in the original NDA 12/3/08; review dated 5/4/09). Briefly, Study CPI-CL-004 was a multi-center, randomized, double-blind, parallel, placebo-controlled trial to evaluate the efficacy, safety, and PK of ibuprofen injection in adult febrile patients (who had temperatures of 101°F (38.3°C) or greater. Doses

were 100 mg, 200 mg and 400 mg of ibuprofen or placebo as a 30-minute infusion, administered Q4h for 24 hours. Blood samples were collected at 0, 0.5, 1, 2, 3, and 4 (before start of second infusion), and 20 (immediately before start of last infusion), 20.5 (at the end of last infusion), 22, 24, and 26 hours. For the comparison purpose, the first 4-h ibuprofen concentrations from the 400 mg dose will be used since the approved dose in adults are 400 mg administered over 30 minutes (the pain and fever indication in adults for Caldolor is 400 to 800 mg intravenous over 30 min Q6h as necessary and 400 mg intravenous over 30 min, followed by 400 mg Q4h to Q6h or 100-200 mg Q4h as necessary, respectively).

The Figure 5 contains individual ibuprofen concentration (µg/mL) profiles from adult 400 mg 30-minute infusion (a) and pediatric groups (b) 10 mg/kg 10-minute infusion. The Figure 6 contains mean ibuprofen concentration (µg/mL) profiles from adult 400 mg 30-minute infusion (a) and pediatric groups (b) 10 mg/kg 10-minute infusion. The overall observation is that the general shapes of ibuprofen plasma profiles from the pediatric febrile groups are very similar to that of the adult 400 mg febrile patients.

Figure 5 Individual ibuprofen concentration (µg/mL) profiles from adult 400 mg 30-minute infusion(a) and pediatric groups(b) 10 mg/kg 10-minute infusion.

a) Adult 400 mg 30-minute infusion



b) Pediatric 10 mg/kg 10-minute infusion

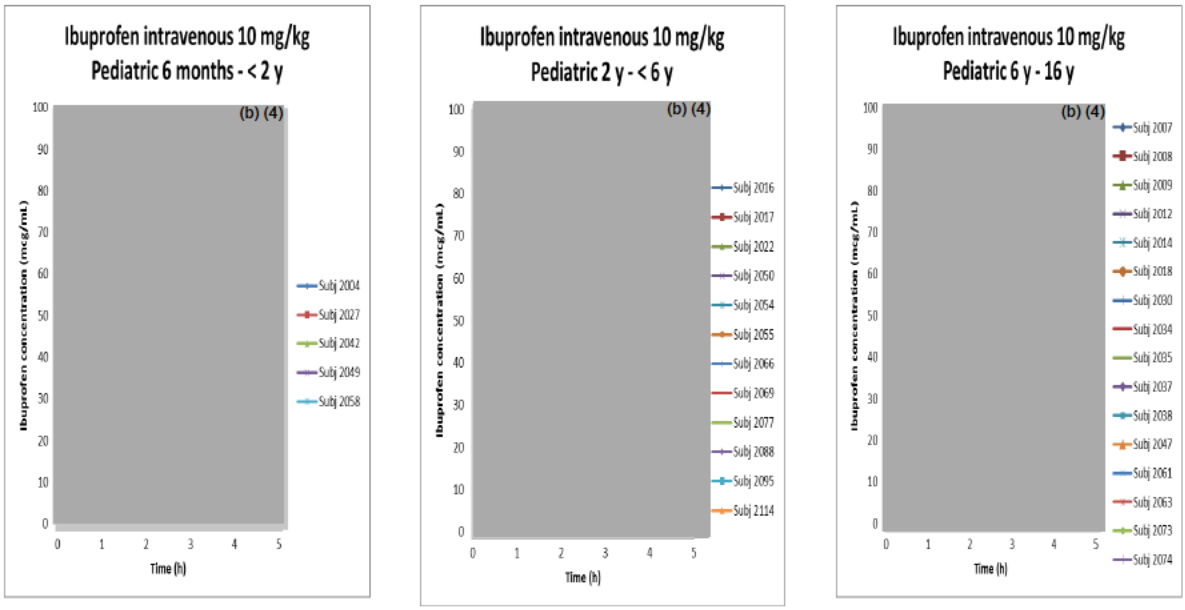
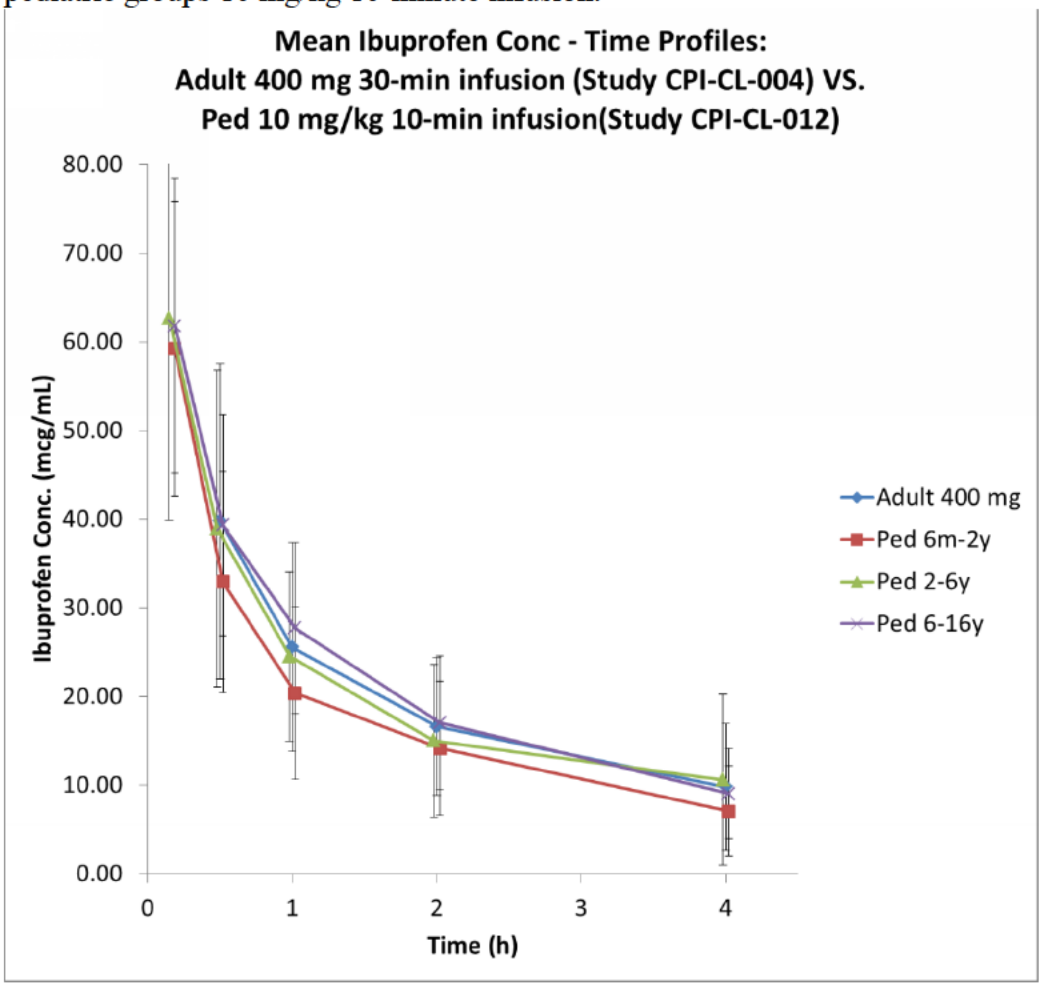


Figure 6 Mean ibuprofen concentration (µg/mL) profiles from adult 400 mg 30-minute infusion and pediatric groups 10 mg/kg 10-minute infusion.



The information used to generate Figure 6 is presented in a table format (Table 6). Comparing 0.5-h mean ibuprofen concentrations across groups showed similar values. The same observation is noted for 4-h mean ibuprofen concentrations.

Table 6 Comparison table of ibuprofen concentrations for adult febrile patients 400 mg 30-minute infusion and pediatric febrile patients 10 mg/kg 10-minute infusion

	Adult 400 mg		Ped 6mo-2y		Ped 2 - 6y		Ped 6 - 16y	
Time (h)	Mean (µg/mL)	SD	Mean (µg/mL)	SD	Mean (µg/mL)	SD	Mean (µg/mL)	SD
0.167	.	.	59.22	20.61	62.62	22.73	61.81	16.59
0.5	**39.76**	17.75	**32.91**	14.31	**38.94**	17.90	**39.31**	12.45
1	25.55	11.77	20.35	7.91	24.49	9.54	27.70	9.71
2	16.59	7.77	14.15	5.88	14.99	8.64	17.02	7.55
4	**9.79**	7.16	**7.05**	3.66	**10.58**	9.63	**9.03**	5.12

The mean pharmacokinetic parameters are presented in Table 7 for adult febrile patients (400 mg 30-minute infusion) and pediatric febrile patients (10 mg/kg 10-minute infusion).

Table 7 Mean pharmacokinetic parameters from adult febrile patients, 400 mg 30-minute infusion and pediatric febrile patients, 10 mg/kg 10-minute infusion

Mean	CPI-CL-004 Adult febrile patients SD 400 mg 30-min infusion	CPI-CL-012 Pediatric febrile patients 10 mg/kg 10-min infusion		
	400 mg N=25	6 mo to < 2 y N=5	2 to < 6 y N=12	6 to 16 y N=25
Cmax (µg/mL)	39.76	59.24	64.18	61.89
AUC0-4 (µg.h/mL)	70.64	70.92	80.25	85.73
Tmax (h)	0.5	10 (range 10-30)	12 (range 10-46)	10 (range 10-40)
T1/2 (h)	2.26	1.78	1.48	1.55

2.4 Extrinsic Factors – Not applicable

2.5 General Biopharmaceutics – Not applicable

2.6 Analytical Section

2.6.1 What active moieties were measured in the plasma in the clinical pharmacology and biopharmaceutics studies and what bioanalytical methods are used to assess concentrations?

Blood samples were analyzed using a validated high performance liquid chromatographic method with tandem mass spectrometry detection (Validation Report No. 115102AEEP: Validation of a High Performance Liquid Chromatographic Method using Tandem Mass Spectrometry Detection for the Determination of Ibuprofen in Human EDTA K2 Plasma; (b) (4)). A typical concentration ranges for standards and quality control samples were 1.00 to 100.00 µg/mL. The typical values obtained from the analytical runs are shown in Tables 8 and 9.

Table 8 Analytical Performance: Back-Calculated Concentrations (µg/mL) of Ibuprofen Calibration Standards in Human EDTA K2 Plasma - 1st Preparation (102002AABP)

Assay Date	Run ID	CS1 1.00 µg/mL	CS2 2.00 µg/mL	CS3 5.00 µg/mL	CS4 10.01 µg/mL	CS5 20.02 µg/mL	CS6 40.04 µg/mL	CS7 80.07 µg/mL	CS8 100.09 µg/mL
2011-09-14	1	1.01	1.70	5.21	9.99	19.30	40.18	77.60	97.42
		1.04	2.01	5.36	10.13	21.18	38.63	78.55	106.12
2011-09-16	2	0.93	1.84	5.37	9.96	19.77	40.68	79.06	103.10
		1.03	2.25	5.06	10.02	19.29	38.67	74.34	103.05
2012-05-18	3	0.94	2.01	5.21	9.81	19.88	40.56	77.78	97.23
		1.04	2.01	5.30	10.21	19.59	38.57	78.99	103.50
2012-05-22	4	1.03	1.92	5.17	9.49	21.19	38.16	80.74	106.18
		1.05	1.87	4.41	9.72	18.98	41.54	84.37	107.53
Mean		1.01	1.95	5.14	9.92	19.90	39.62	78.93	103.02
S.D.		0.05	0.16	0.31	0.23	0.84	1.26	2.86	3.87
% of CV		4.95	8.21	6.03	2.32	4.22	3.18	3.62	3.76
% of Bias		1.00	-2.50	2.80	-0.90	-0.60	-1.05	-1.42	2.93
n		8	8	8	8	8	8	8	8

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Table 9 Analytical Performance of Ibuprofen Quality Control Samples in Human EDTA K2 Plasma - 1st Preparation (102002AABP)

Run Date	Run ID	QC1 3.00 µg/mL	QC4 7.51 µg/mL	QC2 35.02 µg/mL	QC3 75.06 µg/mL
2011-09-14	1	3.05	7.47	32.87	79.25
		3.17	7.58	36.56	72.05
2011-09-16	2	3.39	7.67	36.11	78.92
		3.26	7.93	35.20	76.66
2012-05-18	3	3.16	7.37	36.35	75.15
		3.22	8.22	34.93	74.78
2012-05-22	4	2.98	6.73	33.81	81.09
		3.04	~9.70	35.28	77.19
Mean		3.16	7.83	35.14	76.89
S.D.		0.13	0.87	1.28	2.89
% of CV		4.11	11.11	3.64	3.76
% Theoretical		105.33	104.26	100.34	102.44
% of Bias		5.33	4.26	0.34	2.44
n		8	8	8	8

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3 Detailed Labeling Recommendations

The following revisions (deleted and revised in red fonts) are recommended from clinical pharmacology perspective.

12.3 Pharmacokinetics

Ibuprofen is a racemic mixture of [-]R- and [+]S-isomers. In vivo and in vitro studies indicate that the [+]S-isomer is responsible for clinical activity. The [-]R-form, while thought to be pharmacologically inactive, is slowly and incompletely (~60%) interconverted into the active [+]S species in adults. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. The pharmacokinetic parameters of Caldolor determined in a study with volunteers are presented below.

