CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022450Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA #	22-450/000
Applicant Name	Cadence Pharmaceuticals, Inc.
Date of Submission	May 13, 2009
PDUFA Goal Date	November 13, 2009
Proprietary Name / Established (USAN) Name	Tradename/ Acetaminophen Injection for Intravenous Use
Dosage Forms / Strength	Intravenous/ 10 mg per 1 mL solution
Proposed Indication(s)	Acute pain and fever in adult and pediatric patients
Action/Recommended Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Christina Fang, M.D., M.P.H. - efficacy Jacqueline Spaulding, M.D. - safety
Statistical Review	David Petullo, M.S., Feng Li, Ph.D. Dionne Price, Ph.D.
Pharmacology Toxicology Review	Carlic Huynh, Ph.D., Dan Mellon, Ph.D.
CMC Review/OBP Review	Martin Haber, Ph.D., Ali Al Hakim, Ph.D.
Microbiology Review	Denise Miller, Ph.D.
Clinical Pharmacology Review	Ping Ji, Ph.D., Suresh Doddapaneni, Ph.D.
DDMAC	
DSI	Susan Leibenhaut, M.D., Jean Mulinde, M.D.
OSE/DMEPA	Richard Abate, RPh, Melina Griffis, RPh, Carol Holquist, RPh
Maternal Health Team	Leyla Sahin, M.D., Karen Feibus, M.D.
CDTL Review	Ellen Fields, M.D., M.P.H.
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This application is for a parenteral formulation of acetaminophen intended for intravenous use for pain and fever in adults and children. The applicant has submitted a 505(b)(2) application referencing the Agency's previous findings of efficacy and safety for Tylenol (NDA 19-872) and scientific literature. The applicant had originally also referenced Ultracet (acetaminophen and tramadol) but later withdrew reference to that product as there was an outstanding patent. The product is a sterile, clear, colorless, preservative-free, isotonic formulation of acetaminophen. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL).

As the pharmacokinetic profile for this product differs from oral acetaminophen, clinical studies were conducted to support efficacy and safety. At the time of submission, there were no approved parenteral products for the treatment of fever, so the applicant was granted a priority review.

An IV formulation of acetaminophen was first approved outside the U.S. in 2001, marketed as Perfalgan by Bristol-Myers Squibb, and is approved in approximately 80 countries.

2. Background

Development of this product occurred under IND 58,362. Although the applicant had not initially wanted to seek an indication for pain, the Division of Analgesic, Anti-Inflammatory and Ophthalmic Drug Products asked the applicant to conduct trials in pain as it was likely the product would be used for that purpose.

The application includes five Phase 1 clinical pharmacology studies, one bioequivalence study and fourteen Phase 3 studies. For the pediatric indications, during the End-of-Phase 2 meeting with the applicant, an agreement was reached that it would be acceptable to bridge adult efficacy data with pediatric PK and safety data.

A Pediatric Written Request was issued to the Applicant on August 24, 2007.

The applicant did not request a pre-NDA meeting.

3. CMC/Device

The following section includes material taken from the reviews by Martin Haber, Ph.D. and Ali Al Hakim, Ph.D. and portions of their reviews are included in this summary. The drug substance is manufactured by Mallinckrodt, holder of DMF #5326 which has been reviewed numerous times by the Office of Generic Drugs and is adequate for this NDA. The facilities

inspection EES report for this manufacturing site states that this site has an acceptable cGMP status as of 6/23/2009. As requested by the Agency, the NDA sponsor, Cadence, submitted drug substance specifications for this NDA which include tests for identification, assay, and impurities that include limits for total related substances and individual unidentified impurities.

The drug product is a clear sterile aqueous solution for injection containing 1000 mg of acetaminophen in 100 mL of solution (1% active, concentration 10 mg/mL). Each 100 mL vial also contains mannitol, dibasic sodium phosphate, anhydrous and cysteine hydrochloride, monohydrate. Cysteine is an antioxidant (b) (4) . None of these excipients are novel.

The drug product solution is isotonic with blood with a pH of about 5.5. The drug product is manufactured by Baxter Healthcare Corporation using standard techniques for sterile injectable solutions (b) (4) . Acetaminophen is susceptible to degradation by oxidation (b) (4) . Acetaminophen also (b) (4) to the impurity 4-aminophenol, a potentially genotoxic impurity.

The amount of the 4-aminophenol impurity (b) (4). The amount of 4-aminophenol is (b) (4) at room temperature. The mean amount of the impurity 4-aminophenol in drug substance batches was (b) (4) and the specification limit is NMT (b) (4).

The sterile drug product vials are for single use only and do not contain any (b) (4) preservative. The product is (b) (4) sterilized. The drug product should be administered only as a 15-minute intravenous infusion.

A compatibility study was performed with a number of other drugs, however, only visual observation and turbidity were measured and chemical testing was not performed. The study was repeated and found that there were no changes in the acetaminophen concentration with six different infusion solutions and with 27 other drugs. However, the stability of the other drug in the test solution was not tested, and only one commercial supplier's material was tested while most of the drugs are available from many generic manufacturers with possibly slightly different formulations. Therefore, Dr. Haber recommended deleting reference to mixing with other drugs from the labeling. There was increased turbidity and color changes when mixed with diazepam and chlorpromazine, although chemical reactions are considered unlikely. Both compounds are known to be sparingly soluble in water and the observed turbidity upon mixing with acetaminophen injection probably results from precipitation of the diazepam and chlorpromazine.

An additional inspection of the drug manufacturer, Baxter Healthcare Corporation (Cleveland, MS), was conducted by the Office of Compliance from January 15, 2010 to February 5, 2010. Particulates were again found in the drug product, including fibers and what appeared to be skin cells. A number of cGMP problems were identified by the office of

Compliance inspectors that were part of the written 483 issued to the site manager and are listed below.

1. Control procedures are not established which validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in-process material and the drug product as evidenced by variability in the lots produced, including fill volumes, presence of particulates and foreign matter.
2. A change of procedures relative to the processing (b) (4) was submitted to the Sponsor but was not included in the Sponsor's submission to FDA
3. Records are not kept for the maintenance and inspection of equipment.
4. Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release.
5. Products that do not conform to specifications are not adequately controlled.

Based on the above findings, the Office of Compliance has recommended an overall withhold status for the application as of February 10, 2009. These findings are of sufficient concern that they preclude approval pending adequate resolution and re-inspection. I concur with the conclusions reached by the chemistry reviewer regarding the lack of acceptability of the manufacturing of the drug substance.

4. Nonclinical Pharmacology/Toxicology

The reference drug, Tylenol, has an OTC label and not a prescription label. As noted by Dr. Mellon, a single entity prescription drug label for acetaminophen has not previously been approved by the Agency. Therefore, although a 505(b)(2) application, the Applicant needed to provide full support for the proposed labeling, including pregnancy category. The literature studies originally submitted by the Applicant were not sufficient to support adequately labeling. Additional information was submitted and constituted a major amendment to the application.

There is evidence that acetaminophen is clastogenic based on existing genotoxicity data, but a NOEL can be obtained that provides an apparent safety margin based on body surface area comparisons. There is a carcinogenicity signal based on mononuclear cell leukemias in the female rats, but it has been determined by the Executive Carcinogenicity Assessment Committee to be of limited relevance. Acetaminophen does have effects on reducing fertility based on studies in mice with a dose is equivalent to 1.7 times the maximum human daily dose based on body surface area.

Acetaminophen as a drug substance is known to contain two impurities that have structural alerts for mutagenicity, p-aminophenol (PAP; aka 4-aminophenol or 4-AP) and p-chloroacetanilide. These two impurities have been restricted in the drug substance as per the USP to NMT 0.005% and 0.001%, respectively, since ~1970. Dr. Mellon notes that the

review team has not been able to determine what information resulted in USP establishing such extremely low specifications. One possibility for why the British Pharmacopeia limited p-aminophenol to NMT 0.005% may be due to concern for nephrotoxicty effects. The DMF for the drug substance has been previously found adequate by the Agency for numerous acetaminophen drug products.

The drug substance impurity p-chloroacetanilide (b) (4) in the drug product. However, p-aminophenol is a drug product degradant in addition to a drug substance impurity. The Applicant originally proposed a specification of NMT (b) (4) for p-aminophenol in the drug product, based primarily on their stability data where levels reached (b) (4) in some batches over the submitted 36 months. For a maximum daily dose of 4 grams of acetaminophen per day, a specification of NMT (b) (4) will result in a maximum exposure to 4 mg of p-aminophenol. It is not possible to reduce this impurity to NMT (b) (4) in the formulation due to the inherent instability of acetaminophen in solution. Therefore, this impurity should have undergone safety qualification which usually requires data from a minimal genetic toxicology screen and a repeat-dose toxicology study in a single species of a duration adequate to support the proposed indication, between 14 and 90 days duration in this case, as per ICHQ3B(R2). This requirement for adequate safety qualification of this drug product degradant was communicated to the Applicant in the 74-day filing letter.

The Applicant submitted a response to the requirement for safety qualification in the 74-day letter on August 12, 2009 consisting of a literature review arguing that p-aminophenol is a metabolite of acetaminophen, and summarized existing toxicology data for p-aminophenol from the published literature. No new toxicology studies were conducted. While ICH Q3B(R2) describes the threshold for safety qualification for a drug with a maximum daily dose of > 1 g (b) (4) as a potentially genotoxic impurity and with the long history of very low drug substance specifications listed in the USP, standard qualification thresholds are not applicable. In a submission dated September 10, 2009, the Applicant revised their drug product specification for p-aminophenol to NMT (b) (4), but this still results in a maximum (b) (4)

The Applicant has also argued that p-aminophenol is a human metabolite. As noted by Dr. Mellon, according to ICHQ3B(R2), "Degradation products that are also significant metabolites present in animal and/or human studies are generally considered qualified." The submission cites four references to support that p-aminophenol is a metabolite, however, these were review articles and the review team has not been able to access some of the sources cited within the summary articles. In addition, a submission dated July 28, 2009, contained a literature review of the general toxicology of p-aminophenol. However, this was based on summary articles using oral administration, rather than original publications, and so was inadequate to justify the safety of the proposed specification.

There is evidence that PAP is clastogenic, however, based on the most conservative NOEL for clastogenicity, there appears to be a safety margin of approximately 7.5-times the maximum human daily dose using extrapolation from oral dosing. A definitive determination of the safety margin for the IV formulation would require a GLP in vivo clastogenicity study conducted via the IV route of administration, as the NOEL may differ

via this route pending target tissue examined. An adequate carcinogenicity study given the positive findings to date would also clear this up. Assuming the worst case scenario, the NOEL for heterogeneous malignant lymphomas found in female rates could be estimated to be the 12 mg/kg/day dose, which, based on body surface area comparisons, would represent 36-times the maximum human daily dose of PAP dosed as 4 g/day of acetaminophen if the specification was set to NMT (b) (4). The data support the conclusion that positive genotoxic effects reported in the literature with PAP do not translate into carcinogenicity at exposures that would result from use of this product.

The Applicant has submitted the results of two-week toxicology studies performed with acetaminophen, but the levels of p-aminophenol in the product administered are not known and so these studies cannot adequately qualify the impurity. Dr. Mellon was able to deduce that while a NOAEL for IV PAP could not be extrapolated from the submitted literature, and an IV study should be conducted, it was possible to use a report describing studies by the Japanese National Institute of Health Sciences that provide the most definitive characterization of the general toxicity of oral PAP. This report support a NOAEL for general toxicity in a 28-day repeat-dose toxicology study of 60-times the maximum human daily dose of PAP from an acetaminophen dose of 4 g/day if the specification was set to NMT (b) (4) as is currently proposed. While in a reproductive toxicology study, a dose of 500 mg/kg resulted in mortality with evidence of tubular necrosis of the kidney, the reported 60x safety margin in the rat 28-day study would be adequate to support the safety of an oral formulation. For the IV route, in addition to the normal 10x safety margin factor for species extrapolation, even if an additional 3x uncertainty factor was added based on different route of administration, the data suggests an adequate safety margin for general toxicity.

Reproductive toxicology studies using oral dosing found that acetaminophen will produce both maternal and fetal rat liver and kidney histopathology at a dose between 0.3 and 1.2-times the maximum recommended human dose based on body surface area. This indicates that the rat model is unlikely to provide an adequate safety margin to justify a Pregnancy Category (b) (4) based on nonclinical data. In the absence of adequate clinical data with an IV acetaminophen formulation, these adverse findings would dictate a Pregnancy Category C.

I concur with the conclusions reached by the pharmacology/toxicology supervisor that, using the available literature, there is adequate data to support the application and labeling and that there are no outstanding pharm/tox issues.

5. Clinical Pharmacology/Biopharmaceutics

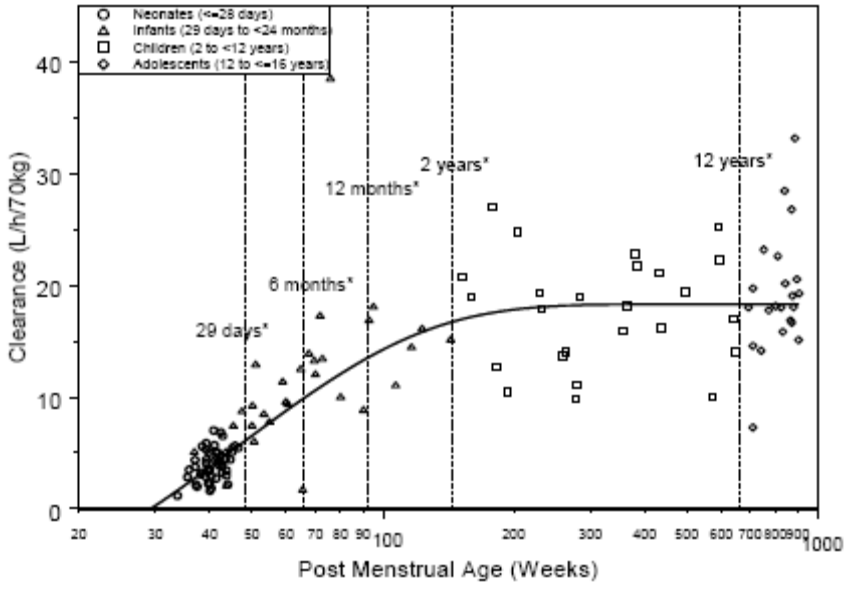
Five Phase 1 clinical pharmacology studies and one bioequivalence study were reviewed. The clinical pharmacology studies included comparisons of repeated doses of IV acetaminophen 1000 mg administered every four hours (q4h) and every six hours (q6h) to PO acetaminophen 1000 mg administered q4h and q6h, respectively, the single dose PK of IV and PO acetaminophen 1000 mg, the single dose PK of IV acetaminophen 1000 mg and 500 mg with 2000 mg of IV propacetamol, a prodrug that is converted to acetaminophen in the blood (2000 mg to 1000 mg) and two studies in pediatric patients that utilized population

methods for PK assessment. The bioequivalence study was intended to evaluate the bioequivalence of the clinical formulation to the proposed commercial formulation.

In adults, the mean maximum plasma concentration of 1000 mg of IV acetaminophen was approximately 70% higher than that following a single dose oral dose of 1000 mg. Mean Tmax values for IV acetaminophen 1000 mg were approximately 30 minutes faster compared with oral acetaminophen 1000 mg. Mean AUC values at steady state were comparable between IV and oral acetaminophen, with the oral bioavailability greater than 90%.

In pediatric patients, ranging from premature neonates to adolescents, following a body weight normalized dosing regimen, the population PK model predicted values were consistent across age groups, with the exception of neonates, who displayed higher exposure values following both single and repeated treatments. Age and body weight were found to be significant PK covariates in the pediatric patients and a body weight and age adjusted dosing regimen was proposed for pediatric patients based on the data presented in the figure below from Dr. Ji's review.

Figure 1. Maturation of standardized clearance versus post-menstrual age (Study CPI-APA-102 and the Palmer Study).



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Note: Individual data points represent the standardized post hoc individual clearances from the final model
The y-axis on the right represents the ratio of the standardized CL over 18.3 L/h/70 kg
* Age represents PNA assuming a gestational period of 40 weeks
Full line represents the equation of standardized clearance: $CL(L/h/70\,kg)=18.3\times\left[1-0.796\times\exp\left(-(PMA-40)\times\frac{\ln(2)}{32.6}\right)\right]$

Source: CADE-RAS-003 Figure 6.3:7.

The route of administration did not appear to have a clinically significant impact on urinary excretion of free or unconjugated acetaminophen or the various acetaminophen metabolites assessed. Specifically, the appearance of NAPQI metabolites in urine was comparable for IV q6h vs. PO q6h. The percent of dose excreted in the urine in pediatric patients for NAPQI appeared to be comparable among different age groups and also comparable to the adults.

Drug-drug interactions and use in patients with hepatic or renal impairment were not evaluated by the applicant. The labeling relies on the Agency's prior findings and information in the publicly available literature.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

The microbiology sterility assurance review determined that the manufacture and (b) (4) sterilization of this product are acceptable, and recommended approval from a quality microbiology standpoint. I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The Applicant has submitted fourteen Phase 3 studies in support of this application. Two studies to support the analgesic efficacy if IV acetaminophen in adults were reviewed in detail by Dr. Fang, Dr. Li and Mr. Petullo, and summarized by Dr. Fields. Patients undergoing orthopedic surgery and abdominal laparoscopic surgery were studied in randomized, double-blind, placebo controlled studies. IV acetaminophen was administered as 1 g every 6 hours in both studies and 650 mg every 4 hours in one study. Opioid analgesics were available as rescue. A randomization error occurred in one study but was noted by the CRO and a correction was instituted. This error was found not to be sufficient to raise concern about the validity of the study results.

Both of these studies demonstrated a statistically significant improvement in pain intensity using a summed pain intensity difference over 24 hours as the primary efficacy analysis. The primary analyses were supported by numerous secondary analyses including a reduction in the amount of morphine rescue in acetaminophen treated patients in one study and several time specific analyses of pain intensity and pain relief in both studies.

Evidence of antipyretic efficacy in adults was provided by a single randomized, double-blind, placebo-controlled, single-dose Phase 3 study in healthy male volunteers treated with endotoxin to induce fever. The formulation of IV acetaminophen used in this study was comparable to the final to-be-marketed formulation with the exception of (b) (4) and this is not a difference sufficient to negate the results of the study to support the indication with the final formulation. Rescue was available with a nonsteroidal anti-inflammatory drug. The active treatment, 1000 mg of IV acetaminophen was statistically superior to placebo in reducing fever with a difference ranging from 0.8 to 1.3ºF.

As noted by Dr. Fields, the additional studies submitted were either not of adequate design to support a finding of efficacy or were unsuccessful. Given what is already known about the efficacy of acetaminophen as an analgesic and as an antipyretic, the studies described are sufficient to support a finding of efficacy for this new formulation and route. The data support the following dosing in adults:

Adults weighing 50 kg and over:

- 650 to 1000 mg every 4 to 6 hours e.g. 1000 mg q6h or 650 mg q4h to a maximum of 4000 mg in 24 hours. Minimum dosing interval of 4 hours.

Adults weighing under 50 kg:

- 12.5 to 15 mg/kg every 4 to 6 hours e.g. 15 mg/kg q6h or 12.5 mg/kg q4h to a maximum of 75 mg/kg in 24 hours. Minimum dosing interval of 4 hours.

8. Safety

The major safety concern with acetaminophen is hepatotoxicity and with a higher Cmax following use of the intravenous formulation compared oral administration, repeated doses in hospitalized patients who might be volume depleted and hemodynamically compromised, especially a debilitated elderly population, were of concern in terms of a possible increased risk of hepatotoxicity. Therefore, the Division requested that the Applicant evaluate high risk populations for liver toxicity, studying the effects of IV acetaminophen during conditions of fasting and hemodynamic instability, and summarizing hepatic adverse events following the use of IV acetaminophen in controlled studies and from foreign post marketing experience. The requirement for the safety database was a total of 300 subjects with 50 exposed for at least five days in both adults and pediatric patients. The applicant submitted a safety database with 1,020 adult patients, 380 of whom received at least five doses, 173 received at least 10 doses, and 183 received five days of treatment. There were 335 pediatric patients who received at least one dose, 212 of whom received five doses, 153 received at least 10 doses and 100 five to seven days of treatment.

As noted by Dr. Fields, the two different, earlier formulations were sufficiently similar to the final formulation that the safety data from studies using those formulations are appropriate to consider in the overall safety database.

No deaths were attributed as related to study drug. There was no excess of serious adverse number of events or adverse events leading to discontinuation in patients treated with IV acetaminophen. However, four patients had elevated ALT and/or AST with normal bilirubin levels. Two of these patients and four others had hepatic events leading to study discontinuation. Two patients met criteria for Hy's law with AST/ALT greater than three times the upper limit of normal and total bilirubin more than two times the upper limit of normal. One of these patients suffered multisystem failure as a result of prolonged hypotension following a CABG, likely to be the cause of the liver enzyme abnormalities. The second patients was a 39 year old man how had a spinal orthopedic procedure with a history of 18 alcoholic drinks per week. This patient had elevated liver enzymes prior to receiving IV acetaminophen, although not at screening. His enzyme elevations peaked on

Day five of IV acetaminophen treatment with an ALT of 3.8x ULN, an AST of 14.9x ULN and a total bilirubin of 2.6x ULN. It is likely that this was related to exposure to acetaminophen, however, it is also likely that this would have occurred with exposure to oral acetaminophen as well.

The nonserious adverse events were consistent with what is known about acetaminophen and what can be expected in a post surgery patient population. The most common adverse events of nausea and constipation were actually lower than placebo. This may reflect greater use of opioids in the placebo group. Placebo patients also had a higher rate of pyrexia reflecting the antipyretic effect of acetaminophen. Care will need to be taken when acetaminophen is used to treat pain in the postoperative period that fever is not masked as it can be an important sign of postoperative complications.

Safety data from pediatric patients was obtained from five studies conducted. Exposure by age group is shown in the table below from Dr. Fields' review.

