CLINICAL REVIEW

Application Type	NDA
Submission Number	22-450 Supplement 10
Priority or Standard	Standard
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Division / Office	DAAAP/CDER/OND/ODE II
Reviewer Name	Christina Fang, M.D., M.P.H.
Review Completion Date	January 19, 2017
Established Name	Acetaminophen IV injection
Trade Name	OFIRMEV® (b) (4) injection
Therapeutic Class	Analgesic and antipyretic
Applicant	Mallinckrodt IP
Formulation	IV solution containing acetaminophen (10 mg/mL)
Dosing Regimen	(b) (4)-15 mg/kg every 6 hours in patients <two years of age
Indication	(b) (4) fever
Intended Population	Hospitalized patients

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1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

(b) (4)

(b) (4) updates for the age group of less than two years may be included in the pediatric section of labeling.

1.2 Risk Benefit Analysis

For pediatric patients less than two years of age hospitalized with need for IV analgesia, benefits from IV acetaminophen could not be demonstrated in terms of the expected reduction in the amount of rescue opioid.

The findings revealed sizable treatment group imbalance at baseline in terms of the amount of loading dose (30-40% more loading opioid given to the active treatment groups than placebo group) and imbalance in pain intensity before and after the loading dose prior to study drug infusion, and thus, invalid treatment comparison of effects of the study drug. The results showed very small and not clinically meaningful treatment differences in all efficacy endpoints and no consistent pattern or trend across dosing groups and age strata. There were conflicting findings with results shown in favor of active treatment for one dosing group versus in favor of placebo (standard care) for the other dosing group and in favor of active treatments in two age strata versus in favor of placebo treatment in other two age strata.

The response to the single dose of loading opioid was overwhelming (40-80% PI reduction from PI of 2.1-4.5 to PI of 0.6 to 2.2) in all the treatment groups across age strata. Low PI scores were maintained throughout the study duration with frequent use of rescue opioid (2-3 doses averaged over patients with or without rescue) in a large proportion (about 80%) of the study population.

The key confounding factor appeared to be the use of a large dose of opioid (more than the total amount of 24-hour rescue) given 30 minutes before the study drug infusion, leading to very low levels of pain at baseline. The variation in institutional practice of opioid usage among 18 different study sites (15 of which had $\leq$12 patients) and variation in individual habit between different investigators and caregivers might have played a major role in inability of study to use opioid consumption as primary and key secondary endpoints for efficacy evaluation.

Based on review of pediatric safety data obtained from 198 pediatric patients with 128 patients exposed to IV acetaminophen and mostly (109) to four doses, there were no new safety signals or major safety issues identified. (b) (4)

1.3 Recommendations for Post marketing Risk Management Activities

None.

1.4 Recommendation for other Post marketing Study Commitments

None.

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

OFIRMEV® (b) (4) is an IV formulation containing 1000 mg acetaminophen in 100 mL solution (10 mg/mL) approved for U.S. marketing in November, 2010 for the management of acute pain and fever in adults and pediatric patients at least two years old.

According to the labeling at the time of NDA approval OFIRMEV (acetaminophen) injection is indicated for
- Management of mild to moderate pain
- Management of moderate to severe pain with adjunctive opioid analgesics
- Reduction of fever

The recommended dosage is summarized by age group in the table below.

Table 1 Dosage by Age Group

Age group	Dosage	Maximum single dose	Maximum total daily dose (by all routes)	Minimum dosing interval
Adults and adolescents (≥13 years old), weighing ≥ 50 kg	650 mg q4h or 1000 mg q6h	1000 mg	4000 mg **in 24 hours**	4 hours
Adults and adolescents (≥13 years old), weighing <50 kg	12.5 mg/kg q4h or 15 mg/kg q6h	15 mg/kg (up to 750 mg)	75 mg/kg **in 24 hours** (up to 3750 mg)	4 hours
Children: 2-12 years old	12.5 mg/kg q4h or 15 mg/kg q6h	15 mg/kg (up to 750 mg)	75 mg/kg **in 24 hours** (up to 3750 mg)	4 hours

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

For the indications of both pain management and fever reduction, non-parenteral formulations of acetaminophen and a number of drugs in NSAID class are currently available. Only Caldolor® (IV ibuprofen) and OFIRMEV® are currently available analgesic/antipyretic for IV injection. The two drug products have the same set of indications and both were approved for use in pediatric patients. The age limit for use of Caldolor® in pediatric patients is at least six months old.

2.3 Availability of Proposed Active Ingredient in the United States

There are many acetaminophen containing products currently available in the United States. A long list of drug products of various formulations was provided in the review of the original NDA and will not be repeated here. Only the formulations that may be administered to younger pediatric patients such as IV and oral solution, oral suspension, and rectal suppository are summarized in the table below by the active ingredient, dosage form and route of administration, strength of formulation, NDA number, and status as reference list product (RLD).

Table 2 Acetaminophen Containing Solution/Suspension/Suppository Formulations

Active ingredient	Dosage Form	Route	Strength	NDA/ANDA #
Rx products				
Acetaminophen	Solution	IV (Infusion)	1gm/100ml (10mg/Ml)	N204767 A202605 A204052 N022450 RLD
Acetaminophen; Butalbital; Caffeine	Solution	Oral	325mg/15ml; 50mg/15ml; 40mg/15ml	A040387 RLD

Acetaminophen; Codeine Phosphate	Solution	Oral	120mg/5ml; 12mg/5ml	A040119 A089450 A087508 RLD A091238 A087006
Acetaminophen; Hydrocodone Bitartrate	Solution	Oral	300mg/15ml; 10mg/15ml	A040881 RLD A040482 RLD A040834 RLD A040838 A040894 A200343 A090468
Acetaminophen; Oxycodone Hydrochloride	Solution	Oral	325mg/5ml; 5mg/5ml	A040680 RLD A203573
Acetaminophen; Codeine Phosphate	Suspension	Oral	120mg/5ml; 12mg/5ml	A086024 RLD
OTC products				
Acetaminophen	Suppository	Rectal	80mg	N018337
Acetaminophen	Suppository	Rectal	120mg	N018060 A070607 N018337 N016401
Acetaminophen	Suppository	Rectal	325mg	A072344 N018060 N018337
Acetaminophen	Suppository	Rectal	650mg	A072237 N018060 A070608 N018337 RLD

Source: Orange book, 2016 edition.

2.4 Important Issues with Consideration to Related Drugs

The major safety concern with the use of acetaminophen is the drug induced hepatic injury with potentially serious outcomes, especially in high risk groups such as hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, and severe renal impairment. Another important safety concern is unintentional overdose since acetaminophen is widely available in many different prescription and OTC combination and single-ingredient products. Accidental overdose due to medication errors in prescribing, preparing, and administering OFIRMEV Injection had been noticed and associated with increased risks of hepatotoxicity with serious consequences. The updated labeling (Supplement 5) now includes Warning statements about not to confuse dosing in mg versus mL, use of weight based dose only for patients <50 kg, have infusion pumps properly programmed, and not to exceed total daily dose from all sources.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

Under the Pediatric Research Equity Act (PREA) the applicant of NDA 22450 was required to conduct a randomized, double-blind, adequately controlled study of efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of IV APAP for the treatment of acute pain in pediatric patients from 0 to 2 years of age and was granted a deferral at the time of NDA approval (refer to the NDA approval letter of the original NDA dated November 2, 2010). A Pediatric Written Request (PWR) consisted of specific requirements for the study was sent to the Applicant on December 20, 2010 and followed by a revised PWR with minor changes for clarification purpose. A request of deferral extension of the pediatric study was granted to extend the study completion date to October 2015 and the final report submission date to May 2016. The most recent PWR revision was sent on March 30, 2015 and had allowed a reduction of subgroup sample size from 12 to 9 patients per active treatment dose group per age strata and combination of PK data from the study under PREA and prior

pediatric studies conducted in neonates and infants. The final study report was submitted to meet the PWR and to be reviewed as NDA Supplement 10 for incorporating new pediatric data into the labeling. Pediatric Exclusivity was granted for studies conducted on Acetaminophen, effective July 11, 2016 before the completion of the reviews of the NDA Supplement. The results of the study will be used as basis to determine whether the study meet the PREA requirement.

2.6 Other Relevant Background Information

None.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

There were data inconsistencies between different parts of the submission and between submissions on different dates. Some important data such as those related to opioid loading dose were missing from the original submission of the NDA supplement.

3.2 Compliance with Good Clinical Practices

The planned steps to ensure compliance with Good Clinical Practices (GCP) included study site monitoring, record keeping of the Investigator Study Files, source documents, and clinical supplies accountability records, quality assurance inspections by the Applicant, and the Institutional Review Boards (IRBs) oversight. Compliance with GCP could not be adequately evaluated because there would not be a study site inspection by the FDA inspectors.

3.3 Financial Disclosures

The financial disclosure form signed by the Applicant (refer to the submission dated May 20, 2016) certified that no financial arrangement with the listed clinical investigators (a complete list of all clinical investigators involved in clinical studies was attached to the form) had been made whereby study outcomes affected compensation as defined in 21 CFR 54.2(a); certified that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such interests; and certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4. SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

Refer to the CMC Review of the original NDA.

4.2 Clinical Microbiology (if applicable)

Refer to the Microbiology Review of the original NDA.

4.3 Preclinical Pharmacology/Toxicology

There were no animal data included in the current NDA Supplement. Refer to the Pharmacology/Toxicology Review for information related to Labeling update.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action for acetaminophen is not completely understood. Its analgesic activities appear to be due to elevation of the pain threshold. Its antipyretic activities may be related to its effects on the hypothalamic heat-regulating centers.

4.4.2 Pharmacodynamics

Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human studies.

4.4.3 Pharmacokinetics

Pharmacokinetic (PK) data were obtained from pediatric patients aged less than two years in Study CPI-APA-353, which is described in detail in the Review Section 5.3.

PK for infants

Patients in each of the three infant age categories were exposed to either 12.5 or 15 mg/kg. PK data were obtained from 13 to 19 patients per infant age category per exposure level as shown in the table below. Sample size for PK data appeared to be adequate. There appeared to be a small dose response in AUC and Cmax in comparison of 12.5 and 15 mg/kg dose levels. The younger infants appeared to have slightly lower clearance, slightly longer half-life, and slightly higher concentrations as suggested by the trend in comparison of PK data at each dose level across age categories. PK profiles associated with exposure to 15 mg/kg in infants were consistent to those in children and adolescents and similar to adult PK data at 1000 mg exposure level (refer to Table below).

Table 3 PK for Infants based on Population PK Analyses

Infant age category	Exposure level & sample size	AUC0-6 (µg×h/mL)	Cmax (µg/mL)	T1/2 (h)	CL (L/h/kg)	Vss (L/kg)
Younger infant	12.5 mg/kg, n=15	37.0 (10.4)	23.5 (7.1)	2.5 (0.5)	0.32 (0.10)	0.97 (0.18)
	15 mg/kg, n=19	41.6 (13.8)	24.7 (9.5)	3.0 (1.5)	0.31 (0.07)	1.27 (0.98)
Intermediate age	12.5 mg/kg, n=14	30.2 (6.3)	20.8 (4.3)	2.3 (0.6)	0.38 (0.10)	1.04 (0.26)
	15 mg/kg, n=17	45.5 (19.8)	30.0 (9.2)	2.4 (0.6)	0.34 (0.12)	0.96 (0.13)
Older infant	12.5 mg/kg, n=13	27.7 (8.1)	20.2 (6.3)	2.2 (0.7)	0.43 (0.12)	1.17 (0.64)
	15 mg/kg, n=18	38.8 (10.9)	27.1 (6.8)	2.2 (0.5)	0.39 (0.08)	1.09 (0.53)

Source: Table 11-12 on page 91 of the study report.

Table 4 PK from Previous PK Studies as in the Current Product Labeling

b(4)

PK for neonates

Exposure to IV acetaminophen and PK data were limited to two patients in the high dose group in each of the extreme pre-term neonate and pre-term neonate age categories.

PK profiles for full-term neonates were representative of the neonate age category due to the lack of PK data in the extreme pre-term and pre-term neonates and the trends were similar to the other three age categories as discussed above.

Table 5 PK for Neonates based on Population PK Analyses

Neonate category	Exposure level & sample size	AUC0-6 (µg×h/mL)	Cmax (µg/mL)	T 1/2 (h)	CL (L/h/kg)	Vss (L/kg)
Extreme Pre-Term	10 mg/kg, n=2	27.7 (8.1)	20.2 (6.3	3.3 (0.3)	0.19 (0.02)	0.85 (0.03)
Pre-Term Neonate	12.5 mg/kg, n=2	43.2 (11.6)	22.8 (6.6)	3.2 (0.7)	0.22 (0.08)	0.92 (0.13)
Full-Term Neonate	10 mg/kg, n=9	37.0 (8.3)	18.1 (4.3)			
	12.5 mg/kg, n=5	41.8 (22.3)	19.6 (11.7)	3.9 (2.6)	0.22 (0.05)	1.3 (1.3)
Neonate combined	10 mg/kg, n=11	36.7 (7.6)	18.2 (4.0)	3.2 (0.5)	0.22 (0.05)	0.93 (0.09)
	12.5 mg/kg, n=7	42.2 (18.8)	20.5 (10.0)	5.0 (4.1)	0.23 (0.06)	1.76 (2.04)

Source: Table 2 on page 12 and Table 3 on page 15 of the study report for Study MALL-PCS-101 and Table 11-12 on page 91 of the study report for Study CPI-APA-353.

There were a number of issues with the Applicant's population PK analyses as described in the PK review by Dr. Kevin Krudys. Based on graphical comparisons of acetaminophen concentrations in neonates receiving 12.5 mg/kg and infants receiving 15 mg/kg IV dosing to concentrations in healthy adults receiving 1000 mg IV (Study CPI-APA-101) after the first dose, the PK review team concluded that IV acetaminophen doses of 12.5 mg/kg in neonates and 15 mg/kg in infants are expected to result in similar concentrations to the already approved adult and pediatric doses.

5. SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

5.1 Tables of Clinical Studies

Table 6 Overview of Pivotal Efficacy Studies

Study # Site, dates	Study Design	Planned treatments with actual exposure				Study Population Demographics	Review section
CPI-APA-353 18 US sites 8/22/12 to 8/12/15	Randomized Double-blind Placebo-controlled Multiple-dose (q6h x4 doses)	Age category	IV APAP-LD	IV APAP-HD	Placebo	Post-surgical pain or pain due to traumatic injury 127 M/ 71 F Caucasian, n=136 African American, n=30 Asian, n=13 Other, n=13 Missing, n=5 American Indian or Alaska Native, n=1	5-6 for efficacy; 7-8 for safety; 4.4 for PK
		Extreme pre-term neonates	7.5 mg/kg, n=0	10 mg/kg, n=2	n=1		
		Pre-term neonates	10 mg/kg, n=0	12.5 mg/kg, n=3	n=1		
		Full-term neonates	10 mg/kg, n=13	12.5 mg/kg, n=7	n=11		
		Younger infants	12.5 mg/kg, n=16	15 mg/kg, n=20	n=18		
		Intermediate age infants	12.5 mg/kg, n=18	15 mg/kg, n=17	n=20		
		Older infants	12.5 mg/kg, n=14	15 mg/kg, n=18	n=19		

Source: Study report for Study CPI-APA-353.

5.2 Review Strategy

Efficacy review consists of review of data submitted in the original submission of NDA supplement and data requested from the Applicant for clarifications of incompleteness, inconsistency, and missing information (e.g., data on loading opioid was not provided in the original submission). Additional post hoc analyses were requested in terms of number of doses of rescue opioid (since the amount of opioid did not appear to be a

sensitive measure), findings with respect to the actual exposure level of acetaminophen (because of the overlap of exposure levels in the low dose and high dose groups), and distribution of the number of rescue doses at specific pain intensity levels (due to suspected disconnection between PI and the use of rescue) based on issues identified during the review process.