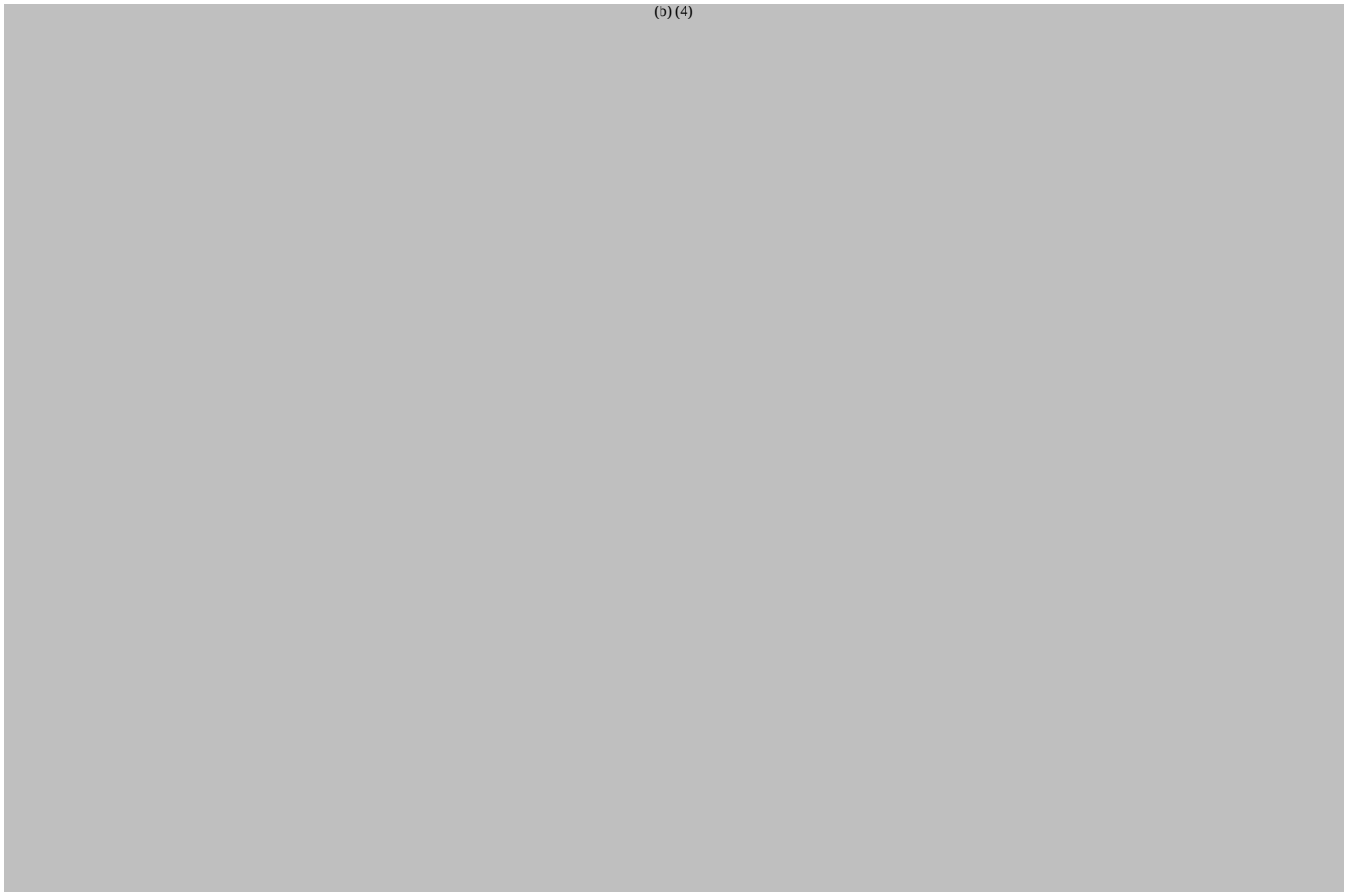
Table 3: Pharmacokinetic Parameters of Intravenous Ibuprofen, Adults

	Caldolor	
	400 mg* Mean (CV%)	800 mg* Mean (CV%)
Number of Subjects	12	12
AUC (mcg·h/mL)	109.3 (26.4)	192.8 (18.5)
C_{max} (mcg/mL)	39.2 (15.5)	72.6 (13.2)
KEL (1/h)	0.32 (17.9)	0.29 (12.8)
$T_{1/2}$ (h)	2.22 (20.1)	2.44 (12.9)

AUC = Area-under-the-curve
Cmax = Peak plasma concentration
CV = Coefficient of Variation
KEL = First-order elimination rate constant
$T_{1/2}$ = Elimination half-life

* = 60 minute infusion time

(b) (4)



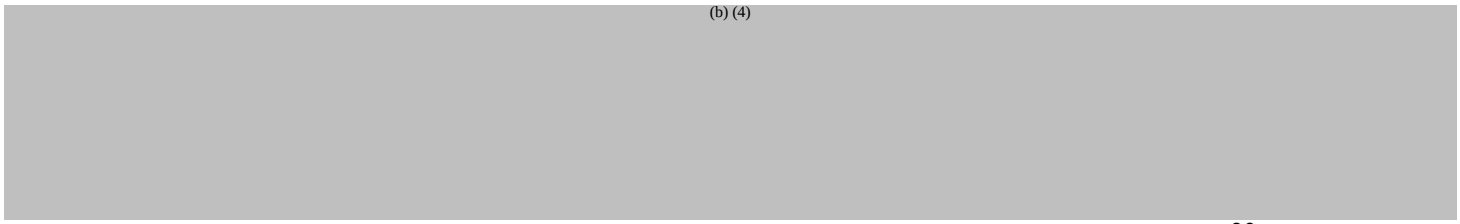
Ibuprofen, like most NSAIDs, is highly protein bound (>99% bound at 20 mcg/mL). Protein binding is saturable, and at concentrations >20 mcg/mL binding is nonlinear. Based on oral dosing data, there is an age- or fever-related change in volume of distribution for ibuprofen.

4 Appendices

4.1 Proposed Package Insert (Original and Annotated)

The following Label is proposed by the Applicant.

(b) (4)



11 pages of draft labeling have been withheld in full as b4 immediately following this page

(b) (4)

4.2 Individual Study Review

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

This study was a multi-center, randomized, open-label, parallel, active comparator, single or multiple-dose clinical study assessed the efficacy, safety, and pharmacokinetics (PK) of ibuprofen administered intravenously to hospitalized febrile pediatric patients less than or equal to 16 years of age. The review write-up will mainly focus on PK exposure.

Patients were randomized in a 1:1 ratio to receive one of two treatments. Treatments were either intravenous ibuprofen or oral/suppository acetaminophen (APAP).

Treatments

Group 1: Initial single dose of 10.0 mg/kg intravenous ibuprofen followed by dosing as needed (maximum 400 mg per dose and maximum 2400 mg daily)

Group 2: Initial single dose of 10.0 mg/kg acetaminophen, oral solution or suppository, followed by dosing as needed (maximum 650 mg per dose and maximum 3900 mg daily).

The primary objective of this study was to determine the superiority of a single dose of intravenous ibuprofen compared to APAP (oral solution or suppository) for the treatment of fever as measured by the area under the change (AUC) in temperature versus time curve during the first two hours of treatment (AUC0-2).

The secondary objectives of this study were to evaluate the change in temperature in patients receiving intravenous ibuprofen and APAP after the first 30 minutes of treatment; to evaluate the change in temperature in patients receiving intravenous ibuprofen and APAP after the first 60 minutes of treatment; to evaluate the change in temperature in patients receiving intravenous ibuprofen and APAP after the first four hours of treatment; to evaluate the change in temperature during the first four hours of treatment in patients receiving intravenous ibuprofen and APAP by assessing the area under the change in temperature versus time curve during the first four hours of treatment (AUC0-4); to evaluate the change in temperature during the first 24 hours of treatment in patients receiving intravenous ibuprofen and APAP by assessing the area under the change in temperature versus time curve during the first 24 hours of treatment (AUC0-24); to evaluate the time to afebrility (temperature less than 100.4 ºF [38 ºC]) in patients receiving intravenous ibuprofen and APAP; to evaluate the percentage of patients becoming afebrile (temperature less than 100.4 ºF [38 ºC]) after four hours in patients receiving intravenous ibuprofen and APAP; to evaluate the safety and tolerability of repeated doses of intravenous ibuprofen administered to hospitalized febrile pediatric patients by assessing treatment-emergent adverse events (TEAEs) and changes in temperature, vital signs, clinical chemistry, hematology, and coagulation, as compared to patients receiving APAP; *to evaluate the pharmacokinetic profile of a single dose of intravenous ibuprofen administered approximately 10 minutes*.

Two hundred patients (100 patients in each treatment group) were targeted for enrollment. Randomization was stratified according to age group. Efforts were made to enroll at least 12 patients (6 per treatment group) in each of the following age categories:

- Birth to < 2 months
- 2 months to < 6 months
- 6 months to < 2 years
- 2 years to < 6 years
- 6 years to ≤ 16 years.

Inclusion Criteria
Per the original protocol, to be considered eligible to participate in this study, a patient should have met the following inclusion criteria:
1. Have written informed consent provided by legal parent, guardian, or authorized agent prior to participation in the study or study-only related procedures.
2. Be between birth (28 weeks to < 40 weeks gestational age) to ≤ 16 years of age
3. Be hospitalized or have an admission scheduled and will soon become hospitalized.
4. Have 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.

Protocol Amendment #3 modified the exclusion criteria to indicate that to be eligible for entry into the study; the patient should not have met any of the following exclusion criteria:
1. Have written informed consent provided by legal parent, guardian, or authorized agent prior to participation in the study or study-only related procedures.
2. Be between birth (28 weeks to < 40 weeks gestational age) to ≤ 16 years of age.

3. Have 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
Per the original protocol, to be eligible for entry into the study, the patient should not have met any of the following exclusion criteria:
1. Have inadequate intravenous access.
2. Have received antipyretic drug therapy within two hours before dosing.
3. Have any history of allergy or hypersensitivity to NSAIDs or aspirin.
4. Have received another investigational drug within the past 30 days.
5. Be otherwise unsuitable for the study, in the opinion of the Investigator.
6. Have a fever due to hyperthermia

Protocol Amendment #2 modified the exclusion criteria to include the following exclusion criteria:
1. Be pregnant or nursing

Protocol Amendment #3 further modified the exclusion criteria to indicate the following exclusion criteria:
1. Have received another investigational drug within the past 30 days (or as directed by local or national laws or regulations).

Be otherwise unsuitable for the study, in the opinion of the Investigator. The determination of the suitability for the study may include but not be limited to a disease, laboratory test, or data which in the opinion of the Investigator makes the subject not acceptable for participation in the study.

Be pregnant or nursing, as confirmed by pregnancy testing (urine or serum).

Administration of treatments

An initial dose (10 mg/kg intravenous ibuprofen administered intravenously over 10 minutes or 10 mg/kg acetaminophen administered orally or per rectum) was administered; four hours following the initial dose, subsequent doses of drugs were administered as needed, at the investigator's discretion, during the Treatment Period. A total of up to 30 doses of drug may have been administered.

Drug was provided to the site pharmacist in an unblinded fashion. The pharmacist prepared each dose of intravenous ibuprofen at a concentration of 4 mg/ml or less by adding 10 mg/kg of product diluted in normal saline. The drug could be administered by regulated gravity free-flow or by infusion or syringe pump. The intravenous catheter was flushed with normal saline before and after each infusion. The 10 mg/kg ibuprofen was administered intravenously over 10 minutes through a central or peripheral catheter.

Efficacy and Safety Measurements Assessed and Flow Chart

Briefly, an overview of the time and events for this study is presented in Table xx; times shown in the table are the times that measurements or evaluations should have been started (e.g., start CTM administration at Hour 0).

Table Overall Schedule of Time and Events

Measurement/ Evaluation	Study Period Screening / Baseline	Treatment					Post-treatment
Time(s)	Hour -24 to Hour 0	Hour 0 to Hour 24	Hour 24 to Hour 48	Hour 48 to Hour 72	Hour 72 to Hour 96	Hour 96 to Hour 120	Hour 120 to Hour 144
Informed Consent	X						
Inclusion and Exclusion Criteria	X						
Complete Medical History	X						
Urine/Serum Pregnancy Test *							
Physical Examination	X						
Age, Weight, Sex	X						
Baseline Signs and Symptoms	X						
Temperature †	X ‡	X §✦	X ✦	X ✦	X ✦	X ✦	X
Vital Signs	X	X ✦	X ✦	X ✦	X ✦	X ✦	X
Safety Lab Sample Collection	X **	X				X	X
Pharmacokinetic Sampling	X	X					
Concomitant Medications	X (-4hr to 0)	Continual					
CTM Administration		A Single, Initial dose then as needed, as determined by the investigator					
AE Monitoring	Continual						

*To be performed for non-sterile females of childbearing potential; only if not previously done as part of normal medical care during current hospitalization.
†Tympanic temperature assessments ONLY; the tympanic route should be used for all temperature measurements.
‡Temperature will be recorded early in the Screening/Baseline Period to determine patient eligibility and again within 15 minutes before patient randomization.
✦Temperature and Vital Sign Assessment are dosing dependent.
§To be collected immediately before CTM administration.
**Laboratory data collected within 24 hours prior to dosing may be used for Screening/Baseline Period laboratory values.

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Primary Efficacy Variable(s)

To evaluate the primary objective of fever reduction within the first 120 minutes of treatment, the following endpoint was measured:

AUC0-2, the area under the change in temperature versus time curve from baseline (Study Hour 0) to 2 hours after the start of the initial dose of CTM (Study Hour 2 Hours).

To evaluate the secondary objective of fever reduction within the first 30 minutes of treatment, the following endpoint was measured:

Change in temperature from baseline (Study Hour 0) to 30 minutes after the start of the initial dose of CTM (Study Hour 30 minutes).

To evaluate the secondary objective of fever reduction within the first 60 minutes of treatment, the following endpoint was measured:

Change in temperature from baseline (Study Hour 0) to 60 minutes after the start of the initial dose of CTM (Study Hour 60 minutes).

To evaluate the secondary objective of fever reduction within the first four hours after of treatment, the following endpoint was measured:

Change in temperature from baseline (Study Hour 0) to 4 hours after the start of the initial dose of CTM (Study Hour 4)

To evaluate the secondary objective of fever reduction during the first four hours of treatment, the following endpoint was measured:

AUC0-4, the area under the change in temperature versus time curve from baseline (Study Hour 0) to 4 hours after the start of the initial dose of CTM (Study Hour 4 Hours)

To evaluate the secondary objective of fever reduction within the first 24 hours of treatment, the following endpoint was measured:

• The AUC0-24, the area under the change in temperature versus time curve from

baseline (Study Hour 0) to 24 hours after the start of the initial dose of CTM (Study Hour 24 Hours).

To evaluate the secondary objective of the time to becoming afebrile during the first 24 hours of treatment, the following endpoint was measured:

The first time at which each patient becomes afebrile (temperature less than 100.4ºF [38ºC]) will be measured.

To evaluate the secondary objective of the percentage of patients becoming afebrile (temperature less than 100.4 ºF [38 ºC]) after 4 hours, the following endpoint was measured:

The percentage of patients who are afebrile (temperature less than 100.4ºF [38ºC]) at 4 hours

Safety: Safety was evaluated on the basis of the following assessments:

- Vital signs (heart rate, respiratory rate, blood pressure)
- Clinical chemistry, hematology, and coagulation measurements
- Treatment-emergent AEs

Treatment period

The following assessments were performed during the Treatment Period (Hour 0 to Hour

120: Day 1 - Hour 0 to Hour 24; Day 2 = Hour 24 to Hour 48; Day 3 = Hour 48 to Hour 72; Day 4 = Hour 72 to Hour 96; Day 5 = Hour 96 to Hour 120)) Time 0 = initiation of administration of first dose of Clinical Trial Material (CTM):
• Temperature: Initial Dose (0, 15, 30, 45, 60, 75, 90, and 105 minutes, then at two hours, 2.5, 3, 3.5, 4, and six hours; The method of temperature measurement was tympanic.
• Temperature: PRN (Pro re nata, as needed) Dosing (pre-dose, 30, 60 minutes, 2, 4 hours after each dose)
• Vital signs: Hour (0, 1, 2, 4, 8, 24 hrs.) then prior to start of and 4 hours after any PRN dosing.
• CTM administration: Hour 0; then PRN as needed (but no sooner than four hours after the initial Hour 0 dose) until Hour 120.
• Blood sample collection for pharmacokinetic assessment: Immediately post-dose, 30 minutes, 1, 2, and 4 hrs. (sparse sampling to be assigned for patients < 6 months of age).
• Blood sample collection for safety laboratory assessments: Day 1 and Day 5 or End of Study.
• Concomitant medications and procedures, including antipyretic treatment (continual)
• AE monitoring (continual; Section 6.0 describes the procedures for handling AEs.)