Table 1 Age of pediatric patients in safety database

Age Group	Number Exposed to IV acetaminophen
Neonates (≤ 28 days old, premature and full term)	47
Infants (29 days to < 2 years)	64
Children (2 to < 12 years)	171
Adolescents (12 to < 18 years)	73

There were no pediatric deaths and as noted by Drs. Spaulding and Fields, the serious adverse events did not appear to be related to exposure to IV acetaminophen. There were five patients who were discontinued from receiving additional IV acetaminophen due to elevated liver enzymes, however causality from exposure to study drug is uncertain as there were additional factors that could have been responsible in each case.

According to the Maternal Health Team (MHT), the application does not provide adequate human and/or animal data sources and analysis to support the requested pregnancy category (b) (4) designation or to adequately inform the pregnancy and nursing mothers subsections of labeling (b) (4)

MHT notes that in a review of …" (b) (4) entries (through Micromedex) for acetaminophen and a PubMED search they found many published studies that evaluate

potential associations between acetaminophen use during various trimesters of pregnancy and fetal and infant outcomes including congenital malformations overall, specific malformations (e.g. gastroschisis or cardiac anomalies), and incidence of asthma in children born to mothers who used acetaminophen during pregnancy. Similarly, LactMed and PubMed are resources you can use to identify published data on levels of acetaminophen in breast milk and actual or calculated infant daily doses of acetaminophen through breast milk."

As noted by Dr. Mellon, the existing animal reproduction studies have shown adverse effects to the fetus. Although the MHT concludes that there are adequate and well controlled studies with oral acetaminophen products to support a Pregnancy Category (b)(4) for oral formulations, there are no adequate and well controlled studies with the IV formulation. Therefore, I concur with the recommendation that this product be designated a Pregnancy Category C.

9. Advisory Committee Meeting

This application was not brought to an advisory committee. Acetaminophen is a well known drug substance and there were no novel concerns raised in this application that required an advisory committee.

10. Pediatrics

The pediatric study requirements for the NDA included cross-study comparison of relative bioavailability between pediatric and adult populations, the use of relative pharmacokinetic profiles to bridge adult efficacy to the pediatric population, in addition to pediatric safety data as basis of approval for pediatric indications. A Pediatric Written Request had been issued to the Applicant on August 24, 2007. The studies submitted adequately support the dosing instructions in the following table.

Table 2 Pediatric dosing recommendations.

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum Single dose	Maximum total daily dose of Acetaminophen
Adults and adolescents (13 years and older) weighing ≥ 50 kg	650 mg	1000 mg	1000 mg	4000 mg in 24 hours
Adults and adolescents (13 years and older) weighing < 50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg /kg in 24 hours (up to 3750 mg)

Age group	Dose	Frequency of use	Maximum Single dose*	Maximum total daily dose of Acetaminophen

Children ≥ 2 to 12 years of age	12.5 mg/kg	every 4 hours	15 mg/kg	75 mg /kg per day
	15 mg/kg	every 6 hours		

(b) (4)

11. Relevant Regulatory Issues

DSI inspections of clinical sites did not reveal any concerns that would impact the overall data reliability.

FDA was contacted about the presence of particulates in product used for clinical trials in 2004. In a telecon on July 29, 2004, the sponsor of the application at the time, Bristol Myers Squibb, informed FDA that three protocols were suspended, that the particulate was in the placebo and active product that were produced on the same line in Italy. No adverse events were identified from this problem and there have been no further concerns about particulates. A DSI inquiry was conducted and no further action was deemed necessary at that time.

An additional inspection of the drug product manufacturer, Baxter Healthcare Corporation (Cleveland, MS), was conducted by the Office of Compliance. Particulates were again found in the drug product, including fibers and what appeared to be skin cells. A number of what appears to be cGMP problems were identified as listed below.

1. Control procedures are not established which validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in-process material and the drug product.
2. Records are not kept for the maintenance and inspection of equipment.
3. Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release.
4. Products that do not conform to specifications are not adequately controlled.

These findings are of sufficient concern that they preclude approval pending adequate resolution and re-inspection.

12. Labeling

Includes:

- The applicant submitted the name Acetavance for review which was found to be unacceptable by DDMAC as this proposed tradename misleadingly overstates the efficacy of the drug.
- DMEPA recommendations were incorporated into the labeling including clarification of the dosing by pediatric ages. DMEPA expressed concern about the risk of air embolism due to the packaging configuration of the product. However, it was unclear that the risk for air embolism with the use of the 100 mL glass vial would be different from other products in glass vials and so was not incorporated into the labeling.

13. Decision/Action/Risk Benefit Assessment

- Complete response

- Risk Benefit Assessment

Although effective and safe in clinical trials, the current manufacturing problems at the drug manufacturing site preclude approval at this time.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	Ofirmev (acetaminophen for injection)

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

/s/

SHARON H HERTZ
02/10/2010

Cross-Discipline Team Leader Review

Date	February 9, 2010
From	Ellen Fields, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-450
Applicant	Cadence Pharmaceuticals, Inc.
Date of Submission	May 13, 2009
PDUFA Goal Date	February 11, 2010
Proprietary Name / Established (USAN) names	Tradename/ Acetaminophen Injection for Intravenous Use
Dosage forms / Strength	Intravenous/ 1000mg per 100ml solution
Proposed Indication(s)	Acute pain and fever adults and pediatric patients
Recommended:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Primary Medical Officer Review	Christina Fang, M.D., M.P.H. - efficacy Jacqueline Spaulding, M.D. - safety
Statistical Reviews	David Petullo, M.S., Feng Li, Ph.D. Dionne Price, Ph.D.
Clinical Pharmacology Review	Ping Ji, Ph.D., Suresh Doddapaneni, Ph.D.
Pharmacology Toxicology Reviews	Carlic Huynh, Ph.D., Dan Mellon, Ph.D.
CMC Reviews	Martin Haber, Ph.D., Ali Al Hakim, Ph.D.
Product Quality Microbiology Review	Denise Miller
DDMAC	
DSI	Susan Leibenhaut, M.D., Jean Mulinde, M.D.
OSE/DMEPA	Richard Abate, RPh, Melina Griffis, RPh, Carol Holquist, RPh
Maternal Health Team	Leyla Sahin, M.D., Karen Feibus, M.D.

1. Introduction

Cadence Pharmaceuticals has submitted a New Drug Application (22-450) for Acetaminophen Injection for Intravenous Use for the proposed indications of the treatment of acute pain and fever in adults and pediatric patients. This NDA was submitted as a 505(b)(2) application relying on previous findings of efficacy and safety for Tylenol (NDA 19-872) and scientific literature. The clinical development for this product was conducted under IND 58,362, and is comprised of 20 studies of healthy subjects and patients ranging in age from premature infants to the elderly. The Applicant requested and was granted a priority review because this product fulfills an unmet medical need for the treatment of fever and acute pain with an intravenous formulation in hospitalized adults and pediatric patients. Although there are many acetaminophen products currently available in the United States, there is not a previously approved intravenous formulation. An IV formulation of acetaminophen was first approved in 2001 for use in France and marketed as Perfalgan® by Bristol-Myers Squibb (BMS) starting in 2002. Currently, Perfalgan® is approved in approximately 80 countries.

2. Background

The initial IND was submitted on May 21, 1999. The Applicant's plan at that time was to conduct clinical studies with IV acetaminophen (APAP), and use data from propacetamol to support the application. Since paracetamol is not an approved product in the United States, the Applicant instead relied on Tylenol (NDA 19-872) and information from literature as the basis for this 505(b)(2) application.

A number of meetings were held between the Division and the Applicant in order to provide advice regarding the clinical development program. The Division recommended that studied pain populations include non-dental post-operative pain along with models where IV APAP could be studied with concomitant use of opioids, since this formulation would be used only in hospitalized patients many of whom may be receiving opioid analgesics, and that pain evaluations in the clinical trials were for at least 24 to 48 hours. Data regarding morphine use would be supportive of primary endpoints related to pain intensity. Data to support dosing interval should be based on time to rescue and end of dosing pain scores during multiple-dose administration. Percentages of rescue medication taken should be documented in all treatment groups.

The Applicant was advised to include all patients who received treatment, regardless of post-dosing assessments, in the intend-to-treat population for analysis, and various methods of imputation for missing data should be included as sensitivity analyses.

In terms of the clinical requirement for the antipyretic indication, the original recommendation was a multiple-dose study on an inpatient population; however the Applicant's later proposal to use an endotoxin induced fever model was accepted by the Division.

The major safety concern for this product is hepatotoxicity, well known to be associated with the use of APAP. Since the intravenous formulation resulted in a higher Cmax compared to that of oral formulation, repeated doses in hospitalized patients who might be volume depleted

and hemodynamically compromised, especially a debilitated elderly population, were of concern in terms of a possible increased risk of hepatotoxicity. The safety information requested by the Division included identifying risks in the target population and in high risk populations for liver toxicity, studying the effects of IV APAP during conditions of fasting and hemodynamic instability, and summarizing hepatic AEs with the use of IV APAP in controlled studies and from foreign post marketing experience. The requirement for the safety database was a total of 300 subjects with 50 exposed for at least 5 days in both adults and pediatric patients.

The pediatric study requirements for the NDA included cross-study comparison of relative bioavailability between pediatric and adult populations, the use of relative pharmacokinetic profiles to bridge adult efficacy to the pediatric population, in addition to pediatric safety data as basis of approval for pediatric indications. A Pediatric Written Request had been issued to the Applicant on August 24, 2007.

3. CMC/Device

The primary CMC review was conducted by Martin Haber, Ph.D., with secondary concurrence from Ali Al Hakim, Ph.D. The following is a brief summary of his review.

The drug product, Acetaminophen Injection, is a clear sterile aqueous solution for injection containing 1000 mg of APAP in 100 mL of solution. Each 100 mL vial also contains the following excipients: 3850 mg mannitol, 10.4 mg dibasic sodium phosphate, anhydrous and 25 mg cysteine hydrochloride, monohydrate. Mannitol is added (b) (4) and cysteine is an antioxidant added (b) (4). The drug product solution is isotonic with blood having an osmolality of about 290 mOsm/kg. The solution pH is about 5.5.

The drug product is manufactured by Baxter Healthcare Corporation at their Cleveland, MS, site. The facility inspection EES report for this site regarding cGMP status was acceptable as of 10/7/2009. Acetaminophen (b) (4) to the impurity 4-aminophenol, a potentially genotoxic impurity. In response to a request from the Agency in the 74-day letter dated 7/22/2009, the firm submitted a toxicological risk assessment regarding the safety of 4-aminophenol in an 8/13/2009 Amendment. The Applicant's risk assessment asserts that the maximum proposed level of 4-aminophenol in both drug substance and product is safe for human use.

The Applicant agreed to tighten in-house limits for drug product impurities and pH. Stability studies demonstrated that during storage, (b) (4) APAP occurs in solution to produce increasing amounts of the impurity, 4-aminophenol, with time. The amount of 4-aminophenol is (b) (4) at room temperature. Cadence is requesting (b) (4) of expiry which is supported by 6 months of long term stability data at 25°C for 3 lots manufactured at their US production site. Supportive stability data for 36 months at 25°C for lots manufactured in Italy was also provided. The limiting factor for shelf life is the allowed amount of 4-aminophenol at expiry, (b) (4).

The container/closure system is typical for an injectable product and consists of a cylindrical Type II clear glass vial of 100 mL nominal capacity, closed with a 32 mm dark grey (b) (4) rubber stopper and sealed with a 32 mm aluminum crimp with a blue plastic flip-off cap.

The drug substance, acetaminophen, is a well characterized compound that is the subject of EP and USP monographs. It is manufactured by Mallinckrodt, holder of DMF #5326, at their Raleigh, NC site. This DMF has been reviewed numerous times by the Office of Generic Drugs and is adequate for this NDA. The facilities inspection EES report for this manufacturing site states that this site has an acceptable cGMP status as of 6/23/2009.

The sterile drug product vials are for single use only and do not contain any (b) (4) preservative. The drug product should be administered only as a 15-minute intravenous infusion. Microbiology sterility assurance review dated 10/13/09 recommended approval from a quality microbiology standpoint.

In August, 2004, a DSI inspection memo noted that particulates were detected in July, 2004 in placebo manufactured in Europe for three of the U.S. clinical trials. The Sponsor terminated these studies, recovered the clinical study materials, and assessed that no adverse events had resulted from the particulates, as per the DSI memo.

An additional inspection of the drug manufacturer, Baxter Healthcare Corporation (Cleveland, MS), was conducted by the Office of Compliance. Particulates were again found in the drug product, including fibers and what appeared to be skin cells. A number of problems were identified as listed below.

1. Control procedures are not established which validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in-process material and the drug product.
2. Records are not kept for the maintenance and inspection of equipment.
3. Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release.
4. Products that do not conform to specifications are not adequately controlled.

The CMC review team has determined that these findings are of sufficient concern that they preclude approval pending adequate resolution and re-inspection.

4. Nonclinical Pharmacology/Toxicology

There are currently no approved single-entity prescription acetaminophen products. Following a review of the vast amount of published nonclinical literature on acetaminophen, the Applicant provided broad statements that were not specifically tied to any particular reference for effects on fertility, genetic toxicology, and reproduction and development studies. The information provided by the Applicant was insufficient to provide labeling that can be clearly documented in terms of source and to include exposure margins to put the data into

perspective. To that end, the Division has requested an adequately detailed annotated labeling as well as copies of pivotal studies that serve as the basis for the proposed labeling.

In addition, the pharmacology/toxicology team has requested additional references regarding the submitted justification for the safety of the 4-aminophenol impurity to support their proposed specification.

The Applicant submitted additional information that constituted a major amendment to the application.

The following is a summary of Dr. Mellon's secondary review of the pharmacology/toxicology aspects of the NDA submission, as stated in Dr. Hertz's Deputy Director Memo.

There is evidence that acetaminophen is clastogenic based on existing genotoxicity data, but a NOAEL can be obtained that provides an apparent safety margin based on body surface area comparisons. There is a carcinogenicity signal based on mononuclear cell leukemias in the female rats, but it has been determined by the Executive Carcinogenicity Assessment Committee to be of limited relevance. Acetaminophen does have effects on reducing fertility based on studies in mice with a dose is equivalent to 1.7 times the maximum human daily dose based on body surface area.

Acetaminophen as a drug substance is known to contain two impurities that have structural alerts for mutagenicity, p-aminophenol (PAP; aka 4-aminophenol or 4-AP) and p-chloroacetanilide. These two impurities have been restricted in the drug substance as per the USP to NMT 0.005% and 0.001%, respectively, since ~1970. Dr. Mellon notes that the review team has not been able to determine what information resulted in USP establishing such extremely low specifications. One possibility for why the British Pharmacopeia limited p-aminophenol to NMT 0.005% may be due to concern for nephrotoxicty effects. The DMF for the drug substance has been previously found adequate by the Agency for numerous acetaminophen drug products.

The drug substance impurity p-chloroacetanilide does not increase in the drug product. However, p-aminophenol is a drug product degradant in addition to a drug substance impurity. The Applicant originally proposed a specification of NMT (b) (4) for p-aminophenol in the drug product, based primarily on their stability data where levels reached up to (b) (4) in some batches over the submitted 36 months. For a maximum daily dose of 4 grams of acetaminophen per day, a specification of NMT (b) (4) will result in a maximum exposure (b) (4) of p-aminophenol. It is not possible to reduce this impurity to NMT (b) (4) in the formulation due to the inherent instability of acetaminophen in solution. Therefore, this impurity should have undergone safety qualification which usually requires data from a minimal genetic toxicology screen and a repeat-dose toxicology study in a single species of a duration adequate to support the proposed indication, between 14 and 90 days duration in this case, as per ICHQ3B(R2). This requirement for adequate safety qualification of this drug product degradant was communicated to the Applicant in the 74-day filing letter.

The Applicant submitted a response to the requirement for safety qualification in the 74-day letter on August 12, 2009 consisting of a literature review arguing that p-aminophenol is a metabolite of acetaminophen, and summarized existing toxicology data for p-aminophenol from the published literature. No new toxicology studies were conducted. While ICH Q3B(R2) describes the threshold for safety qualification for a drug with a maximum daily dose (b) (4) as a potentially genotoxic impurity and with the long history of very low drug substance specifications listed in the USP, standard qualification thresholds are not applicable. In a submission dated September 10, 2009, the Applicant revised their drug product specification for p-aminophenol to NMT (b) (4), but this specification still results in a maximum of (b) (4).

The Applicant has also argued that p-aminophenol is a human metabolite. As noted by Dr. Mellon, according to ICHQ3B(R2), "Degradation products that are also significant metabolites present in animal and/or human studies are generally considered qualified." The submission cites four references to support that p-aminophenol is a metabolite, however, these were review articles and the review team has not been able to access some of the sources cited within the summary articles. In addition, a submission dated July 28, 2009, contained a literature review of the general toxicology of p-aminophenol. However, this was based on summary articles using oral administration, rather than original publications, and so was inadequate to justify the safety of the proposed specification.

There is evidence that PAP is clastogenic, however, based on the most conservative NOEL for clastogenicity, there appears to be a safety margin of approximately 7.5-times the maximum human daily dose using extrapolation from oral dosing. A definitive determination of the safety margin for the IV formulation would require a GLP in vivo clastogenicity study conducted via the IV route of administration, as the NOEL may differ via this route pending target tissue examined. An adequate carcinogenicity study given the positive findings to date would also clear this up. Assuming the worst case scenario, the NOEL for heterogeneous malignant lymphomas found in female rates could be estimated to be the 12 mg/kg/day dose, which, based on body surface area comparisons, would represent 36-times the maximum human daily dose of PAP dosed as 4 g/day of acetaminophen if the specification was set to NMT (b) (4). The data support the conclusion that positive genotoxic effects reported in the literature with PAP do not translate into carcinogenicity at exposures that would result from use of this product.

The Applicant has submitted the results of two-week toxicology studies performed with acetaminophen, but the levels of p-aminophenol in the product administered are not known and so these studies cannot adequately qualify the impurity. Dr. Mellon was able to deduce that while a NOAEL for IV PAP could not be extrapolated from the submitted literature, and an IV study should be conducted, it was possible to use a report describing studies by the Japanese National Institute of Health Sciences that provide the most definitive characterization of the general toxicity of oral PAP. This repots support a NOAEL for general toxicity in a 28-day repeat-dose toxicology study of 60-times the maximum human daily dose of PAP from an acetaminophen dose of 4 g/day if the specification was set to NMT (b) (4) as is currently proposed. While in a reproductive toxicology study, a dose of 500 mg/kg resulted in mortality with evidence of tubular necrosis of the kidney, the reported 60x safety margin in the rat 28-

day study would be adequate to support the safety of an oral formulation. For the IV route, in addition to the normal 10x safety margin factor for species extrapolation, even if an additional 3x uncertainty factor was added based on different route of administration, the data suggests an adequate safety margin for general toxicity.

Reproductive toxicology studies using oral dosing found that acetaminophen will produce both maternal and fetal rat liver and kidney histopathology at a dose between 0.3 and 1.2-times the maximum recommended human dose based on body surface area. This indicates that the rat model is unlikely to provide an adequate safety margin to justify a Pregnancy Category (b) (4) based on nonclinical data. In the absence of adequate clinical data with an IV acetaminophen formulation, these adverse findings would dictate a Pregnancy Category C.

Dr. Mellon has concluded that, using the available literature, there is adequate data to support the application and labeling and that there are no outstanding pharm/tox issues.

5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology review was performed by Ping Ji, Ph.D., with secondary concurrence from Suresh Doddapaneni, Ph.D. The following is a brief summary of Dr. Ji's review.

The results of five Phase 1 clinical pharmacology studies and one bioequivalence study were submitted by the Applicant. The five Phase 1 clinical pharmacology studies were designed to establish PK and safety in adults (Study CPI-APA-101, Study 116-01-03, and Study 98051C-CIS) and in pediatric patients (Study CPI-APA-102 and Study EHRC #26095). Study CPI-APA-101 compared repeated doses of IV APAP 1000 mg administered every four hours (q4h) and every six hours (q6h) to PO APAP 1000 mg administered q4h and q6h, respectively. Study 116-01-03 compared the single dose PK of IV and PO APAP 1000 mg. Study 98051C-CIS compared the single dose PK of IV APAP 1000 mg and 500 mg with 2000 mg of IV propacetamol (PPA), a prodrug that is converted to APAP in the blood (2000 mg to 1000 mg). Two studies (CPI-APA-102 and Study EHRC #26095) in pediatric patients utilized population methods for PK assessment. The bioequivalence study (Study CPI-APA-103) was conducted to determine the bioequivalence of the clinical formulation to the proposed commercial formulation.

Mechanism of Action

Although the exact mechanism of action of acetaminophen is not clearly defined, its effectiveness as an antipyretic agent has been attributed to its effect on the hypothalamic heat-regulating center, while its analgesic effect is due to raising the pain threshold.

The pharmacokinetic findings as reviewed by Dr. Ji are as follows. Please refer to his review for additional details.

PK in Adults

The following table from Dr. Ji's review illustrates the mean PK parameters following single and multiple doses of IV APAP 1000 mg in adults.

Mean (SD) pharmacokinetic parameters following single and multiple doses of intravenous and oral acetaminophen 1000 mg (Study CPI-APA-101).