Efficacy data were analyzed for comparison of acetaminophen low dose and acetaminophen high dose groups against placebo (standard care) for the entire study population and for each of the four age strata and for comparison of different actual exposure levels. Pain curves were presented per age stratum because of the use of different age-dependent pain scales and dose overlap between age strata.

5.3 Discussion of Individual Studies

5.3.1 Pediatric Study CPI-APA-353)

5.3.1.1 Protocol

The original protocol will be described in detail. Protocol amendments will be summarized. The protocol summary table will include key elements of the final version of the protocol.

Study CPI-APA-353 was planned as a multiple-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose (four doses in 24 hours), efficacy and PK/PD study of acetaminophen (APAP) 15-minute IV infusion in hospitalized pediatric patients aged less than two years with acute postsurgical pain or pain due to traumatic injuries requiring opioid treatments.

Eligible patients were to have been pediatric patients in the age range of birth (≥28 weeks gestational age) to less than two years at the time of randomization who would have been expected to have moderate to severe pain due to surgery or traumatic injury requiring IV analgesic for 24 hours and reliable vascular access for study drug infusion and PK sampling. Patients were to have been required to have pain intensity (PI) score of ≥3 on the LNPS (0-14 points for patients aged <6 months) or FLACC scale (0-10 points for patients aged 6 to <24 months and need at least one dose of IV opioid within eight hours prior to randomization and anticipated to require at least one dose of rescue IV opioid during the 24-hour treatment period.

Eligible patients were to have been treated with a standard opioid analgesic regimen according to each center's pediatric anesthesia protocol and rated as "moderate opiate dosing" (≤2 IV opioid doses or <30 mcg/kg/h morphine equivalent) or "high opiate dosing" (≥3 IV opioid doses or ≥30 mcg/kg/h morphine equivalent) based on opioid consumption in the preceding eight hours. They were to have been stratified according to age (see table below) and opioid consumption and randomized to receive either IV acetaminophen (group A of low dose and group B of high dose) or placebo (groups C and D with match volume to A and B, respectively) in a 2:2:1:1 ratio, every six hours for 24 hours (four doses). The planned procedure included sequentially the following: pain intensity (PI) assessment at randomization, a loading opioid dose of Investigator's choice 30 minutes before study drug infusion, and baseline PI prior to the first dose of study drug.

Table 7 Weight-Based Acetaminophen IV Dose Level per Age Strata

	IV acetaminophen (mg/kg)	
Age Category	**Low dose**	**High dose**
Extreme pre-term (28 to <32 weeks gestational age at birth) or neonates with ↑bilirubin	7.5	10
Pre-term (32 to <37 weeks gestational age at birth) or neonates with normal bilirubin	10	12.5
Full term (37 to 40 weeks gestational age at birth) neonates	10	12.5
Younger infants: 29 days to <6 months of age	12.5	15

Intermediate age infants: 6 months to <12 months of age	12.5	15
Older infants/Children: 12 months to <24 months of age	12.5	15

Source: Tables 5 and 6 on pages 53-54 of the original protocol.

Standard care opioid was planned to be given as a loading dose 30 minutes before study drug and as rescue (at least 30 minutes) following the initial dose of study drug. The examples of opioid medication were listed as morphine 0.1 mg/kg (100 mcg/kg), fentanyl 1 mcg/kg, and hydromorphone 0.015 mg/kg (15 mcg/kg). The planned use of opioid rescue was specified inconsistently as "p.r.n. (as needed) for adjunctive treatment of moderate to severe pain (*LNPS or FLACC >4*)" and then as prn "at the Investigator or Caregiver's discretion" "any time the assessed pain intensity is severe (LNPS or FLACC ≥5)' in the next paragraph. The planned method of opioid delivery was up to "Investigator's choice or local standard of care either as q2-3h bolus doses with the initial weight-based loading doses or as healthcare provider-controlled analgesia using a patient-controlled analgesia (PCA) device with appropriate limits on incremental and hourly doses." The planned dose of loading opioid was based on standard of care and the dose of rescue opioid up to Investigator's discretion. The goal of rescue was planned as to achieve LNPS or FLACC <3 on page 9 of the protocol and ≤3 on page 51 of the protocol.

Efficacy data to be collected were to have included information about the use of opioid, pain intensity (PI) measurements at -0.5, 0, 0.5, 1, 2, 3, 4, 6, 12 hours from the start of study drug infusion and prior to each rescue dose (also pre and post heel stick), assessor global and caregiver global evaluation using 11-point numerical scale at the end of the treatment period or early termination, and sedation assessments using the University of Michigan Sedation Scale (UMSS, 5-point categorical scale of 0-4) every three hours until Hour 12. There were two pain scales planned for PI measurements in different age groups: the Face, Legs, Activity, Cry, and Consolability (FLACC) for patients 1 to <2 years of age (the older infant group) and the Leuven Neonatal Pain Scale (LNPS) for patients <1 year of age (the three younger age groups). A 0 to 2-point scale would be used to score each of five categories consisted of facial appearance, leg movement, activity, crying and consolability with a maximum score of 10 in FLACC and each of seven variables including sleep, facial appearance, crying, increase in heart rate, motor tone, motor activity, and consolability with a maximum score of 14 in LNPS.

The planned primary efficacy endpoint was the total amount of rescue opioid (mg/kg morphine or morphine equivalent) over 24 hours from the start of the initial infusion to six hours after the last dose. The planned secondary efficacy endpoints included pharmacodynamic/pharmacokinetic (PD/PK) correlation between acetaminophen concentration and pain scores at one hour; PD/PK correlation between acetaminophen concentration and amount of rescue opioid in the first 12 hours after the initial dose; weighted sum of pain intensity differences in the first three hours (SPID3); total amount of rescue opioid over the first 12 hours; total amount of rescue opioid in each dosing interval; time to the first rescue after the initial dose; percentage of patients requiring rescue opioids; mean pain intensity scores adjusted for corresponding quantity of rescue opioids; assessor global and caregiver global evaluation; Correlation between plasma acetaminophen concentration and change in pain intensity for heel stick (pre to post heel stick procedure).

PK blood sampling was to have been collected in a subset of patients at 0, 0.5, 2, 7, 12 hours from the start of study drug infusion and at any time routine blood work is obtained (randomly, use nominal time after last dose) and urine sampling during each dosing interval corresponding to blood sampling time if applicable.

Safety monitoring was planned to consist of reports of adverse events (AEs), vital signs at screening, pre randomization, prior to and immediately after the first infusion of study medication, and at study completion/early termination, physical examination at screening, pre randomization, and at study completion/early termination, and clinical laboratory tests. Laboratory tests planned for qualification purpose included renal function (BUN and creatinine), hematocrit, and liver function tests (LFTs) such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), direct bilirubin, alkaline phosphatase (ALP) and planned at the time of study completion were focused on liver function and liver

enzymes. Clinically significant elevations in ALT/AST or TBL were to have been followed with additional testing such as ALT, TBL, ALP, International Normalized Ratio (INR) or prothrombin time (PT) within 48-72 hours after the last dose of study medication and to be repeated until resolution to pretreatment baseline level or normalization (<ULN).

Statistical Analysis

Population for analysis

The planned population for efficacy analyses was modified intent-to-treat (mITT), which was to have included all randomized patients who received at least one completed dose of study medication and had at least one pain assessment after randomization.

The planned population for PK/PD analyses was to have included patients who have received at least two full doses of study medication on Day 1, have provided ≥3 PK blood samples, and had ≥3 pain assessments with PK sampling and PI at baseline and additional PK/PI conducted close in time to each other.

The planned population for safety analyses was to have included patients who received any portion of infusion with study medication.

Efficacy analysis

The planned primary efficacy parameter, total opioid consumption during the treatment period (T0-24) was to be analyzed using an analysis of variance (ANOVA) model with treatment group, age group, and opioid consumption group as factors.

The statistical model planned for secondary analyses included Logrank test for time to rescue, Kaplan-Meier for proportion taking rescue, Cochran-Mantel-Haenszel (CMH) for global evaluations, ANOVA for SPID3, and descriptive statistics for time-specific PI measurements. Analyses of PD/PK correlation were to have been based on mean slope of the linear regression comparing acetaminophen concentration in the effect compartment and total opioid consumption.

Additional analyses were planned for subsets of with or without rescue during the study, after the first dose, and after the second dose if data would allow.

Missing data management

Missing data were to have been replaced by LOCF for taking medication that would have a confounding effect (e.g., ibuprofen for management of fever).

Sample size

Under the assumption that the standard deviation (SD) would be approximately equal to the mean in this pediatric population, planned sample size was 64 patients per dose group (192 in total) based on the use of a two-sided two-sample comparison of means at the 5% level of significance to provide 81% power to detect a 50% reduction in total opioid consumption over 24 hours.

Table 8 Summary of Protocol Amendments

	Amendment 1	Amendment 2	Amendment 3	Amendment 4
Protocol date	3-30-12	10-3-12	7-10-13	12-8-14
Submission date	4-3-12	10-11-12	7-11-13	Not submitted to IND
SD	372	377	382	
Design		Blinding removed for PK assignment	Pre-randomization time interval reduced from 8 to 6 hours	

Key inclusion		Timing of age changed from enrollment to randomization	Removal of limit on body weight	
Key exclusion		Window for prohibited drug narrowed from 12 to 8 hours; APAP from breast feeding and ketamine were added to the list	Window for prohibited drug narrowed to 6 hours; removal of 12-hour limit on use of IV corticosteroids	
Sample size			Sample size reduced from 64 to 48 per dose group	
Rescue				
Efficacy data	More time points added for PI including 18 and, 24 hours after T0, and at early termination; Scale for global evaluation changed from 11-point numerical to 4-point categorical	Age appropriate pain scales redefined with LNPS for age <6 months and FLACC for age 6-<24 months;	Removal of PI assessments pre and post heel stick; Use of LNPS and FLACC only required after randomization and replaced by institution's pain scale during 6-hour pre randomization period	
Secondary endpoints	Standard PK and sedation T0-12 added			
Safety				
Other	Administrative changes	PK sampling: five-minute window added for blood collection and change of blood volume	IV line for study drug infusion allowed for PK sampling if proceeded by line flushing	Administrative changes

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

Table 9 Reviewer's Summary of the Protocol

Study #	CPI-APA-353
Objectives	To study efficacy and safety, to characterize the concentration-effect (PK/PD) relationship, and to determine PK profile of IV acetaminophen in management of acute pain in neonates and infants (aged < 2 years).
Design	Multiple-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose (4 doses in 24 hours)
Sample population	Screening 1. ≥ 28 weeks to ≤40 weeks gestational age at birth and up to < 2 years old at time of randomization 2. Undergoing surgery or having a traumatic injury expected to produce moderate to severe pain and expected to require analgesic treatment for acute pain for the 24-hour study period 3. Having a medically reasonable need and expectation for IV treatment due to underlying procedure or medical condition for the duration of the study 4. Bodyweight suitable for participation in the study in the opinion of the Investigator 5. Having reliable vascular access for administration of study medication and blood sampling 6. Free of other physical, mental, or medical conditions interfering with study participation or efficacy/safety evaluation Pre-randomization 1. Having moderate to severe pain assessed by qualified personnel based on PI≥4 on the LNPS or FLACC scales or based on institution's pain scale within 6 hours prior to randomization 2. Requiring use of parenteral opioid of at least one dose (i.e., not pre-emptive therapy) during the 6-hour pre-randomization period, and at least one dose during the 24-hour treatment period
Treatment	**15-minute IV infusion every 6 hours x 4 doses** with 2:2:1:1 ratio for assignment to four treatment groups: acetaminophen group A (low dose), acetaminophen group B (high dose), placebo group C (low volume match to group A), placebo group D (high volume match to group B); 4:4:3:1 ratio with respect to PK groups (4 in each acetaminophen PK group: 3 in the placebo non-PK group: 1 in the placebo PK group in each randomization block).

	Weight based dosing for acetaminophen groups	**APAP (mg/kg)**	
		A	**B**
	Extreme pre term (28 to <32 weeks) or neonates with ↑bilirubin	7.5	10
	Pre term (32 to 36 weeks) or neonates with normal bilirubin	10	12.5
	Full term (≥ 37 to ≤ 40 weeks gestational age) neonates	10	12.5
	Younger infants: ≥29 days to <6 months of age	12.5	15
	Intermediate age infants: ≥6 months to <12 months of age	12.5	15
	Older infants/Children: ≥12 months to <24 months of age	12.5	15
Opioid use	Opioid use was going to be required during 6-hour pre randomization, as a loading dose 30 minutes before study drug infusion, and as rescue during 24-hour treatment period given as needed for moderate pain (PI≥4 on LNPS or FLACC) and mandatory for severe pain (PI≥6 on LNPS or FLACC). The use of opioid, type of opioid, mode of delivery, dose level, and dosing frequency were all up to individual institution's standard of care and individual Investigator's choice.		
Efficacy data	• PI using the LNPS scale (0-14 for <6 months of age) and the FLACC scale (0-10 for 6 months to <2 years of age) at -0.5, 0, 0.5, 1, 2, 3, 4, 6, 12, 18, and 24 hours after the start of study drug infusion, prior to each rescue, and at early termination • Sedation using the University of Michigan Sedation Scale (a 5-point categorical scale of 0-4) at 0, 3, 6, 9, and 12 hours post dose and prior to the first dose of rescue • Global Evaluation of Satisfaction with Study Treatment to be completed by a blinded assessor and a caregiver using a 4-point categorical scale (0 = poor, 1 = fair, 2 = good, 3 = excellent) at the end of study (about 24 hours post dose) or at early termination		
Efficacy parameter	<u>Primary efficacy endpoint</u> • Total rescue opioid (mg/kg IV morphine or morphine equivalent) over 24 hours <u>Secondary and other endpoints</u> • PD/PK correlation between Ceff (effect compartment acetaminophen concentration) and pain scores at 1 hour • PD/PK correlation between Ceff and total opioid rescue during first 12 hours • Standard PK parameters • SPID3 • Sedation score in first 12 hours • Total Rescue Medication consumption over first 12 hours • Total Rescue Medication consumption over 6 hours of each dosing interval • Time to First Rescue Medication • Assessor and Caregiver Global Evaluation at the end of treatment period or early termination • Percentage of patients requiring rescue opioids • Mean pain intensity scores adjusted for corresponding quantity of rescue opioids		
Safety monitoring	• AE throughout • Vital signs and PE at screening, prior to randomization), and at study completion or early termination • Clinical laboratory tests at study entry ALT, AST, ALP, TBL, direct bilirubin, blood urea nitrogen, serum creatinine, hematocrit (for conventional, non-heel stick PK subjects), and INR and prothrombin time (for neonates); ALT, AST; ALP, TBL, and direct bilirubin at study completion Note: Clinically significant elevation in ALT/AST or TBL at study completion were to be followed with additional safety laboratory testing within 48 to 72 hours after the last study drug dosing; Follow-up safety laboratory tests were to be repeated until resolution to pretreatment baseline or a level below ULN (frequency to be determined by Investigator's assessment of the patient's condition and in consultation with the Medical Monitor, but at least every 7 days).		
Safety parameter	• Spontaneous adverse events (incidence, type, severity, and relationship to study medication) • Percentage of subjects withdrawn due to Adverse Events (AEs) • Percentage of subjects with serious AEs (SAEs) • Clinically meaningful changes from baseline in liver function test and/or liver enzymes		

5.3.1.2 Results

Demographic and other baseline characteristics

The study sample population consisted of 198 pediatric patients less than two years of age who received at least one dose of the study medication, with an age range of 1 to 725 days (two years) and a mean of 232 days (i.e., 33 weeks, <8 months, or 0.64 years). Patient distribution by age group included 38 neonates (age <29 days), 54 younger infants (ages 29 days to <6 months), 55 intermediate age infants (ages 6 months to <12 months), and 51 older infants/children (ages 12 months to <24 months).

Of the 198 patients, 69% were Caucasian, 15% were African American, 7% were Asian, 7% were other races combined, <1% were American Indian or Alaska Native and 23% were Hispanic. The ethnic and racial distributions of the study population were very similar to that of the general US population (2014 statistics).