Post-treatment Period (Hour 120 to Hour 144)

The following assessments were performed during the Post-treatment Period:
• Temperature (via the same route used during the Screening/Baseline Period and Treatment Period, if possible)
• Vital signs
• Blood sample collection for safety laboratory assessments
• Concomitant medications and procedures, including antipyretic treatment (continual)
• AE monitoring (continual)

Drug Concentration Measurements

Pharmacokinetic sampling for measurement of plasma ibuprofen concentration was performed on all patients randomized to receive intravenous ibuprofen at the following time points.

• For subjects less than six months of age, samples were taken immediately following administration of the first dose of intravenous ibuprofen; then alternating subject had pharmacokinetic sampling performed at 30 minutes and 2 hours or at 1 hour and 4 hours following the first dose.

• For subjects of six months of age or older, samples were taken immediately following administration of the first dose of intravenous ibuprofen; then at 30 minutes, 1 hour, 2 hours, and 4 hours following the first dose of intravenous ibuprofen.

Blood was collected into Lavender top K2EDTA tubes. Tubes were gently inverted 8 to 10 times and immediately placed into crushed ice and water until centrifugation. The vials were centrifuged at 4º C at 3000 RPM within 50 minutes of collection. The plasma was divided

into duplicate aliquots placed in plasma storage tubes and then stored at or below - 20º C until transfer to the bioanalytical laboratory.

The PK population included every patient for whom sufficient data were collected to calculate the PK parameters.

Pharmacokinetic Data Analysis

The PK population included every patient for whom sufficient data were collected to calculate the PK parameters (N=43). Data from Patients 2001 and 2059 are presented in the concentrations and PK tables but excluded from the descriptive statistics due to insufficient data collected.

PK parameters were estimated with standard non-compartmental methods using WinNonlin® version 5.3 software (Pharsight Corporation) in accordance with the current version of the inVentiv Standard Operating Procedure (SOP).

Plasma concentration values from ibuprofen were used to calculate the following parameters:

AUC0-t: Area under the concentration-time curve from time zero to the last measurable concentration using linear-log trapezoidal rule.
AUC0-4: Area under the concentration-time curve from time zero to 4 hours.
Cmax: Maximum observed concentration.
Tmax: Time of observed Cmax.
T½ el: Elimination half-life, calculated as ln(2)/Kel
Cl: Total body clearance, calculated as Dose/AUC0-inf.
Vz: Volume of distribution, calculated as Dose/(Kel x AUC0-inf).

The terminal rate constant was calculated for all patients when possible. The value of Kel was determined by the slope of the regression line of ln-transformed concentration vs. time profile with the following constraints: at least four non-zero observations during the terminal elimination phase were used to calculate the Kel. A minimum of three observations was used if fewer than four observations were available. If the constant (Kel) could not be measured (e.g.: fewer than three non-zero concentrations in the terminal elimination phase) or the determination coefficient (r2 value) from the regression of the ln linear elimination phase was less than 64% (or 0.64) for some patients (or r value positive or less than 80% or 0.80 in absolute value), then the parameters related to the elimination were not calculated for that individual pharmacokinetic profile.

For Patient 2016, 2022, and 2034, the elimination rate constant could not be properly estimated due to a low correlation coefficient of the ln linear portion of the terminal elimination phase. The Kel derived PK parameters (T½.el, Cl, and Vz) were not calculated for these patients.

Individual and mean concentrations versus time curves were presented using linear and semi-log scales. Listings and descriptive statistics [number of observations (N), arithmetic mean, standard deviation (SD), coefficient of variation (CoV), median, minimum value (Min.), maximum value (Max.), and geometric mean] of the plasma concentrations versus time were provided for ibuprofen data.

Pharmacokinetic parameter data (AUC0-t, AUC0-4, Cmax, Tmax, T1/2 el, Cl, and Vz,) were tabulated for all patients and for each age category. Descriptive statistics including N, arithmetic mean, SD, CoV, median, minimum, maximum and geometric mean were presented. A copy of the Pharmacokinetic Data Analysis Plan (DAP) is provided in Appendix 16.1.9.1

Results

Demographic and Baseline Characteristics by Treatment Group, ITT

Demographic and baseline characteristics are presented in Table 11-2

	Intravenous ibuprofen (n=47)	**Acetaminophen** (n=53)	**Total** (n=100)
Age (years)			
Mean (SD)	7 (4.6)	6 (4.4)	7 4.5)
Min, Max	<1, 16	<1, 15	<1, 16
Gender			
Male	27 (57%)	26 (49%)	53 (53%)
Female	20 (43%)	27 (51%)	47 (47%)
Race			
Caucasian	42 (89%)	42 (79%)	84 (84%)
Black or African American	5 (11%)	8 (15%)	13 (13%)
American Indian/Alaska Native	0	2 (4%)	2 2%)
Other	0	1 (2%)	1 1%)
Ethnicity			
Hispanic or Latino	29 (62%)	24 (45%)	53 (53%)
Not Hispanic or Latino	18 (38%)	29 (55%)	47 (47%)
Weight (kg)			
Mean (SD)	30.2 (19.50)	24.2 (15.18)	27.0 (17.52)
Min, Max	7.3, 80.1	7.2, 63.0	7.2, 80 1

The age (months) information per groups:

Age group		< 6 months Months	6 months to < 2 years Months	2 to < 6 years Months	6 to 16 years Months
Overall	Mean	-	11.1	39.2	122.2

	SD	-	5.04	14	38.4
Males subject	Mean	1	11.4 (N=8)	39 (N=8)	125.3 (N=18)
	SD	-	5.7	15.4	38.2
	Range	-	6 - 11	24 - 60	72 - 156
Females subject	Mean	-	10 (N=2)	39.4 (N=7)	118.4 (N=15)
	SD	-	1.4	13.4	39.5
	Range		9 and 11	24 – 60	72 – 180

The weight (kg) information per groups:

Age group		< 6 months kg	6 months to < 2 years kg	2 to < 6 years kg	6 to 16 years kg
Overall	Mean	-	10.3	16.4	39.3
	SD	-	2.5	4.5	17.6
Males subject	Mean	4.8	10.6 (N=8)	16.3 (N=8)	39.8 (N=18)
	SD	-	2.6	3.8	16.3
	Range	-	7.1 – 14.5	11.3 – 21.1	20 – 80.1
Females subject	Mean	-	9.3 (N=2)	16.5 (N=7)	38.7 (N=15)
	SD	-	2.8	3.8	19.6
	Range	-	7.3 and 11.3	11.9 – 27.2	16.3 – 75.3

Baseline vital signs included temperature, heart rate, respiratory rate and blood pressure. Serial measurements were then taken during the study. As shown in Table 11-3 and Table 11- 4 discussed below, there was no difference between treatment groups with respect to baseline vital signs.

Table 11–3 Baseline Temperature, ITT

Vital Sign	**Intravenous ibuprofen** (n=47)	**Acetaminophen** (n=53)
Temperature °C Mean (SD)	39.0 (0.68)	38.8 (0.48)

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Table 11–4 Baseline Vital Signs, Safety Population

Vital Sign, Mean (SD)	**Intravenous ibuprofen** (n=47)	**Acetaminophen** (n=53)	**Total** (n=100)
Heart Rate (Radial Pulse Rate)	136 (25.5)	134 (27.4)	135 (26.4)

Respiration Rate	26 (6.8)	26 (10.4)	26 (8.8)
Systolic Blood Pressure (mm Hg)	108 (17.3)	107 (13.5)	108 (15.3)
Diastolic Blood Pressure (mm Hg)	59 (15.1)	59 (9.9)	59 (12.5)

Study report CPI-CL-012

Analysis of Efficacy
Primary Endpoint: AUC0-2

For the ITT, there was a significant difference seen in the AUC values for Change from Baseline Versus Time Curve for 0 to 2 hours for patients receiving 10 mg/kg intravenous ibuprofen compared to those acetaminophen (-1.5 + 1.11 vs. -0.9 + 0.89, p=0.005). Table 11-6 presents a summary of AUC0-2 for the ITT population.

Table 11-6 Summary of AUC0-2 by Treatment Group, ITT

AUC_{0-2}	**Intravenous ibuprofen** n=47	**Acetaminophen** n=53
N	46	50
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
Comparison to Acetaminophen		
p-value[2]	0.005	

Missing values at time t are imputed using linear interpolation prior to calculating AUC0-t.
[1] LS Means are from an ANOVA model with fixed effect for treatment.
[2] The data are not normally distributed. The p-value is based on Wilcoxon Rank-Sum test for differences in treatment.
Study report CPI-CL-012

Analysis of the primary efficacy parameters was also evaluated by age group (6 months to <2 years, 2 years to < 6 years, and 6 years to 16 years). There was a significant difference seen for patients in the 6 years to 16 year age group receiving intravenous ibuprofen compared to those receiving acetaminophen (-1.4 + 0.89 vs. -0.8 + 0.78; p=0.016). There was a numerical difference seen for patients in the 6 months to < 2 years age group receiving intravenous ibuprofen compared to acetaminophen (-1.7 + 1.19 vs. -1.4 + 0.88; p=0.481) and in the 2 years to < 6 years age group receiving intravenous ibuprofen compared to acetaminophen (-1.6 + 1.51 vs. -0.7 + 0.97; p=0.059), however these differences were not statistically significant.

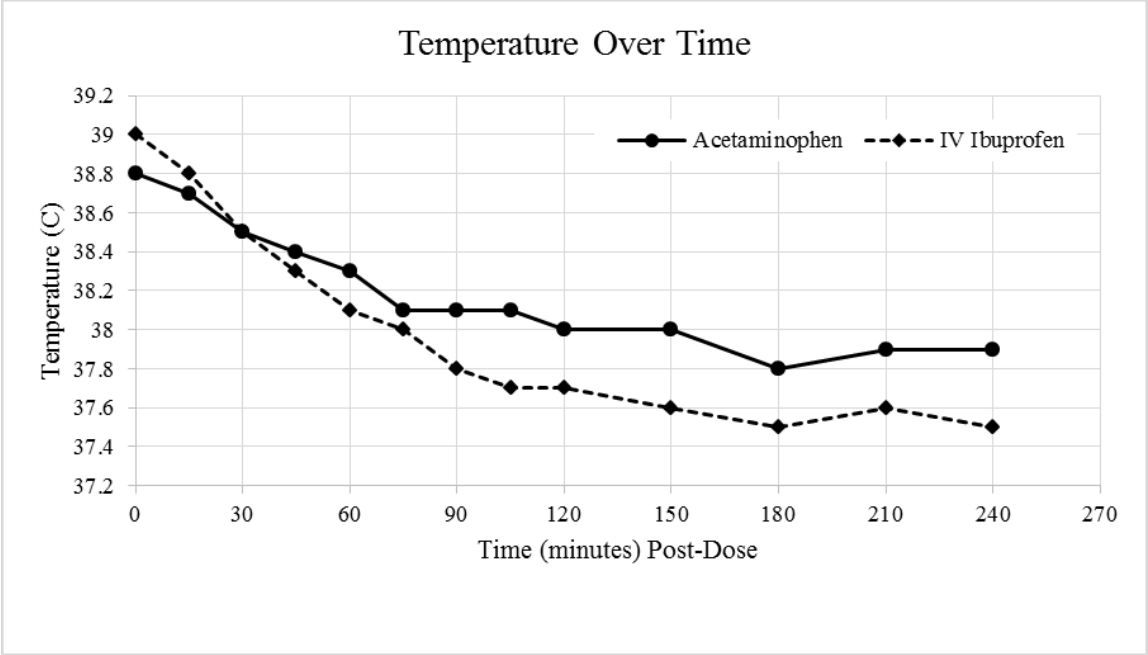
Table 11-7 presents a summary of AUC0-2 for the ITT population by age group (6 months to < 2 years, 2 years to < 6 years, and 6 years to 16 years).

Table 11–7 Summary of Area under the Change from Baseline Vs Time Curve by Age Subgroup

Age 6 months to < 2 years	**Intravenous ibuprofen** n=47	**Acetaminophen** n=53
AUC_{0-2}		
N	6	14
Mean (SD)	-1.7 (1.19)	-1.4 (0.88)
LS Means (SE)1	-1.7 (0.40)	-1.4 (0.26)
Median	-1.6	-1.3
Min, Max	-3.4, -0.2	-3.0, -0.3
Comparison to Acetaminophen		
p-value[2]	0.481	
Age 2 to < 6 years AUC_{0-2}		
AUC_{0-2}		
N	13	13
Mean (SD)	-1.6 (1.51)	-0.7 (0.97)
LS Means (SE)[1]	-1.6 (0.35)	-0.7 (0.35)
Median	-1.0	-0.3
Min, Max	-4.4, 0.1	-2.5, 0.7
Comparison to Acetaminophen		
p-value[2]	0.059	
Age 6 to < 6 years AUC_{0-2}		
AUC_{0-2}		
N	27	23
Mean (SD)	-1.4 (0.89)	-0.8 (0.78)
LS Means (SE)[1]	-1.4 (0.16)	-0.8 (0.18)
Median	-0.9	-0.9
Min, Max	-2.3, 0.6	-2.3, 0.6
Comparison to Acetaminophen		
p-value[2]	0.016	

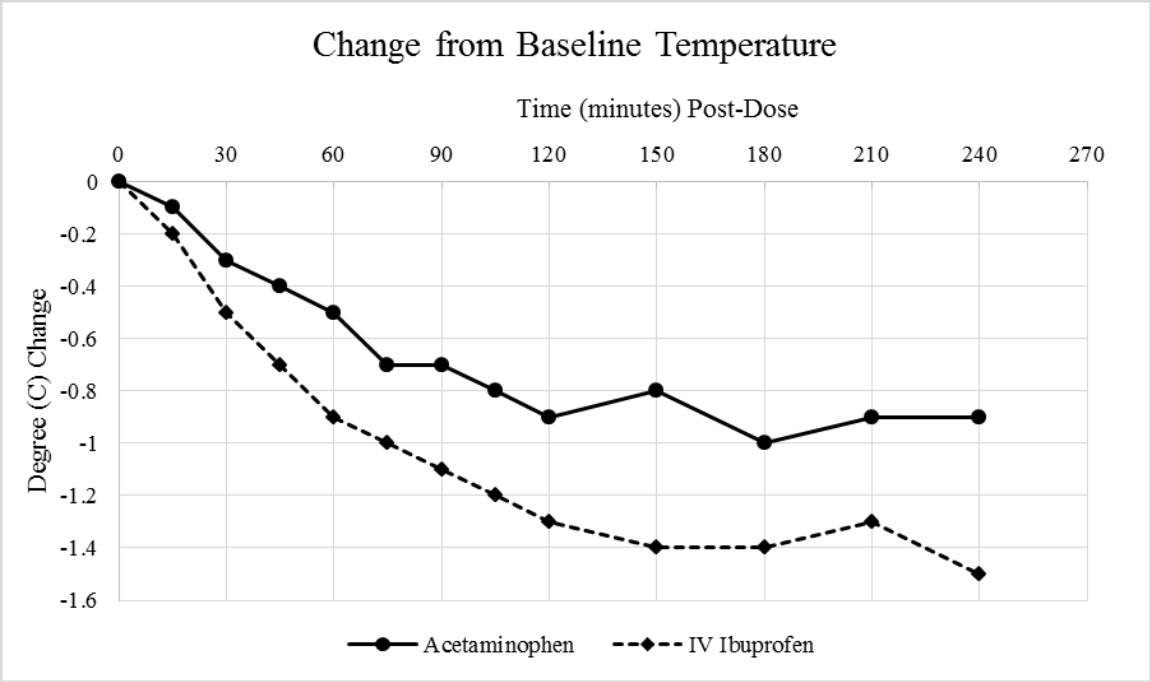
Missing values at time t are imputed using linear interpolation prior to calculating AUC0-t.
[1] LS Means are from an ANOVA model with fixed effect for treatment.
[2] Data are not normally distributed. The p-value is based on Wilcoxon Rank-Sum test for differences in treatment.
AUC= area under the curve; SD= standard deviation; SE= standard error; Min= minimum; Max= maximum
Study report CPI-CL-012

Figure 11–1 Temperature over Time



Study report CPI-CL-012

Figure 11–2 Change from Baseline Temperature



Study report CPI-CL-012

Secondary Endpoint: AUC0-4 and AUC0-24

AUC0-t, the area under the changed in temperature from baseline verse time was calculated using a linear trapezoidal rule on all available change from baseline in temperature data to t hour post-dose for each patient. If any intermediate temperature values were missing during the period, linear interpolation between the adjacent values were used as imputed values.