Day Parameter	IV Acetaminophen 1000 mg q4h (N = 32)	IV Acetaminophen 1000 mg q6h (N = 34)	PO Acetaminophen 1000 mg q4h (N = 35)	PO Acetaminophen 1000 mg q6h (N = 33)
Day 1, Dose 1				
AUC (µg·h/mL)	34.6 (7.98)	42.3 (10.58)	32.6 (7.22)	39.4 (9.57)
$C_{1,max}$ (µg/mL)	26.0 (7.67)	28.4 (21.17)	15.1 (5.36)	15.1 (4.37)
T_{max} (h)	0.25 (0.00)	0.28 (0.10)	0.84 (0.58)	0.72 (0.42)
$t_{1/2}$ (h)	2.28 (0.52)	2.39 (0.57)	2.91 (0.98)	2.66 (0.68)
Day 2, Dose 4 (8^{th} Dose)				
AUC (µg·h/mL)	53.0 (20.83)	59.2 (22.73)	55.3 (23.45)	64.5 (31.20)
$C_{4,max}$ (µg/mL)	36.2 (7.31)	32.4 (10.81)	18.4 (6.25)	21.2 (6.86)
T_{max} (h)	0.25 (0.00)	0.26 (0.02)	0.84 (0.58)	0.66 (0.42)
$t_{1/2}$ (h)	2.7 (1.10)	2.8 (1.03)	3.2 (0.91)	3.1 (0.80)
CL (L/h)	21.1 (7.30)	18.5 (4.73)	20.3 (5.89)	17.7 (5.37)
V_{SS} (L)	29.5 (9.2)	37.2 (8.92)	37.3 (10.8)	42.2 (11.9)

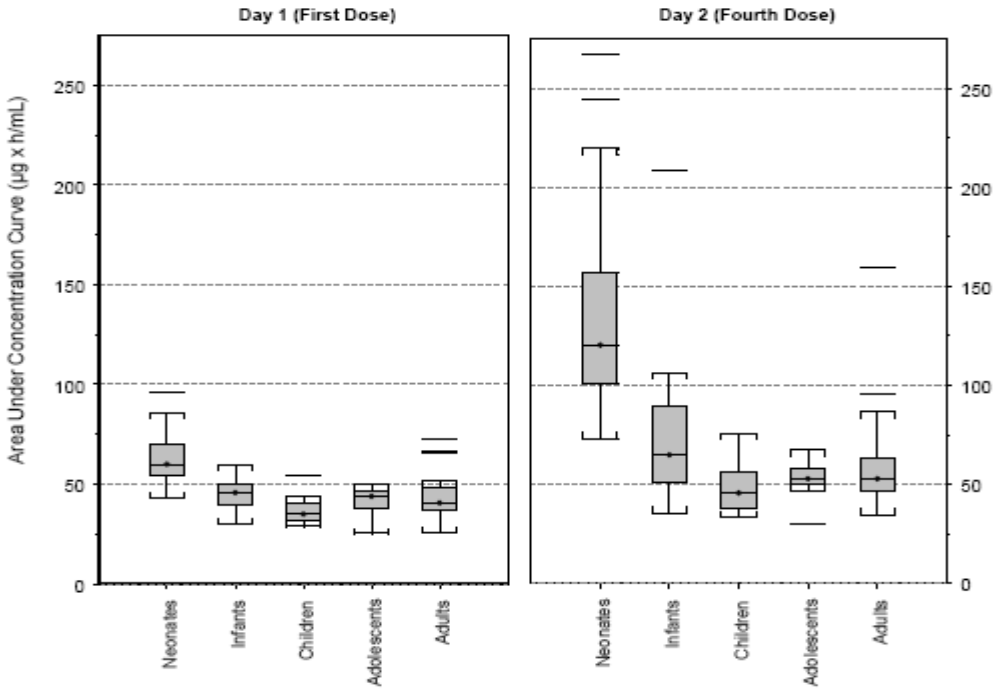
- After single-dose administration of 1000mg the mean Cmax was approximately 70% higher for IV APAP than for oral APAP.
- Mean Tmax values for IV APAP 1000ng were approximately 30 minutes faster than PO APAP 1000 mg.
- Mean AUC values at steady state were comparable between IV and PO APAP.
- Oral BA is greater than 90%

Results from study 98051C-CIS showed that dose proportionality was established between 500mg and 1000mg doses after IV administration. The route of administration did not appear

to have a clinically significant impact on fractional excretion in urine of free or unconjugated acetaminophen or the various acetaminophen metabolites assessed [acetaminophen glucuronide), acetaminophen sulfate and N-acetyl-p-benzoquinone imine (NAPQI,)].

PK in Neonates, Infants, Children, and Adolescents

The PK profile for IV APAP for pediatric patients, ranging from premature neonates to adolescents, was evaluated in two studies. Following body weight normalized dosing regimen, a population PK model predicted acetaminophen AU_T values were consistent across age groups, with the exception of neonates, who displayed higher exposure values following both single and repeated treatments (i.e., Day 2, 4th dose).



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The percent of dose excreted in the urine in pediatric patients metabolites appeared to be comparable among different age groups and also comparable to adults.

A population PK analysis was conducted based on data from the two pediatric studies. A two-compartment model with linear elimination was found to best fit the plasma concentration time profiles. Age and body weight were identified as significant covariates for PK parameter clearance (CL). Body weight was also a significant covariate for central volume of distribution (Vc), inter-compartmental clearance (Q) and peripheral volume of distribution (Vp).

Biopharmaceutics

Three formulations of IV APAP (referred to as the initial, current, and proposed commercial formulations) were used in the development program. The two pivotal efficacy trials (Studies CPI-APF-302 and CPI-APA-304) used the current formulation. Bioequivalence of the current formulation manufactured by BMS in Anagni, Italy and used in the Cadence-sponsored clinical trials to the proposed commercial formulation manufactured by Baxter in Cleveland,

Mississippi was established in Study CPI-APA-103. In terms of formulation, the current formulation (also known as Perfalgan), and the proposed commercial formulation are essentially identical according to the CMC review team.

Relationship between acetaminophen metabolites and liver function markers
The levels of liver function markers (AST, ALT, and Bilirubin) were independent of percent (amount) excreted as NAPQI production (acetaminophen mercapturate, 3'-[S-cysteinyl] acetaminophen, and 3'-S-methylacetaminophen) in both adult and pediatric populations based on analyses of data obtained from Study CPI-APA-101 and CPI-APA-102

The submission was found acceptable from the Clinical Pharmacology perspective with no findings that would preclude approval.

6. Clinical Microbiology

Microbiology sterility assurance review dated 10/13/09 determined that the manufacture and (b) (4) sterilization of this product are acceptable, and recommended approval from a quality microbiology standpoint

7. Clinical/Statistical- Efficacy

A total of 14 clinical studies were submitted in support of the efficacy of IV APAP for the treatment of pain and fever, three of which were identified by the clinical review team as essential, and were subsequently fully reviewed by Dr. Christina Fang. Dr. Fang's review also includes a brief discussion of the additional studies.

Analgesic indication in adults
Two Phase 3 clinical trials were reviewed to support the efficacy of IV APAP for the treatment of pain in adults. Study REC10-3-002 was a mulit-center, randomized double-blind, active and placebo-controlled trial that compared the use of IV APAP 1000mg with IV propacetamol (PPA) 2000mg and placebo every six hours in post-orthopedic surgical patients. The patient population consisted of adult patients undergoing elective unilateral or bilateral, primary or uncomplicated secondary total replacement of hip or knee joint who had postoperative pain of moderate-to-severe intensity on the morning following surgery. Patients were randomized equally to one of three treatment groups; IV APAP 1000mg, IV PPA 2000mg, or placebo, to receive a 15 minute IV infusion of study drug every six hours for a total of four doses in 24 hours. Patients were allowed rescue medication via PCA with morphine sulfate 1mg every 6 minutes up to 25mg every 4 hours, with 2mg IV push boluses if needed in addition. Pain intensity (4-point categorical scale and 100mm VAS) was collected at baseline and every 15 minutes for the first hour and hourly for 6 hours. The planned primary efficacy endpoint was time-specific measurements of pain relief during the first six hours after initial dose. A number of secondary endpoints were collected to further assess single and multiple dosing efficacy of IV APAP.

The "initial" IV APAP formulation was used in this study, which is identical to the proposed to-be-marketed formulation except (b) (4) It is also bioequivalent to the proposed formulation. This would not be expected to affect efficacy. (b) (4) .

The study sample population consisted of 151 adult patients enrolled who received the study medication, The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight and with regard to baseline pain intensity. Greater than 90% of the patients completed the study, and the same proportion received all four doses of study medication.

The protocol specified primary efficacy endpoint, time specific mean pain relief scores over six hours after the initial dose, showed small but statistically significant treatment differences between IV APAP 1000mg and placebo during the entire 6-hour period. Since PPA is not an approved drug in the U.S., this arm was not used as a comparator. Although there were no adjustments made for multiple comparisons at subsequent time points, multiplicity was less of a concern here because the same endpoint evaluated each time in close proximity, and were therefore highly correlated with each other, according to Mr. Petullo's statistical review. He also confirmed the Applicant's statistical analyses.

The figure and table that follow, from Dr. Fang's review, illustrate the primary and secondary endpoint results.

Figure 5.3.1-1 Time-Specific PR during the First Six Hours

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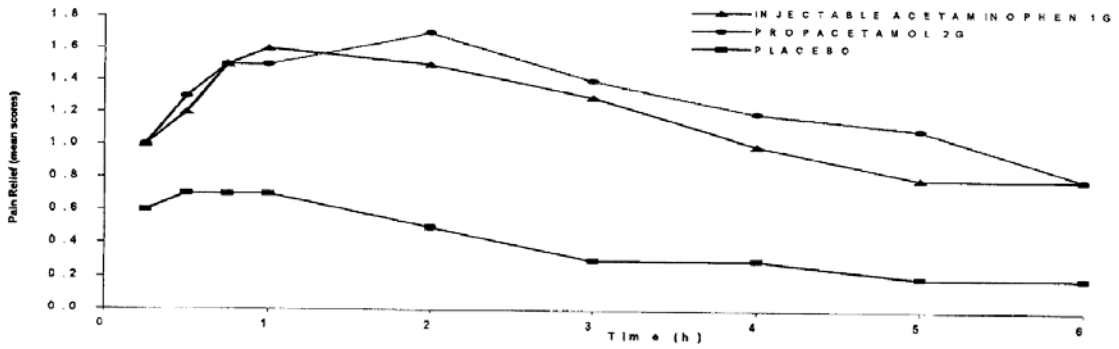

Summary of Efficacy Findings

Study 3-002 **Efficacy summary**	**Treatment differences between APAP 1 g & placebo**	
	Effect size	**p < 0.05**
Primary efficacy endpoint (single-dose effect)		
Time-specific PR in 6 hours after initial dose	0.5-1.0 (0.5-6 hours)	Yes (0.5-6 hours)
Secondary efficacy endpoints: single-dose effects		
Time-specific PID (100 mm VAS) in 1st 6 hours	~15-30 mm (0.5-6 hours)	Yes (0.5-6 hours)
Time-specific PID (categorical) in 1st 6 hours	0.5-0.7 (0.75-4 hours) 0.4 (at Hours 5 and 6)	Yes (0.5-6 hours)
Summation of pain scores		
TOTPAR6	4.4	Yes
SPID6 (VAS)	132.4	Yes
SPID6 (categorical)	2.9	Yes
SPRID6	7.4	Yes

Rescue		
Median time to 1st rescue in 6 hours	2.2 (3 vs. 0.8) hours	Yes
Number (%) of patients requested rescue	-12.2% (87.8 vs. 100%)	
Secondary efficacy endpoints: multiple-dose effects		
Rescue		
Median time to 1st rescue in 24 hours	2.2 hours	Yes
Number (%) of patients requested rescue	0 (100% in both groups)	No
Amount of rescue medication	mg (%↓ from placebo)	
Morphine in 24 hours,	-19.08 (33%↓)	Yes
Morphine in 1st dosing interval	-8.17 (46%↓)	Yes
Morphine in 2nd dosing interval	-2.72 (18%↓)	No
Morphine in 3rd dosing interval	-3.78 (31%↓)	Yes
Morphine in 4th dosing interval	-4.26 (34%↓)	Yes
Pain scores		
Time-specific PI (VAS) at 18, 20, & 24 hours	1.2, -4.6, -2.6	
Time-specific PI (categorical) at 18, 20, & 24 hours	0.11, -0.14, 0	
Average PI over 24 hours, MPI (VAS)	-8	Yes
Average PI over 24 hours, MPI (categorical)	-0.16	Yes
MPI (VAS) adjusted for rescue	-63.1	Yes
MPI (categorical) adjusted for rescue	-53.32	Yes

A post-hoc analysis of multiple-dose efficacy was conducted by the Applicant using SPID24 as the endpoint. The following table from Mr. Petullo's review shows confirmation of the Applicant's results, which were statistically significant in favor of IV APAP.

Analysis of SPID24-multiple doses

Imputation Method	AUC (PID/hour)			p-value
	Placebo	APAP	Difference	
LOCF	407	658	250	0.005
BOCF	374	640	266	< 0.001
Rescue/Withdrawal Score/LOCF	-158	218	376	< 0.001

Source: Reviewer

The primary efficacy findings are supported by multiple secondary endpoints (based on single and multiple dosing) including a 33% greater reduction in morphine consumption in the IV APAP group in the first 24 hours compared with patients receiving placebo. Medan time to rescue was three hours for the IV APAP group compared to 0.8 hours for those receiving placebo. There was no correction for multiple comparisons for the secondary endpoints.

The second Phase 3 study that demonstrated the analgesic efficacy of IV APAP in adults was study A-304. This was a multiple-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose (24 hours) analgesic study of two different dosing regimens (1 g q6 hours and 650 mg q4 hours) of IV APAP in hospitalized patients undergoing abdominal laparoscopic surgery. This study was reviewed in full, and it was the only adequate and well-controlled trial that demonstrated the efficacy of IV APAP 650mg.

The study population consisted of adult patients undergoing abdominal laparoscopic surgery who had moderate-to-severe postoperative pain. Patients were to have been randomized to one of the four treatment groups, APAP 1000mg every six hours, APAP 650mg every four hours, and matching placebo for each of the two dosing regimens, to receive a 15-minute IV infusion of study drug for 24 hours, with an open label extended use of APAP on the same dosing regimen for up to five days. Opioid analgesics were allowed post operatively until the morning of the day after surgery and then allowed as rescue medication during the treatment period. Pain intensity data (PI on 100mm VAS and 4-point categorical scale) was collected at baseline and PI and pain relief was collected hourly for the first 12 hours, then every 2 hours for the next 12 hours, in addition to before rescue. The primary endpoint was SPID24.

A randomization error occurred during enrollment of the first 109 study subjects. The Applicant's original allocation scheme was to randomize patients in a 2:2:1:1 ratio to APAP 1000 mg, APAP 650 mg, Placebo 1000, or Placebo 650. However, during a scheduled quality check by the Applicant's contract research organization (CRO), it was discovered that patients were only being randomized to APAP 1000mg and Placebo 650mg in a 1:1 fashion. The Applicant explained this was due to a programming error in the integrated voice response system (IVRS). The CRO implemented an interim randomization scheme where a subset of patients (selected randomly) had the yes /no field for APAP 1000 mg and P650 changed to yes. Meanwhile, the Applicant implemented a new randomization scheme that allocated patients to APAP 1000mg, APAP 650mg, Placebo 1000mg, and Placebo 650mg in a 6:5:5:2 ratio. In conjunction with the Agency's statistical review team, the appropriate primary efficacy comparison was defined as SPID24 for the pooled placebo group versus the APAP 1000mg group.

The following tables from Dr. Fang's review illustrate the efficacy findings for each dosing group (IV APAP 1000mg q 6 hours and 650mg q 4 hours).

Statistically significant treatment differences between IV APAP 1000mg and placebo were shown in summation of pain scores, SPID and TOTPAR over 24 hours and over first dosing interval and in time-specific PR and mean PR per dosing interval during the first three dosing intervals and mean PI per dosing interval during the first two dosing intervals.

Summary of Efficacy Findings in Support of IV APAP 1000mg

Study A-304 Efficacy summary	Statistically significant treatment differences: APAP 1000mg versus placebo				
Efficacy endpoint	24 hours	Dosing interval			
		1st	2nd	3rd	4th
Primary efficacy endpoint					
SPID24 WOCF	x				
Secondary and other efficacy endpoint					
SPID24 BOCF	x				
TOTPAR24	x				
SPID6		x			
TOTPAR6		x			

Time-specific PR		x	x	x	
Time-specific PI					
Mean PR/dosing interval		x	x	x	
Mean PI/dosing interval		x	x		

Noticeable treatment difference in the proportion of patients taking rescue per dosing interval (10% difference with 42% on APAP versus 52% on matching placebo) was only shown during the first dosing interval. Median time to rescue after the initial dose could not be determined because it was beyond 6 hours in both treatment groups.

Statistically significant treatment differences between IV APAP 650mg and placebo were shown in summation of pain scores, SPID and TOTPAR over 24 hours and SPID over first dosing interval, in time-specific PR from 2nd to 4th dosing interval, in mean PR per dosing interval from 2nd to 6th dosing interval, and in time-specific PI and mean PI per dosing interval from 1st to 3rd dosing interval. Although there were no corrections for multiple comparisons for these endpoints, Mr. Petullo applied post-hoc correction for the SPID24, and found it to be statistically significant in favor of IV APAP.

Table 5.3.2-12 Summary of Efficacy Findings in Support of IV APAP 650 mg

Study A-304 Efficacy summary	Statistically significant treatment differences: APAP 650 mg versus placebo						
Efficacy endpoint	24 hours	Dosing interval					
		1st	2nd	3rd	4th	5th	6th
SPID24 WOCF	x						
SPID24 BOCF	x						
TOTPAR24	x						
SPID4		x					
TOTPAR4							
Time-specific PR			x	x	x		
Time-specific PI		x	x	x			
Mean PR/dosing interval			x	x	x	x	x
Mean PI/dosing interval		x	x	x			x

Noticeable treatment difference in proportion of patients taking rescue per dosing interval (13% difference with 22% on APAP versus 35% on matching placebo) was only shown during the first dosing interval. Median time to rescue after the initial dose could not be determined because it was beyond 6 hours in both treatment groups.

Statistical significance of treatment difference in primary efficacy endpoint was confirmed by Mr. Petullo's reanalyses of data as is illustrated in the table below excerpted from his review. Although there was no correction for multiple comparisons for the APAP 650mg SPID24, Mr. Petullo applied a post-hoc correction, and found the result to be statistically significant in favor of IV APAP.

Comparison of SPID24 (PID/hr) -in Study CPI-APA-304

Treatment Group, (n)	Mean AUC, (SD)	Range	P-value of comparison to placebo
Pooled placebo, (n=110)	-44 (509)	[-1396, 1921]	-
APAP 1000 mg, (n= 92)	-194 (593)	[-1432, 1589]	0.02
APAP 650 mg, (n=42)	-315 (613)	[-1673, 848]	0.009

Source: Reviewer

Conclusions regarding analgesic efficacy

I am in agreement with Dr. Fang's conclusions that IV APAP at 1000mg q 6 hours and 650mg q4 hours is effective in treating acute pain in post-operative patients receiving morphine. The key evidence in support of analgesic efficacy for APAP IV 1000mg in Study 3-002 is the demonstration of statistically significant and clinically meaningful treatment differences in time-specific pain measurements for 6 hours in the first dosing interval supported by a 33% reduction of morphine consumption (compared to placebo) and significantly lower pain intensity adjusted for morphine consumption over 24 hours in comparison to placebo. The key evidence in support of analgesic efficacy for APAP IV 1000mg and 650 mg in Study A-304 are the statistically significant treatment differences in SPID24 supported by significant treatment differences in time-specific pain measurements and in derived mean pain scores per dosing interval. The sizes of subpopulations were too small to allow meaningful subpopulation analyses with regard to age, gender, or race. Treatment differences in end-of-dosing assessments of PR in Study A-304 provided support for every 6-hour dosing of APAP 1000mg and every 4-hour dosing of APAP 650 mg.

Fever indication in adults

A single Phase 3 clinical trial was reviewed to provide evidence of antipyretic efficacy for IV APAP 1000mg. Study CPI-APF-302 was a randomized, double-blind, placebo-controlled, parallel, single-dose study of IV APAP infusion of 1000mg for the treatment of endotoxin-induced fever in healthy adult males. The "initial" formulation of IV APAP was used in this study, which is identical to the proposed to-be-marketed formulation except [redacted] This would not be expected to affect efficacy, [redacted].

Eligible subjects, who tolerated the IV endotoxin test dose of 1 ng/kg with no more than a moderate cardiovascular response within the first hour, received a standard dose of endotoxin of 4 ng/kg. Subjects with a temperature elevation to ≥38.6°C (101.5°F) within 4 hours of 4 ng/kg endotoxin dose were randomized to receive a 15-minute IV infusion of either APAP 1 g or matching placebo.

Rescue treatments were allowed for severe fever-associated symptoms and included ibuprofen 600mg and aspirin 650mg orally or ketorolac 30mg IV as an alternative for those unable to take PO medication.

Efficacy data included measurements of core temperature at multiple time points up to 360 minutes after the start of IV infusion, time to rescue, and patient global evaluations. The primary efficacy endpoint was WSTD6 (weighted sum of temperature differences through 6

hours from baseline). The secondary efficacy endpoints included WSTD3, maximum temperature reduction during 6 hours, Subject's Global Evaluation at 6 hours, and percentage of subjects with temperature reaching <38°C (100.4°F) at any time during the 6-hour evaluation period.

The treatment groups were balanced with regard to demographic characteristics such as age, gender, race, height, and weight and with regard to mean temperature at baseline, which was about 39.3 ºC (102.8 ºF). Four subjects discontinued from the study due to use of rescue medication.

The efficacy results are summarized in the table below from Dr. Fang's review. The treatment differences were statistically significant for the primary and the key secondary efficacy endpoints (no correction for multiple comparisons). The effect sizes of treatment differences of 0.8 to 1.3 °F in mean temperature reduction from baseline up to 5.5 hours and 32% more subjects in the IV APAP group than the placebo group with temperature reduced to <38ºC (100.4ºF), are all considered clinically meaningful.