There were more males (about two thirds of the study population) than females, an imbalance due to the limitation on the number of patients undergoing major surgeries with respect to sex.

The acetaminophen and placebo treatment groups were approximately balanced with regard to demographic characteristics such as age, sex, race, and weight at screening and with regard to the amount of total opioid consumption during the 8-hour period before randomization.

Table 10 Demographics and Baseline Characteristics, Safety Population

Study CPI-APA-353 Demographics	IV APAP Low Dose	IV APAP High Dose	IV APAP Combined	Placebo	Total
Post Natal Age (Days)					
N	61	67	128	70	198
Mean	223.1	245.7	234.9	225.8	231.7
SD	175.20	208.66	193.02	179.65	188.00
Median	202.0	187.0	199.0	194.5	195.5
Minimum	2	3	2	1	1
Maximum	643	725	725	664	725
Post Natal Age Categories					
Neonates	13 (21.3%)	12 (17.9%)	25 (19.5%)	13 (18.8%)	38 (19.3%)
Extreme Preterm	0	2 (16.7%)	2 (8.0%)	1 (7.7%)	3 (7.9%)
Preterm	0	3 (25.0%)	3 (12.0%)	1 (7.7%)	4 (10.5%)
Full term	13 (100.0%)	7 (58.3%)	20 (80.0%)	11 (84.6%)	31 (81.6%)
Younger Infants	16 (26.2%)	20 (29.9%)	36 (28.1%)	18 (26.1%)	54 (27.4%)
Intermediate Age Infants	18 (29.5%)	17 (25.4%)	35 (27.3%)	20 (29.0%)	55 (27.9%)
Older Infants	14 (23.0%)	18 (26.9%)	32 (25.0%)	19 (27.1%)	51 (25.8%)
Sex					
Male	44 (72.1%)	40 (59.7%)	84 (65.6%)	43 (62.3%)	127 (64.5%)
Female	17 (27.9%)	27 (40.3%)	44 (34.4%)	27 (38.6%)	71 (35.9%)
Race					
Caucasian	40 (65.6%)	49 (73.1%)	89 (69.5%)	47 (67.1%)	136 (68.7%)
African American	12 (19.7%)	9 (13.4%)	21 (16.4%)	9 (13.0%)	30 (15.2%)
American Indian or Alaska Native	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Asian	3 (4.9%)	4 (6.0%)	7 (5.5%)	6 (8.7%)	13 (6.6%)
Other	4 (6.6%)	4 (6.0%)	8 (6.3%)	5 (7.2%)	13 (6.6%)
Missing	1 (1.6%)	1 (1.5%)	2 (1.6%)	3 (4.3%)	5 (2.5%)
Ethnicity					
Hispanic or Latino	12 (19.7%)	18 (26.9%)	30 (23.4%)	15 (21.4%)	45 (22.7%)
Not Hispanic or Latino	46 (75.4%)	47 (70.1%)	93 (72.7%)	50 (72.5%)	143 (72.6%)
Not Reported	0	0	0	1 (1.4%)	1 (0.5%)

Unknown	2 (3.3%)	1 (1.5%)	3 (2.3%)	2 (2.9%)	5 (2.5%)
Missing	1 (1.6%)	1 (1.5%)	2 (1.6%)	2 (2.9%)	4 (2.0%)
Weight at Screening (kg)					
N	60	67	127	70	197
Mean	6.97	6.96	6.96	7.03	6.99
SD	2.789	3.051	2.919	2.727	2.845
Median	6.75	7.00	7.00	7.20	7.00
Minimum	2.6	1.0	1.0	0.8	0.8
Maximum	13.7	14.3	14.3	12.0	14.3
Opioid Dose pre-randomization (µg/kg)					
N	60	67	127	70	197
Mean	45.871	49.689	47.885	47.201	47.642
SD	36.0773	36.2196	36.0596	31.6172	34.4663
Median	48.284	50.000	50.000	49.786	50.000
Minimum	0.00	0.00	0.00	0.00	0.00
Maximum	170.45	204.82	204.82	116.28	204.82

Source: Table 14.1.4.1 on page 5 of response to information request in the submission dated June 15, 2016 and Table 1 on page 2 of response to information request in the submission dated August 8, 2016

The study was conducted at 18 sites. Most had few patients, ranged from 1 to 12 patients at 15 of 18 sites. The distribution of patients per site is listed in the table below.

Table 11 Distribution of Patients by Study Sites

Number of patients per site	66	26	21	12	11	10	8	7	6	5	4	1
Number of sites	1	1	1	2	2	1	1	2	1	2	1	3

Patient disposition

About 80% of 198 pediatric patients completed the study. There were 39 cases of dropouts, 21 from the IV APAP treatment groups and 18 from the placebo group. The reasons for dropouts included 12 cases of adverse events (10 reported in the placebo group), six cases in each of the following categories: withdrawal of consent, loss of IV access or unable to draw blood, early discharge, and physician's decision, and four cases of non-compliance. The main treatment group differences were more AE-related dropouts in the placebo group and all dropouts due to withdrawal in the IV acetaminophen groups.

Table 12 Patient Disposition

Study CPI-APA-353 Patient Disposition	**IV APAP Low Dose**	**IV APAP High Dose**	**IV APAP combined**	**Placebo**	**Total**
All Treated Patients	61	67	128	70	198
Discontinued n **(%)**	9 (14.8%)	12 (17.9%)	21 (16.4%)	18 (25.7%)	39 (19.7%)
Main reason for discontinuation					
Adverse event	0	2 (3.0%)	2 (1.6%)	10 (14.3%)	12 (6.1%)
Withdrawal by subject	4 (6.6%)	2 (3.0%)	6 (4.7%)	0	6 (3.0%)
Loss of IV access or unable to draw blood	1 (1.6%)	3 (4.5%)	4 (3.1%)	2 (2.9%)	6 (3.0%)
Early discharge	2 (3.3%)	2 (3.0%)	4 (3.1%)	2 (2.9%)	6 (3.0%)
Physician's decision	1 (1.6%)	2 (3.0%)	3 (2.3%)	3 (4.3%)	6 (3.0%)
Non-compliance	1 (1.6%)	1 (1.5%)	2 (1.6%)	2 (2.9%)	4 (2.0%)

Source: Table 14.1.1.2.1 on page 12 of the response to information request in the submission dated June 15, 2016 and Table 2 on page 3 of the response to information request in the submission dated August 8, 2016.

Protocol violations

About 45% of the study population had protocol deviations and the proportions were similar between the active and placebo treatment groups. The most frequently reported protocol deviation was in the categories of error in use of rescue (23%), especially in terms of rescue given with no pain score (12%) and missing rescue after pain assessment. The other more frequently (10-15%) reported protocol deviations included missing pain intensity assessment, taking exclusionary medications, missing laboratory test, and deviation from eligibility criteria. Interestingly, only one subject was reported as having acetaminophen containing product in six hours pre-dose though a number of placebo subjects were reported as having baseline acetaminophen levels (refer to PK review for detail). There were no dramatic differences between the IV acetaminophen and placebo treatment group for the deviations in these major categories as shown in the table below.

Table 13 Summary of Protocol Deviations

Study CPI-APA-353 Protocol deviations	**IVAPAP LD (N = 61)**	**IVAPAP HD (N = 67)**	**IV APAP (N = 128)**	**Placebo (N = 70)**	**Total (N = 198)**
# Subjects with ≥1 violation	31 (50.8%)	28 (41.8%)	59 (46.1%)	31 (44.3%)	90 (45.5%)
Deviation Category					
Inclusion criteria	6 (9.8%)	7 (10.4%)	13 (10.2%)	6 (8.6%)	19 (9.6%)
Exclusion criteria	1 (1.6%)	0	1 (0.8%)	2 (2.9%)	3 (1.5%)
Post-surgical inclusion criteria	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Exclusionary medications	9 (14.8%)	10 (14.9%)	19 (14.8%)	7 (10.0%)	26 (13.1%)
Exclusionary medication – 6 hours prior to T0	2 (3.3%)	3 (4.5%)	5 (3.9%)	2 (2.9%)	7 (3.5%)
Using other APAP containing product – 6 hours pre-dose	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Exclusionary medication – during 24- hours treatment	7 (11.5%)	6 (9.0%)	13 (10.2%)	4 (5.7%)	17 (8.6%)
Other exclusionary medication usage	1 (1.6%)	3 (4.5%)	4 (3.1%)	1 (1.4%)	5 (2.5%)
Dose window missed	3 (4.9%)	1 (1.5%)	4 (3.1%)	1 (1.4%)	5 (2.5%)
No baseline opioid given	5 (8.2%)	4 (6.0%)	9 (7.0%)	2 (2.8%)	11 (5.5%)
Error in use of rescue	16 (26.2%)	14 (20.9%)	30 (23.4%)	16 (22.9%)	46 (23.2%)
Rescue given with no pain score	7 (11.5%)	7 (10.4%)	14 (10.9%)	10 (14.3%)	24 (12.1%)
Rescue given with low pain score	1 (1.6%)	1 (1.5%)	2 (1.6%)	0	2 (1.0%)
Rescue given for wrong reason	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Missing rescue after pain assessment	5 (8.2%)	3 (4.5%)	8 (6.3%)	6 (8.6%)	14 (7.1%)
Wrong choice of rescue: oxycodone	3 (4.9%)	2 (3.0%)	5 (3.9%)	0	5 (2.5%)
Missed pain intensity assessment	7 (11.5%)	8 (11.9%)	15 (11.7%)	13 (18.6%)	28 (14.1%)
Missed some PI before hour 6	0	1 (1.5%)	1 (0.8%)	1 (1.4%)	2 (1.0%)
Use of wrong pain scale	0	0	0	1 (1.4%)	1 (0.5%)
Laboratory test not performed	8 (13.1%)	7 (10.4%)	15 (11.7%)	5 (7.1%)	20 (10.1%)
Missed baseline liver function tests	5 (8.2%)	4 (6.0%)	9 (7.0%)	3 (4.3%)	12 (6.0%)
Missed end-of-study liver function tests	2 (3.3%)	3 (4.5%)	5 (3.9%)	2 (2.8%)	7 (3.5%)
Missed other lab tests	1 (1.6%)	1 (1.5%)	2 (1.6%)	0	2 (1.0%)
Vital signs not performed	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Physical exam not performed	0	1 (1.5%)	1 (0.8%)	1 (1.4%)	2 (1.0%)
Other- Incorrect ICF version signed	1 (1.6%)	1 (1.5%)	2 (1.6%)	1 (1.4%)	3 (1.5%)

Source: Table 3 on pages 4-5 of the response to information request in the submission dated August 8, 2016.

Exposure

The exposure information is summarized in the table below in terms of number of doses exposed. About 85% of the IV acetaminophen group and 79% placebo group received all four doses. Drug exposure was similar between the treatment groups.

Table 14 Number of Doses Exposed

Study CPI-APA-353 Exposure	**IV APAP LD (N = 61)**	**IV APAP HD (N = 67)**	**IV APAP (N = 128)**	**Placebo (N = 70)**	**Total (N = 198)**
#Doses, n (%)					
1	4 (6.6%)	4 (6.0%)	8 (6.3%)	7 (10.0%)	15 (7.6%)
2	2 (3.3%)	5 (7.5%)	7 (5.5%)	4 (5.7%)	11 (5.6%)
3	2 (3.3%)	2 (3.0%)	4 (3.1%)	4 (5.7%)	8 (4.0%)
4	53 (86.9%)	56 (83.6%)	109 (85.2%)	55 (78.6%)	164 (82.8%)

Source: Table 12-1 on page 103 of the study report for Study CPI-APA-353.

Efficacy results

Baseline opioid use before and after randomization

To better interpret the results of the primary endpoint, the total amount of opioid rescue in 24 hours post the start of study drug infusion, the amount of prior use of opioid over 8 hours before randomization and the amount of single loading dose of opioid given at 30 minutes before the start of IV infusion of the study drug are summarized.in the table below to see if they have potential impact on the primary endpoint.

The opioid use before randomization was basically balanced between the treatment groups. The loading dose was expected to be given as a standard opioid dose at 30 minutes before the infusion of the study drug based on pain level of PI≥3 by LNPS scale of 0-14 for the two younger age categories or by FLACC scale of 0-10 for the two older age categories at the time of randomization. The low dose and high dose IV acetaminophen groups received 50 µg/kg (20%) and 93 µg/kg (38%), respectively, more opioid loading dose than the placebo group.

Table 15 Prior Use of Opioid and Opioid Loading Dose

Study CPI-APA-353 Opioid use before study drug infusion	IV APAP Low Dose	IV APAP High Dose	IV APAP combined	Placebo
Opioid over 8 hours prior to randomization, µg/kg				
N	60	67	127	70
Mean	45.871	49.689	47.885	47.201
SD	36.0773	36.2196	36.0596	31.6172
Median	48.284	50.000	50.000	49.786
Minimum	0.00	0.00	0.00	0.00
Maximum	170.45	204.82	204.82	116.28
Single loading dose at 0.5 hour prior to study drug infusion				
N	61	67	128	69
Mean	**296.5**	**339.8**	**319.2**	**246.5**
SD	322.8	346.4	334.8	261.5
Median	200.0	300.0	250.0	200.0
Minimum	0	0	0	0
Maximum	1500	1700	1700	1000
Difference active treatment and placebo: amount	50	93.3	72.7	
Relative difference using placebo as a denominator for comparison	20.3%	37.8%	29.5%	
Relative difference using each active treatment as a denominator for comparison	16.9%	27.5%	22.8%	

Source: Table 1.11.3-1 on page 1 of the response to information request in the submission dated August 31, 2016.

Primary efficacy endpoint: total amount of rescue opioid in the time interval of 0 to 24 hours

The total amount of rescue opioid over 24 hours is summarized in the table below. The average amount of 24-hour rescue opioid for each of the treatment groups was relatively small, only 180 µg/kg in the high dose acetaminophen group and placebo group and 167 µg/kg in the low dose acetaminophen group, much less than the amount of opioid received as a single loading dose (about 300 to 340 µg/kg in the IV acetaminophen groups versus about 250 µg/kg in the placebo group). The total amount of rescue opioid received in 24 hours was only 53-73% of the amount received as a single loading dose.

The average use of opioid over 24 hours was similar in the IV acetaminophen and placebo groups. The differences were too small to be noticeable, only a few µg/kg, in contrast to the size of differences of 50-93 µg/kg in opioid loading dose. The results were mixed in that the low dose IV acetaminophen group had 11 µg/kg more rescue opioid than the placebo group and the high dose IV acetaminophen group had 1.4 µg/kg less

total rescue than the placebo group. The findings were inconsistent and not statistically significant or clinically meaningful.

Table 16 Total Amount of Rescue Opioid over 24 Hours

Study CPI-APA-353 Primary endpoint: total rescue over 0-24 hours	IV APAP Low Dose	IV APAP High Dose	IV APAP combined	Placebo
N	61	67	128	69
Mean	**166.9**	**179.9**	**173.7**	**180.2**
SD	225.06	193.47	208.39	184.70
Median	90.9	127.1	105.7	131.6
Minimum	0	0	0	0
Maximum	1364	922	1364	817
ANOVA Analysis				
LS Means	163.4	176.7	170.3	175.3
97.5% CI	(105.6, 221.2)	(121.3, 232.0)	(130.4, 210.3)	(120.8, 229.7)
Difference in LS Means vs Placebo Group	-11.8	1.4	-4.9	
97.5% CI	(-91.0, 67.3)	(-75.9, 78.7)	(-72.0, 62.2)	
P-value	0.736	0.967	0.869	
Difference between loading dose and 24-hour rescue opioid using loading dose as denominator	56.3%	52.9%	54.4%	73.1%

Source: Table 11.1 on page 70 of the study report for Study CPI-APA-353.