For the ITT, there was a significant difference seen in the AUC values for Change from Baseline Versus Time Curve for 0 to 4 hours for patients receiving 10 mg/kg intravenous ibuprofen compared to those acetaminophen (-4.4 + 2.59 vs. -2.6 + 2.02 , p= <0.001).
A summary of AUC0-4 and AUC0-24 are presented on Table 11-9

Table 11–9 Summary of AUC0-4 by Treatment Group, ITT

AUC_{0-4}	**Intravenous ibuprofen** n=47	**Acetaminophen** n=53
N	44	42
Mean (SD)	-4.4 (2.59)	-2.6 (2.02)
LS Means (SE)[1]	-4.4 (0.35)	-2.6 (0.36)
Median	-4.4	-2.7
Min, Max	-12.0, 0.6	-7.4, 1.3
Comparison to Acetaminophen		
p-value[2]	<0.001	
AUC_{0-24}	**Intravenous ibuprofen** n=47	**Acetaminophen** n=53
N	29	24

Mean (SD)	-34.2 (17.97)	-26.6 (14.29)
LS Means (SE)[1]	-34.2 (3.05)	-26.6 (3.35)
Median	-36.9	-25.0
Min, Max	-72.9, 1.3	-66.1, 1.7
Comparison to Acetaminophen		
p-value[2]	0.061	

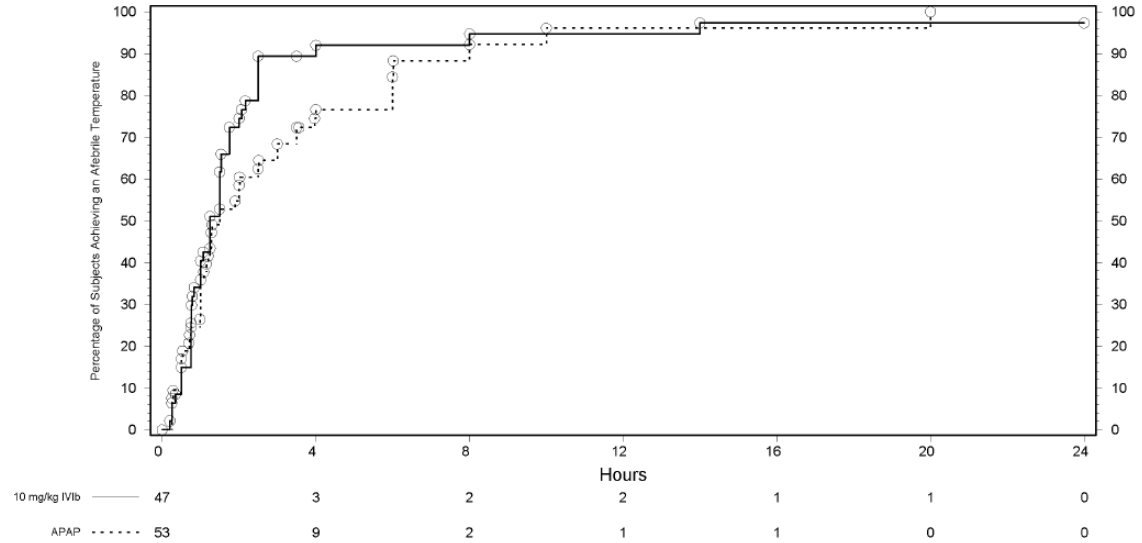
[1] LS Means are from an ANOVA model with fixed effect for treatment.
[2] The p-value is based on a Wilcoxon Rank-Sum test for differences in treatment
SD= standard deviation; SE- standard error
Study report CPI-CL-012

Secondary Endpoint: Time to afebrile (0-24 hour)

The secondary endpoint Time to Afebrility evaluated the time of the patient becoming afebrile (temperature less than 100.4 ºF [38 ºC]) during the first 24 hours of treatment. The secondary efficacy parameter of the time to becoming afebrile was analyzed by using the log-rank test. Any patient who did not complete the study was censored at the time of the last non-missing temperature assessment. Patients who were still febrile at the end of the Treatment Period were censored at the end of the study.

A summary of the time from first dose of CTM to becoming afebrile is presented in Figure 11-3.

Figure 11–3 Time to Achieving an Afebrile Temperature



IVIb= intravenous ibuprofen; APAP= acetaminophen
Study report CPI-CL-012

Secondary Endpoint: Percentage of Afebrile Patients (0-4 hours)

The secondary endpoint of the percentage of patients becoming afebrile (temperature less than 100.4 ºF [38 ºC]) after four hours evaluated the percentage of patients who were afebrile at 4 hours. The secondary efficacy parameter of percentage of subjects who experienced an afebrile temperature (a temperature less than 100.4º F or 38o C) within four hours, post-dose was summarized with descriptive statistics. The secondary efficacy parameter of percentage of patients who are afebrile four hours after initial dosing will be analyzed for differences between treatment groups with the CMH test of general association. A summary of Afebrile Temperature is presented on Tables 11-10, 11-11

Table 11–10 Summary of Afebrile Temperature (temperature less than 100.4º F or 38o C)

Total Subjects Afebrile at 4 Hours Post-Dose	**Intravenous ibuprofen** n=47 N (%)	**Acetaminophen** n=53 N (%)
Yes	43 (91%)	40 (75%)
No	3 (6%)	11 (21%)
p-value [1]	0.036	

[1] The p-value is based on a Cochran-Mantel-Haenszel statistic of difference between treatment groups
Study report CPI-CL-012

Table 11–11 Time to Achieving an Afebrile Temperature (temperature less than 100.4º F or 38o C)

Time to Achieving an Afebrile Temperature	**Intravenous ibuprofen** N (%)	**Acetaminophen** N (%)
N	47	53
Number Censored (%)	2 (4%)	6 (11%)
Mean (SE)	2.2 (0.47)	3.3 (0.67)
p-value [2]	0.156	

[2] The p-value is based on the log rank statistic.
Study report CPI-CL-012

Brief Summary of Adverse Events

Safety was evaluated by analyzing data obtained during the study including vital signs (temperature, heart rate, respiratory rate, and blood pressure), clinical laboratory assessments (chemistry, hematology, and coagulation panels), and treatment–emergent adverse events. Investigators were asked to report any medical event (new events or worsening conditions) that occurred during the study after administration of the first dose of CTM and to grade the event by intensity (mild, moderate, or severe), seriousness (yes or no), outcome (resolved, resolved with sequelae, chronic condition, unknown, or fatal), CTM action taken due to the event (none, study drug interrupted, study drug discontinued), action taken to treat the event (none, concomitant medication, hospitalization, or other action), and investigator's assessment of the relationship of the event to the CTM (not related, related, possibly related, and unlikely related). The date and time of onset and resolution were also recorded. If an event was unable to be followed until resolution, or if the event was ongoing at the time of

discharge, the resolution date and time was left blank and the event was recorded as ongoing.

If the event was a laboratory abnormality, the Investigator was asked to judge the event as to its clinical significance. If the event was determined to be clinically significant the event was followed until resolution or until a new stable baseline was established.

During the study, 131 events were reported by 54 (54%) patients (Appendix 14.3.1.2.1). The most common adverse event overall was vomiting which was reported by 6 (6%) patients (Appendix 14.3.1.6). Infusion site pain was the most frequently reported event in the ibuprofen treatment group (N=5; 11%). In the acetaminophen treated group, diarrhea was the most common event (N=4; 8%). Other events reported by ≥ 3% of patients included nausea, headache, aspartate aminotransferase increased, blood lactate dehydrogenase increased, alanine aminotransferase increased, hypokalemia, and pruritus.
There were no patient deaths during the study. A total of six SAEs were reported for 4 (4%) patients (Appendix 14.3.1.4). Of the six serious adverse events reported, four were considered as not related and two were considered as possibly related (Pancreatitis and Transaminases increased) by the investigator.

During the study, 4 (4%) patients discontinued study drug due to an adverse event. One (1%) patient was discontinued with two events (bradycardia and hypotension) and 3 (3%) patients were discontinued with one event each (thrombocytopenia, headache, and body temperature increased) (Appendix 14.3.1.3).

Table 12-2 displays treatment emergent adverse events by intensity occurring in 3% or more patients

Table 12–2 Treatment Emergent Adverse Events by System Organ Classification and Preferred Term that Occurred in ≥ 3% Patients

System Organ Class **Preferred Term**	**Intravenous Ibuprofen (n=47)**	**Acetaminophen** (n=53)	**Total (n = 100)**
No Events	19 (40%)	27 (51%)	46 (46%)
Any Event	28 (60%)	26 (49%)	54 (54%)
Mild	18 (38%)	19 (36%)	37 (37%)
Moderate	7 (15%)	7 (13%)	14 (14%)
Severe	3 (6%)	0	3 (3%)
Gastrointestinal Disorders	9 (19%)	11 (21%)	20 (20%)
Vomiting	3 (6%)	3 (6%)	6 (6%)
Mild	1 (2%)	2 (4%)	3 (3%)
Moderate	2 (4%)	1 (2%)	3 (3%)
Severe	0	0	0
Diarrhoea	1 (2%)	4 (8%)	5 (5%)
Mild	1 (2%)	1 (2%)	5 (5%)

Moderate	0	0	0
Severe	0	0	0
Nausea	3 (6%)	2 (4%)	5 (5%)
Mild	2 (4%)	2 (4%)	4 (4%)
Moderate	1 (2%)	0	1 (1%)
Severe	0	0	0
Investigations	9 (19%)	9 (17%)	18 (18%)
Aspartate Aminotransferase Increased	2 (2%)	2 (2%)	4 (4%)
Mild	2 (2%)	2 (2%)	4 (4%)
Moderate	0	0	0
Severe	0	0	0
Blood Lactate Dehydrogenase Increased	1 (2%)	3 (6%)	4 (4%)
Mild	1 (2%)	3 (6%)	4 (4%)
Moderate	0	0	0
Severe	0	0	0
Alanine Aminotransferase Increased	2 (4%)	1 (2%)	3 (3%)
Mild	2 (4%)	1 (2%)	3 (3%)
Moderate	0	0	0
Severe	0	0	0
General Disorders and Administration Site Conditions	9 (19%)	1 (2%)	10 (10%)
Infusion Site Pain	5 (11%)	0	5 (11%)
Mild	2 (4%)	0	2 (4%)
Moderate	3 (6%)	0	3 (6%)
Severe	0	0	0
Metabolism and Nutrition Disorder	1 (2%)	4 (8%)	5 (5%)
Hypokalemia	1 (2%)	2 (4%)	3 (3%)
Mild	0	1 (2%)	0 (1%)
Moderate	1 (2%)	1 (2%)	2 (2%)
Severe	0	0	0
Skin and Subcutaneous Tissue Disorders	1 (2%)	4 (8%)	5 (5%)
Pruritus	1 (2%)	2 (4%)	3 (3%)
Mild	1 (2%)	2 (4%)	3 (3%)
Moderate	0	0	0
Severe	0	0	0
Nervous System Disorders	4 (9%)	1 (2%)	5 (5%)
Headache	3 (6%)	1 (2%)	4 (4%)
Mild	2 (4%)	1 (2%)	3 (3%)
Moderate	1 (2%)	0	0
Severe	0	0	0

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Of the 100 total patients, 4 (4%) patients discontinued study drug due to an adverse event. In the ibuprofen treatment group, one (1%) patient was discontinued with two events (bradycardia and hypothermia) and two (2%) patients were discontinued with one event each (thrombocytopenia, and headache). One patient (1%) was discontinued due to body temperature increase in the acetaminophen group (Appendix 14.3.1.3).

Table 12-3 displays treatment emergent adverse events leading to discontinuation of study drug.

Table 12–3 Number and Percentage of Patients with Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug

System Organ Class **Preferred Term**	**Intravenous Ibuprofen (n=47)**	**Acetaminophen (n=53)**	**Total (n=100)**
Any Event Leading to Discontinuation of Study Drug	3 (6%)	1 (2%)	4 (4%)
Blood and Lymphatic System Disorders	1 (2%)	0	1 (1%)
Thrombocytopenia	1 (2%)	0	1 (1%)
Cardiac Disorders	1 (2%)	0	1 (1%)
Bradycardia	1 (2%)	0	1 (1%)
General Disorders and Administrative Site Conditions	1 (2%)	0	1 (1%)
Hypothermia	1 (2%)	0	1 (1%)
Investigations	0	1 (2%)	1 (1%)
Body Temperature Increase	0	1 (2%)	1 (1%)
Nervous System Disorders	1 (2%)	0	1 (1%)
Headache	1 (2%)	0	1 (1%)

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There were four patients for whom six serious treatment emergent adverse events were reported. Two patients in the ibuprofen treatment group experienced two events (cardiorespiratory arrest and pneumothorax) (pancreatitis and transaminases increased) and two patients in the acetaminophen treatment group experienced one event each (pleural effusion and abdominal abscess). Four of the events were coded by the investigator as not related and two of the events were coded as possibly related (pancreatitis and transaminases increased).