Table 5.3.3-10 Efficacy Summary for Study F-302

Study F-302 Efficacy summary	**Treatment differences from placebo**	
	p<0.05	**Effect size**
Primary efficacy endpoint, WSTD6		
Difference in LSMeans	x	-4.5 °Fxhr
Secondary efficacy endpoints		
Mean changes from baseline in time-specific temperature measurements	0.5 to 5.5 hours	0.8 to 1.3 °F
% of subjects with temperature <38ºC during 6 hours	x	31.6%

The statistical reviewer, Dr. Feng Li, confirmed the Applicant's primary and secondary efficacy analyses.

Conclusion regarding antipyretic efficacy

IV APAP 1000mg is effective in treating fever induced by endotoxin based on the demonstration of statistically significant and clinically meaningful treatment differences in Study F-302. Since oral APAP is an approved antipyretic, and the Applicant is relying in part on the efficacy of Tylenol for this NDA submission, one clinical trial using the endotoxin based fever model is sufficient evidence of efficacy.

Additional studies

Study reports for eleven additional studies were submitted with this NDA, however the results of these studies could not be used to support efficacy for various reasons, including: no demonstration of statistically significant and clinically meaningful treatment differences, single-dose evaluation in a non-target population, incomplete studies due to particulates in placebo infusion, open-label studies designed to evaluate safety, and active-controlled studies with no demonstration of superiority. Refer to Dr. Fang's review for additional details regarding these studies.

8. Safety

Aspects of the application related to safety were reviewed completely by Jacqueline Spaulding, M.D. The following summarizes her review.

The safety database consisted of data from 14 studies and included 1,020 adult patients who received at least one dose of IV APAP, of whom 380 patients received at least 5 doses and 173 at least 10 doses. One hundred eighty-three adults received IV APAP for five days. A total of 335 pediatric patients were administered at least one dose of IV APAP, of whom 212 received at least 5 doses, and 153 at least 10 doses. One-hundred pediatric patients received five to seven days of IV APAP treatment. These numbers satisfy the requirements agreed upon between the Division and the Applicant at the EOP2 meeting.

Three formulations of IV APAP were used in trials during the clinical development program, the "initial formulation", "current formulation" (Perfalgan), and the proposed to-be-marketed formulation. Both the initial formulation and current formulation were found to be bioequivalent to the to-be-marketed formulation. The initial and current formulations (Perfalgan) are essentially identical to the proposed formulation, except that the proposed formulation contains dibasic sodium phosphate anhydrous, and the initial and current formulations (b) (4), and the initial formulation (b) (4). The initial formulation (b) (4) was used in three studies that exposed 126 adult subjects out of the total 1020 adults in the safety database. Both the CMC and pharmacology/toxicology team have reviewed these formulation issues and determined that the safety profile would be unaffected by these differences.

Adult Safety

In the adult clinical trials, a total of eight deaths occurred, none of which were determined to be causally related to study drug, as per Dr. Spaulding's review. The incidence of serious adverse events in the IV APAP group (5.6%) was essentially the same as in those receiving placebo (5.7%). The overall incidence of adverse events leading to discontinuation was similar in patients who received IV APAP (3%) and in patients who received placebo (4%).

Accidental overdose defined as greater that 4g of APAP in a 24 hour period was the most commonly reported SAE (n = 12) both in the IV APAP group (4) and placebo groups (8, theoretical overdose). The majority of the cases of accidental overdose involved concomitant dosing with a combination opioid/APAP medication. There were no medical consequences as a result of these errors. The occurrence of these overdoses during a clinical trial with trained study personnel overseeing patient safety emphasizes the importance of proper labeling of this product to avoid inadvertent overdoses in routine hospital situations.

Four IV APAP patients in the adult patient safety pool had liver function tests elevations that were assessed as serious adverse events. Three of these patients were enrolled in the open-label study and were receiving IV APAP 650mg q4h. One patient was enrolled in the randomized, active/placebo controlled, 24 hour study and was receiving IV APAP 1000mg q6h. All four of these patients had undergone surgery and were receiving IV APAP for pain post-operatively. Three of the four patients had elevations in ALT and/or AST > 3x ULN and 1 patient had ALT/AST elevation 2x ULN with a normal total bilirubin in all four patients.

Three of the four events were determined by Dr. Spaulding to be possibly related to the administration of IV APAP. Six IV APAP patients had hepatic events that led to discontinuation, including two of the six patients assessed with serious TEAEs.

A MedDRA SMQ was performed by the Applicant to assess hepatic adverse events. There were 2 cases that met laboratory criteria for Hy's Law (concurrent elevation in AST/ALT > 3x ULN with TNL > 2x ULN). One patient was a 70 year old woman status post CABG who suffered severe post operative prolonged hypotension and multi-organ failure, which was the likely cause of the hepatic lab abnormalities. The second was a 39 year old man with a history of 18 alcoholic drinks per week status post a spinal orthopedic procedure. His pretreatment LFTs were elevated and continued to elevate through day five of IV APAP administration. In this case it is likely that his history of alcohol abuse, a well known risk factor, put him at risk for APAP toxicity.

The most common adverse events in adult patients treated with IV APAP (incidence ≥ 5% or greater than placebo) were nausea, vomiting, headache, and insomnia as shown in the following table excerpted from Dr. Spaulding's review.

Common (≥1%) Incidence of Treatment-Emergent Adverse Events by Frequency in IV APAP Study Group: All Randomized, DB, PC Adult Patient Studies Safety Population

Preferred Term	IV APAP[a] (N=783)	Placebo (N=525)
Nausea	151 (19.3%)	131 (25.0%)
Constipation	93 (11.9%)	95 (18.1%)
Headache	73 (9.3%)	45 (8.6%)
Vomiting	69 (8.8%)	46 (8.8%)
Procedural pain	67 (8.6%)	9 (1.7%)
Fatigue	42 (5.4%)	9 (1.7%)
Flatulence	39 (5.0%)	39 (7.4%)
Pyrexia	35 (4.5%)	57 (10.9%)
Pruritus	34 (4.3%)	37 (7.0%)
Insomnia	34 (4.3%)	28 (5.3%)
Anaemia	28 (3.6%)	23 (4.4%)
Dizziness	27 (3.4%)	25 (4.8%)
Abdominal distension	19 (2.4%)	14 (2.7%)
Post procedural haemorrhage	17 (2.2%)	4 (0.8%)
Tachycardia	15 (1.9%)	18 (3.4%)
Alveolar osteitis	15 (1.9%)	4 (0.8%)
Aspartate aminotransferase increased	14 (1.8%)	8 (1.5%)
Trismus	14 (1.8%)	1 (0.2%)
Diarrhoea	11 (1.4%)	18 (3.4%)
Injection site extravasation	11 (1.4%)	10 (1.9%)
Infusion site pain	11 (1.4%)	4 (0.8%)
Gamma-glutamyltransferase increased	10 (1.3%)	11 (2.1%)
Alanine aminotransferase increased	10 (1.3%)	8 (1.5%)
Abdominal pain	10 (1.3%)	7 (1.3%)

Laboratory assessments and vital signs

There were no clinically meaningful differences noted between IV APAP and placebo groups in terms of hematology or chemistry lab values, except for one patient noted to have an increased serum creatinine who had a previous history of renal insufficiency. He underwent a

radical cystectomy and received 16 doses of IV APAP 1000mg. His creatinine normalized following discontinuation of IV APAP.

Because the issue of APAP-induced liver damage is the primary safety concern for this product the Applicant and Dr. Spaulding performed a detailed analysis of liver function tests and determined there were no clinically meaningful changes in mean LFT values (ALT, AST, GGT, and ALP) from baseline to end of trial for the all adult patient pool. The percentage of patients with elevations in ALT or ALT, TBL, or GGT> 3x ULN was slighter higher in the IV APAP group as compared to the placebo group.

The only vital sign abnormality found to be greater in the IV APAP group compared to placebo was a higher incidence of hypotension (2.8% vs. 0.4 %). The reason for this could not be determined. Otherwise, there were no clinically meaningful differences between IV APAP and placebo groups in TEAEs associated with vital sign abnormalities.

Overall, no new safety information related to the administration of APAP in adults was identified in this review, including no new signals regarding the hepatotoxicity of IV APAP. There were some cases of inadvertent overdose of APAP (>4gms/day) due to co administration of opioid/APAP combination products. This reinforces the need for appropriate labeling in order to mitigate the risk of accidental overdose during routine hospital use of IV APAP.

Pediatric Safety
Safety data from five studies conducted in pediatric patients were included in this application, none of which were placebo-controlled trials. Two of the five pediatric studies were Phase 3, randomized, double-blind, active-control, single-dose efficacy and safety studies, one study was an open- label, repeated-dose efficacy and safety study for up to 7 days for the treatment of either pain or fever, and the remaining two studies were Phase 1, open-label, repeated dose, PK evaluations.

Data was pooled for four age categories: neonates (≤ 28 days old, premature and full term), infants (29 days to < 2 years), children (2 to < 12 years), and adolescents (12 to < 18 years). Exposure by age group is shown in the table below.

Age Group	Number Exposed to IV Acetaminophen
Neonates	47
Infants	64
Children	171
Adolescents	73

Forty-three of the 47 neonates exposed to IV APAP were exposed to Perfalgan, the EU formulation. A side-by-side table of the Applicant's proposed formulation and Perflagan was requested by the Division on October 22, 2009. The table was reviewed by the CMC team who determined that there was a very minor difference between the two formulations and they were essentially identical, allowing the data on the 43 exposed neonates to be included in the safety database.

Overall, 60% (212/355) of pediatric patients received at least five doses of IV APAP, including: 96% of neonates, 58% of infants, 35% of children and 96 % of adolescents.

No deaths were reported in any study, and the overall incidence of serious adverse events was 8.5%, including 2.1% of neonates, 6.3 % of infants, 10.5 % of children and 9.6% of adolescents. There was no evidence these SAEs were associated with IV APAP, as they were consistent with the underlying disease processes. In pediatric patients, the overall incidence of adverse events leading to discontinuation was 1.4% (5/355), however all five of these discontinuations were secondary to liver function test elevations. All five cases had confounding factors (concomitant hepatotoxic medications, posterior spinal fusion surgery) that may have contributed to hepatic enzyme elevations.

The MedDRA SMQ of hepatic disorders was used to assess the incidence, severity, and baseline characteristics of pediatric patients who experienced a hepatic event. The overall incidence of hepatic events was 3.9%, with a higher incidence in adolescents (8.2%) compared to children (4.1%), infants (1.6%) and neonates (0%). There were no deaths related to a hepatic TEAE. The incidence of serious hepatic TEAE was 1.1 % (4/355). The incidence of hepatic TEAE resulting in discontinuations was 1.4 % (5/355). There were no cases that met Hy's law criteria. No new safety information related to hepatic laboratory analyses and hepatic related adverse events were identified.

The most common adverse events in pediatric patients treated with IV APAP (incidence $\geq$ 5%) were nausea, vomiting, constipation, pruritus, agitation and atelectasis. Adverse events by age group are shown in the table below from Dr. Spaulding's review. As there is no placebo group for comparison, the actual association of these events with IV APAP is unknown.

Most Common ≥1 % of All Patients TEAEs Pediatric Safety Population

MedDRA Preferred Term	Neonates (N=47) n (%)	Infants (N=64) n (%)	Children (N=171) n (%)	Adolescents (N=73) n (%)	Total (N=355) n (%)
Nausea	0	2 (3.1)	19 (11.1)	33 (45.2)	54 (15.2)
Vomiting	0	1 (1.6)	18 (10.5)	18 (24.7)	37 (10.4)
Constipation	0	3 (4.7)	12 (7.0)	14 (19.2)	29 (8.2)
Pruritus	0	3 (4.7)	13 (7.6)	12 (16.4)	28 (7.9)
Agitation	0	9 (14.1)	8 (4.7)	3 (4.1)	20 (5.6)
Atelectasis	2 (4.3)	6 (9.4)	7 (4.1)	4 (5.5)	19 (5.4)
Pyrexia	0	0	9 (5.3)	6 (8.2)	15 (4.2)
Hypokalaemia	0	8 (12.5)	5 (2.9)	1 (1.4)	14 (3.9)
Hypomagnesaemia	1 (2.1)	4 (6.3)	4 (2.3)	5 (6.8)	14 (3.9)
Pleural effusion	1 (2.1)	5 (7.8)	3 (1.8)	4 (5.5)	13 (3.7)
Anaemia	0	4 (6.3)	3 (1.8)	4 (5.5)	11 (3.1)
Injection site pain	0	1 (1.6)	11 (6.4)	0	12 (3.4)
Headache	0	0	1 (0.6)	8 (11.0)	9 (2.5)
Hypotension	0	1 (1.6)	5 (2.9)	3 (4.1)	9 (2.5)
Pulmonary oedema	1 (2.1)	4 (6.3)	3 (1.8)	1 (1.4)	9 (2.5)
Wheezing	0	7 (10.9)	1 (0.6)	0	8 (2.3)
Diarrhoea	0	0	5 (2.9)	3 (4.1)	8 (2.3)
Muscle spasms	0	0	1 (0.6)	6 (8.2)	7 (2.0)
Stridor	0	4 (6.3)	3 (1.8)	0	7 (2.0)
Hypoalbuminaemia	0	1 (1.6)	4 (2.3)	1 (1.4)	6 (1.7)
Hypophosphataemia	0	1 (1.6)	2 (1.2)	2 (2.7)	5 (1.4)
Oliguria	0	3 (4.7)	1 (0.6)	1 (1.4)	5 (1.4)
Abdominal pain	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Hepatic enzyme increased	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Hypertension	0	2 (3.1)	2 (1.2)	0	4 (1.1)
Hypervolaemia	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Hypoxia	0	0	1 (0.6)	3 (4.1)	4 (1.1)
Insomnia	0	1 (1.6)	2 (1.2)	1 (1.4)	4 (1.1)
Oedema peripheral	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Pain in extremity	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Periorbital oedema	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Rash	0	1 (1.6)	3 (1.8)	0	4 (1.1)
Tachycardia	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Wound infection	0	0	4 (2.3)	0	4 (1.1)

Definitions: TEAE = Treatment-Emergent Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities

Laboratory findings and vital signs

There were no clinically meaningful findings regarding hematology or chemistry lab values, and as with the adverse events, there was no placebo group for comparison. It was difficult to assess a trend in mean LFT parameters due to no comparative placebo population for each age category and physiologic differences across pediatric age categories. There were no identifiable trends in vital sign abnormalities.

Foreign Marketing Experience

Dr. Spaulding performed an extensive review of the ex-U.S. post-marketing safety data submitted by the Applicant. Use of IV APAP appears to show a similar pattern of adverse

events compared to oral APAP; the drug has the potential to increase hepatic adverse outcomes when used in "high risk" conditions (alcoholic disease, and prior and current liver dysfunction) at therapeutic doses and when given in excess of the recommended dose (accidental overdose). Overall, IV APAP accidental overdoses were more prevalent in the pediatric population compared to adults. In the majority of the pediatric accidental overdose cases the most common adverse sequelae involved LFT elevations. In the severe overdose cases a hepatotoxic picture was observed requiring anecdotal (n-acetyl-cysteine) treatment in some cases.

Safety summary
No new safety signals in adults or pediatric patients were detected for IV APAP upon review of the data presented in this submission. Hepatotoxicity and accidental overdose continue to be the most serious potential adverse events.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held regarding this application, however in June, 2009, a joint advisory committee meeting of the Drug Safety and Risk Management Advisory Committee, the Agency's Nonprescription Drugs Advisory Committee and the Anesthetic and Life Support Drugs Advisory Committee was convened by the Agency to discuss safety issues related to the use of acetaminophen. The consensus of the meeting was that preventing and decreasing the misuse and overdose of acetaminophen is critical.

Recommendations put forth included:

- Decrease the maximum total daily dose of APAP in non-prescription single ingredient and combination products to less than 4 grams/day
- Decrease the maximum non-prescription single adult dose of APAP to 650 mg
- Require a boxed warning for prescription APAP combination products
- Unbundle prescription APAP narcotic combination products
- Provide label dosing directions for pediatric patients < 2 years of age
- Limit the non-prescription APAP liquid suspension to a single concentration

10. Pediatrics

As per agreement between the Division and the Applicant, the pediatric study requirements for the NDA included cross-study comparison of relative bioavailability between pediatric and adult populations, the use of relative pharmacokinetic profiles to bridge adult efficacy to the pediatric population, and pediatric safety data as basis of approval for pediatric indications. The Applicant submitted pharmacokinetic and safety data for the pediatric population that is sufficient to establish dosing for premature neonates through patients aged 17 years, and has therefore fulfilled their requirements for studies under the Pediatric Research Equity Act (PREA).

The pediatric studies submitted with the NDA fulfilled two of the study requirements put forth in the Written Request issued August 24, 2007. At a meeting between the Division and the Pediatric Research Committee (PeRC), it was determined that the studies submitted in the NDA could also serve to fulfill the requirements of the WR, and could be reviewed on a

"rolling" basis. One study specified in the WR has not been submitted as of yet, and will be reviewed upon submission of the final study report to the Agency.

Refer to Section 12 below for the dosing regimen in pediatric patients.

11. Other Relevant Regulatory Issues

DSI inspections
The inspections of four investigators (Drs. Reynolds, Wininger, Daniels and Miller) did not find regulatory violations. The inspection of Dr. Jahr found minor violations. Data from all sites appear acceptable in support of the proposed indications.

12. Labeling

DMEPA has reviewed three proprietary names proposed by the Applicant (Acetavance, (b) (4)). Aectavance was rejected based on promotional concerns, and the other two were rejected based on the potential for medical errors.

DMEPA has also reviewed the label and provided comments regarding vulnerabilities in the label that could lead to medication errors. These include the proposed packaging configuration, wording in the Dosage and Administration Section, and the presentation of the name and strength on the container and carton labeling.

Pregnancy and Lactation Labeling
A consult was sent to the Maternal Health Team in order to assess the Applicant's proposed Pregnancy Category (b) (4) which the Applicant based on historical use of APAP in pregnant women; however they provided insufficient data or literature in support. As a result, the Division has requested an adequately performed comprehensive literature review to support the proposed Pregnancy Category in the product label.

According to the Maternal Health Team (MHT), the application does not provide adequate human and/or animal data sources and analysis to support the requested pregnancy category (b) (4)

(b) (4)

MHT notes that in a review of …"the Reprotox and TERIS entries (through Micromedex) for acetaminophen and a PubMED search they found many published studies that evaluate potential associations between acetaminophen use during various trimesters of pregnancy and fetal and infant outcomes including congenital malformations overall, specific malformations (e.g. gastroschisis or cardiac anomalies), and incidence of asthma in children born to mothers who used acetaminophen during pregnancy. Similarly, LactMed and PubMed are resources

you can use to identify published data on levels of acetaminophen in breast milk and actual or calculated infant daily doses of acetaminophen through breast milk."

The proposed dosing regimen is as follows and has been found acceptable:

Adults and adolescents weighing 50 kg and over:

- 650 to 1000 mg every 4 to 6 hours e.g. 1000 mg q6h or 650 mg q4h to a maximum of 4000 mg in 24 hours. Minimum dosing interval of 4 hours.

Adults and adolescents weighing under 50 kg and all children:

- 12.5 to 15 mg/kg every 4 to 6 hours e.g. 15 mg/kg q6h or 12.5 mg/kg q4h to a maximum of 75 mg/kg in 24 hours. Minimum dosing interval of 4 hours.

(b) (4)

[redacted]

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response

- Risk Benefit Assessment

The clinical studies submitted in this application successfully demonstrated the efficacy and safety of IV APAP for the treatment of acute pain and fever in hospitalized adults and children. Efficacy for the analgesic indication in adults was based on two studies that showed 1000mg of IV APAP given every 6 hours and 650mg given every 4 hours was effective for the treatment of pain in two post operative pain models compared to placebo, in patients receiving IV Morphine sulfate as rescue medication. Efficacy for the antipyretic indication in adults was demonstrated in one adequate and well controlled study using an endotoxin based fever model. Pediatric efficacy for both indications was based on cross-study comparison of relative bioavailability between pediatric and adult populations, and the use of relative pharmacokinetic profiles to bridge adult efficacy to the pediatric population.

The safety of IV APAP in adults and children was demonstrated in the safety database submitted in this application as well as post-marketing data from outside the United States for this formulation. Extensive review of all data revealed no new or unexpected safety signals. Hepatotoxicity, in healthy patients receiving more than the labeled maximum dose

and in patients predisposed to liver toxicity when receiving the labeled dose, and unintended overdose remain serious and concerning adverse events associated with this product. However, these risks can be mitigated by appropriate product labeling.

Based on the risk benefit balance for IV APAP, this product is approvable. Although effective and safe in clinical trials, the current manufacturing problems at the drug manufacturing site preclude approval at this time. As a consequence, I recommend this application receive a Complete Response.

Recommendation for Postmarketing Risk Management Activities

The product label appears sufficient to manage the potential risks of this product. Should new safety information become available, additional risk management activities may be considered.

- Recommendation for other Postmarketing Study Commitments

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	Ofirmev (acetaminophen for injection)

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/s/

ELLEN W FIELDS
02/09/2010

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Addendum to Clinical Review (Safety)

NDAs #:	**022-450**
Drug Name (generic):	**Intravenous acetaminophen**
Sponsor:	**Cadence**
Indication:	**Relief of acute pain and fever**
Type of Submission:	**NDA**
Date of Review:	**October 26, 2009**
Reviewer:	**Jacqueline A. Spaulding, M.D.**
Project Managers:	**Ramani Sista and Sharon Rinehardt-Turner**

This document will serve to update the Clinical Review of NDA 22-450, IV acetaminophen, regarding additions to the adult clinical studies table and a description of a protocol violation.

Table 1 is a corrected tabulation of all studies submitted to the NDA.