Reviewer's comments:

- A much reduced need for subsequent rescue opioid after the loading dose and similar amount of rescue opioid use in all three treatment groups (primary efficacy endpoint) suggested that the loading opioid had a major impact on analgesic response.
- The treatment group imbalance of 20%-40% more loading opioid in the acetaminophen than placebo group 30 minutes before the start of study drug would make the rest of treatment comparison invalid.

Secondary and other efficacy endpoints

Rescue data, global evaluation, and sedation score

Rescue data are summarized in the table below, in terms of the amount of rescue, number of rescue doses, and proportion of the treatment group using rescue over various dosing intervals and in terms of median time to initial rescue. The other endpoints such as assessor's and caregiver's global evaluation and sedation scores are also included in the same table.

Treatment differences for all these endpoints were very small and showed no consistent trends. Median time to initial rescue opioid of one-hour earlier in the placebo group in comparison to the active treatments is still considered a very small and clinically insignificant treatment difference.

Table 17 Rescue Data and Other Secondary Endpoints

Study CPI-APA-353 Secondary & other endpoints	IVAPAP LD (N = 61)	IVAPAP HD (N = 67)	IV APAP (N = 128)	Placebo (N = 70)	Difference from placebo			Reference
					Low	High	IV	
Amount of rescue: 0–12h, µg/kg	98.8	106.7	103.0	100.7	-1.9	6.0	2.2	T14.2.1.2
Amount of rescue: 0–6h	55.7	53.3	54.4	53.4	2.3	-0.1	1	T14.2.1.2
Amount of rescue: 6–12h	43.2	53.4	48.6	46.4	-3.2	7	2.2	T14.2.1.2
Amount of rescue: 12-18h	33.3	33.1	33.2	37.4	-4.1	-4.3	-4.2	T14.2.1.2
Amount of rescue: 18–24h	31.4	34	32.7	36.3	-4.9	-2.3	-3.6	T14.2.1.2
# of rescue doses: 0–24h, n	2.4	2.5	2.4	2.7	-0.3	-0.2	-0.3	new
# of rescue doses: 0–6h	0.8	0.8	0.8	0.8	-0.1	-0.1	-0.1	new
# of rescue doses: 6–12h	0.6	0.8	0.7	0.8	-0.2	-0.0	-0.1	new

# of rescue doses: 12-18h	0.6	0.5	0.6	0.7	-0.1	-0.1	-0.1	new
# of rescue doses: 18–24h	0.6	0.6	0.6	0.7	-0.1	-0.2	-0.2	new
Proportion rescued: 0-24h, %	77.0%	79.1%	78.1%	82.6%	-5.6%	-3.5%	-4.5%	T14.2.2
Proportion rescued: 0–6h	57.4%	61.2%	59.4%	62.3%	-4.9%	-1.1%	-2.9%	new
Proportion rescued: 6–12h	49.1%	58.7%	54.2%	58.1%	-8.9%	0.7%	-3.9%	new
Proportion rescued: 12-18h	45.5%	44.8%	45.1%	48.3%	-2.8%	-3.5%	-3.2%	new
Proportion rescued: 18–24h	41.5%	42.9%	42.2%	53.7%	-12.2%	-10.8%	-11.5%	new
Time to first rescue (median), hrs	4.78	4.75	4.76	3.78	**1.00**	**0.97**	**0.97**	new
Assessor's global, LSmean	2.3	2.4	2.4	2.3	-0.0	0.1	0.1	new
Caregiver global, LSmean	2.4	2.6	2.5	2.5	-0.1	0.2	0.0	new
Sedation Score, 0-12h, LSmean	1.2	1.3	1.2	1.3	-0.1	-0.0	-0.1	new

Source: Table 4a on page 6 of the response to information request in the submission dated August 8, 2016.

Reviewer's comments:

- Further analyses of rescue data in terms of amount of rescue, number of doses, and proportion rescued would still not help in identifying any trend and have confirmed the finding of no treatment differences in rescue.
- One-hour difference in time to an event would have been considered clinically significant if it were used for measuring an acute analgesic onset but not considered clinically meaningful in terms of single-dose duration in general in adult analgesic studies.
- Global assessments are not generally used for evaluation of acute analgesia in adult studies.

Time-specific pain measurements over 24 hours

Pain curves formed by time-specific pain measurements usually provide very useful information about the time course of analgesic response if the scales are valid and are used properly. Accurate pain measurements are especially important in this study because the decisions on giving opioid as loading dose or as rescue were expected to be based on pain intensity, i.e., PRN opioid for moderate pain (PI≥4 on LNPS or FLACC) and mandatory opioid for severe pain (PI≥6) as described in the protocol.

Pain intensity data are summarized by dosing group for each age stratum (different scales were used for different age strata) as shown in the table and figures below.

There was treatment group imbalance in mean PI at randomization that the low dose IV acetaminophen group was consistently below 3 (on both scales) across all age strata, and much lower than the other two treatment groups (the high dose IV acetaminophen group and placebo group) in three of the four age strata.

Mean PI scores were much reduced, by about 40-80% in most cases in response to opioid loading dose and became low, ranging from 0.6 to 2.2 at baseline before the start of study drug infusion. Subsequent PI measurements fluctuated up and down in the same range as baseline PI with no clear trend to suggest treatment effects from IV acetaminophen.

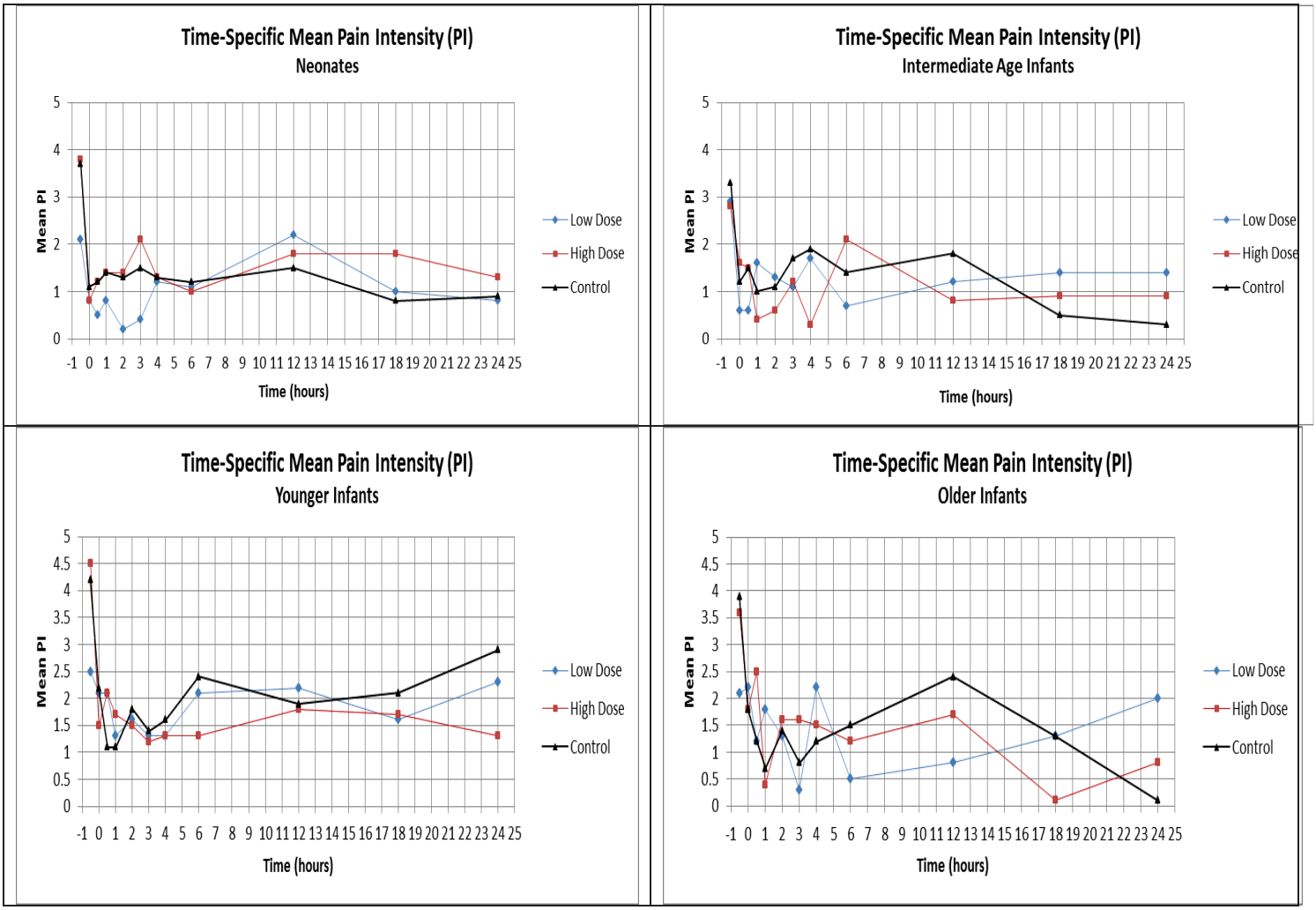
Table 18 Mean Pain Intensity by Measurement Time

Study group	**Dose level, #exposed**	***-0.5***	***0***	***0.5***	***1***	***2***	***3***	***4***	***6***	***12***	***18***	***24***
Neonates PI by LNPS scale of 0-14												
APAP-LD	10mg/kg, n=13	2.1	0.8	0.5	0.8	0.2	0.4	1.2	1.1	2.2	1.0	0.8
APAP-HD	10 mg/kg, n=2 12.5 mg/kg, n=10	3.8	0.8	1.2	1.4	1.4	2.1	1.3	1.0	1.8	1.8	1.3
Placebo		3.7	1.1	1.2	1.4	1.3	1.5	1.3	1.2	1.5	0.8	0.9
Younger infants, PI by LNPS scale of 0-14												
APAP-LD	12.5 mg/kg, n=16	2.5	2.1	2.1	1.3	1.6	1.3	1.3	2.1	2.2	1.6	2.3
APAP-HD	15 mg/kg, n=20	4.5	1.5	2.1	1.7	1.5	1.2	1.3	1.3	1.8	1.7	1.3

Placebo		4.2	2.2	1.1	1.1	1.8	1.4	1.6	2.4	1.9	2.1	2.9
Intermediate Age Infant, PI by FLACC scale of 0-10												
APAP-LD	12.5 mg/kg, n=18	2.9	0.6	0.6	1.6	1.3	1.1	1.7	0.7	1.2	1.4	1.4
APAP-HD	15 mg/kg, n=17	2.8	1.6	1.5	0.4	0.6	1.2	0.3	2.1	0.8	0.9	0.9
Placebo		3.3	1.2	1.5	1.0	1.1	1.7	1.9	1.4	1.8	0.5	0.3
Older infants, PI by FLACC scale of 0-10												
APAP-LD	12.5 mg/kg, n=14	2.1	2.2	1.2	1.8	1.3	0.3	2.2	0.5	0.8	1.3	2.0
APAP-HD	15 mg/kg, n=18	3.6	1.8	2.5	0.4	1.6	1.6	1.5	1.2	1.7	0.1	0.8
Placebo		3.9	1.8	1.2	0.7	1.4	0.8	1.2	1.5	2.4	1.3	0.1

Source: Table 14.2.3.1 on pages 208-251 of the study report for Study CPI-APA-353.

Figure 1 Pain Curves for Each Age Stratum



Source: Pain data in the table above

Reviewer's comments:

- The only finding that was consistent across dose levels and age strata, was the dramatic response to the opioid loading dose by a sizable PI reduction of 40-80% (from Hour -0.5 to Hour 0), leading to low baseline PI (≤2.2 on the scales of 0-14 and 0-11 at Hour 0) before study drug infusion.
- The treatment group imbalance in pain intensity both before and after loading opioid dose at baseline prior to study drug infusion, made it invalid to use pain curves to evaluate treatment effects in this study.
- The dramatic confounding effects from the loading opioid dose on top of the treatment group imbalance in loading opioid dose and imbalance in baseline PI before the start of study drug had all contributed to no treatment differences in amount of rescue and random and unpredictable pain curve fluctuation around baseline pain levels in the next 24 hours. It explains why the study as designed could not be used to adequately evaluate effects of acetaminophen treatment in the current setting.
- Low PI levels in all treatment groups while opioid were given frequently (2-3 rescue doses on the average including those not taking rescue) to a large proportion of patients (about 80% patients) might indicate effective pain control by rescue opioid or could be explained as unnecessary overuse of opioid since low level pain did not seem to require heavy use of rescue (which supposed to be given only for PI≥4 according to the protocol).

Efficacy findings in each age stratum

For each age stratum the findings are summarized in terms of the amount of opioid loading dose, mean group PI before and after opioid loading dose, PI score reduction and percentage of reduction in response to opioid loading dose before the study drug infusion, and rescue information such as the amount of rescue, number of rescue doses, proportion of patients receiving rescue, and time to initial rescue during the 24-hour evaluation period.

Neonate

For neonates (<29 days old), mean PI scores before opioid loading dose were similar between the high dose IV acetaminophen group and placebo group (PI of 3.8 versus 3.7) and much lower in the low dose IV acetaminophen group (PI of 2.1). The low dose and high dose IV acetaminophen groups received 29 µg/kg (19%) and 51 µg/kg (33%) less opioid loading dose than the placebo group. All three treatment groups responded to opioid loading dose as shown in PI reduction by 1.3 point (62%) in the low dose IV acetaminophen group, by 3.0 point (79%) in the high dose IV acetaminophen group, and by 2.6 point (70%) in the placebo group. With such low PI (0.8-1.1) at baseline before the start of study drug infusion it is hard to explain why a majority of patients (62-69%) were still treated with rescue opioid. Treatment differences measured by opioid rescue (amount of opioid, number of doses, proportion rescued, and time to first rescue) were in favor of the IV acetaminophen treatments than placebo and the treatment differences were larger for the low dose acetaminophen group.

Table 19 Efficacy Summary for Neonates

Study CPI-APA-353 Efficacy findings in neonates	IVAPAP-LD (N = 13)	IVAPAP-HD (N = 12)	IV APAP (N = 25)	Placebo (N = 13)	Difference from placebo		
					Low dose	High dose	IV APAP
Before the start of study drug infusion							
Amount of opioid loading dose µg/kg	***127.7***	***105.4***	***117.0***	***156.7***	***-29***	***-51.3***	***-39.7***
% difference from placebo					-18.5%	-32.7%	-25.3%
PI before opioid loading dose	2.1	3.8		3.7			
PI after opioid loading dose	0.8	0.8		1.1			
Reduction in PI score	1.3	3.0		2.6			
% PI reduction from initial PI	61.9%	78.9%		70.3%			
After the start of study drug infusion							
Amount of rescue: 0–24h, µg/kg	60.3	144.3	100.6	165.3	-105.0	-21.0	-64.7
# of rescue doses: 0–24h, n	0.9	1.9	1.4	2.7	-1.8	-0.8	-1.3
Proportion rescued: 0-24h, %	61.5%	66.7%	64.0%	69.2%	-7.7%	-2.6%	-5.2%
Time to first rescue (median), h0urs	6.00	5.30	6.00	4.23	**1.77**	**1.07**	**1.77**

Source: Table 14.2.3.1 on page 208 of the original study report; Table 1.11.3-1 on pages 2-3 of the response to information request (IR) in the submission dated September 9, 2016; Table 4c on pages 8-10 of the response to IR in the submission dated August 8, 2016.

Younger infant

For younger infants (29 day to <6 months old), mean PI scores before opioid loading dose were higher for the high dose IV acetaminophen group and placebo group (PI of 4.5 versus 4.2) than that of the low dose IV acetaminophen group (PI of 2.5). The low dose and high dose IV acetaminophen groups received 42 µg/kg (18%) and 33 µg/kg (14%), respectively, more opioid loading dose than the placebo group. The high dose IV acetaminophen group and placebo group responded to the opioid loading dose as shown in PI reduction by 3.0 point (67%) in the high dose IV acetaminophen group and by 2.0 point (48%) in the placebo group. The low dose IV acetaminophen group had much smaller response to opioid loading dose as shown in PI reduction by only 0.4 point (16%). Baseline PI before the start of study drug infusion was in the range of 1.5-2.2. Treatment differences measured by opioid rescue (amount of opioid, number of doses, proportion rescued, and time to first rescue) were in favor of placebo treatment than active treatments.