Table 12-4 displays the serious treatment emergent adverse events

Table 12–4 Number and Percentage of Patients with Serious Treatment-Emergent Adverse Events

System Organ Class **Preferred Term**	**Intravenous Ibuprofen (n=47)**	**Acetaminophen (n=53)**	**Total (n=100)**

Any Serious Event	2 (4%)	2 (4%)	4 (4%)
Respiratory, Thoracic, and Mediastinal Disorders	1 (2%)	1 (2%)	2 (2%)
Pleural Effusion	0	1 (2%)	1 (1%)
Pneumothorax	1 (2%)	0	1 (1%)
Cardiac Disorders	1 (2%)	0	1 (1%)
Cardio-Respiratory Arrest	1 (2%)	0	1 (1%)
Gastrointestinal Disorders	1 (2%)	0	1 (1%)
Pancreatitis	1 (2%)	0	1 (1%)
Infections and Infestations	0	1 (2%)	1 (1%)
Abdominal Abscess	0	1 (2%)	1 (1%)
Investigations	1 (2%)	0	1 (1%)
Transaminases Increased	1 (2%)	0	1 (1%)

Study report CPI-CL-012

Analysis of Adverse Events

All patients greater than six months of age who were enrolled in the study and received at least one dose of CTM (100 total) are included in the safety analysis population (identical to the ITT population). There were 54 of the 100 patients for whom 131 treatment-emergent adverse events (serious and non-serious) were reported. In the intravenous ibuprofen group 28 patients experienced treatment-emergent adverse events; mild 18, moderate 7 and severe 3. In the acetaminophen group, 26 patients experienced treatment-emergent adverse events; mild 19, moderate 7 and severe 0 (Appendix 14.3.1.1).

The most common adverse event overall experienced by patients was vomiting 6/100 (6%). Other events reported by $\geq$ 3 % of patients included diarrhoea, nausea, infusion site pain, aspartate aminotransferase increased, blood lactate increased, headache, alanine aminotransferase increased, hypokalemia, and pruritus.

Adverse events and clinical laboratory assessments commonly associated with oral ibuprofen were specifically examined, including gastrointestinal effects (hemoglobin, hematocrit, platelets, prothrombin time, activated partial prothrombin time [aPTT] and international normalized ration [INR]), hepatic effects (total bilirubin, albumin, total protein, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase), hypertensive effect (blood pressure), renal effects (blood urea nitrogen and creatinine), and hematological effects (hemoglobin, hematocrit, platelets, prothrombin time, activated partial prothrombin time and INR).

There were no patient deaths during the six day study. There were four patients for whom six serious treatment emergent adverse events were reported. Two patients experienced two events (cardio-respiratory arrest and pleural effusion) (pancreatitis and transaminases increased) and two patient experienced one event each. Four of the events were coded by the

investigator as not related and two of the events were coded as possibly related (pancreatitis and transaminases increased).

Laboratory Values over Time

Laboratory assessments were performed for safety analyses at Screening, Day 1, and Day 5 or End of Study. Summary statistics of individual laboratory measurements (n, mean, standard deviation, median, minimum, maximum), laboratory assessments, and treatment groups can be found in Appendix 14.3.4.1 through Appendix 14.3.4.24. Select laboratory assessments are presented in Table12-5 below. Baseline, Endpoint (defined as the last assessment taken during the Treatment Period) and change from Baseline to Endpoint are presented.

Table 12-5 Select Laboratory Values over Time.

	Intravenous ibuprofen (n=47)		**Acetaminophen (n=53)**	
	n	Mean (SD)	n	Mean (SD)
BUN (mg/dL)				
Baseline (BL)	46	9 (5.2)	50	10 (6.7)
Endpoint	42	8 (6.3)	45	9 (4.0)
Change from BL to Endpoint	41	-1 (6.1)	42	-1 (6.3)
Creatinine (mg/dL)				
Baseline (BL)	46	0.50 0.346)	50	0.47 (0.195)
Endpoint	42	0.43 0.180)	45	0.40 (0.185)
Change from BL to Endpoint	41	-0.09 (0.310)	42	-0.07 (0.180)
Hemoglobin (g/dL)				
Baseline (BL)	47	11 4 1.73)	50	11.4 (2.01)
Endpoint	43	10 6 1.57)	44	11.0 (1.45)
Change from BL to Endpoint	43	-0.6 (1.11)	41	-0.4 (1.90)
Hematocrit (%)				
Baseline (BL)	47	33 4 4.77)	50	33.5 (5.58)
Endpoint	43	31 4 4.51)	11	32.6 (4.08)
Change from BL to Endpoint	43	-1.6 (3.64)	41	-0.8 (6.04)
Platelets ($x10^3/mm^3$)				
Baseline (BL)	46	290 (136.9)	50	278 (121.0)
Endpoint	43	305 (134.0)	44	295 (157.6)
Change from BL to Endpoint	42	18 (97.0)	41	20 (106.3)
Prothrombin Time (seconds)				
Baseline (BL)	39	14 9 2.59)	43	15.1 (2.37)
Endpoint	35	14 0 2.98)	37	14.8 (4.30)
Change from BL to Endpoint	31	-0.9 (3.49)	32	-0.6 (1.57)
Activated Partial Prothrombin Time (APPT) (seconds)				
Baseline (BL)	41	34 4 5.48)	46	39.6 (45.42)
Endpoint	37	34 1 10.25)	40	34.0 (10.76)
Change from BL to Endpoint	33	-0.2 (9.68)	34	-8.4 (52.59)

There were no significant differences between treatment groups in regards to the change from Baseline to Endpoint (defined as the last assessment taken during the Treatment Period) for sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, albumin, total protein, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, white cell count, total neutrophil count, monocytes, eosinophils, basophils, hematocrit, hemoglobin, platelets, and activated partial prothrombin time. There was a significant difference between treatment groups in regards to the change from Baseline to Endpoint for Lymphocytes.

Vital Signs, Physical Findings and other Observations Related to Safety

Vital signs were collected at Screening, between 15 minutes prior to hour 0, hour 0, hour 0 plus 15 minutes, hour 0 plus 30 minutes, hour 0 plus 45 minutes, hour 1, hour 1 plus 15 minutes, hour 1 plus 30 minutes, hour 1 plus 45 minutes, hour 2, hour 2 plus 30 minutes, hour 3, hour 3 plus 30 minutes, hour 4, hour 6, hour 8, hour 24, and between hour 120 and hour 144 following the initial single dose of CTM. For subsequent PRN CTM dosing, if administered, vital l signs were taken only prior to the PRN dose, then at 30 minutes post dose, 60 minutes post dose, 2 hours post dose, and 4 hours post dose for PRN CTM dosing.

Vital signs collected included pulse rate, respiratory rate, and systolic and diastolic blood pressure. Appendix 16.2.4.5 provides listings of each vital sign for each participant over time. Appendix 14.2.2.1 (temperature), Appendix 14.3.3.1 (pulse rate), Appendix 14.3.3.2 (respiratory rate), Appendix 14.3.3.3 (systolic blood pressure), and Appendix 14.3.3.4 (diastolic blood pressure), and Appendix 14.3.3.5 (mean arterial pressure) provide summary data of each of the vital signs including mean, median, standard deviation and change from Baseline.

There were no significant differences between treatment groups in regards to the change from Baseline to Endpoint (defined as the last assessment taken during the Treatment Period) for pulse rate, respiratory rate, and systolic and diastolic blood pressure.

Safety Conclusions

Fifty-four of the 100 patients reported treatment-emergent adverse events (serious and nonserious): 37 (37%) were mild, 14 (14%) were moderate and 3 (3%) were severe. In the intravenous ibuprofen group, 28 (60%) patients experienced treatment-emergent adverse events; 18 (38%) mild, 7 (15%) moderate and 3 (6%) severe. In the acetaminophen group, 26 (49%) patients experienced treatment-emergent adverse events; 19 (36%) mild, 7 (13%) moderate and none were severe.

In the treatment-emergent adverse events occurring in 3% or more patients, the most common event was vomiting 6 (6%); 3 (6%) in the intravenous ibuprofen group and 3 (6%)

in the acetaminophen group. One event, infusion site pain, was reported significantly more patients in the intravenous ibuprofen group 5 (11%) than in the APAP group (0).

There were no deaths reported in this study. There were four (4%) subjects for whom six serious adverse events were reported. In the intravenous ibuprofen group, two (2%) subjects experienced four serious adverse events. In the acetaminophen group, two (2%) subjects experienced two serious adverse events. Four of the events were coded as not related; two of the events were coded as possibly related.

There were four (4%) subjects who discontinued CTM due to an adverse event. Of the subjects who discontinued, one (2%) subject was discontinued due to thrombocytopenia, one (2%) subject was discontinued due to bradycardia, and hypothermia, one (2%) subject was discontinued due to body temperature increased, and one (2%) subject was discontinued due to headache.

There were no significant differences between treatment groups in regards to the change from Baseline to Endpoint (defined as the last assessment taken during the Treatment Period.) for pulse rate, respiratory rate, and systolic and diastolic blood pressure.

There were no significant changes between treatment groups in regards to the change from Baseline to Endpoint (as defined as the last assessment taken during the Treatment Period) for any laboratory assessment except for Lymphocytes (p=0.034).

Overall, treatment with 10 mg/kg intravenous ibuprofen over 10 minutes was considered safe and well tolerated in pediatric subjects.

Pharmacokinetic Parameters

PK parameters were estimated with standard non-compartmental methods using WinNonlin® version 5.3 software (Pharsight Corporation) in accordance with the current version of the inVentiv Standard Operating Procedure (SOP).

Plasma concentration values from ibuprofen were used to calculate the following parameters:

AUC0-t: Area under the concentration-time curve from time zero to the last measurable concentration using linear-log trapezoidal rule.
AUC0-4: Area under the concentration-time curve from time zero to 4 hours.
Cmax: Maximum observed concentration.
Tmax: Time of observed Cmax.
T½ el: Elimination half-life, calculated as ln(2)/Kel
Cl: Total body clearance, calculated as Dose/AUC0-inf.
Vz: Volume of distribution, calculated as Dose/(Kel x AUC0-inf).

Analysis of Pharmacokinetic Parameters

Mean plasma concentration-time profile for intravenous ibuprofen is presented in Figure 11-4. Mean Values, by age group, are summarized in Table 11-11.

Figure 11-4 Mean Plasma Concentration-Time

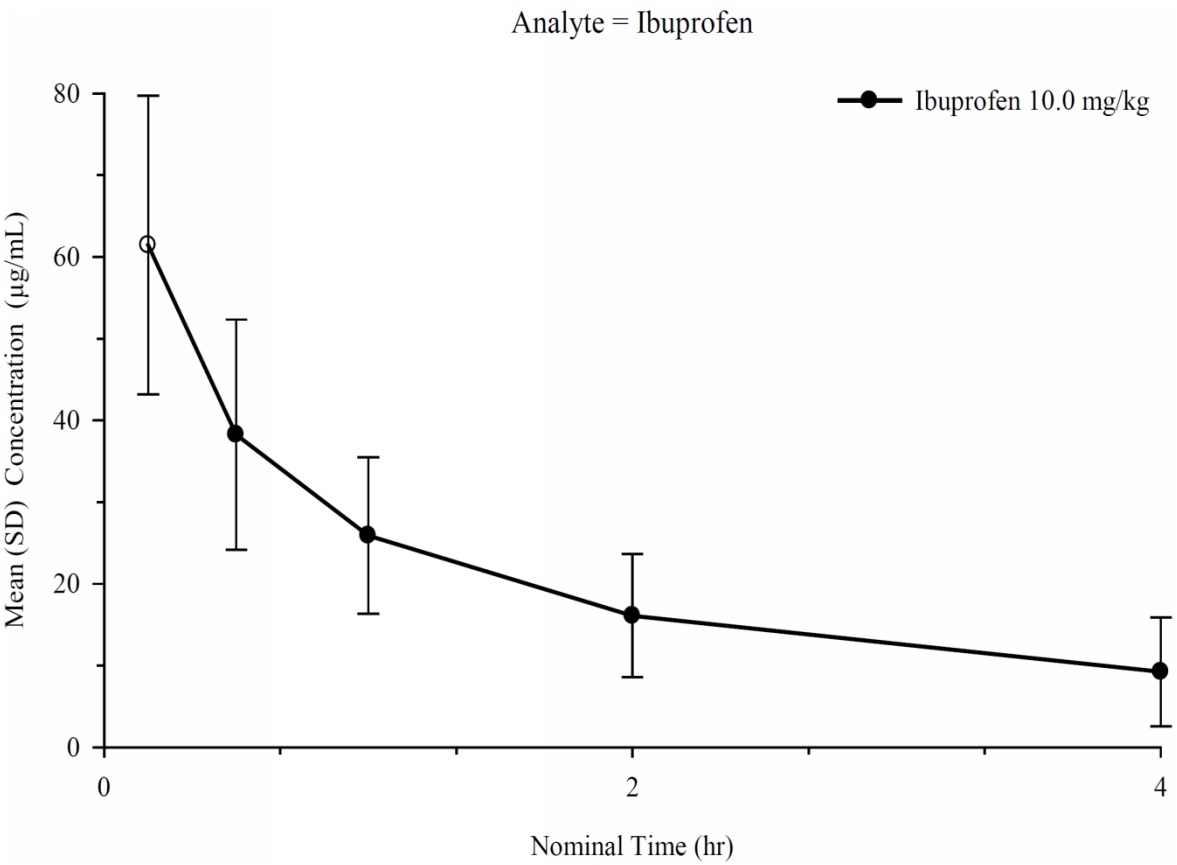

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Table 11-11 Mean Pharmacokinetic Parameters, by Age Group

Age Category	N	AUC_{0-t}	AUC_{0-4}	C_{max}	T_{max}	$T_{½\ el}$	Cl	V_z
		(µg•hr/mL)	(µg•hr/mL)	(µg/mL)	(hr)	(hr)	(mL/hr)	(mL)

Birth to < 2 months	1	51.18	69.14	49.83	0.167	1.18	619.97	1053.72
6 months to < 2 years	5	71.15	70.92	59.24	0.234	1.78	1172.50	2805.73
2 to < 6 years	12	79.19	80.25	64.18	0.309	1.48	1967.27	3695.76
6 to 16 years	25	80.67	85.73	61.89	0.212	1.55	4878.47	10314.21

AUC0-t: Area under the concentration-time curve from time zero to the last measurable concentration using linear-log trapezoidal rule.
AUC0-4: Area under the concentration-time curve from time zero to 4 hours.
Cmax: Maximum observed concentration.
Tmax: Time of observed Cmax.
T½ el: Elimination half-life, calculated as ln(2)/Kel
Cl: Total body clearance, calculated as Dose/AUC0-inf.
Vz: Volume of distribution, calculated as Dose/(Kel x AUC0-inf).
Study report CPI-CL-012

For patients Nos. 2016, 2022, and 2034, the elimination rate constant could not be properly estimated due to a low correlation coefficient of the ln-linear portion of the terminal elimination phase. The Kel derived PK parameters (T½.el, Cl, and Vz) were not calculated for these patients. These low correlation coefficients of the ln-linear portion of the terminal elimination phase are due to an increase in ibuprofen plasma concentration at the 4 hours sample. According to the clinical data, the 4 hours samples were collected before the second administration of the treatment, thus these samples were kept in the calculation of AUC0-t, AUC0-4, Cmax, and Tmax.