Table 1: Overview of Clinical Studies of IV Acetaminophen in Adults

Protocol	Phase	Population	Indication	Study Design	Single (S) Repeated (R) dose/ Duration	IV APAP	Control	Total
116-01-03	1	Healthy males	N/A	Randomized, O/L, 2 way, crossover PK, safety	S/6h	21	PO APAP n=22	22
98051C-CIS	1	Healthy males	N/A	Randomized, O/L, 3 way, crossover PK, safety	S/6h	26	IV PPA n=25	27
CPI-APA-101	1	Healthy males	N/A	Randomized, O/L, 4 way, crossover PK, safety	R/48h	34	PO APAP n=36	38
CPI-APF-302	3	Healthy males	Fever	Randomized, ,DB, PC, endotoxin-induced fever, efficacy, safety	S/6h	31	Placebo n=29	60
CPI-APF-303	3	Healthy males	Fever	Randomized, DB, PC, endotoxin-induced fever, efficacy, safety	S/6h	54	PO APAP N=51	105
CPI-APA-301	3	Inpatient	Pain	Randomized, DB, PC, abdominal gynecological surgery, efficacy, safety	R/48h	166	Placebo N=165	331
CPI-	3	Inpatient	Pain	Randomized, DB, PC,	R/24h	134	Placebo	244

APA-304				abdominal laparoscopic surgery, efficacy safety			N=110	
Protocol	**Phase**	**Population**	**Indication**	**Study Design**	**Single (S) Repeated (R) dose/ Duration**	**IV APAP**	**Control**	**Total**
CN 145-004	3	Outpatient	Pain	Randomized, DB, PC, 3rd molar extraction, efficacy, safety	S/6h	264	Placebo N=33	297
RC 210 3 001	3	Outpatient	Pain	Randomized, DB, PC, hip arthroplasty, PK efficacy, safety	S/6h	51	IV PPA n=51 Placebo N=50	152
136-01-03	3	Inpatient	Pain	Randomized, DB, PC & AC, hip arthroplasty, PK, efficacy, safety	S/6h	35	Placebo N=34	69
RC 210 3 002	3	Inpatient	Pain	Randomized, DB, PC, hip or knee arthroplasty, efficacy, safety	R/24h	49	IV PPA N=50 Placebo N=52	151
136-02-03	3	Inpatient	Pain	Randomized, DB, PC hip arthroplasty, efficacy, safety	R/24h	30	Placebo N=31	61
136-03-03	3	Inpatient	Pain	Randomized, DB, PC, vaginal hysterectomy, efficacy, safety	R/24h	23	Placebo N=21	44
CPI-APA-351	3	Inpatient	Pain/ Fever	Randomized, O/L, AC, safety	R/5days	183	SRX N=30	213

Study CN 145-004 and Study CPI-APA-351 were inadvertently omitted from the table during my initial review.

Protocol Violation

On 6 November 2009 an information request was sent to the Applicant regarding Patient 001-02 in Study CPI-APA-351 at Site #001. This patient had pretreatment liver function tests that were elevated and continued to increase through day 5 of IV acetaminophen administration as displayed in Table 80 that follows:

Table 80: Patient 001-02, Study CPI-APA-351, LFT Assessments

Value (X ULN)	T0/Day 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8
ALT	81 (1.5)	48 (0.9)	39 (0.7)	83 (1.5)	134 (2.4)	208 (3.8)	102 (1.9)
AST	310 (6.9)	262 (5.8)	253 (5.6)	361 (8.0)	456 (10.1)	670 (14.9)	238 (5.3)
TBL	0.9 (0.6)	0.8 (0.5)	0.8 (0.5)	2.3 (1.5)	2.6 (1.7)	3.9 (2.6)	1.4 (0.9)
ALP	87 (0.6)	71 (0.5)	74 (0.5)	267 (1.8)	264 (1.8)	320 (2.2)	252 (1.7)

Definitions: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = alanine or aspartate transaminase; TBL = total bilirubin.

Source: CSR CPI-APA-351, Section 16.2, Listing 16.2.1.21.4

This patient met Exclusion Criterion #4 for Study CPI-APA-351. The complete list of exclusion criteria for this study follow:

1. Had a significant medical disease, laboratory abnormality or condition that, in the Investigator's judgment, could have compromised the Subject's welfare or otherwise contraindicate study participation

2. Was expected to have difficulty in communicating with the study staff or completing study requirements (including follow up visits)

3. Had known hypersensitivity to acetaminophen or the inactive ingredients (excipients) of IV acetaminophen or any contraindication to receiving acetaminophen

4. Had impaired liver function, *eg*, alanine aminotransferase (ALT) greater than or equal to three times the upper limit of normal (ULN), bilirubin greater than or equal to three times ULN, known active hepatic disease (*eg*, hepatitis), evidence of clinically significant chronic liver disease or other condition affecting the liver (*eg*, alcoholism as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, cirrhosis or chronic hepatitis)

5. Had participated in an interventional clinical study (investigational or marketed product) within 30 days of study entry

After further review of the above information, the Division queried the Applicant as to why this patient did not represent a protocol violation. The specific questions were:

1. Provide rationale as to why Patient 001-02 was allowed to proceed on study treatment as well as continue treatment until day five of IV APAP administration.

2. Provide rationale as to why inclusion of Patient 001-02 into the study and his continuing on study drug treatment despite LFT abnormalities was not reported as a protocol violation.

On 23 November 2009, the Applicant responded as follows.

As described in SN 0009, this subject was a 39-year-old male with no prior medical history of liver disease who underwent an extensive spinal reconstructive surgery for a mid-thoracic fracture-dislocation secondary to ankylosing spondylitis and received numerous blood product transfusions. The Investigator enrolled the subject based upon his interpretation of Exclusion criterion #4 that the predominantly AST elevation combined with a low level ALT elevation could reasonably be inferred as being due to muscular trauma from the surgery and/or multiple transfusions and not the result of an active liver process. A waiver was not requested by the Investigator at the time of enrollment and Cadence agrees with the Investigator's interpretation of eligibility. As the subject's baseline AST value was already (>5 X ULN), the early termination provision in Section 3.4.3 of the protocol did not apply. Cadence applied a significant (>2 X baseline value) change in the baseline value as an alternate criterion in such situations. ALT and AST values were > 2X baseline from the day 5 laboratory collection; however the Investigator did not feel that these values met the criteria for an SAE, nor did he discontinue the subjects from treatment or request a waiver. In retrospect, Cadence agrees that a protocol deviation occurred on Day 5. Note, however, that by the time Cadence became aware of the Day 5 values, the subjects had already been terminated from study participation.

Reviewer Recommendation:

The addendum to my clinical review does not substantially change the overall impression of the safety profile of intravenous acetaminophen.

Jacqueline A. Spaulding, M.D., Medical Officer

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	ACETAMINOPHEN FOR INJECTION FOR IV USE

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

/s/

JACQUELINE A SPAULDING
01/21/2010

ROBERT B SHIBUYA
01/22/2010
I concur with Dr. Spaulding's review.

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-450
Submission Code	N000
Letter Date	May 13, 2009, June 23, 2009, June 26, 2009
Stamp Date	May 15, 2009, June 23, 2009, June 26, 2009
PDUFA Goal Date	November 13, 2009
Reviewer Name	Christina Fang, M.D., M.P.H.
Review Completion Date	October 17, 2009
Established Name	Acetaminophen IV injection
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Analgesic and antipyretic
Applicant	Cadence Pharmaceuticals, Inc.
Priority Designation	3P
Formulation	IV solution containing acetaminophen (10 mg/mL)
Dosing Regimen	1 g every 6 hours or 650 mg every 4 hours in adults 7.5-15 mg/kg by age and body weight in pediatric
Indication	Acute pain and fever
Intended Population	Hospitalized patients

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1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

IV acetaminophen injection is recommended for a regulatory action of approval based on clinical findings, pending adequate response from the Applicant to address all the non clinical deficiencies.

The recommendation for approval is based on an acceptable benefit/risk ratio according to my review of clinical efficacy data and Dr. Spaulding's review of clinical safety data submitted in NDA 22-450.

The antipyretic efficacy of IV acetaminophen injection for treating fever is supported by positive findings from the fever study (Study CPI-APF-302), which addressed the concerns with durability of treatment effects toward the end of dosing interval, when higher Cmax coupled with earlier Tmax were identified in comparison of relative bioavailability between the IV and oral acetaminophen formulations. The strength of evidence in support of antipyretic efficacy of IV acetaminophen injection was provided through the demonstration of statistically significant treatment differences in primary analyses and clinically meaningful effect sizes of treatment differences in the degrees of temperature reduction and the percentage of patients with temperature reduction to a lower degree.

The analgesic efficacy of IV acetaminophen injection for treating mild to moderate pain is supported by positive findings from the study of post operative pain associated with laparoscopic surgery (Study CPI-APA-304). The strength of evidence for efficacious use of IV acetaminophen injection, given 1 g every 6 hours or 650 mg every 4 hours, was indicated by statistically significant treatment differences in primary analyses and was supported by treatment differences in terms of the end-of-dosing pain measurements upon repeated dosing as basis for the proposed dosing interval. The therapeutic benefit of IV acetaminophen injection for use as supplemental analgesia to opioid treatment in managing moderate to moderately severe pain is supported by the statistically significant treatment differences in primary analyses in Study RC210 3 002 in combination with treatment effects on reduction of morphine consumption and on pain reduction adjusted for the use of morphine over 24 hours.

The use of IV acetaminophen at recommended dosage is considered reasonably safe based on the lack of new safety signals or unexpected events in clinical trial database, the known safety profile of the acetaminophen moiety, and the anticipated short-term use of the IV formulation and close safety monitoring in a hospital setting.

The Applicant should provide information on Perfalgan® with regard to its quantitative composition and drug product specification in comparison to the IV formulation of acetaminophen under NDA review. The information will help to determine the adequacy of safety exposure in neonates (b) (4) .

1.2 Risk Benefit Analysis

The benefits of treating fever with IV acetaminophen have been shown in terms of clinically meaningful treatment differences from placebo in the degree of temperature reduction and the percentage of patients with temperature reduction to a lower degree.

In comparison to placebo, treatment with IV acetaminophen 1 g resulted in statistically significant and clinically meaningful treatment difference in weighted sum of temperature reduction over six hours (equivalent to an hourly average temperature reduction of 0.6ºC or 1.1ºF more than placebo), 0.8°F to 1.3°F more temperature

reduction than placebo in the time interval of 40 minutes to 5.5 hours, and 32% more subjects with temperature reduced to <38ºC (100.4ºF) than placebo.

The benefits of using IV acetaminophen injection of 1 g q6 hours or 650 mg q4 hours in treating mild to moderate pain have been shown in terms of statistically significant treatment differences from placebo in 24-hour cumulative pain reduction and clinically noticeable effect sizes of treatment differences in pain scores measuring pain relief and pain reduction upon repeated dosing, including pain scores measured at end-of-dosing time points.

The benefits of using IV acetaminophen injection in supplementing opioid analgesia for treating moderate to moderately severe post surgical pain have been shown in reduction of morphine consumption (38 mg morphine in the IV acetaminophen group versus 57 mg morphine in the placebo group over 24 hours) and reduction of pain. Although IV acetaminophen alone is not expected of capable of treating post-operative pain that is severe in nature, it is considered therapeutically beneficial in use as a supplement to opioid treatment in patients who might not be able to use larger doses of opioid analgesics.

In evaluation of safety data collected from hospitalized patients, acetaminophen-induced toxicities might overlap with clinical abnormalities associated with surgical complications, concurrent illness, and concomitant medication, making it a challenge to assess the causal relationship between the study drug and adverse events.

Safety data were pooled from 14 adult clinical studies in 1020 subjects exposed to IV acetaminophen for up to 30 doses or 5.4 days. One adult PK formulation study (CPI-APA-103) in 26 healthy subjects had no safety data collected or reported (request for explanation is sent to the Applicant). In the pooled safety database the median exposure was four doses or one day of treatment. The longest exposure was about five days in 132 patients and 67 of them were exposed to 1 g q6 hours and 65 to 650 mg q4 hours (refer to Table 4.2 on page 109 of the study report) in Study CPI-APA-351, which was the only adult study with more than three days of actual exposure. According to Dr. Spaulding's safety review there were no IV acetaminophen treatment-related deaths and basically no treatment differences between IV acetaminophen and placebo in the incidences of serious AEs (5.6% versus 5.7%), AE-related dropouts (3% versus 4%), and total AEs (69% versus 71%). The most common AEs reported in ≥5% subjects exposed to IV acetaminophen at rates greater than that of placebo included nausea, vomiting, headache, and insomnia. There were no new safety signals or unexpected adverse events identified in the adult studies.

Safety data were pooled from five pediatric clinical studies in 355 subjects (47 neonates, 64 infants, 171 children, and 73 adolescents), including 305 treated with the IV acetaminophen under NDA review and 50 (43 neonates and 7 infants) treated with Perfalgan® in the population PK study by Palmer et. al. The longest exposure was about five days in 61 pediatric patients (1 neonate, 5 infants, 26 children, and 33 adolescents) and more than six days in four pediatric patients (refer to Listing 16.2.1.15 of the study report) in Study CPI-APA-352, which was the only pediatric study with more than two days of exposure. Neonates appeared to be the subpopulation with the least exposure to the proposed formulation of IV acetaminophen (exposure in four neonates with the longest exposure of about 5 days in one of the four neonates). Based on pooled safety data from the five studies there were no reports of deaths and 30 (8.5%) reports of serious AEs, which were not considered as caused by acetaminophen treatment according to Dr. Spaulding's safety review. AE-related dropouts occurred in five cases (1.4%), all due to elevation of liver function parameters that might be related to multiple contributing factors. The most common AEs reported in ≥ 5% pediatric subjects exposed to IV acetaminophen were nausea, vomiting, constipation, pruritus, agitation and atelectasis. There were no new safety signals or unexpected adverse events identified in the pediatric studies.

The most important safety concern with the use of IV acetaminophen is the potential risks for hepatic toxicities associated with much higher peak exposures (72 to 88% higher Cmax after a single 1 g dose, 53% higher Cmax after q6 hour repeated dosing and 97% higher Cmax after q4 hour repeated dosing of 1 g IV acetaminophen)

compared to that of oral formulation, in the subpopulation of hospitalized patients with increased risks to drug-induced liver toxicities due to volume depletion, concurrent illness, multiple treatments, and hepatic and/or renal impairments. In adult clinical studies of IV acetaminophen the overall incidence of hepatic AEs (4.4% of subjects on IV acetaminophen and 5.7% on placebo) and the type of AEs were similar between the two treatment groups based on pooled data across studies. There were four cases (0.4%) of serious hepatic AEs and six dropout cases (0.6%), including two of the cases classified as serious AEs, all due to hepatic AEs in the IV acetaminophen group whereas none was reported in the placebo group. All eight cases had various combinations of hepatic enzyme elevations and normal total bilirubin. According to Dr. Spaulding's safety assessments two cases in the adult database had laboratory abnormality meeting the criteria for Hy's Law (concurrent elevation in AST/ALT > 3x ULN with total bilirubin > 2x ULN) and one of the two had shock induced multi-organ failure contributing to the lab abnormalities.

In pediatric clinical studies of IV acetaminophen (none had a placebo control) the overall incidence of hepatic AEs was 3.9% (14 reported in 355 pediatric patients). There were four cases (1.1%) of serious hepatic AEs and five dropout cases (1.4%) due to hepatic AEs. Hepatic abnormalities in all nine cases involved liver enzyme elevations and normal total bilirubin, and were judged to be possibly related to acetaminophen treatment. No cases in the pediatric database were identified based on the criteria of Hy's Law based on Dr. Spaulding's safety review.

Unintentional overdose from co-administration of IV acetaminophen and combination products containing acetaminophen is another major safety concern. Because acetaminophen alone is not capable of treating surgical pain that is severe in nature (pain associated with major surgical procedures), there is a strong need for opioid analgesics, which have been commonly prescribed as opioid/acetaminophen combination agents. For example, accidental overdose was reported in 18 (1.2%) patients, five (0.5%) in the IV acetaminophen group and 13 (2.5%) in the placebo group in the adult clinical studies of IV acetaminophen (refer to page 64 of the Summary of Clinical Safety of the NDA submission). The accidental overdose in these cases was characterized by co-administration of acetaminophen/opioid combination oral formulations for break-though pain. Not all cases had the total daily dose of acetaminophen exceeding 4 g and none of the cases was associated with an adverse event or LFT elevation. The more than 1% incidence of occurrence in a tightly controlled clinical trial setting predicts a higher risk of potential overdose once the drug is available on the market.

In general, the use of IV acetaminophen in a hospital setting is considered reasonably safe as supported by the safety findings from clinical studies with the consideration of known safety profile of acetaminophen established from extensive clinical studies and the OTC marketing experience in the U.S. for many years. The duration of use is anticipated to be limited to two to three days when IV access is still available. Close monitoring of the amount of IV infusion and safety monitoring of adverse events and laboratory abnormalities with the use of IV acetaminophen are expected to be available around the clock in a hospital setting. Warnings in the product labeling about the use of IV acetaminophen in patients at high risks for liver toxicities and about the concomitant administration of other acetaminophen containing drug products should help to reduce the risks.

The benefit/risk ratio is considered acceptable in my opinion.

1.3 Recommendations for Postmarketing Risk Management Activities

None.

1.4 Recommendation for other Postmarketing Study Commitments

None.

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

IV acetaminophen injection (IV APAP) is an IV formulation containing 1000 mg acetaminophen in 100 mL solution (10 mg/mL) for the management of acute pain and fever.

The established name of the product is acetaminophen IV injection and the proposed trade names Acetavance™ (b) (4) were not considered acceptable by DMEPA. The review of the newly submitted trade names is still pending. The active ingredient of the product, acetaminophen is the acetate amide of p-aminophenol. The proposed dosage for acetaminophen IV injection is 1000 mg q6 hour or 650 mg q4 hours up to a maximum daily dose of 4000 mg in *adults and adolescents weighing ≥ 50 kg*; 15 mg/kg q6 hours or 12.5 mg/kg q4 hours up to a maximum daily dose of 75 mg/kg in *adults and adolescents weighing <50 kg as well as in children age ≥2 to 12 years old*; (b) (4) as summarized in the table below.

Table 2.1-1 Dosage by Age Group

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

(b) (4)

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

Non parenteral formulations of acetaminophen and a number of drugs of the NSAID class are currently available for treating fever and mild to moderate pain. IV formulation of ketorolac and ibuprofen are available for treating mild to moderate pain and IV ibuprofen is available for treating fever in the U.S.

2.3 Availability of Proposed Active Ingredient in the United States

There are many acetaminophen containing products currently available in the United States. The information on these products is summarized in the table below by the active ingredient, dosage form and route of administration, strength of formulation, and NDA number of the reference list product (RLD) of the formulation.

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

Active ingredient	Dosage Form; Route	Strength	RLD, NDA#
Rx			
Acetaminophen; aspirin; codeine phosphate	Capsule; oral	150mg;180mg;30mg	081096
Acetaminophen;	Capsule; oral	650mg;50mg	088831

Active ingredient	Dosage Form; Route	Strength	RLD, NDA#
butalbital	Tablet; oral	650mg;50mg 325mg;50mg	089988 087811
Acetaminophen; butalbital; caffeine	Capsule; oral	500mg;50mg;40mg 325mg;50mg;40mg	040085 089007
	Solution; oral	325mg/15ml;50mg/15ml;40mg/15ml	040387
	Tablet; oral	750mg;50mg;40mg 500mg;50mg;40mg 325mg;50mg;40mg	040496 089451 088616
Acetaminophen; butalbital; caffeine; codeine phosphate	Capsule; oral	325mg;50mg;40mg;30mg	020232
Acetaminophen; caffeine; dihydrocodeine bitartrate	Capsule; oral	356.4mg;30mg;16mg	040109
	Tablet; oral	712.8mg;60mg;32mg	040316
Acetaminophen; codeine phosphate	Solution; oral	120mg/5ml;12mg/5ml	085861
	Suspension; oral	120mg/5ml;12mg/5ml	086024
	Tablet; oral	650mg;60mg 650mg;30mg 300mg;60mg 300mg;30mg 300mg;15mg	089363 089231 088629 085055 040223
Acetaminophen; hydrocodone bitartrate	Capsule; oral	500mg;5mg	Not RLD
	Solution; oral	500mg/15ml;10mg/15ml 500mg/15ml;7.5mg/15ml 325mg/15ml;10mg/15ml 325mg/15ml;7.5mg/15ml	040508 081051 040834 040482
	Tablet; oral	750mg;10mg 750mg;7.5mg 660mg;10mg 650mg;10mg 650mg;7.5mg 500mg;10mg 500mg;7.5mg 500mg;5mg 500mg;2.5mg 400mg;10mg 400mg;7.5mg 400mg;5mg 325mg;10mg 325mg;7.5mg 325mg;5mg 300mg;10mg 300mg;7.5mg 300mg;5mg no	040094 089736 040084 081223 089689 040100 089699 088058 089698 040288 040288 040288 040148 040148 040099 040556 040556 Not RLD
Acetaminophen; oxycodone hydrochloride	Capsule; oral	500mg;5mg	088790
	Solution; oral	325mg/5ml;5mg/5ml	089351
	Tablet; oral	650mg;10mg 500mg;10mg 500mg;7.5mg 500mg;5mg 400mg;10mg 400mg;7.5mg 400mg;5mg 400mg;2.5mg 325mg;10mg 325mg;7.5mg 325mg;5mg 325mg;2.5mg	040341 Not RLD 040341 089775 040692 040698 040687 040679 040434 040434 040330 040330

Active ingredient	Dosage Form; Route	Strength	RLD, NDA#
		300mg;10mg 300mg;7.5mg 300mg;5mg 300mg;2.5mg	040608 040608 040608 040608
Acetaminophen; pentazocine hydrochloride	Tablet; oral	650MG;EQ 25MG BASE	018458
Acetaminophen; propoxyphene hydrochloride	Tablet; oral	650MG;100MG 500MG;100MG 325MG;100MG 325MG;50MG	017122 Not RLD Not RLD Not RLD
Acetaminophen; tramadol hydrochloride	Tablet; oral	325MG;37.5MG	021123
OTC			
Acetaminophen	Suppository; rectal	650mg 325mg, 120mg, 80mg	018337 Not RLDs
	Tablet (caplet), ER; oral	650mg	019872
	Tablet (geltab), ER; oral	650mg	019872
Acetaminophen; aspirin; caffeine	Tablet; oral	250mg;250mg;65mg	020802
Acetaminophen; clemastine fumarate; pseudoephedrine hydrochloride	Tablet; oral	500mg;eq 0.25mg base;30mg	021082
Acetaminophen; dexbrompheniramine maleate; pseudoephedrine sulfate	Tablet, ER; oral	500mg;3mg;60mg	019453

Source: Orange book, 2009 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.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

The initial IND was submitted on May 21, 1999 with a general investigational plan of conducting a few clinical studies of IV acetaminophen and using propacetamol data to support IV acetaminophen application. In terms of the type of pain to be studied the recommendations from the Division included studying non dental post operative pain models to provide replicable results (minutes for the meeting on April 30, 2003), exploring wider pain populations for potential use and choosing the pain models where IV APAP could be studied alone and studied with concomitant use of opioids (minutes for the meeting on July 16, 2003). In terms of the duration of the study the Division's recommendation was at least 24 to 48 hours of pain evaluation (minutes for the meeting on August 14, 2006). In terms of the use of morphine the Division cautioned about not to under dose morphine, commented on that the reduction of morphine use should be coupled with improved efficacy (minutes for the meeting on April 30, 2003). In terms of generating data to support proposed dosing interval the Division recommended collection of more efficacy data points during the multiple-dose period in Study 3-002 (medical review of the initial IND submitted on May 21, 1999), pointed out that data on median time to rescue in Study 3-002 did not appear to support every 6-hour dosing interval (minutes for the meeting on April 30, 2003), recommended evaluation of end-of-dosing pain (minutes for the meeting on August 14, 2006), and requested data analyses to include time to rescue and percentage of patients taking rescue in 24 hours (letter to the Sponsor dated July 21, 2008). In terms of the choice of efficacy endpoints the early recommendation on single-dose study was the 5-parameter summary of PR, PID, PRID, onset, and duration (minutes for the meeting on

September 20, 2000), patient global evaluation was not considered acceptable and multiple-dose endpoints should be designed based on questions to be answered (minutes for the meeting on April 30, 2003).