Table 20 Efficacy Summary for Younger Infants

Study CPI-APA-353 Efficacy findings in younger infants	IVAPAP-LD (N = 16)	IVAPAP-HD (N = 20)	IV APAP (N = 36)	Placebo (N = 18)	Difference from placebo		
					Low dose	High dose	IV APAP
Before the start of study drug infusion							
Amount of opioid loading dose µg/kg	***276.3***	***267.0***	***271.1***	***234.4***	***41.9***	***32.6***	***36.7***
% difference from placebo					17.9%	13.9%	15.7%
PI before opioid loading dose	2.5	4.5		4.2			
PI after opioid loading dose	2.1	1.5		2.2			
Reduction in PI score	0.4	3.0		2.0			
% PI reduction from initial PI	16.0%	66.7%		47.6%			
After the start of study drug infusion							
Amount of rescue: 0–24h, µg/kg	192.7	169.2	179.7	110.2	82.5	59.1	69.5
# of rescue doses: 0–24h, n	3.2	2.7	2.9	2.1	1.1	0.6	0.8
Proportion rescued: 0-24h, %	87.5%	80.0%	83.3%	77.8%	9.7%	2.2%	5.5%
Time to first rescue (median), hours	4.78	4.03	4.78	5.43	-0.64	-1.39	-0.64

Source: Table 14.2.3.1 on page 219 of the original study report; Table 1.11.3-1 on pages 2-3 of the response to information request (IR) in the submission dated September 9, 2016; Table 4c on pages 8-10 of the response to IR in the submission dated August 8, 2016.

Intermediate age infant

For intermediate age infants (6 months to <1 year old), mean PI scores before receiving opioid loading dose were close (PI of 2.8 to 3.3) for the three treatment groups. The low dose and high dose IV acetaminophen groups received 90 µg/kg (33%) and 67 µg/kg (24%), respectively, more opioid loading dose than the placebo group. All three treatment groups responded to opioid loading dose as shown in PI reduction by 2.3 (79%) in the low dose IV acetaminophen group, by 1.2 (43%) in the high dose IV acetaminophen group, and by 2.1 (65%) in the placebo group. Baseline PI before the start of study drug infusion was low in the range of 0.6-1.6. Treatment differences measured by opioid rescue (amount of opioid, number of doses, proportion rescued, and time to first rescue) were in favor of IV acetaminophen treatments than placebo treatment.

Table 21 Efficacy Summary for Intermediate-Age Infants

Study CPI-APA-353 Efficacy findings, intermediate-age infant	IVAPAP-LD (N = 18)	IVAPAP-HD (N = 17)	IV APAP (N = 35)	Placebo (N = 20)	Difference from placebo		
					Low dose	High dose	IV APAP
Before the start of study drug infusion							
Amount of opioid loading dose µg/kg	***363.6***	***339.8***	***352.0***	***273.3***	***90.3***	***66.5***	***78.7***
% difference from placebo					33.0%	24.3%	28.8%
PI before opioid loading dose	2.9	2.8		3.3			
PI after opioid loading dose	0.6	1.6		1.2			
Reduction in PI score	2.3	1.2		2.1			
% PI reduction from initial PI	79.3%	42.9%		63.6%			
After the start of study drug infusion							
Amount of rescue: 0–24h, µg/kg	210.9	177.2	194.5	265.2	-54.3	-88.0	-70.7
# of rescue doses: 0–24h, n	3.1	2.6	2.9	3.5	-0.4	-0.9	-0.6
Proportion rescued: 0-24h, %	77.8%	88.2%	82.9%	90.0%	**-12.2%**	**-1.8%**	**-7.1%**
Time to first rescue (median), hours	3.96	5.43	4.25	3.24	**0.72**	**2.19**	**1.01**

Source: Table 14.2.3.1 on page 230 of the original study report; Table 1.11.3-1 on pages 2-3 of the response to information request (IR) in the submission dated September 9, 2016; Table 4c on pages 8-10 of the response to IR in the submission dated August 8, 2016.

Older infants/young children

For older infants/young children (1 to <2 years old), mean PI scores before opioid loading dose were similar between the high dose IV acetaminophen group and placebo group (PI of 3.6 versus 3.9) and much lower in the low dose IV acetaminophen group (PI of 2.1). The low dose and high dose IV acetaminophen groups received 96 µg/kg (33%) and 284 µg/kg (97%), respectively, more opioid loading dose than the placebo group. The high

dose IV acetaminophen group and placebo group responded to the opioid loading dose as shown in PI reduction by 1.8 point (50%) in the high dose IV acetaminophen group and by 2.1 point (54%) in the placebo group, but not the low dose IV acetaminophen group (PI increase by 0.1 point). Baseline PI before the start of study drug infusion was in the range of 1.8-2.2. Treatment differences measured by opioid rescue were mixed that differences in the amount of rescue opioid and time to first rescue were in favor of placebo treatment and differences in proportions receiving rescue were in favor of IV acetaminophen treatments.

Table 22 Efficacy Summary for Older Infants

Study CPI-APA-353 Efficacy findings in older infants	IVAPAP-LD (N = 14)	IVAPAP-HD (N = 18)	IV APAP (N = 32)	Placebo (N = 18)	Difference from placebo		
					Low dose	High dose	IV APAP
Before the start of study drug infusion							
Amount of opioid loading dose µg/kg	***390.0***	***577.1***	***495.2***	***293.6***	***96.4***	***283.5***	***201.6***
% difference from placebo					32.8%	96.6%	68.7%
PI before opioid loading dose	2.1	3.6		3.9			
PI after opioid loading dose	2.2	1.8		1.8			
Reduction in PI score	-0.1	1.8		2.1			
% PI reduction from initial PI	-4.8%	50.0%		53.8%			
After the start of study drug infusion							
Amount of rescue: 0–24h, µg/kg	179.8	218.0	201.3	166.6	13.2	51.4	34.7
# of rescue doses: 0–24h, n	2.2	2.7	2.5	2.7	-0.5	0.1	-0.2
Proportion rescued: 0-24h, %	78.6%	77.8%	78.1%	88.9%	-10.3%	-11.1%	-10.8%
Time to first rescue (median), hours	2.49	2.18	2.18	2.58	-0.08	-0.40	-0.40

Source: Table 14.2.3.1 on page 241 of the original study report; Table 1.11.3-1 on pages 2-3 of the response to information request (IR) in the submission dated September 9, 2016; Table 4c on pages 8-10 of the response to IR in the submission dated August 8, 2016.

Summary of findings by age stratum

The active treatment groups received less opioid loading dose in neonates and more opioid loading dose in the three infant groups in comparison to the corresponding placebo group of the same age stratum. The treatment group received larger amount of loading opioid also received larger amount of rescue opioid in the younger and older infants. Most treatment groups across age strata responded to the opioid loading dose as shown in PI reduction by1.2 to 3.0 points (about 40-80%) except the low dose IV acetaminophen treatment in the younger and older infant strata. Baseline PI before the start of study drug infusion was generally low in the range of 0.6 to 2.2. Treatment differences measured by opioid rescue in terms of the amount of opioid, number of doses, proportion rescued, and time to first rescue, were basically in favor of acetaminophen treatments for neonates and intermediate-age infants and in favor of placebo treatment in younger infants and older infants. In three of the four age strata, neonates and younger and older infants, the treatment group on higher loading opioid received more rescue opioid as summarized in the table below.

Table 23 Summary of Loading Opioid versus Rescue Opioid by Age Group

Study CPI-APA-353	IVAPAP-LD	IVAPAP-HD	IV APAP	Placebo
Neonates				
Amount of opioid loading dose µg/kg	***127.7***	***105.4***	***117.0***	***156.7***
Amount of rescue: 0–24h, µg/kg	60.3	144.3	100.6	165.3
Younger Infants				
Amount of opioid loading dose µg/kg	***276.3***	***267.0***	***271.1***	***234.4***
Amount of rescue: 0–24h, µg/kg	192.7	169.2	179.7	110.2
Intermediate-Age Infants				
Amount of opioid loading dose µg/kg	***363.6***	***339.8***	***352.0***	***273.3***
Amount of rescue: 0–24h, µg/kg	210.9	177.2	194.5	265.2
Older Infants				
Amount of opioid loading dose µg/kg	***390.0***	***577.1***	***495.2***	***293.6***
Amount of rescue: 0–24h, µg/kg	179.8	218.0	201.3	166.6

Source: Four tables on age-related findings above.

Reviewer's comments:

- Small treatment differences and conflicting results between different age strata suggested randomness of the findings.
- The pattern of opioid use that the treatment groups on relatively higher loading dose also received larger dose of rescue, suggested individualized/institutionalized practice habit rather than PI based use of rescue.
- The possibility of a disconnection between opioid use and pain intensity scores would be difficult to evaluate because of uncertainty about validity of pain measurements in patients <2 years old.

Additional analyses on relationship between the use of rescue and PI before rescue

Additional data were requested from the Applicant to explore relationship between the use of rescue opioid and the level of PI before each rescue use (refer to submission dated September 23, 2016). The data are summarized in the table below. Most patients received rescue opioid at PI≥4. Rescue was given at low PI or no PI in some cases in all the treatment groups per age strata. The proportion of patients given opioid rescue ranged 62-69% in neonates and 78-90% in the three infant groups. The mean number of rescue doses was about 2 to 3 doses for most of the treatment group/age strata (averaged over patients receiving and not receiving the rescue) during the 24-hour treatment period and higher (2.6-3.8 doses) in the subpopulation that received rescue opioid.

Table 24 Number of Rescue versus PI

Study CPI-APA-353	Neonate			Younger Infant			Intermediate Age Infant			Older Infant		
	IV APAP		Placebo	IV APAP		Placebo	IV APAP		Placebo	IV APAP		Placebo
	LD	HD		LD	HD		LD	HD		LD	HD	
Number of patients	N=13	N=12	N=13	N=16	N=20	N=18	N=18	N=17	N=20	N=14	N=18	N=18
No rescue	N=5	N=4	N=4	N=2	N=4	N=4	N=2	N=2	N=2	N=3	N=4	N=2
Rescued	N=8	N=8	N=9	N=14	N=16	N=14	N=16	N=15	N=18	N=11	N=14	N=16
Proportion rescued	61.5%	66.7%	69.2%	87.5%	80.0%	77.8%	88.9%	88.2%	90.0%	78.6%	77.8%	88.9%
Count of rescue based on PI level												
PI 4 to ≥6	9	15	33	44	40	36	48	41	52	26	42	33
PI 0 to <4 (rescue at low PI)	1	8	1	2	4	4	7	12	5	3	4	8
Rescue with no PI scores	0	1	0	2	5	1	1	0	0	0	0	0
Total #rescue	10	24	34	48	49	41	56	53	57	29	46	41
Mean # rescue per group	0.8	2.0	2.6	3.0	2.5	2.3	3.1	3.1	2.9	2.1	2.6	2.3
Mean # rescue among subgroup rescued	1.3	3.0	3.8	3.4	3.1	2.9	3.5	3.5	3.2	2.6	3.3	2.6

Source: Table 1.11.3.1 on page 1 of the response to information request (IR) in the submission dated September 23, 2016

Reviewer's comments:

- The relatively large amount (in comparison to the amount of rescue) of opioid loading dose given 30 minutes prior to study drug infusion plus frequent dosing of rescue opioid during the 24-hour evaluation period made it basically impossible to evaluate treatment effects of IV acetaminophen (a much weaker analgesic) dosed every six hours.
- The frequent use of rescue opioid in a large proportions of study population with the use of opioid reported as to be based mostly on PI≥4 did not appear to match the average PI recorded before opioid loading dose (PI of 2.1 to 4.5, mostly below 4) and low PI levels after loading opioid (PI fluctuating between 0.6 and 2.2 on 0-10 and 0-14 scales). Possible explanations for the mismatch might be data inaccuracy, inappropriate use of pain scales, and/or misinterpretation of signs of irritation as pain in this youngest population for

which it is a challenge in determining whether irritation is caused by pain or many other factors. Habitual overuse of opioid as a routine practice in a hospital setting is also suspected.

- Data quality is problematic as evidenced by data inconsistency between data submitted on different dates as examples given in the table below. It would be impossible to have a total of 10 counts of rescue doses given with no pain scores (submission on September 23) in a total of 14 patients identified as the number of patients receiving rescue with no pain scores (submission on August 8). Similarly, it would be very unlikely to have a total of 59 counts of rescue doses given at low pain scores (submission on September 23) in a total of only two patients identified as the number of patients receiving rescue at low pain scores (submission on August 8).

Table 25 Examples of Data Inconsistency

Study CPI-APA-353	IVAPAP LD (N = 61)	IVAPAP HD (N = 67)	Placebo (N = 70)
Data about protocol violation submitted on August 8, 2016			
Rescue given with no pain score, n (%)	7 (11.5%)	7 (10.4%)	10 (14.3%)
Rescue given with low pain score, n (%)	1 (1.6%)	1 (1.5%)	0
Data summarized from PI based rescue dosing submitted on September 23, 2016			
Number of rescue doses given with no pain scores	3	6	1
Number of rescue doses given at low pain scores (PI<4)	13	28	18

Additional analyses by exposure levels

According to the protocol low dose was 7.5-10 mg/kg and high dose was 10-12.5 mg/kg for neonates and low dose was 12.5 mg/kg and high dose was 15 mg/kg for the three infant groups. Because nobody received 7.5 mg/kg, the actual exposure to acetaminophen was 10 to 12.5 mg/kg in the low dose group and 10 to 15 mg/kg in the high dose group for the entire study population. There was an overlap of weight based exposure levels between the low dose and high dose groups when the neonate group was combined with the three infant groups. It would be interesting to see if there might be any dose response to the actual weight based exposure level. Weight based exposure distribution to IV acetaminophen (a total of 128 patients) included no subjects to 7.5 mg/kg, 15 (12%) to 10 mg/kg, 58 (45%) to 12.5 mg/kg, and 55 (43%) to 15 mg/kg. The exposure to 12.5-15 mg/kg accounted for 88% of the study population. Basically, neonates (up to four weeks old) were exposed to 10 to 12.5 mg/kg and infants/young children (about 1-24 months old) were exposed to 12.5 to 15 mg/kg.

Table 26 Selected Demographics for Patients Exposed to Each Weight Based Exposure level

Volume	0.75 mL/kg		1.0 mL/kg				1.25 mL/kg				1.5 mL/kg	
Treatment	IV APAP 7.5 mg/kg	Pla	IV APAP 10 mg/kg			Pla	IV APAP 12.5 mg/kg			Pla	IV APAP 15 mg/kg	Pla
Age Group	Neonate (extreme pre-term)		Neonate (extreme pre-term)	Neonate (full-term)	Total		Neonate (pre to full-term)	Infant	Total		Infant	
# Exposed	0	0	2	13	15	8	10	48	58	30	55	32
Sex												
Male			1	11	12	6	7	33	40	18	32	19
Female			1	2	3	2	3	15	18	12	23	13
Weight at screening (kg)												
Mean			1.2	3.5	3.2	3	3.2	7.9	7.1	7	7.9	8.1
SD			0.28	0.65	1	0.98	0.72	2.33	2.81	2.49	2.57	2.28
Median			1.2	3.3	3.2	3.25	3.3	8.2	7	6.8	8	7.9
Minimum			1	2.6	1	0.8	2	3.1	2	2.2	2.8	4
Maximum			1.4	4.8	4.8	4	4.1	13.7	13.7	11.7	14.3	12

Source: Table 2 on page 17 of the response to information request in the submission dated June 15, 2016.

The number of doses exposed at each weight based dose level is summarized in the table below. All 25 neonates received a full exposure of four doses of IV acetaminophen at 10 mg/kg in 15 patients and at 12.5 mg/kg in 10 patients. The three infant groups had the full exposure at 12.5 mg/kg in 40 of 48 patients (83%) and at 15 mg/kg in 44 of 55 patients (80%).