For patients Nos. 2001, 2008, 2009, 2012, 2014, and 2030, the 4 hours sample was collected after the start of the second infusion. Thus these samples were were judged unacceptable and were recorded as DEV (deviation) in the concentration tables. These samples were set as missing for pharmacokinetic analyses.

Pharmacokinetic Discussions

This was a multi-center, randomized, open-label, parallel, active-comparator, multiple dose trial to determine the efficacy, safety, and pharamacokinetics of intravenous ibuprofen in pediatric patients.

The objective under the scope of inVentiv was to define the pharmacokinetics of ibuprofen in plasma.

The exposure to ibuprofen following a 10.0 mg/kg IV infusion in 43 pediatric patients was evaluated. The extent (AUC0-4) and rate of absorption (Cmax) ranged respectively from 22.96 to 162.03 µg*hr/mL and 15.91 to 96.31 µg/mL.

The median time of observed maximum concentration was 10 minutes, which corresponds to the end of the infusion.

The elimination half-life was short and ranged from 0.79 to 2.87 hours with a mean of 1.55 hours.

The PK parameters were also stratified by age category. The mean extent of absorption increased with age. The mean Cmax, Tmax, and T1/2 el were similar among age categories.

The clearance (CL) and volume of distribution (Vz) increased with age which was expected when taking into consideration the common size-related change in clearance for small chemical entities.

Pharmacokinetic Conclusions

The pharmacokinetics of ibuprofen following a 10.0 mg/kg IV infusion was evaluated. It was observed that the median Tmax was at the end of the infusion and that ibuprofen has a short elimination half-life. As expected the clearance and volume of distribution increased with age. Details of the pharmacokinetic analysis are provided in Appendix 16.2.5.

==========

Appendix

Table 9-1: Ibuprofen Actual Times

Ibuprofen Actual Time (hr) over Nominal Time (hr)

Patient	(b) (4)
1005	
2001	
2004	
2007	
2008	
2009	
2012	
2014	
2016	
2017	
2018	
2022	
2027	
2030	
2034	
2035	
2037	
2038	
2042	
2047	
2049	
2050	
2054	
2055	
2058	
2059	

(b) (4)

2061
2063
2066
2069
2073
2074
2077
2078
2088
2091
2095
2098
2099
2102
2104
2106
2110
2114
2116

NS = No Sample

Table 9-2: Ibuprofen Concentration over Nominal Time

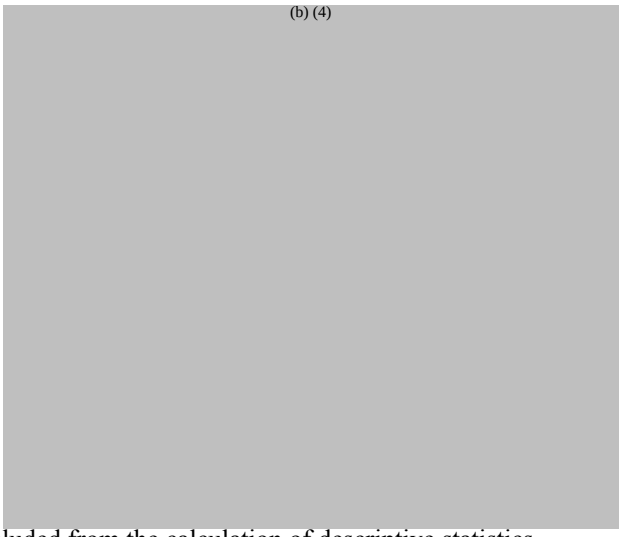
Ibuprofen Concentration (μg/mL) over Nominal Time (hr)

Patient	0.00	0.167	0.500	1.00	2.00	4.00

(b) (4)

1005
*2001
2004
2007
2008
2009
2012
2014
2016
2017
2018
2022
2027
2030
2034
2035
2037
2038
2042
2047
2049
2050
2054
2055
2058
*2059
2061
2063
2066

(b) (4)



* = Excluded from the calculation of descriptive statistics
NS = No Sample
DEV = Deviation
NCSS = Not Calculated, Small Sample Size

Table 9-3: Ibuprofen Pharmacokinetic Parameters

Ibuprofen

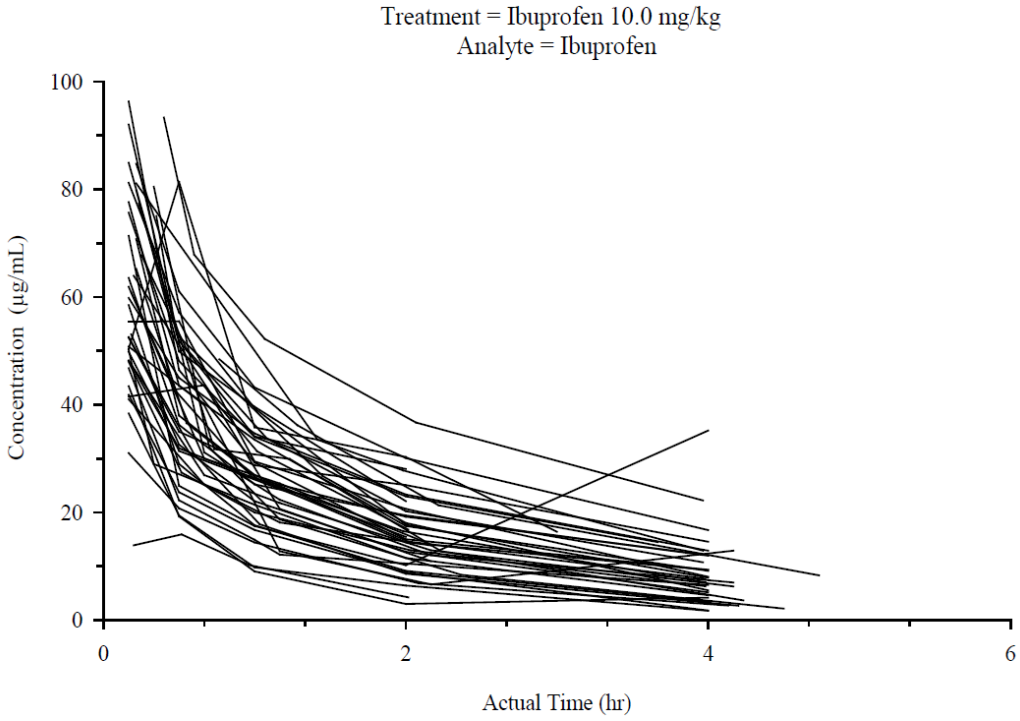
Patient	AUC0-t (µg•hr/mL)	AUC0-4 (µg•hr/mL)	Cmax (µg/mL)	Tmax (hr)	T½ el (hr)	Cl (mL/hr)	Vz (mL)
1005	(b) (4)						
*2001							
2004							
2007							
2008							
2009							
2012							
2014							
2016							
2017							
2018							
2022							
2027							
2030							
2034							
2035							
2037							
2038							
2042							
2047							
2049							
2050							
2054							
2055							
2058							
*2059							
2061							
2063							

(b) (4)

Patient	AUC0-t (µg•hr/mL)	AUC0-4 (µg•hr/mL)	Cmax (µg/mL)	Tmax (hr)	T½ el (hr)	Cl (mL/hr)	Vz (mL)
N	43	43	43	43	40	40	40
Mean	78.46	82.09	61.94	0.240	1.55	3580.96	7489.52
SD	28.73	28.97	18.14	0.143	0.48	3171.01	6428.80
CV%	36.62	35.29	29.28	59.65	30.74	88.55	85.84
Min	19.00	22.96	15.91	0.167	0.79	619.97	1053.72
Median	80.96	83.10	60.84	0.167	1.57	2208.68	4639.07
Max	161.30	162.03	96.31	0.767	2.87	12536.67	23964.19
Geometric Mean	72.86	76.59	58.93	0.215	1.48	2587.63	5528.86

Figure 10-47: Ibuprofen Individual Concentration – Time Profiles

a) Linear Scale



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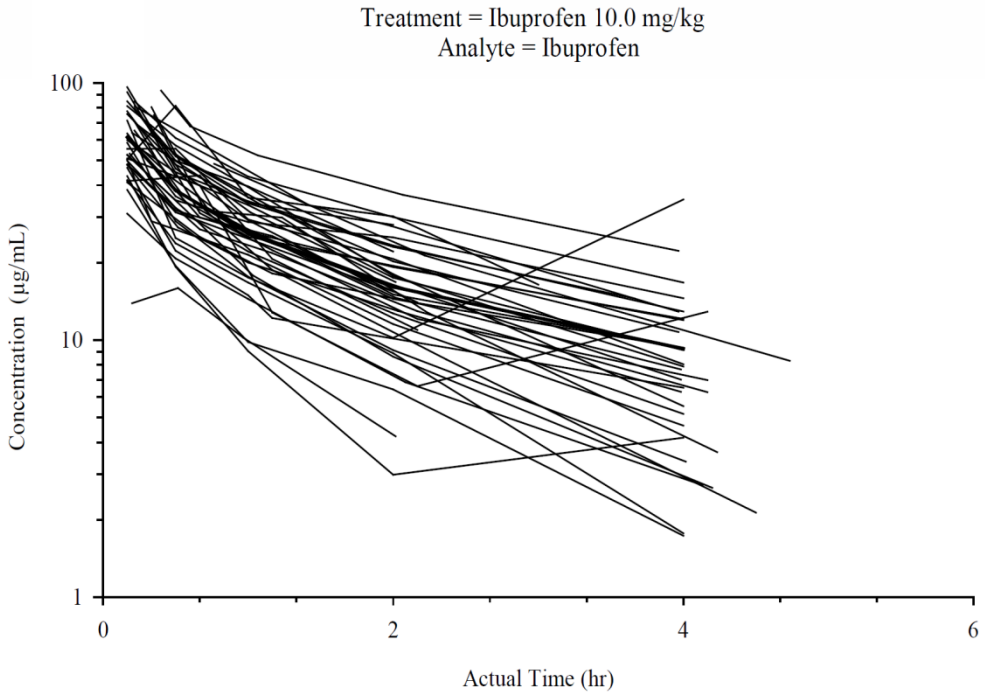
b) Log Scale



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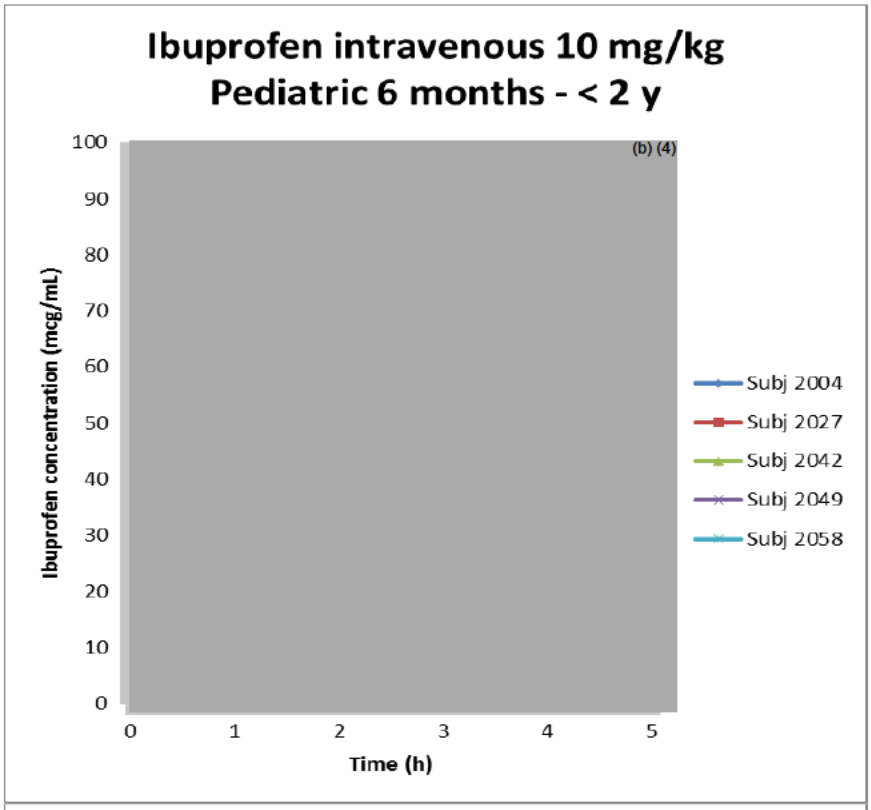
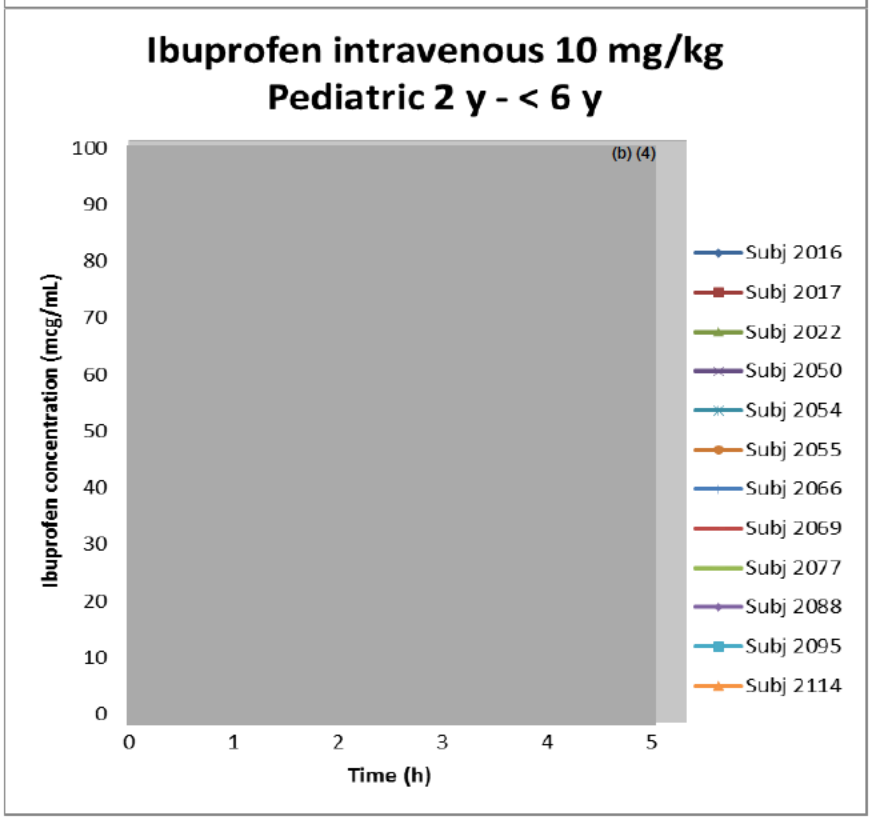
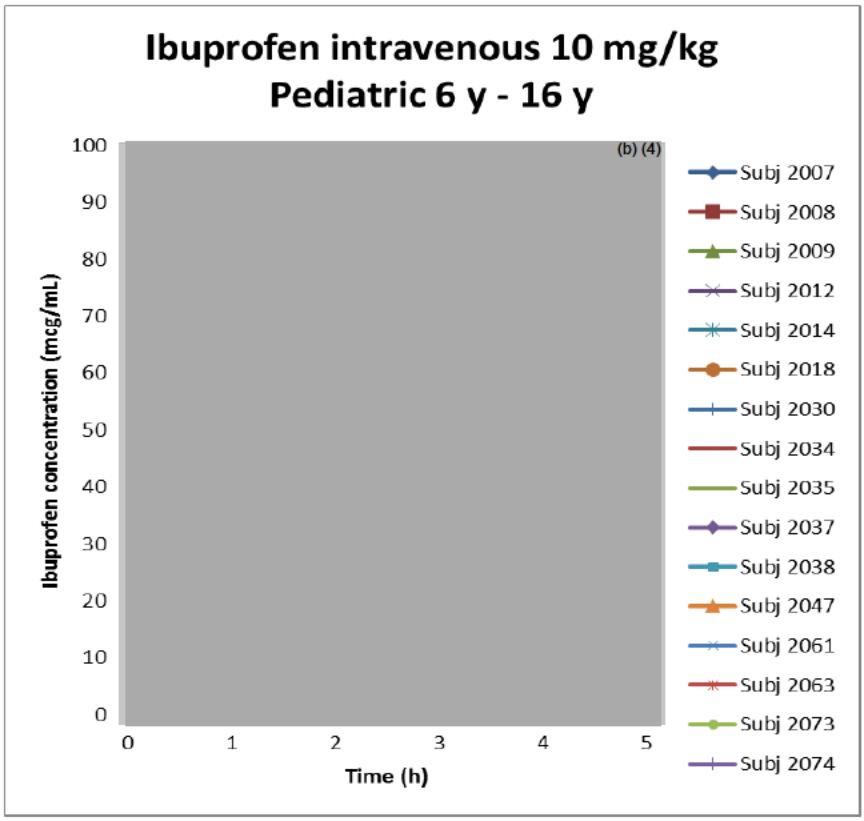