In terms of statistical analysis plan the Sponsor was advised of including all patients having received treatments regardless post dosing assessment status in ITT population for analysis and using various methods in missing data imputation (letter to the Sponsor dated April 9, 2007) and discussed potential issues in data analysis due to randomization allocation error (letter to the Sponsor dated November 20, 2008).

In terms of fever study requirement the original recommendation was multiple-dose study on an inpatient setting (minutes for the meeting on August 14, 2006). The Sponsor's later proposal on studying endotoxin induced fever was accepted by the Division (letter to the Sponsor dated January 29, 2007).

In terms of safety issues the major concerns were the repeated exposure of relatively high Cmax of IV acetaminophen (compared to that of oral formulation) in hospitalized patients who might be volume depleted and hemodynamically compromised, especially in the debilitated elderly population, the higher exposure associated with 4-hour dosing interval of 1 g dose, and higher percentage of cases of liver enzyme elevation than the placebo group in Study 3-002 (minutes for the meeting on November 14, 2003). The safety information requested included identifying risks in the target population and in high risk population for liver toxicities (minutes for the meeting on November 14, 2003); studying effects of drug with the conditions of fasting and hemodynamic instability (minutes for the meeting on April 30, 2003); summarizing hepatic AEs with the use of IV acetaminophen in controlled studies and from foreign post marketing experience (letter dated December 1, 2004); reporting liver safety data from the use of paracetamol, including information on the use of paracetamol in patients with hepatic impairment and/or history of alcohol abuse (minutes for the meeting on September 20, 2000). In terms of safety exposure the requirements had been the duration and the number of subjects specified in the ICH guideline (any exposure in 1500 subjects with 300 exposed for 24 hours and 100 exposed for proposed duration of use) (minutes for the meeting on September 20, 2000); 300 subjects exposed at the maximum dose (minutes for the meeting on April 30, 2003); repeated dosing at regular intervals for at least a week in 300 subjects (minutes for the meeting on November 14, 2003). The final requirement on safety database was 300 subjects with 50 exposed for 5 days (minutes for the meeting on August 14, 2006). In terms of particulates detected in the placebo injection the Sponsor terminated all the studies involved as reported by DSI (memo filed on August 17, 2004).

In terms of the pediatric study requirements the Division agreed with the Sponsor's proposal on cross-study comparison of relative bioavailability between pediatric and adult populations (letter dated January 29, 2007), the use of relative PK profiles to bridge adult efficacy to pediatric population in addition to pediatric safety data as basis of approval for pediatric indications, and treating data required for PWR and data required for pediatric approval separately (letter dated July 21, 2008).

2.6 Other Relevant Background Information

IV formulation of acetaminophen developed by Bristol-Myers Squibb (BMS) was first approved as Perfalgan® in France in 2001 and had been approved in approximately 80 countries to date.

Perfalgan® might have different quantitative composition, drug product specification, and impurity content (information not provided by the Applicant) from those of the IV acetaminophen formulation used in the current NDA. One population PK study of mostly neonates used Perfalgan®. Safety data from the study of Perfalgan® were pooled with the other pediatric studies in the Applicant's Integrated Safety Summary.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

There were some minor inconsistencies between different parts of the submission. (b) (4) Because the missing information was minor and not considered to change the study outcomes, additional analyses were not requested. The quality of the submission in terms of data organization, retrieval, and completeness was considered acceptable in general.

3.2 Compliance with Good Clinical Practices

The steps to ensure compliance with Good Clinical Practices (GCP) included approval of protocols and informed consent forms by the Institutional Review Boards (IRBs) before the initiation of the study, verification of the original copies of consent forms, checking consistency between CFR data and source documents, monitoring the receipt, storage, dispensing and return of clinical study drugs, etc. A quality assurance system was established in accordance with the current regulations and Good Clinical Practice to conduct study center audit by qualified personnel, to ensure independent and double data entry followed by manual edits and detailed computer-based checks, and to conduct systematic review of the entire database.

Rates of major protocol deviations were relatively low (11% in Study 3-002 and 4% in Study A-304) and of minor protocol deviations were higher (47% in Study 3-002 and 65% in study A-304). About 25% subjects had protocol deviations in the fever study (F-302). The protocol deviations were not considered as having a major differential impact on study outcomes (refer to the individual study review in section 5.3 for detail).

Five clinical sites lead by the Investigators Dr. Jonathan Jahr (Study 3-002), Dr. Lowell Reynolds (Study 3-002), Dr. Steven Wininger (Study A-304), Dr. Howard Miller (Study A-304), and Dr. Stephen Daniels (Study F-302), were selected for DSI inspection based on the number of patients enrolled, the percentage of protocol violation/deviations, and the site's influence to the efficacy outcomes.

According to a preliminary review by Dr. Susan Leibenhaut dated October 7, 2009, the inspections of the sites lead by Drs. Reynolds, Wininger, Miller, and Daniels did not find regulatory violations. The inspection of Dr. Jahr found violations not considered significant to impact overall data reliability from the site. Her conclusion was that "the data from all sites appear acceptable in support of the proposed indication.

3.3 Financial Disclosures

The financial disclosure form signed by the Applicant certified that no financial arrangement with the listed clinical investigators (a complete list of all clinical investigators involved in 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

Acetaminophen IV injection is a clear sterile aqueous solution containing 1000 mg acetaminophen in 100 mL solution (10 mg/mL). The solution also contains a number of excipients such as mannitol (b) (4) (b) (4), anhydrous dibasic sodium phosphate (b) (4)), monohydrate cysteine hydrochloride (antioxidant (b) (4) and pH adjusting agents. It is isotonic with blood with pH at about 5.5.

The Applicant had address all deficiencies identified by the chemistry reviewer, agreed to tighter in-house limits for impurities (shelf life acceptance limits for the impurity 4-aminophenol to NMT (b) (4)) and pH (b) (4), and provided risk assessments of the major impurity of safety concerns (4-aminophenol, which is potentially genotoxic). In-process controls, drug product specifications (including identification, assay, impurities, cysteine, cysteine, pH, osmolality, particulate matter and bacterial endotoxins), and container/closure system are all considered acceptable according to the chemistry reviewer, Dr. Martin Haber's review of the original submission and subsequent amendments (refer to Dr. Haber's review for detail). Drug stability at room temperature for (b) (4) was base on 6-month stability data from the U.S. sites and supported by 36-month stability data from the Italian sites.

CMC portion of the application is considered adequate and acceptable to support a market approval of the product by the chemistry review team.

4.2 Clinical Microbiology (if applicable)

The manufacture and (b) (4) sterilization of acetaminophen injection is considered acceptable according to the Microbiology Reviewer Denise Miller (refer to the Microbiology Review for detail).

4.3 Preclinical Pharmacology/Toxicology

There were a number of issues identified per conversation with Dr. Dan Mellon and the review and recommendations from the pharmacology and toxicology review team is still pending.

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 six PK studies, four studies of crossover design in adults and two open label studies in pediatric populations. The four adult PK studies were Studies CPI-APA-101, 116-01-

03, 98051C-CIS, and CPI-APA-103. Study CPI-APA-101 was designed to evaluate relative bioavailability between IV and oral formulations given as acetaminophen 1 g every 4 hours or every 6 hours for 48 hours. Study 116-01-03 was designed to evaluate relative bioavailability between IV and oral formulations after a single dose of acetaminophen 1 g. Study 98051C-CIS was designed to evaluate dose proportionality between IV acetaminophen 500 mg and 1000 mg doses after a single-dose exposure, using IV propacetamol as a comparator. Study CPI-APA-103 was designed to evaluate single-dose relative bioavailability between the formulation used in clinical trial and to-be-marketed formulation. The two pediatric PK studies were Study CPI-APA-102 (48-hour study) and Study EHRC #26095 (study of Perfalgan® conducted by Palmer et. al. in Australia) and served as database for population PK analyses.

Key findings in adult PK studies

In comparison to oral formulation, IV acetaminophen had much higher peak exposures (72 to 88% higher Cmax), earlier time to peak level (about half hour shorter Tmax), and comparable total exposure (AUC) and half life ($t_{1/2}$ of 2-3 hours). The trend persisted at steady state with Cmax being 97% higher than oral APAP on a dosing regimen of 1 g q4 hours and 53% higher on a dosing regimen of 1 g q6 hours, based on findings of PK Study CPI-APA-101. Dose proportionality in Cmax and AUC between IV acetaminophen 500 mg and 1000 mg doses was shown in the single-dose PK Study 98051C-CIS. There were a number of metabolites identified in the urine such as acetaminophen glucuronide (the highest percentage), acetaminophen sulfate (the second highest percentage), and N-acetyl-p-benzoquinone imine (NAPQI, which represents a group of metabolites). Fractional urine excretion of free acetaminophen or its metabolites appeared to be independent of the route of drug administration as demonstrated in Study CPI-APA-101.

Key findings in pediatric studies and their comparison to adult PK profile

Using PK data obtained from Study CPI-APA-102 and the Palmer Study with normalization of dosing regimen by body weight, analyses by population PK model predicted consistency in AUC across age groups (infants, children, adolescents, and adults) after a single-dose exposure and at steady state. Only the neonate group had higher AUC than the other age groups in response to both single and repeated exposure. In comparison of urine metabolites between the age groups the percent of dose excreted in the urine as NAPQI appeared to be comparable among different pediatric age groups in Study CPI-APA-102 and comparable to that of adults. Age and body weight were identified as significant covariates for clearance (CL) and body weight alone as a significant covariate for central and peripheral volume of distribution (Vc and Vp) and for inter-compartmental clearance (Q).

Relationship between acetaminophen metabolites and liver function markers

The levels of liver function markers (AST, ALT, and Bilirubin) were independent of the percent (amount) excreted as NAPQI production (acetaminophen mercapturate, 3'-[S-cysteinyl] acetaminophen, and 3'-S-methylacetaminophen) in both adult and pediatric populations based on the analyses of data obtained from Study CPI-APA-101 and CPI-APA-102.

5. SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

5.1 Tables of Clinical Studies

Table 5.1-1 Overview of Pivotal Efficacy Studies

Study # Phase	Study Design	Sites	Treatments	N	Study Population Demographics	Use of Data	Review section
Analgesic studies in adults							
RC210 3 002 (3-002) Phase 3	Randomized double-blind active- and placebo-controlled	8 US	APAP 1g IV PPA 2g IV Placebo Q6h x 4 (24h evaluation) Rescue IV-PCA MS	49 50 52 T 151	Post orthopedic surgical pain 77 M/ 74 F Mean age 60 yr (range 22-87)	Data reviewed in detail in support of efficacy	5.3.1
CPI-APA-304 (A-304) Phase 3	Randomized double-blind placebo-controlled	17 US	APAP 1g q6h APAP 650 mg q4h Placebo q6 Placebo q4 24h, followed with open label APAP for up to 5d	92 42 43 67 P110 T 244	Post abdominal laparoscopic surgical pain 46 M/ 198 F Mean age 46 yr (range 18-78)	Data reviewed in detail in support of efficacy	5.3.2
Antipyretic study in adults							
CPI-APF-302 (F-302) Phase 3	Randomized double-blind placebo-controlled	1 US	APAP 1g Placebo Single dose	31 29 T 60	Endotoxin-induced fever in healthy male volunteers Mean age 30 yr (range 18-55 yr)	Data reviewed in detail in support of efficacy	5.3.3

Source: Tabular listing of all clinical studies in section 5.2 of the NDA submission and individual study reports.

Table 5.1-2 Overview of Other Efficacy Studies

Study # Phase	Study Design	Sites	Treatments	N	Study Population	Note	Review section
Analgesic studies in adults							
CPI-APA-301 Phase 3	Randomized double-blind placebo-controlled	27 US	APAP 1g IV Placebo Q6h x 8 (48h evaluation) open label with APAP q6 for up to 5d	166 165 T 331	Post abdominal gynecological surgical pain	Outcomes did not support efficacy	5.3.4
RC210 3 001 Phase 3	Randomized double-blind active- and placebo-controlled	1 Denmark	APAP 1g IV PPA 2g IV Placebo Single dose (6h evaluation)	51 51 50 T 152	Dental pain	Outpatient setting for studying pain	5.3.4
CN145-004 Phase 3	Randomized double-blind placebo-controlled	1 Denmark	APAP 1g APAP 2g Placebo Single dose (8h evaluation)	132 132 33 T 297	Dental pain	Outpatient setting for studying pain	5.3.4
136-01-03 Phase 3	Randomized double-blind Placebo-controlled PK/PD	11 US	APAP 1g Placebo Single dose (6h evaluation)	35 34 T 69	Post total hip arthroplastic surgical pain	Early termination due to particulates in placebo injection	5.3.4
136-02-03 Phase 3	Randomized double-blind placebo-controlled	16 US	APAP 1g IV Placebo 4 doses at 0, 4, 10, 16h	30 31 T 61	Post total hip arthroplastic surgical pain	Early termination due to particulates in placebo injection	5.3.4
136-03-03 Phase 3	Randomized double-blind placebo-controlled	14 US	APAP 1g IV Placebo 4 doses at 0, 4, 10, 16h	23 21 T 44	Post vaginal hysterectomy surgical pain	Early termination due to particulates in placebo injection	5.3.4
CPI-APA-351 Phase 3	Randomized open label,	15 US	APAP 1g APAP 650mg	92 91	Acute pain and fever	Open label study	5.3.4

Study # Phase	Study Design	Sites	Treatments	N	Study Population	Note	Review section
	standard of care controlled		Standard of care x 5 days	30 T 213			
Antipyretic study in adults							
CPI-APF-303 Phase 3	Randomized double-blind active-controlled	1 US	APAP 1g IV APAP 1g oral Single dose	54 51 T 105	Endotoxin-induced fever in healthy male volunteers	Active-controlled	5.3.4
Pediatric studies							
RC210 3 006 Phase 3	Randomized double-blind (non-inferiority) active-controlled	18 France	APAP 1g IV PPA 2g IV Single dose	95 88 T 183	Pediatric inguinal herniorrhaphy	Active-controlled	5.3.4
CN145-001 Phase 3	Randomized, double-blind (non-inferiority) active-controlled	11 France	APAP 1g IV PPA 2g IV Single dose	35 32 T 67	Acute fever of infectious origin Inpatients	Active-controlled	5.3.4
CPI-APA-352 Phase 3	Open label	12 US	APAP; 40-75 mg/kg q4 or 6 h; 30-50 mg/kg q6 or 8 h, neonates IV	100	Pediatric Inpatients	Open label study	5.3.4

Source: Tabular listing of all clinical studies in section 5.2 of the NDA submission and individual study reports.

5.2 Review Strategy

A total of 14 clinical studies submitted in the NDA 22-450 were Phase 3 efficacy and safety studies. Eight studies were conducted by Bristol-Myers Squibb, the original sponsor and six by Cadence. Three studies were identified as the pivotal studies (one study by Bristol-Myers Squibb and two studies by Cadence) based on the study designs and outcomes. Each of the three studies is reviewed in detail. The other efficacy studies are discussed briefly in terms of study designs and major findings.

5.3 Discussion of Individual Studies

5.3.1 Pain Study 3-002

5.3.1.1 Protocol

The study protocol described in Amendment 1 dated August 6, 1999 had major changes from the original protocol dated March 31, 1999. The major changes included the change of type of surgery from lower abdominal surgery to orthopedic surgery, the change of timing of the initial dose of study medication from immediately post operation to the morning of the day following surgery, the change of primary efficacy evaluation from morphine sparing upon multiple dosing to time-specific pain relief over the first six hours after the initial dose. Because the Amendment 1 was submitted before the study initiation date of September 13, 1999, Protocol Amendment 1, instead of the original protocol is presented in the review.

Study RC210 3 002 was planned as a multiple-center, randomized, double-blind, active- and placebo-controlled, parallel, multiple-dose (4 doses in 24 hours), analgesic study of acetaminophen (APAP) 1 g IV infusion in hospitalized patients undergoing orthopedic surgery.

Eligible patients were to have been adult patients undergoing elective unilateral or bilateral, primary or uncomplicated secondary total replacement of hip or knee joint following standard surgical and anesthetic procedures, who had postoperative pain of moderate to severe intensity on the morning of the day post surgery (refer to the complete list of the eligibility criteria attached in the Appendix of the study review).

Eligible patients were planned to be randomized to one of the three treatment groups, acetaminophen 1g, propacetamol (PPA) 2g, and matching placebo, to receive a 15-minute IV infusion of study drug every six hours for a total of four doses in 24 hours.

Post operative IV morphine was planned to be given as 1 mL (1.0 mg) boluses every six minutes up to a total of 25 mg every four hours by PCA and given as 2 mg boluses by IV push if there were additional needs. The use of IV morphine was to have been withheld for baseline assessment until the completion of the initial infusion of study drug and subsequently allowed to be used as rescue analgesics at the same dosing regimen as described above.

Efficacy data to be collected were to have included the measurements of pain intensity (PI) on a 4-point categorical scale and on an 100 mm visual analogue scale (VAS) at baseline, every 15 minutes for up to one hour, hourly for up to 6 hours, and at 18, 20, and 24 hours after the initial dose, measurements of pain relief (PR) on a 5-point categorical scale every 15 minutes for up to one hour and hourly for up to 6 hours, rescue information, and patient global.

The planned primary efficacy endpoint was time-specific measurements of PR during the first six hours after the initial dose. The planned secondary efficacy endpoints for the evaluation of single-dose effects included time-specific PID (categorical scale and VAS), peak pain scores (MAXPR, MAXPID, and MAXPRID) and time to peak scores, summation of pain scores (TOTPAR, SPID, and SPRID), median time to first rescue medication and number and percentage of patients requesting rescue, and patient global evaluation. The planned secondary efficacy endpoints for the 24-hour evaluation of multiple-dose effects included mean PI (categorical scale and VAS), amount of rescue medication (IV morphine per dosing interval and over 24 hours), number of request and actual administrations of rescue medication, median time to first rescue medication, number and percentage of patients requesting rescue medication, mean PI adjusted for the amount of rescue, and patient global evaluation.

Safety monitoring was planned to consist of reports of adverse events (AEs) during the study, where all serious AEs would have been followed until resolution; vital signs at baseline, two hours after the initial dose, and in the morning of Day 2; routine laboratory tests (hematology and chemistry) before surgery and on Day 4 (or at the time of early withdrawal from the study).

Statistical Analysis

Population for analysis

The planned intent-to-treat (ITT) population was to have included all treated patients with at least one dose of study medication.

The planned per protocol analysis population was to have been a subset of the ITT population with no major protocol violations prior to study drug administration. Per protocol analysis was not planned to be performed if there were <5% of major protocol violations.

Efficacy analysis

The planned primary efficacy parameter, time-specific measurements of PR during the first six hours after the initial dose, was to have been analyzed using the analysis of covariance, ANCOVA with treatment and center as fixed effects and baseline PI as covariate.

Missing data management

Missing data were to have been replaced by LOCF for dropouts, taking rescue, or missing 6-hour score, by BOCF for dropouts in the first 15 minutes, and by WOCF for missing score at time of rescue.

Sample size

The planned sample size was 50 patients per treatment group based on an estimated effect size of treatment difference in PR score of 1, mean placebo response of 1.7 at Hour 1, 2, 3, and 4 post-dosing times, and estimated common standard deviation between 1.4 and 1.6, to provide 90% power and 5% level of significance.

Protocol Amendments

There was one additional protocol amendment dated September 27, 1999. The amendment had deletion of the upper age limit of 70 years for inclusion and deletion of the use of anticoagulants as exclusion criteria.