Table 27 Number of Doses Exposed at Each Dose Level

Volume	1.0 mL/kg				1.25 mL/kg				1.5 mL/kg	
Treatment	IV APAP 10 mg/kg			Pla	IV APAP 12.5 mg/kg			Pla	IV APAP 15 mg/kg	Pla
Age Group	Neonate (extreme pre-term)	Neonate (full-term)	Total		Neonate	Infant	Total		Infant	
#patient exposed	2	13	15	8	10	48	58	30	55	32
1 dose	0	0	0	0	0	4	4	2	4	5
2 doses	0	0	0	0	0	2	2	3	5	1
3 doses	0	0	0	0	0	2	2	0	2	4
4 doses	2	13	15	8	10	40	50	25	44	22

Source: Table 3 on page 19 of the response to information request in the submission dated June 15, 2016.

The results per exposure level are summarized in terms of the amount of opioid loading dose given at baseline before study drug infusion and in terms of the treatment differences in terms of rescue opioid including the amount, number of doses, proportion rescued, and time to the first rescue as shown in the table below. The group exposed to 10 mg/kg IV acetaminophen had less opioid loading dose than placebo and the groups exposed to 12.5 and 15 mg/kg had more opioid loading dose than placebo. Treatment differences measured by rescue opioid were in favor of the IV acetaminophen 10 mg/kg than corresponding placebo and were very small at the two higher dose levels 12.5 and 15 mg/kg to which most (close to 90%) patients were exposed. There was no trend to suggest a dose response.

Table 28 Efficacy Summary per Dose Level

Study CPI-APA-353	IV APAP 10mg/kg	Placebo	Diff	IV APAP 12.5mg/kg	Placebo	Diff	IV APAP 15mg/kg	Placebo	Diff
	N=15	N=8		N=58	N=30		N=55	N=32	
Amount of opioid loading dose	**120.0**	**189.0**	-69	**302.6**	**250.8**	51.8	**391.0**	**258.2**	132.8
Amount of rescue: 0–24h, µg/kg	95.6	214.8	-119.2	171.3	152.7	18.6	188.9	181.8	7.2
# of rescue doses: 0–24h, n	1.3	3.3	-2.0	2.5	2.3	0.2	2.7	2.9	-0.2
Proportion rescued: 0-24h, %	66.7%	75.0%	-8.3%	77.6%	82.8%	-5.2%	81.8%	84.4%	-2.6%
Time to first rescue, hours	6.00	4.30	1.70	4.19	4.13	0.06	3.55	2.51	1.04

Source: Tables 1.11.3-2 and 1.11.3-3 on pages 4-6 of the response to information request (IR) in the submission dated September 9, 2016

Reviewer's comments:

In addition to issues already discussed above, the three doses 10, 12.5, and 15 mg/kg are very close to each other and are not likely to have a dose response even in an adult analgesic study.

5.3.1.3 Summary of Findings and Discussion

Study conduct

The treatment groups were approximately balanced with regard to demographic characteristics such as age, sex, race, and weight at screening and with regard to the amount of total opioid consumption during the 6-hour period before randomization.

Dropouts were reported in about 20% (39/198) of the study population, mainly due to AEs (nine of 11 cases in the placebo group), withdrawal of consent (six cases all in the acetaminophen group), loss of IV access or unable to draw blood, early discharge, and physician's decision.

The reported protocol deviations involved about 45% of the study population. They were mainly in the categories of error in use of rescue (23%, including 13% rescue given with no PI or low PI), missing pain intensity assessment (14%), taking exclusionary medications (13%), missing laboratory test, and deviation from eligibility criteria. Although the proportion of total protocol deviation and deviations in the major categories were similar between the treatment groups, the noticeable proportion of patients receiving rescue incorrectly, missing PI, and taking excluded medication could potentially make the differentiation of true treatment effects difficult.

Treatment group imbalanced in mean pain intensity at randomization before opioid loading dose was noticed that the low dose IV acetaminophen group had much lower group mean PI than the placebo group in three of the four age strata. Treatment group imbalance was also detected in terms of the amount of opioid received as a single loading dose 30 minutes before the study drug infusion, that acetaminophen groups receiver 50 and 93 μg/kg (20 to 38%) more opioid loading dose than placebo patients.

Efficacy

There were no consistent findings or clear trend overall or across age strata (b) (4) treatment effects of IV acetaminophen. Treatment differences measured by primary and all the secondary efficacy endpoints were very small in general and the results were mixed in that some findings were in favor of the active treatment groups and other findings were in favor of the placebo treatment. For example, the treatment comparison in primary efficacy endpoint showed that the low dose IV acetaminophen group had 11 μg/kg more 24-hour rescue opioid than the placebo group and the high dose IV acetaminophen group had 1.4 μg/kg less rescue opioid than the placebo group. Treatment differences measured by opioid rescue in terms of the amount of opioid, number of doses, proportion rescued, and time to the first rescue, were in favor of IV acetaminophen treatments for neonates and intermediate-age infants and in favor of placebo treatment in younger and older infants.

The most remarkable and consistent findings in all the treatment groups were dramatic PI reduction (40-80%) in response to the loading dose of opioid regardless of PI before loading dose and maintenance of low PI (<2.2 on 0-14 and 0-10 scales) with frequent use of rescue opioid (2-3 doses on the average) in all treatment groups.

The large confounding effects from loading opioid given 30 minutes before study drug and the unpredictable individualized opioid dosing (based on institution's standard of care and up to Investigator's choices in a study conducted at 18 sites, 15 of which had only 1-12 patients (refer to table 11) made it impossible to use the amount of rescue or any rescue data to evaluate efficacy of acetaminophen treatment in this kind of setting. The observation that treatment groups on higher loading opioid dose also received larger dose of rescue regardless of PI level suggested disconnection between the use of rescue and PI score though the rescue use should have been based on PI.

5.3.1.4 Conclusion

Analgesic effects of IV acetaminophen could not be adequately evaluated due to the overwhelming analgesic response to the opioid loading dose given shortly before study drug infusion and inter-center variations in opioid usage pattern.

5.3.1.5 Appendix

Eligibility criteria copied from the final version of the protocol

Inclusion Criteria
To be eligible for entry into the Study, Subjects must meet, or Subjects' Parent or Guardian must meet, agree with, or confirm all of the following criteria:

1. Subject is ≥ 28 weeks to ≤ 40 weeks gestational age and < 2 years old at study randomization.
2. Subject will undergo surgery or had a traumatic injury expected to produce moderate to severe pain and patient is expected to require analgesia for acute pain for 24 hours.
3. Subject has a medically reasonable need and expectation for IV treatment due to their underlying procedure(s) or medical condition(s) for the duration of the study.
4. Subject has a bodyweight which, in the opinion of the Investigator does not preclude participation in the study.
5. Subject has reliable vascular access for administration of study medication and PK sampling.
6. Subject is free of other physical, mental, or medical conditions which, in the opinion of the Investigator, make study participation inadvisable or make it impossible to accurately assess efficacy or safety endpoints.
7. Subject's parent or guardian must provide written informed consent prior to participation in the study.
8. Subject's parent or guardian must have the ability to read and understand the study procedures and have the ability to communicate meaningfully with the study investigator and staff.

Exclusion Criteria
A subject is NOT eligible for entry into the study if ANY of the following criteria are met:

1. Subject is not able to comply with the sampling requirements of the study.
2. Subject has known or suspected hypersensitivity to acetaminophen or the excipients of IV acetaminophen.
3. Subject has any significant medical condition that in the opinion of the Investigator contraindicates participation in the study or impairs the assessment of efficacy or safety (for example, neurologic diseases such as hemiplegia, demyelinating disorders, or neuromuscular paralysis, or requirement for prolonged mechanical ventilation making it impossible to assess pain scales using the LNPS or the FLACC).
4. Subject has participated in another interventional clinical study within 30 days of the planned study randomization date.

Pre-Randomization Eligibility (Qualification) Criteria
To be eligible to be randomized into the study, subjects must meet the following criteria prior to randomization:
1. Subject has not been administered the following:
   a. Any acetaminophen-containing product, NSAIDs, central alpha-adrenergic agents (e.g., clonidine, dexmedetomidine) or ketamine within 6 hours of T0.
   b. Regional or neuraxial (caudal, epidural or spinal) anesthetic with local anesthetics within 6 hours of T0.
2. Subject does not have abnormal LFTs and/or liver enzymes from a sample obtained postoperatively/post-trauma and prior to randomization above the following limits:
   a. TBL > 3 X ULN, OR
   b. ALT > 3 X ULN, OR
   c. TBL > 2 X ULN) AND ALT > 3 X ULN, OR
   d. If neonate, in the absence of intentional anticoagulation, INR > 1.5 X ULN or PT > 1.5 X ULN.
3. Subject does not have significantly impaired renal function or known significant renal disease, which in the opinion of the Investigator would contraindicate study participation.
4. Subject had a pain assessment performed by qualified nursing, anesthesia or other clinical or research staff documenting moderate to severe pain (i.e., pain score of at least 4 on the LNPS or FLACC, or moderate to severe pain using the institution's preferred validated observational pain scale) within 6 hours prior to randomization.
5. Subject required at least one dose of parenteral opioid for pain management (i.e., not preemptive therapy) during the 6-hour pre-randomization period, and is anticipated to require at least one dose of parenteral opioid during the 24-hour treatment period.
6. If subject is breast feeding, mother has not been administered any acetaminophen containing product in the previous 6 hours prior to T0 and throughout the treatment period.

6. INTEGRATED REVIEW OF EFFICACY

Efficacy summary

There were no consistent findings or clear trend overall or across age strata [redacted] (b) (4) treatment effects of IV acetaminophen. Treatment differences measured by primary and all the secondary efficacy endpoints were very small in general and the results were mixed in that some findings were in favor of the active treatment groups and other findings were in favor of the placebo treatment. For example, the treatment comparison in primary efficacy endpoint showed that the low dose IV acetaminophen group had 11 µg/kg more 24-hour rescue opioid than the placebo group and the high dose IV acetaminophen group had 1.4 µg/kg less rescue opioid than the placebo group. Treatment differences measured by opioid rescue in terms of the amount of opioid, number of doses, proportion rescued, and time to the first rescue, were in favor of IV acetaminophen treatments for neonates and intermediate-age infants and in favor of placebo treatment in younger and older infants.

The most remarkable and consistent findings in all the treatment groups were dramatic PI reduction (40-80%) in response to the loading dose of opioid regardless of PI before loading dose and maintenance of low PI (<2.2 on 0-14 and 0-10 scales) with frequent use of rescue opioid (2-3 doses on the average) in all treatment groups.

The large confounding effects from loading opioid given 30 minutes before study drug and the unpredictable individualized opioid dosing (based on institution's standard of care and up to Investigator's choices in a study conducted at 18 sites, 15 of which had only 1-12 patients (refer to table 11) made it impossible to use the amount of rescue or any rescue data to evaluate efficacy of acetaminophen treatment in this kind of setting. The observation that treatment groups on higher loading opioid dose also received larger dose of rescue regardless of PI level suggested disconnection between the use of rescue and PI score though the rescue use should have been based on PI.

6.1 Proposed Indication

The proposed indication for acetaminophen IV injection is for the [redacted] (b) (4) reduction of fever.

6.2 Methods/Study Design

There was only one efficacy study of the youngest age group of less than two years old in the NDA submission and the Review Section 5.3 should be referred to for detailed review of the study. The Review Section 6 will contain brief summaries of what have already been presented in Review Section 5.3.

Study CPI-APA-353 was a multiple-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose (4 doses in 24 hours) analgesic study of acetaminophen (APAP) 15-minute IV infusion in hospitalized patients undergoing surgery or experiencing traumatic injury.

Patients with pain of moderate (PI≥4) to severe (PI≥6) intensity, where PI was measured by 15-point LNPS scale for the age group of <6 months old or by 11-point FLACC scale for the age group of 6 months to <2 years old, were given a single loading dose of opioid. IV infusion of study drug as low dose acetaminophen, high dose acetaminophen, or placebo, was started 30 minutes after the opioid loading dose.

The primary efficacy parameter was total rescue opioid over 24 hours from the start of the initial infusion to 6 hours after the last dose. The secondary efficacy parameters consisted of PD/PK correlation, time-specific pain intensity measurements and SPID3, amount of rescue over various time intervals, time to first rescue, proportion of patient requiring rescue, assessor and caregiver's global evaluation, and sedation scores.

6.3 Demographics

Of 198 pediatric patients treated there were 38 neonates (age <29 days), 54 younger infants (ages 29 days to <6 months), 55 intermediate age infants (ages 6 months to <12 months), and 51 older infants/children (ages 12 months to <24 months). The ethnic and racial distributions of the study population were very similar to that of the general US population. Inclusion of more males than females (2:1 ratio) was due to the limitation on the number of patients available after major surgeries.

The acetaminophen and placebo treatment groups were approximately balanced with regard to demographic characteristics such as age, sex, race, and weight at screening and with regard to the amount of total opioid consumption during the 8-hour period before randomization.

6.4 Patient Disposition and Protocol Deviations

Dropouts were reported in about 20% (39/198) of the study population, mainly due to AEs (nine of 11 cases in the placebo group), withdrawal of consent (six cases all in the acetaminophen group), loss of IV access or unable to draw blood, early discharge, and physician's decision.

About 45% of the study population had protocol deviations, mainly in the categories of error in use of rescue (23%), missing pain intensity assessments (14%), taking exclusionary medications (13%), missing laboratory tests, and deviation from eligibility criteria. The proportion of total protocol deviation and deviations in the major categories were similar between the treatment groups.

6.5 Analysis of the Primary Endpoint(s)

Primary efficacy endpoint was the total amount of rescue opioid in 24 hours after start of study drug infusion. The results showed no trend that the low dose IV acetaminophen group had 11 μg/kg more rescue opioid than the placebo group and the high dose IV acetaminophen group had 1.4 μg/kg less rescue opioid than the placebo group. The treatment differences in 24-hour rescue opioid were very small in comparison to the differences in the opioid loading dose with 50-93 μg/kg more received in the acetaminophen groups than the placebo group.

6.6 Secondary and Other Endpoint(s)

Treatment differences measured by opioid rescue in terms of the amount of rescue, number of rescue doses, proportion receiving rescue, and median time to initial rescue and by global evaluation and sedation score were very small and showed no clear trends to suggest treatment effects of IV acetaminophen.

Mean PI scores were not balanced between the treatment groups at randomization and were much reduced, by about 40-80% in most cases (all age strata for the high dose acetaminophen group and placebo group and in neonates and intermediate age infants for the low dose acetaminophen group) in response to opioid loading dose. Baseline PI scores before the start of study drug infusion were low, ranging from 0.6 to 2.2 and subsequent PI measurements fluctuated up and down in the same range as baseline PI with no clear trend to suggest treatment effects from IV acetaminophen.

6.7 Subpopulations

Age strata based subpopulation analyses are described in detail in Review Section 5.3. In terms of treatment group imbalance in the amount of opioid loading dose active treatment groups received less opioid loading dose in neonates and more opioid loading dose in the three infant groups in comparison to the corresponding placebo group of the same age stratum. Most treatment groups across age strata responded to the opioid loading dose as shown in PI reduction by1.2 to 3.0 point (about 40-80%) except the low dose IV acetaminophen treatment in the

younger and older infant strata. Baseline PI before the start of study drug infusion was generally low in the range of 0.6 to 2.2. Treatment differences measured by opioid rescue in terms of the amount of opioid, number of doses, proportion rescued, and time to the first rescue, were in favor of acetaminophen treatments for neonates and intermediate age infants and in favor of placebo treatment in younger infants, and results were mixed in older infants.

Subpopulation analyses by sex or race are not applicable because of the very small subpopulation size for female and racial/ethnic minorities in each age stratum.

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The efficacy analyses based on age strata or weight based exposure level did not show consistent results (b) (4) (refer to the Review Sections 5.3, 6.7, and 6.10).