Ibuprofen intravenous 10 mg/kg
Pediatric 6 months - < 2 y
(b) (4)
Ibuprofen concentration (mcg/mL)
Time (h)
Subj 2004
Subj 2027
Subj 2042
Subj 2049
Subj 2058


Ibuprofen intravenous 10 mg/kg
Pediatric 2 y - < 6 y
(b) (4)
Ibuprofen concentration (mcg/mL)
Time (h)
Subj 2016
Subj 2017
Subj 2022
Subj 2050
Subj 2054
Subj 2055
Subj 2066
Subj 2069
Subj 2077
Subj 2088
Subj 2095
Subj 2114



Treatment = Ibuprofen 10.0 mg/kg
Age Category = Birth to < 2 months

Table 9-4: Ibuprofen Pharmacokinetic Parameters - Stratified by Age Categories

Treatment = Ibuprofen 10.0 mg/kg
Age Category = Birth to < 2 months

		Ibuprofen						
Patient	Age (months)	AUC_{0-t} (µg•hr/mL)	AUC_{0-4} (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hr)	$T_{½\ el}$ (hr)	Cl (mL/hr)	V_z (mL)
1005	1	(b) (4)						

Treatment = Ibuprofen 10.0 mg/kg

Age Category = 6 months to < 2 years

Patient	Age (months)	Ibuprofen AUC_{0-t} (µg•hr/mL)	AUC_{0-4} (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hr)	$T_{½ el}$ (hr)	Cl (mL/hr)	V_z (mL)
2004	19	[redacted]						(b) (4)
2027	9							
2042	10							
2049	21							
2058	6							
*2059	10							
N		5	5	5	5	5	5	5
Mean		71.15	70.92	59.24	0.234	1.78	1172.50	2805.73
SD		26.42	26.28	20.61	0.149	0.53	456.47	565.74
CV%		37.14	37.06	34.79	63.75	29.89	38.93	20.16
Min		34.67	34.67	38.37	0.167	1.06	844.83	2036.38
Median		84.29	83.10	55.47	0.167	1.66	1092.00	2866.45
Max		95.20	95.20	92.02	0.500	2.35	1955.92	3568.56
Geometric Mean		66.45	66.26	56.62	0.208	1.71	1114.34	2758.67

* = Excluded from the calculation of descriptive statistics

NC = Not Calculated

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Treatment = Ibuprofen 10.0 mg/kg

Age Category = 2 to < 6 years

Patient	Age (months)	Ibuprofen AUC_{0-t} (µg•hr/mL)	AUC_{0-4} (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hr)	$T_{½ el}$ (hr)	Cl (mL/hr)	V_z (mL)
*2001	59	[redacted]						(b) (4)
2016	28							
2017	26							
2022	39							
2050	45							
2054	50							
2055	65							
2066	59							
2069	29							
2077	68							
2088	34							
2095	61							
2114	26							
N		12	12	12	12	10	10	10
Mean		79.19	80.25	64.18	0.309	1.48	1967.27	3695.76
SD		29.29	30.23	22.05	0.195	0.62	1101.25	1108.01
CV%		36.99	37.67	34.35	63.23	41.81	55.98	29.98
Min		19.00	22.96	15.91	0.167	0.79	1098.93	1850.84
Median		88.54	88.54	73.19	0.200	1.34	1672.42	3870.06
Max		109.50	123.58	96.31	0.767	2.87	4744.56	5410.57
Geometric Mean		71.49	72.94	59.11	0.264	1.38	1772.28	3529.17

* = Excluded from the calculation of descriptive statistics

NC = Not Calculated

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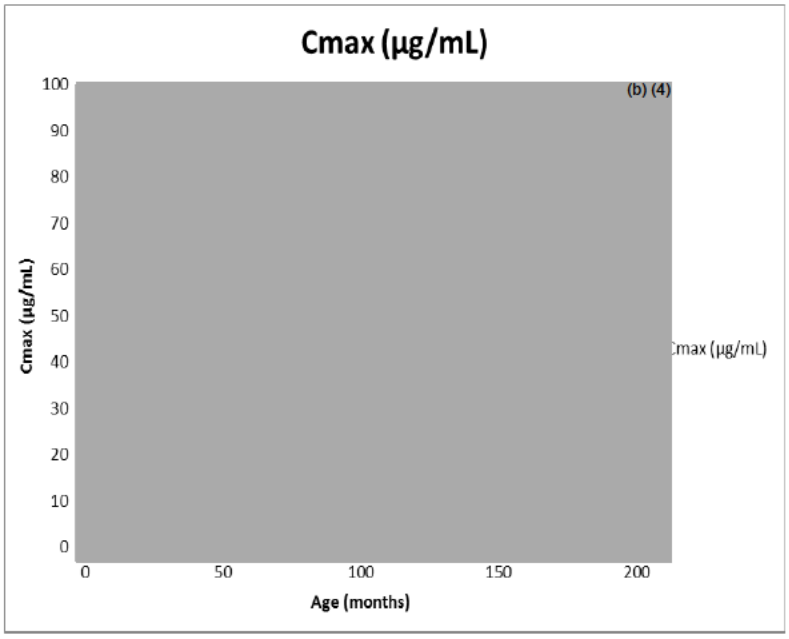
Treatment = Ibuprofen 10.0 mg/kg
Age Category = 6 to 16 years

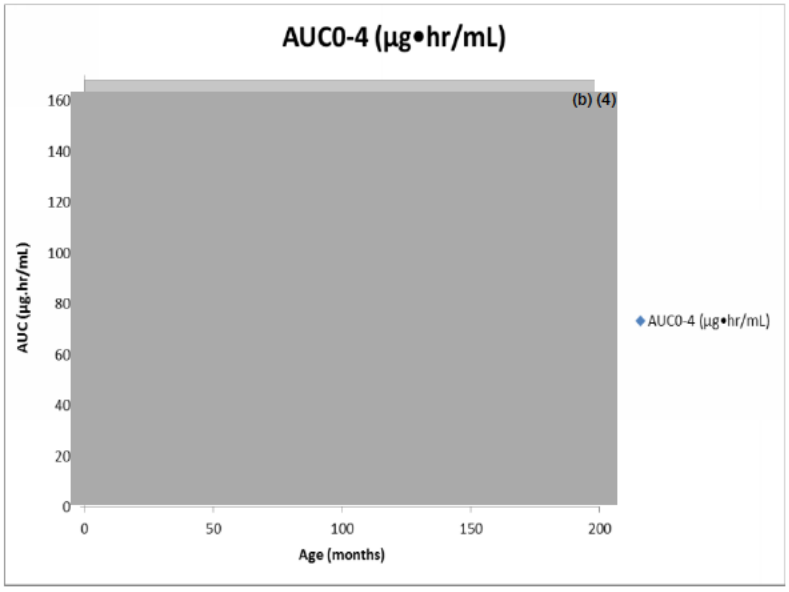
		Ibuprofen						
Patient	Age (months)	AUC_{0-t} (µg•hr/mL)	AUC_{0-4} (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hr)	$T_{½\ el}$ (hr)	Cl (mL/hr)	V_z (mL)
2007	158	(b) (4)						
2008	135							
2009	77							
2012	191							
2014	147							
2018	184							
2030	104							
2034	82							
2035	161							
2037	105							
2038	90							
2047	105							
2061	94							
2063	78							
2073	73							
2074	151							
2078	175							
2091	97							
2098	158							
2099	189							
2102	164							
2104	79							
2106	150							
2110	110							
2116	149							
N		25	25	25	25	24	24	24
Mean		80.67	85.73	61.89	0.212	1.55	4878.47	10314.21
SD		29.79	29.77	16.49	0.107	0.41	3465.32	6956.36
CV%		36.93	34.72	26.64	50.35	26.36	71.03	67.44
Min		40.00	39.62	31.03	0.167	0.79	998.60	2638.76
Median		78.95	80.96	60.84	0.167	1.55	3372.63	7457.67
Max		161.30	162.03	93.32	0.667	2.54	12536.67	23964.19
Geometric Mean		75.97	81.04	59.72	0.199	1.49	3832.41	8256.00

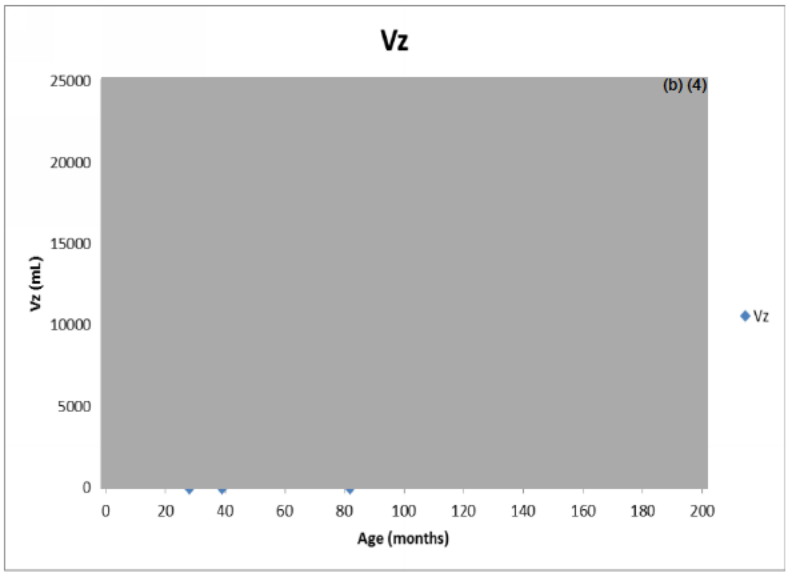
NC = Not Calculated

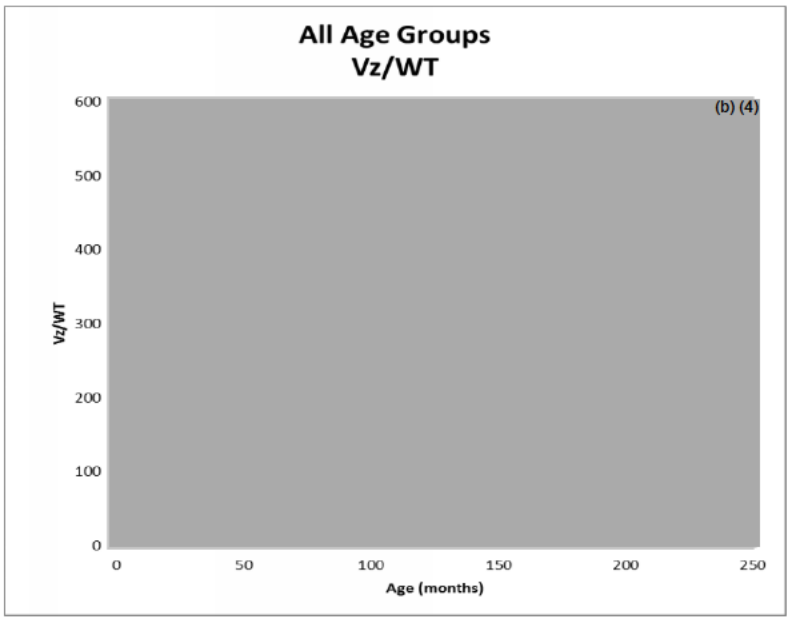
Study report CPI-CL-012

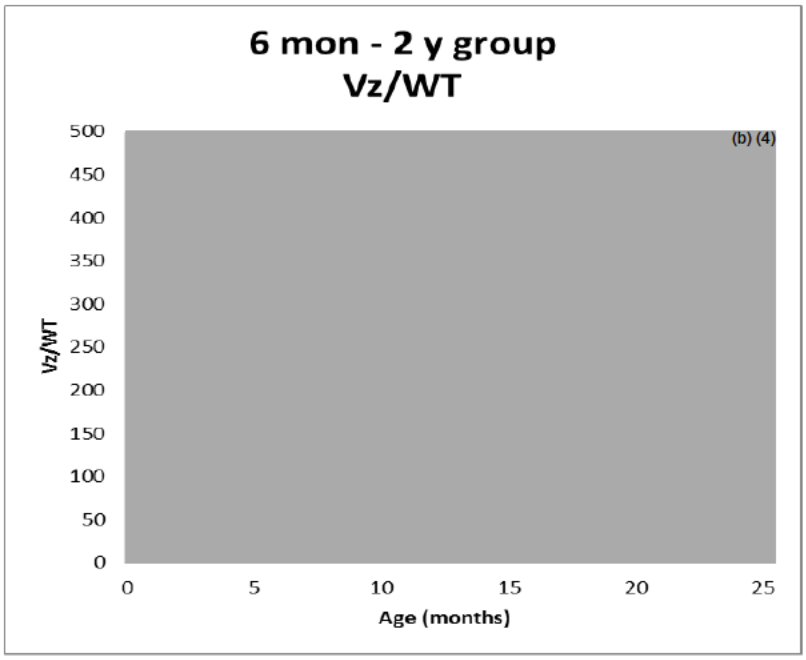
Plots of individual Cmax, AUC, Vz, and CL values vs. age (months)