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

Table 5.3.1-1 Reviewer's Summary of the Protocol

Study #	RC210 3 002
Objectives	To study single-dose and multiple-dose analgesic effects, tolerability and safety of IV acetaminophen 1 g, in comparison to placebo and propacetamol 2 g, in patients with postoperative pain following total hip or knee replacement
Design	Multiple-center, randomized, double-blind, active- (propacetamol) and placebo-controlled, parallel, multiple-dose (4 doses in 24 hours)
Sample population	Hospitalized adult patients with post- orthopedic (total hip or knee replacement) surgical pain of moderate to severe intensity in the morning of day after surgery
Treatment	Acetaminophen (APAP) 1 g, propacetamol (PPA) 2 g, or matching placebo 15-minute IV infusion every six hours for a total of four doses in 24 hours
Rescue medication	IV Morphine 1 mg/per 6 minute up to 25 mg/in a 4-hour period by PCA and additional 2 mg by IV push for adequate pain relief (use of morphine as concomitant analgesic treatment)
Efficacy data	PR and PI at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours (single dose) PI at 18, 20, and 24 hours (repeated dose) Rescue: time to 1st request, time to 1st administration, and amount of rescue Patient global
Efficacy parameter	**Primary efficacy endpoint:** time-specific PR during the first six hours after the initial dose **Secondary efficacy endpoints** ***Single dose: measured and derived pain scores*** . Time-specific pain scores: PIDcat, PIDvas, PRID . Peak pain scores: MAXPR, MAXPID, and MAXPRID . Time to peak scores . Summation of pain scores: TOTPAR, SPID, and SPRID over six hours ***Single dose: rescue information*** . Time to first rescue (median, 95% confidence interval) in first six hours . Number and percentage of patients requiring rescue in first six hours. ***Singled dose:*** patient global evaluation ***Repeated dose: derived pain scores*** . Mean PI (MPIcat and MPIvas) over 24 hours (the average of all PI recorded in 24 hours) ***Repeated dose: rescue information*** . Amount of rescue medication per dosing interval and in 24 hours . Number of requested and actual administrations of rescue medication . Time to first rescue over the 24-hr period . Number and percentage of patients requiring rescue medication over the 24-hr period ***Repeated dose: composite endpoint*** . MPI (categorical scale and VAS) adjusted for amount of rescue over the 24-hr period, ***Repeated dose:*** patient global evaluation
Safety monitoring	• Adverse events • Vital signs at baseline, two hours after the initial dose, and in the morning of Day 2; • Routine laboratory tests before surgery and on Day 4 (or at time of early withdrawal)

5.3.1.2 Results

Demographic and other baseline characteristics

The study sample population consisted of 151 patients enrolled who received the study medication, with an age range of 22 to 87 years and a mean of 60 years. Of the 151 patients, 86% were Caucasian, 7% were African American, 5% were Hispanic, and 49% were female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight and with regard to baseline pain intensity. About ¾ of patients had moderate pain and ¼ of patients had severe pain at baseline when PI was measured by a 4-point categorical scale and the mean baseline PI was 2.2 on a categorical scale and 58 mm on a 100 mm VAS scale.

Table 5.3.1-2 Demographics and Baseline Characteristics

Study 3-002 Baseline Characteristics	IV APAP 1g (n=49)	IV PPA 2g (n=50)	Placebo (n=52)	Total (n=151)	p-value
Age (years)					
Mean (SD)	61.7 (16.9)	59.5 (14.2)	59.2 (13.4)	60.1 (14.8)	0.6556
Median	66.0	64.0	61.0	63.0	
Minimum, Maximum	22, 87	25, 82	24, 81	22, 87	
Gender, n (%)					0.288
Male	28 (57.1)	27 (54)	22 (42.3)	77 (51)	
Female	21 (42.9)	23 (46)	30 (57.7)	74 (49)	
Race, n (%)					0.801
Caucasian	42 (85.7)	42 (84)	46 (88.5)	130 (86.1)	
Black	4 (8.2)	3 (6.0)	4 (7.7)	11 (7.3)	
Hispanic	3 (6.1)	3 (6)	1 (1.9)	7 (4.6)	
Other	0	2 (4)	1 (1.9)	3 (2.0)	
Height (cm)					
Mean (SD)	171.8 (10.7)	171.6 (12.8)	168.7 (10.6)	170.7 (11.4)	0.3168
Weight (kg)					
Mean (SD)	85.7 (13.0)	85.7 (18.8)	81 (17.3)	84.1 (16.6)	0.2455
Baseline PI (categorical), n (%)					0.727
Mild	0	0	1 (1.9)	1 (0.7)	
Moderate	36 (73.5)	40 (80.0)	39 (75.0)	115 (76.2)	
Severe	13 (26.5)	10 (20.0)	12 (23.1)	35 (23.2)	
Baseline PI (categorical)	2.27	2.2	2.21	2.23	
Baseline PI (VAS)	62.0 (19.1)	55.7 (17.6)	56.4 (16.9)	58.0 (18.0)	0.156

APAP = acetaminophen; PPA = propacetamol; SD = standard deviation; PI = pain intensity; VAS = Visual Analogue Scale.
Source: Table 11.1 on page 68, Table 14.3.1 on page 118, and Table 11.7 on page of the report for Study 3-002.

Patient disposition

More than 90% of 151 treated patients completed the study. There were 14 cases of dropouts, three from the IV APAP 1 g group, six from the IV PPA 2 g group, and five from the placebo group. The reasons for dropouts included withdrawal of consent in six cases, adverse events in four, lack of compliance in two, not meting eligibility criteria in one, and using APAP to treat fever in one. The number of patient who dropped out was between none and three per treatment group for any particular reason listed as shown in the table below.

Table 5.3.1-3 Patient Disposition

Study 3-002 Patient Disposition	IV APAP 1g (n=49)	IV PPA 2g (n=50)	Placebo (n=52)	Total (n=151)
All Treated Patients				
***Discontinued* n (%)**	3 (6.1)	6 (12.0)	5 (9.6)	14 (9.3)
Reason for discontinuation				
Withdrawal of consent	2 (4.1)	2 (4.0)	2 (3.8)	6 (4.0)
Adverse Event	0	3 (6.0)	1 (1.9)	4 (2.6)
Lack of compliance	1 (2.0)	1 (2.0)	0	2 (1.3)
Not meeting eligibility criteria	0	0	1 (1.9)	1 (0.7)

Other (APAP for treating fever)	0	0	1 (1.9)	1 (0.7)

Source: Table 10.1 on page 66 in Volume 1 and Appendix Table 16.2.1 on pages 478-483 in Volume 4 of the report for Study 3-002.

Protocol violations

There were 11% of patients with a major protocol deviation and 47% with a minor protocol deviation. The most frequent major protocol deviation was the delayed initial dose due to local pain at infusion site, seven cases in the IV PPA 2 g group and one case in the placebo group. The distribution of the type of the protocol deviations was similar between the APAP 1 g and the placebo groups as shown in the table below.

Table 5.3.1-4 Summary of Protocol Deviations

Study 3-002 **Protocol deviations**	**IV APAP 1g (n=51)**	**IV PPA 2g (n=52)**	**Placebo (n=53)**	**Total (n=156)**
Number of patients with a major protocol deviation	3 (5.9)	12 (23.1)	2 (3.8)	17 (10.9)
Major protocol deviations before T0	2 (3.9)	2 (3.8)	1 (1.9)	5 (3.2)
Inclusion criteria not met (not moderate or severe pain)	0	0	1	1
Study drug not given	2	2	1	5
Major protocol deviations after T0	1 (2.0)	10 (19.2)	1 (1.9)	12 (7.7)
Initial dose not given as specified in the protocol	0	7	1	8
Taking NSAIDs or prohibited analgesics prior to 2nd dose (or rescue)	0	1	0	1
Delayed end-of dosing assessments (after 2nd dose instead of at Hour 6)	1	2	0	3
Number of patients with a minor protocol deviation	23 (45.1)	26 (50.0)	25 (47.2)	74 (47.4)
Minor protocol deviations before T0	9 (17.6)	16 (30.8)	12 (22.6)	37 (23.7)
Prohibited NSAIDs/analgesics within specified time windows before initial dose	0	3	0	3
Prohibited other treatments within specified time windows before initial dose	0	0	1	1
Minor anesthetic deviations	7	9	10	26
Inclusion criteria not met	0	3	2	5
Selection criteria before surgery not respected	1	1	0	2
Delay between study drug preparation and the initial dose	1	1	1	3
Minor protocol deviations after T0	17 (33.3)	14 (26.9)	17 (32.1)	48 (30.8)
1st, 2nd, 3rd, & 4th dose not given as specified in the protocol	4	8	4	16
Miss-timed visits and assessment (out of specified windows)	3	2	3	8
Taking NSAIDs or prohibited analgesics between 2nd dose and H24 (or rescue)	4	2	6	12
Having any prohibited treatment during 24-hour treatment period	0	0	1	1
Taking NSAIDs or unauthorized analgesics/concomitant treatment after H24	8	4	5	17

Source: Table 10.2 on page 67 and tables on pages 116 and 117 in Section 14 of the report for Study 3-002.

Exposure

The exposure information is summarized in the table below. About 90% or more in each treatment group received all four doses. Drug exposure was similar between the treatment groups.

Table 5.3.1-5 Exposure

Study 3-002 **Exposure**	**IV APAP 1g (n=49)**	**IV PPA 2g (n=50)**	**Placebo (n=52**	**Total (n=151)**
#Doses, n (%)	**Distribution**			
1	2 (4.1)	4 (8.0)	4 (7.7)	10 (6.6)
2	0	1 (2.0)	1 (1.9)	2 (1.3)
3	1 (2.0)	1 (2.0)	0	2 (1.3)
4	46 (93.9)	44 (88.0)	47 (90.4)	137 (90.7)

Source: Table 12.1 on page 96 of the report for Study 3-002.

Efficacy results

Primary efficacy endpoint:

Time-specific mean pain relief scores over six hours after the initial dose (single-dose effect)

The time-specific mean pain relief scores (PR at multiple time points) during the first six hours after the initial dose are summarized in the table below. Treatment differences between IV APAP 1 g and placebo were statistically significant during the entire six-hour period based on pairwise comparison of the Applicant's

analyses. Although there were no adjustments made for multiple comparisons at subsequent time points, multiplicity was less of a concern here for the reason that the data points on the same parameter were collected so closely in time and were highly correlated with each other, in the statistical reviewer, Dr. Petullo's opinion. In his reanalysis of data using three different methods of adjustment for multiplicity, statistical significance of treatment differences was confirmed. The results were also confirmed by Dr. Petullo's sensitivity analyses.

Effect sizes of the differences in the time interval between 0.5 and 6 hours, ranged from 0.5 to 1.0 on a 5-point categorical scale and were considered clinically meaningful.

Figure 5.3.1-1 Time-Specific PR during the First Six Hours

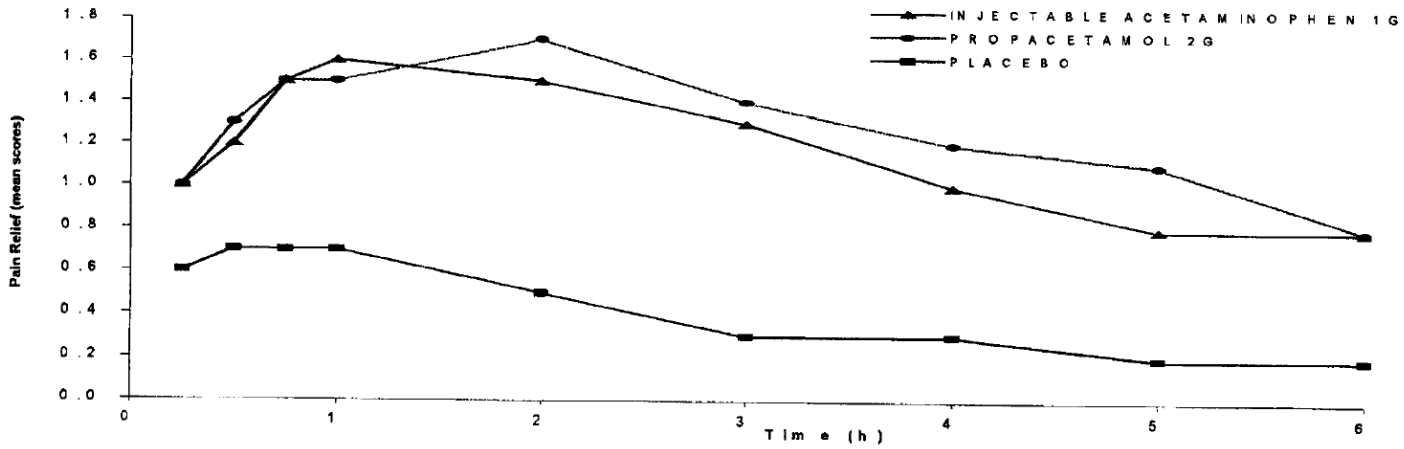


Table 5.3.1-6 Mean Scores of Pain Relief (Categorical Scale), ITT

Study 3-002 PR scores	0.25 hour	0.5 hour	0.75 hour	1 hour	2 hour	3 hour	4 hour	5 hour	6 hour
IV acetaminophen 1g (a)	1.0 (1.0) 49	1.2 (1.1) 44	1.5 (1.3) 36	1.6 (1.3) 35	1.5 (1.3) 29	1.3 (1.3) 24	1.0 (1.2) 18	0.8 (1.1) 9	0.8 (1.1) 6
IV propacetamol 2g (a)	1.0 (1.1) 46	1.3 (1.1) 44	1.5 (1.2) 40	1.5 (1.3) 36	1.7 (1.4) 30	1.4 (1.5) 23	1.2 (1.4) 18	1.1 (1.3) 13	0.8 (1.1) 8
Placebo (a)	0.6 (0.9) 49	0.7 (1.0) 41	0.7 (1.0) 28	0.7 (1.1) 22	0.5 (1.0) 10	0.3 (0.7) 4	0.3 (0.7) 2	0.2 (0.5) 2	0.2 (0.4) 0
Trt. p value (b)	0.0330	0.0114	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0006
Center p-value (b)	0.6037	0.2079	0.4340	0.3759	0.3207	0.0756	0.1434	0.2799	0.2985
Center* Trt p-value (c)	0.3495	0.1664	0.2465	0.4081	0.0852	0.7773	0.1318	0.3860	0.2893
BLPAI * Trt p-value (c)	0.9312	0.2122	0.2148	0.3403	0.2771	0.1300	0.3265	0.2955	0.2866
RMS error (b)	0.97	1.05	1.12	1.19	1.21	1.14	1.09	1.02	0.88
APAP vs placebo, p value	**0.0174**	**0.0161**	**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0008**	**0.0013**	**0.0005**
Effect size	**0.4**	**0.5**	**0.8**	**0.9**	**1.0**	**1.0**	**0.7**	**0.6**	**0.6**
PPA vs placebo, p value	0.0361	0.0065	0.0003	0.0012	0.0001	0.0001	0.0001	0.0001	0.0017
APAP vs PPA, p value	0.7636	0.7624	0.6223	0.2455	0.6545	0.9448	0.3895	0.2610	0.7119

(a) Values presented for each treatment group are (clock wise from upper left): Mean (Standard Deviation) and Sample sizes before processing procedure of handing missing or off-schedule data
(b) PR = BLPAI + center + Trt; (c) PR = BLPAI + center + Trt + (center*Trt) + (BLPAI*Trt), where BLPAI stands for baseline PI
Source: Table 11.10 on page 78 of the report for Study 3-002.

Secondary efficacy endpoints: single-dose effect

Time-specific mean pain intensity difference (PID) scores in the first six hours

The time-specific mean pain intensity scores during the first six hours after the initial dose are summarized in the two tables below as PID by VAS and PID by categorical scale, respectively. In terms of PID by VAS treatment differences between IV APAP 1 g and placebo were statistically significant during the entire six-hour period. The high correlation between the closely measured data points would make multiplicity less of a

concern as explained above. Effect sizes in the time interval between 0.5 and 6 hours, ranged from about 15 to 30 mm on a 100 mm scale and were considered clinically meaningful.

Figure 5.3.1-2 Time-Specific PID (VAS) during the First Six Hours

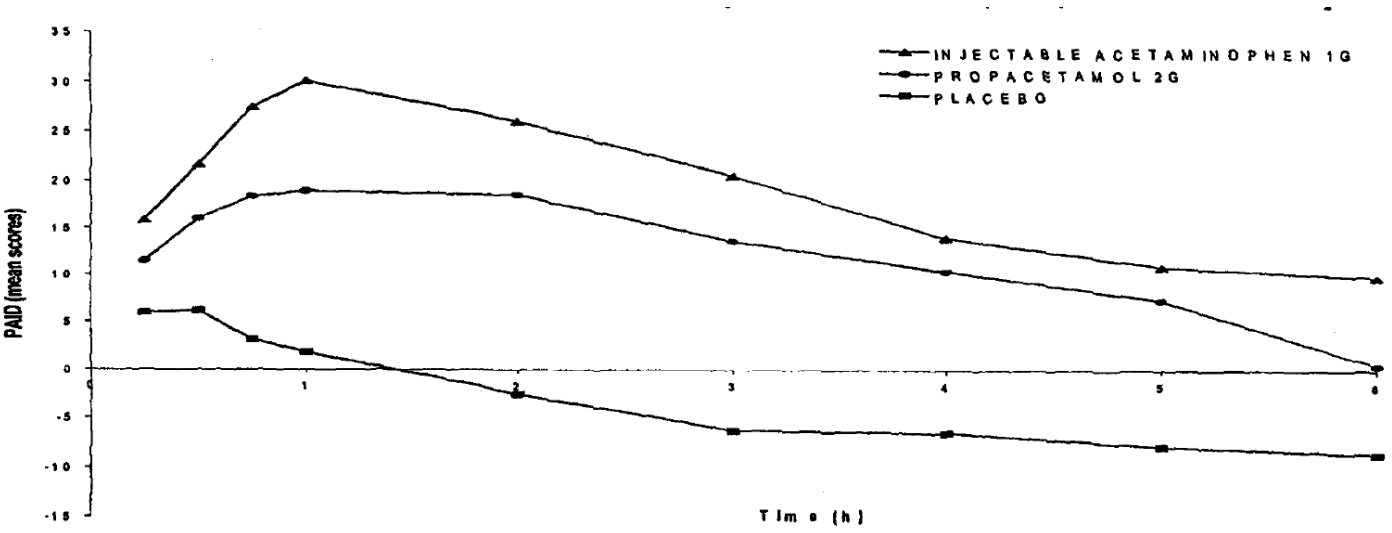


Table 5.3.1-7 Mean Scores of Pain Intensity Differences (Visual Analogue Scale), ITT

Study 3-002 PID scores	0.25 hour	0.5 hour	0.75 hour	1 hour	2 hour	3 hour	4 hour	5 hour	6 hour
IV acetaminophen 1g (a)	15.8 (18.7) 49	21.6 (19.8) 44	27.4 (22.8) 36	30.1 (24.3) 35	25.9 (23.8) 29	20.5 (23.3) 24	14.0 (22.7) 18	10.9 (21.8) 9	9.8 (21.3) 6
IV propacetamol 2g (a)	11.4 (14.2) 46	16.0 (16.8) 44	18.3 (18.5) 40	18.9 (20.7) 36	18.5 (22.8) 30	13.6 (22.9) 23	10.4 (23.0) 18	7.3 (21.8) 13	0.5 (18.8) 8
Placebo (a)	5.9 (16.1) 49	6.1 (18.5) 41	3.1 (20.3) 28	1.8 (21.8) 22	-2.6 (21.5) 10	-6.3 (15.8) 4	-6.5 (17.5) 2	- 7.9 (14.9) 2	-8.6 (15.6) 0
Trt. p value (b)	0.0184	0.0002	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Center p-value (b)	0.2886	0.3512	0.2223	0.4768	0.5355	0.6088	0.8377	0.9706	0.8164
Center* Trt p-value (c)	0.6716	0.1685	0.1221	0.1076	0.0924	0.3410	0.0756	0.0875	0.1338
BLPAI * Trt p-value (c)	0.8071	0.1574	0.2303	0.3217	0.5481	0.2815	0.4931	0.3478	0.3097
RMS error (b)	16.22	18.33	20.50	22.35	22.75	20.86	21.14	19.39	18.30
APAP vs placebo, p value	0.0053	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Effect size	**9.9**	**15.5**	**24.3**	**28.3**	**28.5**	**26.8**	**20.5**	**18.8**	**18.4**
PPA vs placebo, p value	0.0814	0.0064	0.0002	0.0001	0.0001	0.0001	0.0001	0.0001	0.0119
APAP vs PPA, p value	0.2786	0.1797	0.0387	0.0191	0.1456	0.1665	0-5685	0.6089	0.0389

(a) Values presented for each treatment group are (clock wise from upper left): Mean (Standard Deviation) and Sample sizes before processing procedure of handing missing or off-schedule data
(b) PR = BLPAI + center + Trt; (c) PR = BLPAI + center + Trt + (center*Trt) + (BLPAI*Trt), where BLPAI stands for baseline PI.
Source: Table 11.11 on page 80 of the report for Study 3-002

In terms of PID by categorical scale treatment differences between IV APAP 1 g and placebo were statistically significant from 0.5 to 6 hours. The effect sizes of treatment differences ranged from 0.5 to 0.7 on a 4-point categorical scale in the time interval between 0.75 and 4 hours, and decreased to 0.4 at Hours 5 and 6. The effect sizes are still considered clinically meaningful.