6.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance effects could not be adequately evaluated because the trial was one day study of acute pain.

6.10 Additional Efficacy Issues/Analyses

Additional analyses are focused on findings related to actual exposure levels as described in detail in the Review Section 5.3. Of the 128 patients treated with IV acetaminophen, 15 (12%) were exposed to 10 mg/kg, 58 (45%) to 12.5 mg/kg, and 55 (43%) to 15 mg/kg. Neonates (<29 days old) were exposed to 10 to 12.5 mg/kg and infants/young children (about 29 days to 2 years old) to 12.5 to 15 mg/kg. The group exposed to 10 mg/kg IV acetaminophen had less opioid loading dose than placebo and the groups exposed to 12.5 and 15 mg/kg had more opioid loading dose than placebo. Treatment differences measured by opioid rescue were in favor of the IV acetaminophen 10 mg/kg than corresponding placebo and were very small with mixed results for the treatment comparison between 12.5 mg/kg acetaminophen and placebo or comparison between 15 mg/kg acetaminophen and placebo.

7. INTEGRATED REVIEW OF SAFETY

Safety summary

The safety database contains safety data from one pediatric study involving a total of 198 pediatric patients less than two years of age. A total of 128 of them were exposed to IV acetaminophen and 109 of 128 received four doses.

There were no reports of deaths and three reports of nonfatal serious adverse events (SAEs), one of which involving a patient in the IV acetaminophen treatment group, who experienced opioid related respiratory depression. Of the 10 AE-related dropout cases two involved IV acetaminophen treated patients. One was due to opioid related respiratory depression as mentioned above second one due to infection.

The common AEs (reported in at least three IV acetaminophen treated patients) included vomiting, hypokalemia, pyrexia, constipation, pleural effusion, hypertension, body temperature increased, and anemia. In comparison of the incidence of individual and total AEs between the placebo versus low dose acetaminophen and high dose acetaminophen treatment groups, there were no treads suggesting dose-related safety concerns with acetaminophen treatment.

Laboratory testing was focus on evaluation of hepatic and renal function because of limitation on the amount of blood drawing. The most frequently detected lab abnormality in the acetaminophen group at the end of study included elevation in AST, ALT, direct and total bilirubin, BUN, and creatinine. Increase in AST or ALT of 1.5 times from baseline was reported in one or two patients in all three treatment groups. There were no recorded cases of high AST or ALT level at more than three times of upper limit of normal range (ULN) during the study or at least two times increase in AST or ALT from abnormally high baseline values. Cases of liver toxicity were identified in the placebo group and not in the IV acetaminophen treatment group.

Assessment of effects of IV acetaminophen treatment on growth is not applicable because of the short treatment of four doses given within 24 hours.

Accidental drug overdose and medication error had the highest reporting rates based on post-marketing surveillance.

Because of the overlap in acetaminophen exposure level in the low dose and high dose acetaminophen groups and residual acetaminophen levels detected in placebo patients, in addition to variable and individualized amount of opioid, the dose response in safety could not be adequately assessed. Based on review of pediatric safety data there were no new safety signals or major safety issues identified in patients treated with IV acetaminophen and opioid concomitantly for 24 hours.

7.1 Methods

This safety review includes safety data collected from Study CPI-APA-353 reported in the submission dated April 29, 2016 and information update on worldwide safety submitted on June 21, 2016. Safety data from controlled study are summarized in terms of individual cases of Serious Adverse Events (SAEs) and AEs leading to dropouts, commonly occurring AEs, and major findings from clinical laboratory testing, especially liver toxicities. Review of worldwide safety data is focused on the most frequently reported events and cases with fatal outcomes.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study CPI-APA-353 was the only study in the NDA supplement for the safety evaluation of the use of IV acetaminophen in (b) (4) pediatric population of ages less than two years old.

7.1.2 Categorization of Adverse Events

Common AEs were categorized by body systems. The Applicant presented AEs by the three treatment groups, low-dose IV acetaminophen, high-dose IV acetaminophen, and placebo treatment. Because the two dose levels of acetaminophen in each age category were so close in amount (a difference of only 2.5 mg/kg) the low dose and high dose groups are also combined for comparison between the active and placebo treatments. Common AEs are not analyzed further by age category or by actual exposure levels due to low incidence of individual AEs.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling data across studies is not applicable since there was only one study.

7.2 Adequacy of Safety Assessments

Safety assessments included AE monitoring, vital signs, physical examinations, and clinical laboratory tests with emphasis on liver function conducted before and after treatment period with data included in the original submission or available upon request and are considered adequate.

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

The overall exposure to at least one dose of IV acetaminophen was reported in 128 pediatric patients in four age categories, including 25 neonates, 36 younger infants, 35 intermediate age infants, and 32 older infants/young children. Most patients (85%) received a full course of four doses, including all neonates (15 neonates exposed to 10 mg/kg and 10 to 12.5 mg/kg) and 84 of 103 infants in the three older age categories (40 out of 48 infants exposed to 12.5 mg/kg and 44 of 55 infants exposed to 15 mg/kg). Refer to Review Section 5.3.

7.2.2 Explorations for Dose Response

There was an effort in exploration for dose response by including two dose levels in each age category. Safety data were summarized in terms of low dose versus high dose acetaminophen treatment groups.

7.2.3 Special Animal and/or in Vitro Testing

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

7.2.4 Routine Clinical Testing

Safety monitoring consisted of mainly routine clinical testing.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the approved labeling of IV acetaminophen for the information on metabolic, clearance, and interaction.

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

Liver function was monitored to evaluate potential liver toxicity known to be associated with acetaminophen.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the study.

7.3.2 Nonfatal Serious Adverse Events

There were three cases of serious adverse events (SAE), two in the placebo group and one in the high dose IV acetaminophen group. The first case in the placebo group was a six-month old Caucasian female who had hypoxia during open-heart surgery before being started on placebo infusion and the second case was a 16-month old Caucasian Hispanic male, who had leukocytosis detected 35 hours after the last dose of placebo infusion, accompanied by fever and signs suggesting surgical site infection. The third case of SAE was reported in a 21-month old Caucasian female assigned to the high dose IV acetaminophen group. She was hospitalized for replacement of grid strip electrodes via right craniotomy and was given one doses of 0.1 mg hydromorphone about two hours after the initial acetaminophen infusion and a repeated dose of 0.1 mg hydromorphone 38 minutes thereafter. Fifteen minutes after the second dose of opioid she had an episode of apnea with a respiratory rate of nine breaths per minute lasting for 10 seconds and low oxygen saturation of 33%. After receiving treatments with oxygen and biphasic positive airway pressure there were no further episodes of apnea. The SAE was probably due to repeated dosing with hydromorphone as suggested by the time sequence of events and dose-related respiratory depression known to be associated with the use of opioid.

7.3.3 Dropouts and/or Discontinuations

There were 12 cases of early dropouts due to AE, two in the high dose IV acetaminophen group and 10 in the placebo group. One of the two in the acetaminophen group was presented above. The other one occurred in a 19-month old African American male, who had fever and was test positive for respiratory syncytial virus after a number of concurrent cardiovascular surgeries. He was discontinued from the study after the second dose of acetaminophen infusion. His fever responded to systemic antibiotic treatment and was not likely to be due to the study drug. The 10 AE-related early dropouts in the placebo group included seven cases of fever and one case of each of the following: anxiety, tachycardia, and peripheral edema.

7.3.4 Significant Adverse Events

No significant AEs other than known acetaminophen and opioid-related AEs have been identified in the safety database.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common Adverse events (AEs), i.e. ≥2 pediatric patients in any IV acetaminophen treatment group, are summarized in Table 7-1 based on all treatment emergent AEs listed in Table 7-2. The percentage of patient with at least one AE was similar between the low dose acetaminophen group and placebo (53% versus 56%) and was less in the high dose IV acetaminophen group (33%). The percentage was less in the combined acetaminophen treatment group than placebo group.

The most common AEs reported in the low dose acetaminophen group were vomiting (n=7 versus n=2 in the high dose group and n=4 in the placebo group) and pleural effusion (n=5 versus none in the high dose group and n=3 in the placebo group). AEs reported in three patients in at least one acetaminophen treatment group included hypokalemia (versus n=1 in the placebo group), pyrexia (versus n=13 in the placebo group), constipation (n=3 in the low dose group and n=2 in the high dose group versus n=2 in the placebo group), hypertension (in the high dose group only versus n=1 in the placebo group), and body temperature increased (in the low dose group versus none in the other two treatment groups). In comparison of acetaminophen treatment and placebo the noticeable differences were higher proportions with vomiting, constipation, and hypokalemia in patients treated with acetaminophen.

The common AEs reflected known opioid-related AEs and AEs from surgical complications and were not much different between the active and placebo treatments. None suggested dose-related AEs associated with the IV acetaminophen treatment.

Table 29 Common AEs in ≥2 Patients in Any Acetaminophen Dosing Group

		APAP LD (N = 61)	APAP HD (N = 67)	APAP (N=128)	Placebo (N = 70)
Number of Subjects With at Least One TEAE		32 (52.5%)	22 (32.8%)	54 (42.2%)	39 (55.7%)
Organ system involved	**Adverse event**				
Blood and lymphatic system disorders	Anemia	2 (3.3%)	1 (1.5%)	3 (2.3%)	1 (1.4%)
Eye disorders	Periorbital edema	0	2 (3.0%)	2 (1.6%)	1 (1.4%)
Gastrointestinal disorders	Vomiting	7 (11.5%)	2 (3.0%)	9 (7.0%)	4 (5.7%)
	Constipation	3 (4.9%)	2 (3.0%)	5 (3.9%)	2 (2.9%)
General disorders and administration site conditions	Pyrexia	3 (4.9%)	3 (4.5%)	6 (4.7%)	13 (18.6%)
Investigations	Body temperature ↑	3 (4.9%)	0	3 (2.3%)	0
Metabolism and nutrition disorders	Hypokalemia	3 (4.9%)	3 (4.5%)	6 (4.7%)	1 (1.4%)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	5 (8.2%)	0	5 (3.9%)	3 (4.3%)
	Atelectasis	2 (3.3%)	0	2 (1.6%)	2 (2.9%)
Vascular disorders	Hypertension	0	3 (4.5%)	3 (2.3%)	1 (1.4%)

Source: Data extracted from the table below.

Table 30 Treatment Emergent AEs

	APAP LD (N = 61)	APAP HD (N = 67)	APAP (N=128)	Placebo (N = 70)	Total (N = 198)
Number of subjects with ≥1 TEAE	32 (52.5%)	22 (32.8%)	54 (42.2%)	39 (55.7%)	93 (47.0%)
Blood and lymphatic system disorders	2 (3.3%)	2 (3.0%)	4 (3.1%)	2 (2.9%)	6 (3.0%)
Anemia	2 (3.3%)	1 (1.5%)	3 (2.3%)	1 (1.4%)	4 (2.0%)
Coagulopathy	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Leukocytosis	0	0	0	1 (1.4%)	1 (0.5%)
Cardiac disorders	1 (1.6%)	2 (3.0%)	3 (2.3%)	6 (8.6%)	9 (4.5%)
Tachycardia	0	0	0	6 (8.6%)	6 (3.0%)
Cyanosis	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Nodal rhythm	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Sinus tachycardia	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Eye disorders	1 (1.6%)	2 (3.0%)	3 (2.3%)	2 (2.9%)	5 (2.5%)
Periorbital edema	0	2 (3.0%)	2 (1.6%)	1 (1.4%)	3 (1.5%)
Eye swelling	1 (1.6%)	0	1 (0.8%)	1 (1.4%)	2 (1.0%)
Gastrointestinal disorders	11 (18.0%)	5 (7.5%)	16 (12.5%)	10 (14.3%)	26 (13.1%)
Vomiting	7 (11.5%)	2 (3.0%)	9 (7.0%)	4 (5.7%)	13 (6.6%)
Constipation	3 (4.9%)	2 (3.0%)	5 (3.9%)	2 (2.9%)	7 (3.5%)
Flatulence	1 (1.6%)	0	1 (0.8%)	1 (1.4%)	2 (1.0%)
Gastritis	0	1 (1.5%)	1 (0.8%)	1 (1.4%)	2 (1.0%)

Nausea	0	0	0	2 (2.9%)	2 (1.0%)
Hemorrhagic ascites	0	0	0	1 (1.4%)	1 (0.5%)
General disorders and administration site conditions	5 (8.2%)	4 (6.0%)	9 (7.0%)	15 (21.4%)	24 (12.1%)
Pyrexia	3 (4.9%)	3 (4.5%)	6 (4.7%)	13 (18.6%)	19 (9.6%)
Generalized edema	1 (1.6%)	0	1 (0.8%)	1 (1.4%)	2 (1.0%)
Face edema	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Implant site discharge	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Edema peripheral	0	0	0	1 (1.4%)	1 (0.5%)
Hepatobiliary disorders	0	0	0	1 (1.4%)	1 (0.5%)
Hyperbilirubinemia	0	0	0	1 (1.4%)	1 (0.5%)
Infections and infestations	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Viral upper respiratory tract infection	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Injury, poisoning and procedural complications	1 (1.6%)	0	1 (0.8%)	1 (1.4%)	2 (1.0%)
Postoperative fever	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Postoperative ileus	0	0	0	1 (1.4%)	1 (0.5%)
Investigations	5 (8.2%)	2 (3.0%)	7 (5.5%)	2 (2.9%)	9 (4.5%)
Body temperature increased	3 (4.9%)	0	3 (2.3%)	0	3 (1.5%)
Oxygen saturation decreased	1 (1.6%)	1 (1.5%)	2 (1.6%)	0	2 (1.0%)
Hematocrit decreased	0	0	0	1 (1.4%)	1 (0.5%)
Hemoglobin decreased	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Respiratory syncytial virus test positive	0	1 (1.5%)	0	0	1 (0.5%)
Urine output decreased	0	0	0	1 (1.4%)	1 (0.5%)
Metabolism and nutrition disorders	4 (6.6%)	4 (6.0%)	8 (6.3%)	3 (4.3%)	11 (5.6%)
Hypokalemia	3 (4.9%)	3 (4.5%)	6 (4.7%)	1 (1.4%)	7 (3.5%)
Hypocalcaemia	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Hypoglycemia	0	0	0	1 (1.4%)	1 (0.5%)
Hyponatremia	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Metabolic acidosis	0	0	0	1 (1.4%)	1 (0.5%)
Nervous system disorders	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Convulsion	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Psychiatric disorders	1 (1.6%)	0	1 (0.8%)	1 (1.4%)	2 (1.0%)
Agitation	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Anxiety	0	0	0	1 (1.4%)	1 (0.5%)
Renal and urinary disorders	0	1 (1.5%)	1 (0.8%)	2 (2.9%)	3 (1.5%)
Hydronephrosis	0	0	0	1 (1.4%)	1 (0.5%)
Oliguria	0	0	0	1 (1.4%)	1 (0.5%)
Urinary retention	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Respiratory, thoracic & mediastinal disorders	7 (11.5%)	3 (4.5%)	10 (7.8%)	9 (12.9%)	19 (9.6%)
Pleural effusion	5 (8.2%)	0	5 (3.9%)	3 (4.3%)	8 (4.0%)
Atelectasis	2 (3.3%)	0	2 (1.6%)	2 (2.9%)	4 (2.0%)
Apnea	0	1 (1.5%)	1 (0.8%)	1 (1.4%)	2 (1.0%)
Pulmonary edema	1 (1.6%)	0	1 (0.8%)	1 (1.4%)	2 (1.0%)
Stridor	0	1 (1.5%)	1 (0.8%)	1 (1.4%)	2 (1.0%)
Apneic attack	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Hydropneumothorax	0	0	0	1 (1.4%)	1 (0.5%)
Pulmonary hypertension	0	0	0	1 (1.4%)	1 (0.5%)
Rhonchi	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Skin and subcutaneous tissue disorders	2 (3.3%)	1 (1.5%)	3 (2.3%)	1 (1.4%)	4 (2.0%)
Pruritus	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Pruritus allergic	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)
Rash	0	0	0	1 (1.4%)	1 (0.5%)
Subcutaneous emphysema	1 (1.6%)	0	1 (0.8%)	0	1 (0.5%)
Vascular disorders	0	3 (4.5%)	3 (2.3%)	2 (2.9%)	5 (2.5%)
Hypertension	0	3 (4.5%)	3 (2.3%)	1 (1.4%)	4 (2.0%)
Pallor	0	0	0	1 (1.4%)	1 (0.5%)
Superior vena cava syndrome	0	0	0	1 (1.4%)	1 (0.5%)

Source: Table 12-3 on pages 105-107 of the study report.