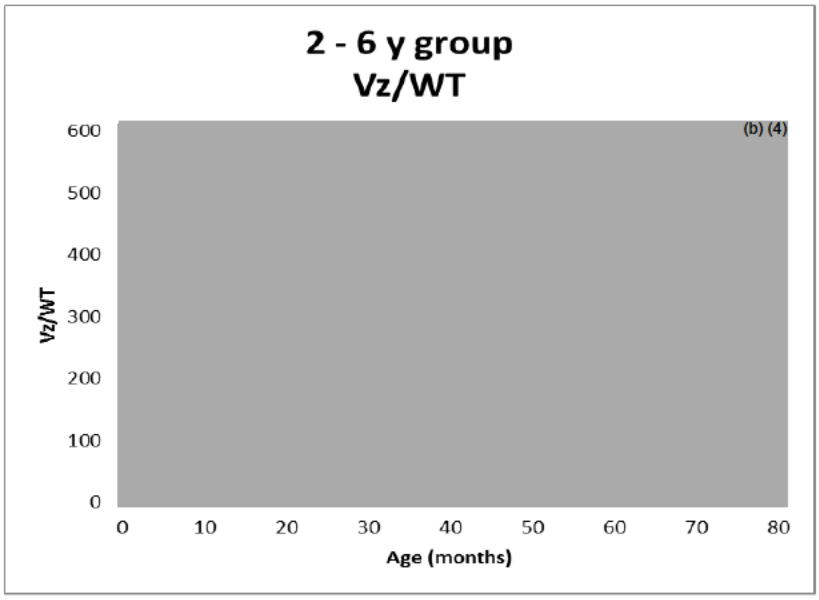


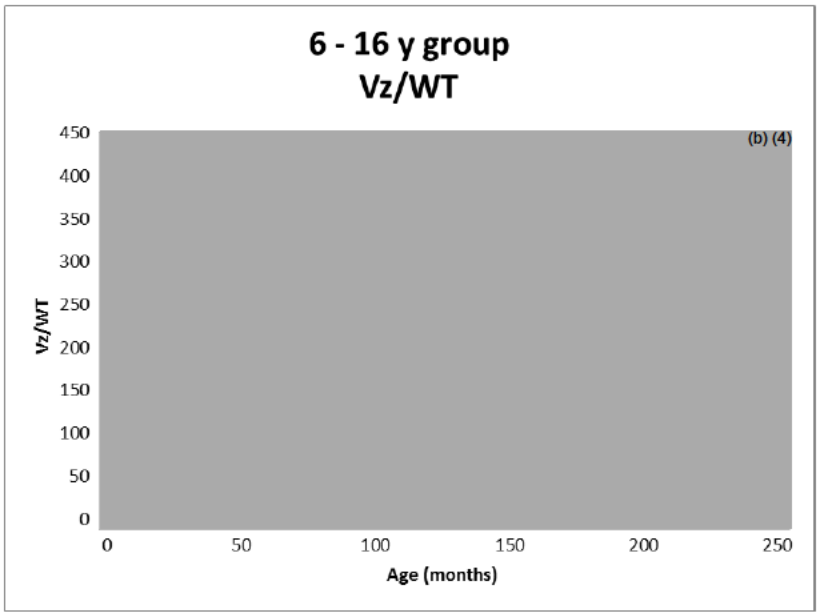


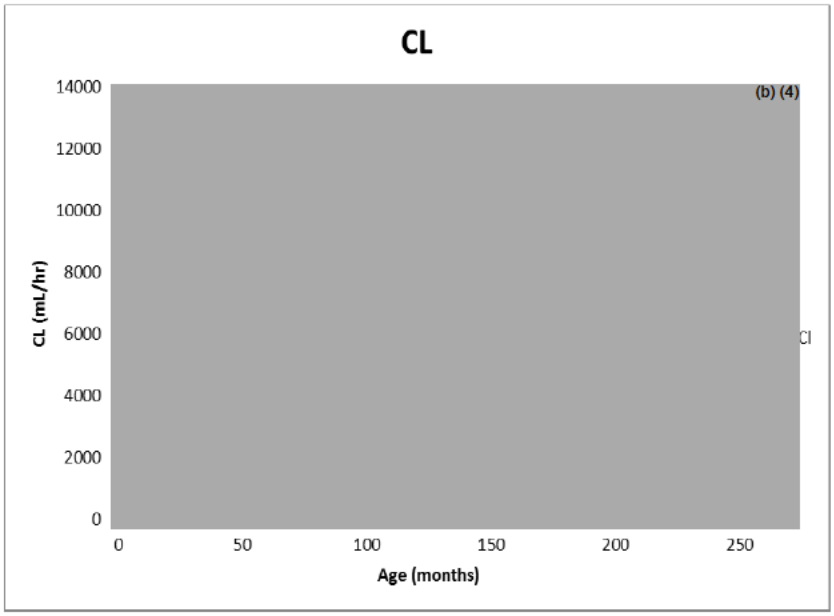

Vz
(b) (4)
25000
20000
15000
10000
5000
0
Vz (mL)
0
20
40
60
80
100
120
140
160
180
200
Age (months)
Vz

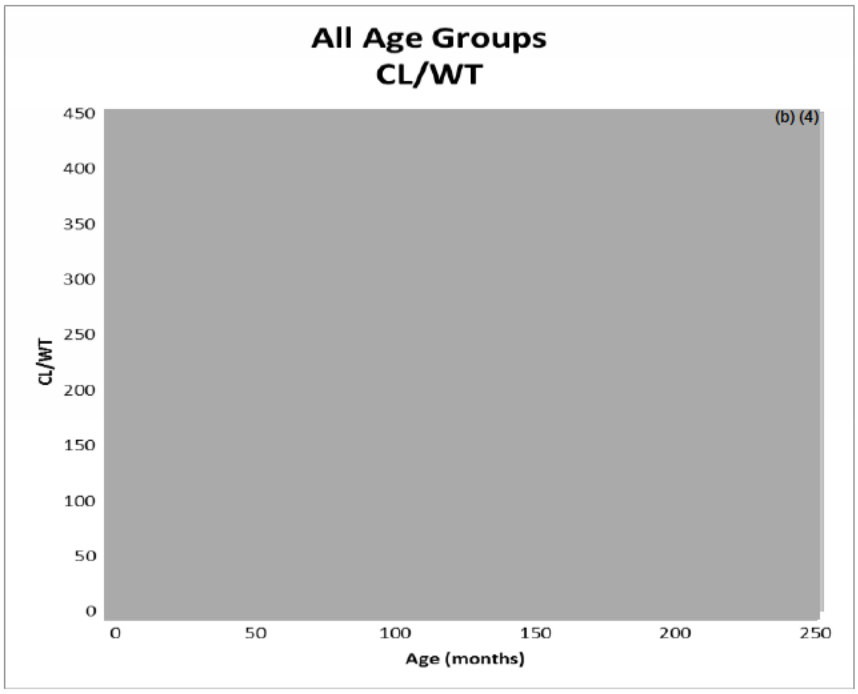

All Age Groups
Vz/WT
(b) (4)
600
500
400
300
200
100
0
Vz/WT
0
50
100
150
200
250
Age (months)

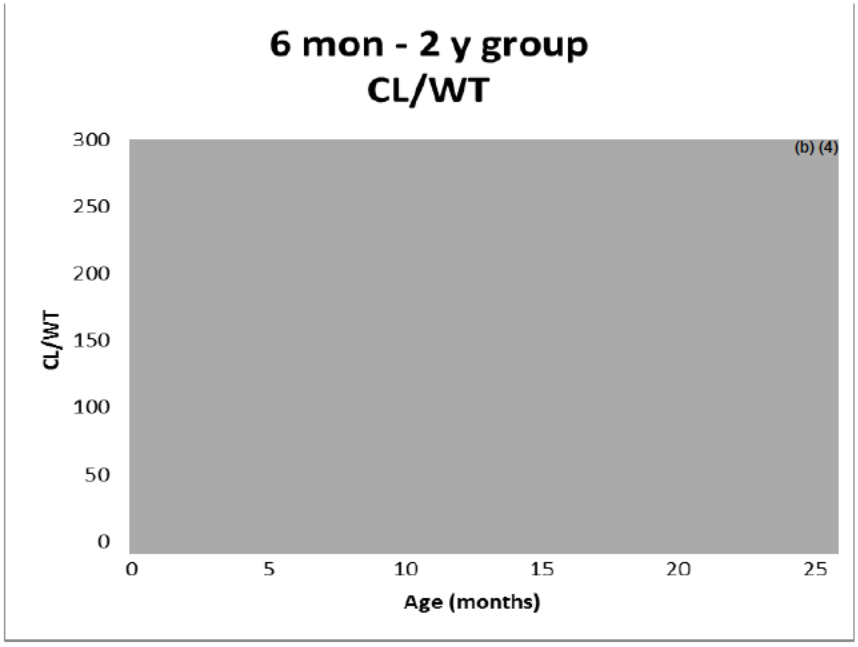

6 mon - 2 y group
Vz/WT
(b) (4)
500
450
400
350
300
250
200
150
100
50
0
Vz/WT
0
5
10
15
20
25
Age (months)

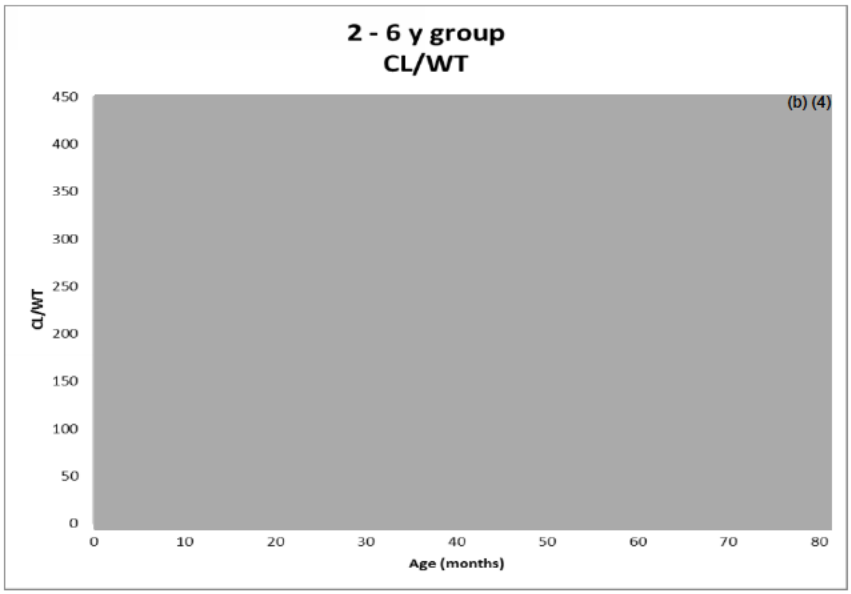

2 - 6 y group
Vz/WT
(b) (4)
600
500
400
300
200
100
0
Vz/WT
0
10
20
30
40
50
60
70
80
Age (months)

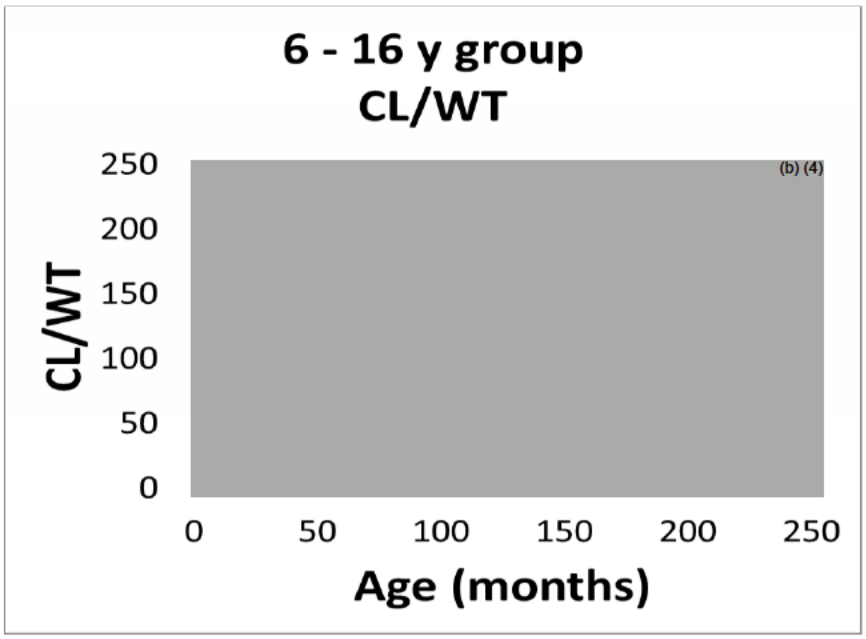

6 - 16 y group
Vz/WT
(b) (4)
Vz/WT
450
400
350
300
250
200
150
100
50
0
0
50
100
150
200
250
Age (months)


CL
(b) (4)
CL (mL/hr)
14000
12000
10000
8000
6000
4000
2000
0
0
50
100
150
200
250
Age (months)


All Age Groups
CL/WT
(b) (4)
450
400
350
300
250
200
150
100
50
0
CL/WT
0
50
100
150
200
250
Age (months)


6 mon - 2 y group
CL/WT
(b) (4)
300
250
200
150
100
50
0
CL/WT
0
5
10
15
20
25
Age (months)


2 - 6 y group
CL/WT
(b) (4)
CL/WT
450
400
350
300
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
Age (months)


6 - 16 y group
CL/WT
(b) (4)
CL/WT
250
200
150
100
50
0
0
50
100
150
200
250
Age (months)

4.3 Consult Review (including Pharmacometric Reviews) – Not applicable

4.4 Cover Sheet and OCP Filing/Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	22348/Supplement 005	**SDN 065, 070**	
Applicant	Cumberland Pharmaceuticals, Inc.	**Submission Date**	1/29/15; 3/20/15
Generic Name	Ibuprofen IV	**Brand Name**	Caldolor®
Drug Class	Analgesic		
Indication	Reduction of fever; the management of mild to moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics		
Dosage Regimen	Pain: Adult-400 to 800 mg IV every 6 hours as necessary; Pediatric-10 mg/kg up to (b) (4) mg IV every 6 hours as necessary. Fever: Adult- 400 mg IV followed by 400 mg every 4 to 6 hours or 100-200 mg every 4 hours as necessary; Pediatric-10 mg/kg up to 400 mg IV every 4 to 6 hours as necessary		
Dosage Form	Solution	**Route of Administration**	Intravenous
OCP Division	DCP 2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	David Lee	Yun Xu	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	3/30/15	**74-Day Letter Date**	4/13/15
Review Due Date	10/29/15	**PDUFA Goal Date**	11/29/15

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in

the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability			Comparator ibuprofen oral 800 mg
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☑ Single Dose	1	Pediatric patients birth to <2 mon (n=1); 6 mon-<2 y (n=5); 2-<6 y (n=12); 6-<16 y (n=25)

	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	1
Total Number of Studies to be Reviewed				1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism	☐Yes ☐No	

and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	The supplement submission if for Change to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the package insert to provide for antipyretic and analgesia use in the pediatric population
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	

Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☑Yes ☐No ☐N/A	
General		

8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo
This is optional, discuss with your TL content and format

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID J LEE
10/21/2015

YUN XU
10/21/2015