7.4.2 Laboratory Findings

Because of concerns with the volume of blood drawing in neonates and infants, only limited blood tests were conducted before and after the study. Summarized below are the number and proportion of patients with end-of-study abnormally high laboratory test values who had normal or abnormally high vales at baseline in Table 7-3 and patients with certain levels of liver enzyme elevation in Table 7-4.

The most frequently reported abnormally high values in the IV acetaminophen groups at the end of study were shown in the following labs: aspartate aminotransferase (AST, n=9 in the low dose and n=7 in the high dose group versus n=9 in the placebo group), alanine aminotransferase (ALT, n=5 in each of the acetaminophen versus n=1 in the placebo group), direct bilirubin (n=3 in the low dose and n=5 in the high dose group versus n=1 in the placebo group), total bilirubin (n=2 in the low dose and n=4 in the high dose group versus n=4 in the placebo group), blood urea nitrogen (n=2 in the low dose and n=4 in the high dose group versus n=2 in the placebo group), and creatinine (n=2 in each of the three treatment group). Treatment differences between the acetaminophen and placebo groups were noticeable in abnormally high end-of-study values of ALT and direct bilirubin in patients with normal or abnormally high baseline values.

Table 31 Shift Table for Laboratory Parameters

Number (%) of patients with abnormally high value for the following lab test at end of study	APAP LD			APAP HD			Pla		
	Normal baseline	Abn high baseline	Total	Normal baseline	Abn high baseline	total	Normal baseline	Abn high baseline	Total
Alanine Aminotransferase (ALT)	5 (10.6%)	0	5 (10.6%)	3 (5.8%)	2 (3.8%)	5 (9.6%)	1 (1.9%)	0	1 (1.9%)
Alkaline Phosphatase (ALKP)	0	1 (2.1%)	1 (2.1%)	0	0	0	0	0	0
Aspartate Aminotransferase (AST)	4 (8.5%)	5 (10.6%)	9 (19.1%)	0	7 (13.2%)	7 (13.2%)	3 (5.7%)	6 (11.3%)	9 (17.0%)
Direct Bilirubin (umol/L)	1 (2.7%)	2 (5.4%)	3 (8.1%)	1 (2.1%)	4 (8.3%)	5 (10.4%)	1 (2.3%)	0	1 (2.3%)
Total Bilirubin (TBL)	0	2 (4.7%)	2 (4.7%)	0	4 (8.2%)	4 (8.2%)	3 (6.0%)	1 (2.0%)	4 (8.0%)
Blood Urea Nitrogen (BUN)	0	2 (5.0%)	2 (5.0%)	1 (2.6%)	3 (7.7%)	4 (10.3%)	0	2 (4.9%)	2 (4.9%)
Creatinine (umol/L)	1 (2.5%)	1 (2.5%)	2 (5.0%)	1 (2.7%)	1 (2.7%)	2 (5.4%)	1 (2.4%)	1 (2.4%)	2 (4.9%)
Prothrombin Intl. Normalized Ratio (INR	0	2 (66.7%)	2 (66.7%)	0	0	0	0	0	0
Prothrombin Time (PT)	0	2 (66.7%)	2 (66.7%)	0	0	0	0	0	0
Hematocrit (Proportion of 1.0)				1 (4.5%)	1 (4.5%)	2 (9.1%)	1 (5.6%)	1 (5.6%)	2 (11.1%)

Source: Table 14.3.6.2 on pages 434-453-107 of the study report.

The lab test results with abnormally high values of transaminase >3 times or >5 times of ULN, or 1.5 times increase at the end of study from baseline were summarized in the table below. No case of ALT/AST >5x ULN was reported. ***For the six cases with AST >3x ULN the Applicant clarified that the elevation occurred only "at the qualification visit and should not have been reported in the original table" in their response to IR dated June 15, 2016.*** Increase in ALT of 1.5 times from baseline was reported in five patients (n=2 for the low dose acetaminophen group, n=1 for the high dose acetaminophen group, and n=2 for the placebo group). Increase in AST of 1.5 times from baseline was reported in four patients (n=1 for the low dose acetaminophen group, n=1 for the high dose acetaminophen group, and n=2 for the placebo group). There were no treatment differences or trend showing dose response in liver enzyme elevation of 1.5 times. ***No cases were identified as having ALT/AST > 3x ULN at end of study or 2x increase in ALT/AST from abnormally high baseline values***.

Table 32 Summary of Elevations in Liver Enzymes

Number (%) of subjects with LFT elevation	APAP-LD	APAP-HD	APAP	Placebo	Total
ALT > 3 x ULN	0	0		0	0
ALT 1.5 x increase from Baseline	2 (3.3%)	1 (1.5%)	3 (2.3%)	2 (2.9%)	5 (2.5%)
ALT > 5 x ULN	0	0	0	0	0
AST > 3 x ULN	1 (1.6%)	1 (1.5%)	2 (1.6%)	4 (5.7%)	6 (3.0%)*

AST 1.5 x increase from Baseline	1 (1.6%)	1 (1.5%)	2 (1.6%)	2 (2.9%)	4 (2.0%)
AST > 5 x ULN	0	0	0	0	0

Note: AST > 3 x ULN at the qualification visit only.
Source: Table 14.3.5.2 on page 413 of the study report.

Of the two liver toxicity cases identified in the study report, one had hyperbilirubinemia and the second one had hemorrhagic ascites, both were in the placebo group.

7.4.3 Vital Signs

There were six cases of tachycardia, all reported in the placebo group; three cases of hypertension, three in the high dose acetaminophen group and one in the placebo group; 19 cases of pyrexia, three in each of the active treatment group and 13 in the placebo group and three cases of body temperature increased and one case of postoperative fever reported in the high dose acetaminophen group. Information on group mean changes in vital signs per treatment group is not that useful because of widely varied normal ranges by age at various study sites. Nevertheless, there were no clear patterns to suggest treatment differences between the groups.

7.4.4 Electrocardiograms (ECGs)

There was no plan for ECG testing.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Refer to product labeling.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency of AEs could not be adequately assessed because of the overlap in the exposure levels between the two IV acetaminophen treatment groups that the low dose group had two exposure levels of 10 and 12.5 mg/kg and the high dose group had three exposure levels of 10, 12.5, and 15 mg/kg. Nevertheless, there were no trends suggesting dose-related AEs based on safety data collected in the study.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse findings could not be adequately assessed due to limited exposure with patients treated for acute condition for up to four doses within 24-hour period.

7.5.3 Drug-Demographic Interactions

Analyses of drug-demographic interactions are not applicable because of the limited subpopulation sizes of the treatment groups divided by age, gender, and race, in addition to relatively low frequency of adverse findings per treatment group.

7.5.4 Drug-Disease Interactions

Refer to the professional drug labeling for IV acetaminophen.

7.5.5 Drug-Drug Interactions

Refer to the professional drug labeling for IV acetaminophen.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to the professional drug labeling for IV acetaminophen.

7.6.2 Human Reproduction and Pregnancy Data

Refer to the professional drug labeling for IV acetaminophen.

7.6.3 Pediatrics and Assessment of Effects on Growth

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The maximum exposure was 15 mg/kg for up to four doses in the study. There were no reports of drug overdose. Acetaminophen is not known to have abuse potential and problems with withdrawal or rebound.

7.7 Additional Submissions / Safety Issues

There were 16 additional submissions dated from May 16 to September 23, 2016, mostly responses to information requests by the NDA reviewers and updates on labeling. Safety data were included in three of these submissions, two for clarification purpose and one as worldwide safety update.

8. POSTMARKETING EXPERIENCE

Since the international marketing of IV acetaminophen by Bristol Myers-Squibb (BMS) in 2001, the drug product has been available in over 80 countries. A search conducted by the Applicant using the global safety database held by BNS revealed 180 AEs in 80 cases involving the use of IV acetaminophen in pediatric patients less than two years of age up to May 2016.

The AEs with more than one occurrence are grouped by SAEs versus Non-Serious events and summarized in order of decreasing reporting frequency as shown in the table below. The most frequently (n>3) reported AEs were overdose, accidental overdose, medication error, aspartate aminotransferase increased, alanine aminotransferase increased, bradycardia, fetal exposure during pregnancy, and drug administration error.

Table 33 Post-Marketing AEs

Preferred Term	Serious AE	Non-Serious	Total
Overdose	18	5	23
Accidental overdose	14	4	18
Medication error	3	8	11
Aspartate aminotransferase increased	8	0	8

Alanine aminotransferase increased	7	0	7
Bradycardia	4	0	4
Fetal exposure during pregnancy	0	4	4
Drug administration error	3	1	4
Cardiac arrest	3	0	3
Incorrect dose administered	3	0	3
International normalized ratio increased	3	0	3
Off label use	0	3	3
Rash	1	2	3
Bronchospasm	2	0	2
Cerebral hemorrhage	2	0	2
Chills	0	2	2
Coagulopathy	2	0	2
Drug prescribing error	1	1	2
Erythema	1	1	2
Fetal growth restriction	2	0	2
Hepatic failure	2	0	2
Malaise	2	0	2
Metabolic acidosis	2	0	2
No adverse event	0	2	2
Oxygen saturation decreased	2	0	2
Seizure	2	0	2
Thrombocytopenia	2	0	2
Transaminases increased	2	0	2

Source: Table on pages 5-7 of the submission dated June 21, 2016.

Some of the AEs listed in the table above were also classified as serious and unlisted. They included bradycardia (n=4), fetal exposure during pregnancy (n=4), cardiac arrest (n=3), and two cases of each of the following: cerebral hemorrhage, fetal growth restriction, coagulopathy, malaise, metabolic acidosis, seizure, thrombocytopenia, and agranulocytosis. A causal relationship between IV acetaminophen treatment and these AEs could not be determined in any of the cases.

Of the 80 cases identified 50 involved medication errors and five had a fatal outcome. The fatal cases are briefly summarized in the table below. Because of insufficient information in the fatal case descriptions and confounding factors from complications of concurrent medical conditions and multiple concomitant medications it is hard to decide the causal relationship between IV acetaminophen treatment and the events leading to death in most of these cases.

In case #1 the final episode of respiratory distress and subsequent events leading to death appeared to be most likely related to pneumonia. There were no descriptions on disease development and complications from pneumonia or descriptions about possibility of any drug allergy from the medications he received. Information about the duration of acetaminophen treatment was not provided other than the timing of the last dose. The impact of IV acetaminophen on the worsening of respiratory status could not be determined.

In case #2 the mother received six medications including a dose of acetaminophen before delivery and one medication after delivery and before breast feeding and there were no tests for drug exposures in the newborn. Other than APGAR score there were no descriptions about whether the newborn was full term or pre-term or whether there were other insults from delivery not immediately reflected by APGAR assessment. The timing for leukocytosis and metabolic acidosis was not clear. It is difficult to determine what would be the most likely explanations for the newborn's death in this case.

In case #3 the extreme pre-term newborn received IV acetaminophen overdose of 10 times due to confusion with dosing calculation based on mL versus mg. He had toxic level of acetaminophen and lab tests related to liver function conducted with most of the results within normal range (according to the reference value listed in Clinical Chemistry http://clinchem.aaccjnls.org/content/43/1/228) other than elevated alkaline phosphatase. The massive GI and pulmonary hemorrhage leading to death were most likely due to prematurity. It appears less likely that IV acetaminophen would be a major contributor to the massive hemorrhage.

In case #4 septic shock and necrotizing enterocolitis as complications of staphylococcal infection appeared to be the major cause of death. IV acetaminophen was not expected to be related to the infectious disease progression in this case.

In case #5 post kidney transplantation complications with hemodynamic instability and multi organ problems leading to cardio-pulmonary dysfunction seemed to be the major cause of death. The contributing effects from so many different medications could not be determined or completely ruled out.

Table 34 Summary of Fatal Cases Based on Post-Marketing Surveillance

Patient	Medical history & reason for hospitalization	Symptoms/signs test results	Concomitant medication	IV APAP	AEs leading to death
Case 1: 1-yr old male	Respiratory distress	Fever, ↑WBC, ↑C-reactive protein, X-ray: pneumopathy	Amoxicillin then ceftriaxone Na, josamycin, and ibuprofen	15 mg/kg 4x/day, last dose 100 min before the onset of acute distress	Respiratory distress, loss of consciousness, then bradycardia and convulsion
Case 2: 2-hr old male	Mother had normal pregnancy, Apgar 10/10 for newborn at birth	Medication to mother: hydroxyzine at 10.5 hrs., nalbuphine & erythromycin at 6.5 hrs., sufentanil & ropivacaine at 80 min before delivery, and oxytocin at 40 min after delivery and 25 min before breast feeding		IV APAP (1 gm) given at 6.5 hours before delivery	Leukocytosis and metabolic acidosis, death 1.5 hours after birth & 22 minutes after breast feeding
Case 3: 3-dy old male	Extreme pre-term, 27 weeks gestational age at birth	IV APAP overdose with 70 mg (75.3mg/kg) over 6 hours (between 6.5-14.5 hours after birth) leading to toxic level of 141 mg/L. Lab tests (units or reference range not available): total bilirubin 64; gamma-glutaryl transferase 38; alkaline phosphatase 453; aspartate transaminase 30; alanine transaminase 16; prothrombin time 25%			↓O_2 saturation with massive GI and pulmonary hemorrhage, bradycardia, and asystole
Case 4: 9-dy old female	Pre-term, 34.4 weeks gestational age at birth with birth weight of 0.93 kg	Blood transfusion 2 weeks before birth & on Day 4; 2 gm human immunoglobulin on Day 1 & 4; Staphylococcal infection on Day 5		IV APAP 30 mg 4x/day for 7 days (Day 1-7)	Septic shock on Day 6, necrotizing enterocolitis on Day 7, cardiac arrest on Day 9
Case 5: 20-mo old male	History of congenital nephrotic syndrome complicated by chronic renal insufficiency, bilateral nephrectomy, peritoneal dialysis, severe arterial hypertension. Hospitalized for kidney transplantation	Bradycardia on induction of anesthesia; <u>Post-op Day 1</u> hemodynamic instability, alveolar syndrome and suspected gastrointestinal hemorrhage	Adrenalin/albumin for bradycardia; midazolam/morphine for sedation; <u>Medication on surgical day</u>: basiliximab, methylprednisolone, midazolam, sufentanil, atracurium, atropine, epinephrine, ceftriaxone, furosemide, esomeprazole,	IV APAP 1.5 hours after surgery	Left ventricular dysfunction, severe bradycardia (<50/ min) with QRS widening and rhythm disorder; <u>Autopsy finding:</u> pulmonary and diffuse edema with bilateral pleural effusion and splenomegaly

			salbutamol, heparin, sevoflurane; <u>Medication on post-op Day 1:</u> ketamine, metronidazole, morphine sulfate, sulfamethoxazole + trimethoprim, norepinephrine, mycophenolate mofetil, human albumin IV, and RBC transfusion		

Post marketing safety data have a lot of limitations such as problems with data quality and underreporting. There did not appear to be clusters of events suggesting new safety signals based on the limited post-marketing safety information available.

9. APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

Literature review was not provided in this submission.

9.2 Labeling Recommendations

Labeling recommendations include a brief description of clinical trial conducted and updates on PK information for pediatric patients less than two years of age.

9.3 Advisory Committee Meeting

There is no Advisory Committee Meeting planned for use of IV acetaminophen in pediatric patients less than two years of age.

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/s/

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