Figure 5.3.1-3 Time-Specific PID (Categorical) during the First Six Hours

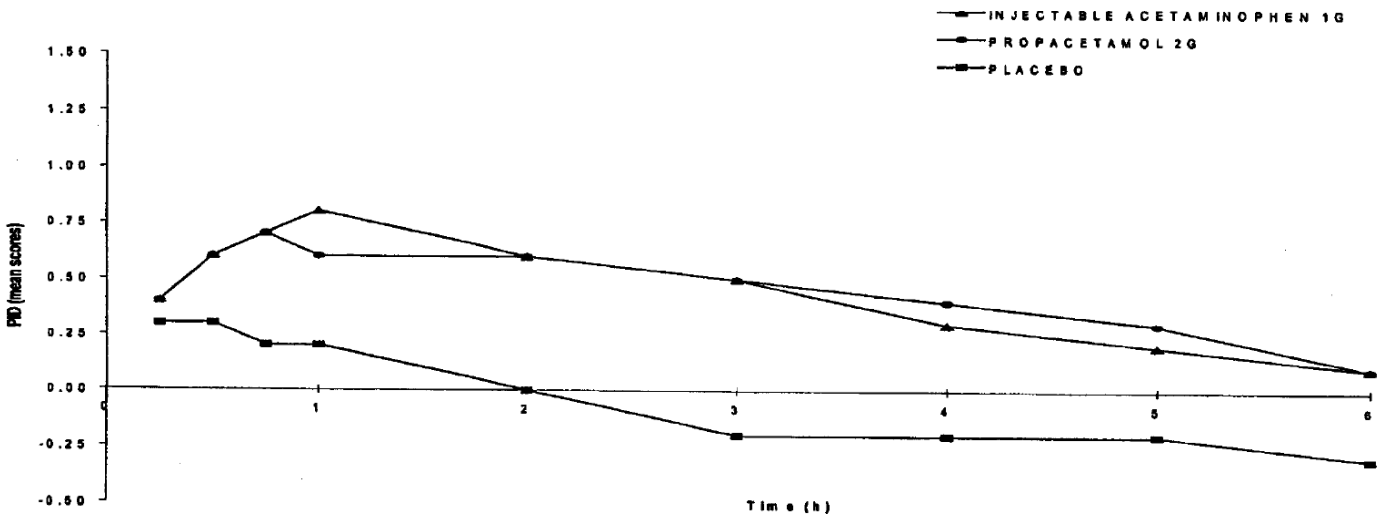


Table 5.3.1-8 Mean Scores of Pain Intensity Differences (Categorical Scale), ITT

Study 3-002 PID categorical	0.25 hour	0.5 hour	0.75 hour	1 hour	2 hour	3 hour	4 hour	5 hour	6 hour
IV acetaminophen 1g (a)	0.4 (0.5) 49	0.6 (0.7) 44	0.7 (0.7) 36	0.8 (0.7) 35	0.6 (0.8) 29	0.5 (0.8) 24	0.3 (0.8) 18	0.2 (0.7) 9	0.1 (0.7) 6
IV propacetamol 2g (a)	0.4 (0.6) 46	0.6 (0.7) 44	0.7 (0.8) 40	0.6 (0.9) 36	0.6 (0.9) 30	0.5 (1.0) 23	0.4 (0.9) 18	0.3 (0.8) 13	0.1 (0.7) 8
Placebo (a)	0.3 (0.6) 49	0.3 (0.8) 41	0.2 (0.8) 28	0.2 (0.9) 22	- 0.0 (0.8) 10	- 0.2 (0.6) 4	- 0.2 (0.7) 2	- 0.2 (0.6) 2	.0.3 (0.6) 0
Trt. p value (b)	0.4288	0.0585	0.0002	0.001	0.001	0.0001	0.0005	0.008	0.0102
Centre p-value (b)	0.1730	0.2208	0.2808	0.2612	0.3941	0.3187	0.6454	0.9607	0.9769
Center* Trt p-value (c)	0.4119	0.6413	0.6825	0.5210	0.2774	0.6099	0.1746	0.3008	0.3183
BLPAI * Trt p-value (c)	0.9841	0.6986	0.2969	0.6556	0.5180	0.2341	0.2534	0.2326	0.3316
RMS error (b)	0.59	0.71	0.75	0.82	0.84'	0.80	0.78	0.72	0.67
APAP vs placebo, p value	0.2276	0.0314	0.0002	0.001	0.001	0.001	0.0026	0.0111	0.0048
Effect size	0.1	0.3	**0.5**	**0.6**	**0.6**	**0.7**	**0.5**	**0.4**	**0.4**
PPA vs placebo, p value	0.3147	0.0526	0.0012	0.0027	0.001	0.0001	0.003	0.0002	0.0194
APAP vs PPA, p value	0.8314	0.8099	0.5615	0.2381	0.9797	0.9645	0.5552	0.2617	0.6007

Source: Table 11.12 on page 81 of the report for Study 3-002.

Secondary efficacy endpoints: single-dose effect

Summation of pain scores by area under the pain curves (AUC) in the first 6 hours

Time-weighted summation of pain scores by area under the PR, PID, and PRID curves are summarized in the table below. Treatment differences between IV APAP 1 g and placebo were statistically significant in all of the summation scores: TOTPAR, SPID (categorical), SPID (VAS), and SPRID.

Table 5.3.1-9 Summation of Pain Scores by AUC

Study 3-002	IV APAP 1g	IV PPA 2g	Placebo	Overall treatment p value	Pairwise comparisons			
					APAP/pla		PPA/pla	APAP/PPA
					Effect size	*p value*	p value	
TOTPAR, n	49	49	52					
Mean	6.6	7.5	2.2	0.0001	***4.4***	***0.0001***	0.0001	0.7224
SD	5.9	6.8	3.8					
SPIDcat, n	49	50	52					
Mean	2.3	2.5	-0.6	0.0001	***2.9***	***0.0001***	0.0001	0.9000
SD	3.6	4.3	3.5					
SPIDvas, n	49	50	52					
Mean	104.7	66.6	-27.7	0.0001	***132.4***	***0.0001***	0.0001	0.1320
SD	112.9	107.1	92.4					

SPRID, n	49	49	52					
Mean	9.0	10.0	1.6	0.0001	***7.4***	***0.0001***	0.0001	0.7540
SD	8.7	10.7	6.2					

Source: Table 11.14 on page 84 of the report for Study 3-002.

Secondary efficacy endpoints: single-dose effect

Time to first rescue medication and percentage rescued during six hours following the initial dose

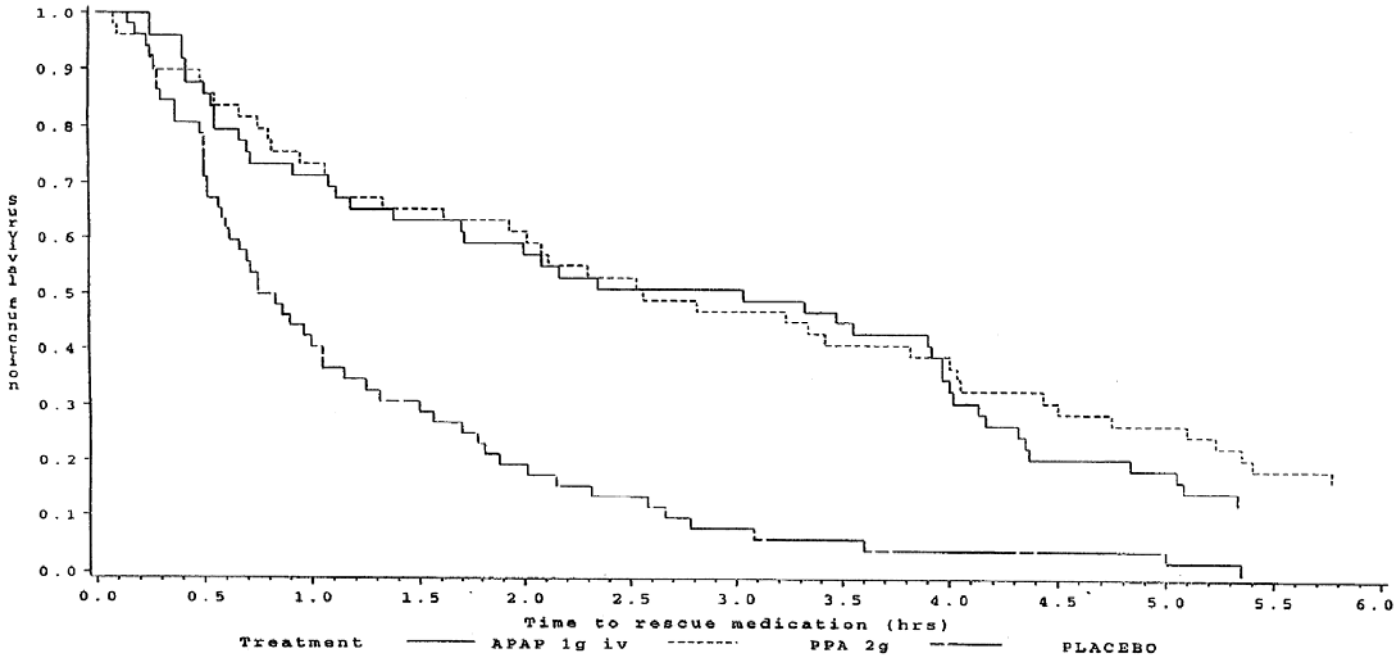
Rescue data are summarized in terms of median time to first rescue medication and number and percentage of patients requesting rescue during the first six hours following the initial dose in the table below. An overwhelming majority of patients, about 88% in the IV APAP 1 g group and 100% in the placebo group, were in need for rescue medication during the first dosing interval. Median time to the first rescue medication was three hours for the IV APAP 1 g group and less than one hour for the placebo group. Treatment differences between IV APAP 1 g and placebo were statistically significant. Effect sizes of the treatment differences, 12.2% less requests and 2.2 hours longer median time to first rescue for the IV APAP treatment in comparison to placebo were clinically noticeable.

Table 5.3.1-10 Time to First Rescue Medication & Number (Percentage) of Patients Rescued

Study 3-002 Rescue data in 1st 6 hours	**IV APAP 1g (n=49)**	**IV PPA 2g (n=50)**	**Placebo (n=52)**	**Overall comparison**	**Pairwise comparisons**			
					APAP/pla		**PPA/pla**	**APAP/PPA**
					Effect size	***p value***	**p value**	
Median time to rescue (hr)	3.0	2.6	0.8	0.0001	***2.2 hr***	***0.0001***	0.0001	0.5739
95% Confidence Interval	[1.4; 4.0]	[1.6; 4.0]	[0.6; 1.1]					
n (%) requested rescue	43 (87.8)	41 (82.0)	52 (100.0)	0.008	***-12.2%***	***0.012***	0.001	0.432

Source: Table 11.18 on page 88 and Table 11.20 on page 89 of the report for Study 3-002.

Figure 5.3.1-4 Time to First Rescue Medication



Source: Figure 11.1 on page 87 of the report for Study 3-002.

Secondary efficacy endpoints: multiple-dose effect

Amount of rescue medication per dosing interval and in 24 hours

Rescue data are summarized for the 24-hour multiple-dose period, in terms of the median time to first rescue medication, number and percentage of patients requesting for rescue, and the amount of rescue (in mg morphine) per dosing interval and in 24 hours in the table below. All patients in the IV APAP 1 g and placebo groups requested rescue, and the median time to requesting for the first rescue in 24 hours had the same numerical value as the median time to rescue in first six hours. The amount of morphine use was reduced by almost half in the first dosing interval and by about 1/3 in the third and fourth dosing interval and in 24 hours on the average. Statistical significance of treatment differences was confirmed by Dr. Petullo's reanalysis of data.

Table 5.3.1-11 Summary of Rescue Data for the Entire 24-Hour Period

Study 3-002 Rescue data in 24 hours	**IV APAP 1g**	**IV PPA 2g**	**Placebo**	**Overall p value**	**Pairwise comparisons**			
					APAP/pla		**PPA/pla**	**APAP/PPA**
	N=49	**N=48**	**N=52**		***Effect size***	***p value***	**p value**	
Median time to rescue (hr)	3.0	2.6	0.8	0.0001	***2.2 hr***	***0.0001***	0.0001	0.4372
n (%) rescued	49 (100.0)	47 (94.0)	52 (100.0)	0.044			0.060	0.096
Amount of rescue								
24-hour period								
Morphine (mg), mean	38.33	40.75	57.41	0.0025	***-19.08 (33%↓)***	***0.0007***	0.0287	0.2125
Morphine (mg), SD	35.14	30.23	52.3					
1st dosing interval								
Morphine (mg), mean	9.66	9.31	17.83	0.0001	***-8.17 (46%↓)***	***0.0001***	0.0001	0.5558
Morphine (mg), SD	9.97	8.94	16.68					
2nd dosing interval								
Morphine (mg), mean	12.09	11.51	14.81	0.1863	***-2.72 (18%↓)***	***0.1053***	0.1270	0.9191
Morphine (mg), SD	10.05	9.16	14.79					
3rd dosing interval								
Morphine (mg), mean	8.38	10.15	12.16	0.0107	***-3.78 (31%↓)***	***0.0028***	0.2626	0.0618
Morphine (mg), SD	9.53	8.76	11.22					
4th dosing interval								
Morphine (mg), mean	8.34	9.78	12.6		***-4.26 (34%↓)***	***0.0010***	0.1947	0.0441
Morphine (mg), SD	10.0	8.23	12.95					

Source: Table 11.20 on page 89, Table 11.21 on page 90, and Table 11.24 on page 91 of the report for Study 3-002.

Multiple-dose efficacy data

Data on time-specific PI after the first six hours were only collected at Hours 18, 20, and 24, corresponding to the end of third dosing period and the peak and the end of the fourth dosing period, respectively. As shown in the table below, there were basically no treatment differences between IV APAP 1 g and placebo at these later evaluation time points.

Table 5.3.1-12 Time-Specific PI Available after the First Dosing Period

Study 3-002 Time-specific PI	**IV APAP 1g**	**IV PPA 2g**	**Placebo**	**Pairwise comparisons**		
				APAP/pla	**PPA/pla**	**APAP/PPA**
	Mean (SD), n			**Difference in mean**		
PI (categorical)						
T18hr	1.62 (0.90), n=47	1.32 (0.93), n=44	1.51 (0.83), n=47	0.11	0.19	0.3
T20hr	1.24 (0.67), n=46	1.12 (0.89), n=42	1.38 (0.78), n=45	-0.14	0.26	0.12
T24hr	1.28 (0.68), n=47	1.36 (0.69), n=44	1.28 (0.77), n=47	0	-0.08	-0.08
PI (VAS)						
T18hr	37.5 (27.2), n=47	30.4 (24.3), n=44	36.3 (23.2), n=47	1.2	5.9	7.1
T20hr	28.4 (21.2), n=46	24.8 (22.6), n=42	33.0 (22.4), n=45	-4.6	8.2	3.6
T24hr	28.2 (20.6), n=47	30.6 (21.8), n=44	30.8 (23.8), n=47	-2.6	0.2	-2.4

Source: Tables on pages 188 and 189 of the report for Study 3-002.

Secondary efficacy endpoints: multiple-dose effect

MPI and MPI adjusted for rescue

The PI scores measured in the first dosing interval and at 18, 20, and 24 hours were averaged over 24 hours as indicated by MPI. MPI and MPI adjusted for the amount of rescue (MPI-res) are summarized in the table below. Treatment differences between IV APAP 1 g and placebo in MPI were very small as expected, mainly due to the contribution of almost no treatment differences at later time points to the 24-hour average, although the differences in MPI were statistically significant. Treatment differences between IV APAP 1 g and placebo in MPI adjusted for the amount of rescue were statistically significant. The results were confirmed by Dr. Petullo's reanalysis of data.

Table 5.3.1-13 PI Averaged over 24 Hours and Average PI Adjusted by Amount of Rescue

Study 3-002	**IV APAP**	**IV PPA 2g**	**Placebo**	**Overall**	**Pairwise comparisons**			
Average PI: MPI & MPI-res	**1g**			**p value**	***APAP/pla***		**PPA/pla**	**APAP/PPA**
MPI in 24 hours	**N=46**	**N=44**	**N=47**		***Effect size***	***p value***	**p value**	
MPI (VAS)	31.6 (17.0)	29.5 (17.1)	39.6 (18.5)	0.0013	***-8***	***0.0006***	0.0050	0.5394
MPI (categorical)	1.42 (0.50)	1.31 (0.57)	1.58 (0.58)	0.0224	***-0.16***	***0.0202***	0.0152	0.9016
MPI adjusted for rescue	**N=45**	**N=44**	**N=47**					
MPI-res (VAS)	-25.3 (91.7)	-14.6 (102.4)	37.8 (91.4)	0.0001	***-63.1***	***0.0001***	0.0072	0.0920
MPI-res (categorical)	-20.2 (94.6)	-14.6 (99.9)	33.1 (95.4)	0.0015	***-53.32***	***0.0004***	0.0176	0.2411

Source: Table 11.25 on page 92, Table 14.5.1.2.2 on page 191, Table 11.26 on page 93, and Table 14.5.1.2.3 on page 192 of the report for Study 3-002.

Reduction of morphine side effects

There were no predefined measures of morphine-related side effects to evaluate the impact of morphine reduction. The most frequently occurring individual adverse events in the APAP 1 g group were minor GI symptoms and pruritus, which could be considered as morphine treatment-related. As shown in the table below the data did not suggest a clear pattern, probably due to short length of treatments and very small sample size of the treatment groups.

Table 5.3.1-14 Most Frequent AEs (n>5 in the APAP group)

Adverse events	**IV APAP 1g (n=49)**	**IV PPA 2g (n=50)**	**Placebo (n=52)**
Constipation	10 (20.4)	8 (16.0)	12 (23.1)
Nausea	13 (26.5)	9 (18.0)	7 (13.5)
Vomiting	6 (12.2)	3 (6.0)	3 (5.8)
Pruritus	5 (10.2)	4 (8.0)	5 (9.6)

5.3.1.3 Summary of Findings and Discussion

Study conduct

The treatment groups in Study 3-002 were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight, and with regard to baseline pain intensity. Majority of patients had moderate pain at baseline and the ratio of moderate to severe pain was 3:1.

Dropouts accounted for less than 10% (14/151) of the study population, mainly due to withdrawal of consent (six cases), AEs (four cases), and lack of compliance (two cases). Very few (≤2) patients dropped out due to a specific reason in the IV APAP 1 g group.

Major and minor protocol deviations were 11% and 47%, respectively. There were few reports of protocol deviations in a specific category. Protocol deviations were balanced between the IV APAP 1 g and the placebo treatment groups and were not considered as having differential impact on study outcomes.

Efficacy

The efficacy results are summarized in the table below in terms of treatment differences from placebo to examine statistically significant and clinically meaningful effect sizes of the findings.

Single-dose effects of IV APAP 1 g were demonstrated by statistically significant and clinically meaningful separation of pain curves from the placebo group. Treatment differences were mainly from 0.5 to 1 point on a 5-point categorical scale for PR, the primary efficacy endpoint, and from 15 to 30 mm on a 100-mm VAS for PID during the first six hours after the initial dose. The magnitude of treatment differences in summation of pain scores were as expected given the sizes of time-specific pain curve separations. The high proportions of patients (88% in the IV APAP 1 g group and 100% in the placebo group) taking rescue and relatively short median time to rescue (three hours for IV APAP 1 g and 0.8 hours for placebo) indicated that the pain was still quite severe on the first post operative day following a very painful surgical procedure that had bony involvement and that the use of APAP (indicated for management of mild to moderate pain) alone was insufficient to control pain of such a severity.

Multiple-dose effects of IV APAP 1 g were demonstrated by statistically significant treatment differences in use of morphine upon repeated dosing in three of the four dosing intervals. These differences represented about 30% to 50% reduction in use of morphine when IV APAP 1 g was compared to placebo treatments. The clinical impact of morphine reduction could not be shown due to mainly small sample sizes. Time-specific pain measurements were collected only at 18, 20, and 24 hours following the first dosing interval and were associated with no significant treatment differences. The totality of data suggested that post orthopedic surgical pain in this study required early rescue with morphine analgesics and that it became difficult to show additional treatment benefits in terms of further pain reduction when APAP, a relatively weak analgesic, was added to background morphine (a strong analgesic) treatment.

Statistical significance of treatment difference in primary and key secondary efficacy endpoints were confirmed by Dr. Petullo's reanalysis of data.

Table 5.3.1-15 Summary of Efficacy Findings

Study 3-002	**Treatment differences between APAP 1 g & placebo**	
Efficacy summary	**Effect size**	**p < 0.05**
Primary efficacy endpoint (single-dose effect)		
Time-specific PR in 6 hours after initial dose	0.5-1.0 (0.5-6 hours)	Yes (0.25-6 hours)
Secondary efficacy endpoints: single-dose effects		
Time-specific PID (100 mm VAS) in 1st 6 hours	~15-30 mm (0.5-6 hours)	Yes (0.25-6 hours)
Time-specific PID (categorical) in 1st 6 hours	0.5-0.7 (0.75-4 hours) 0.4 (at Hours 5 and 6)	Yes (0.5-6 hours)
Summation of pain scores		
TOTPAR6	4.4	Yes
SPID6 (VAS)	132.4	Yes
SPID6 (categorical)	2.9	Yes
SPRID6	7.4	Yes
Rescue		
Median time to 1st rescue in 6 hours	2.2 (3 vs 0.8) hours	Yes
Number (%) of patients requested rescue	-12.2% (87.8 vs 100%)	
Secondary efficacy endpoints: multiple-dose effects		
Rescue		
Median time to 1st rescue in 24 hours	2.2 hours	Yes
Number (%) of patients requested rescue	0 (100% in both groups)	No
Amount of rescue medication	mg (%↓ from placebo)	
Morphine in 24 hours,	-19.08 (33%↓)	Yes
Morphine in 1st dosing interval	-8.17 (46%↓)	Yes
Morphine in 2nd dosing interval	-2.72 (18%↓)	No
Morphine in 3rd dosing interval	-3.78 (31%↓)	Yes
Morphine in 4th dosing interval	-4.26 (34%↓)	Yes
Pain scores		
Time-specific PI (VAS) at 18, 20, & 24 hours	1.2, -4.6, -2.6	
Time-specific PI (categorical) at 18, 20, & 24 hours	0.11, -0.14, 0	
Average PI over 24 hours, MPI (VAS)	-8	Yes
Average PI over 24 hours, MPI (categorical)	-0.16	Yes
MPI (VAS) adjusted for rescue	-63.1	Yes
MPI (categorical) adjusted for rescue	-53.32	Yes

Refer to all the efficacy tables in this section.

The three-hour median time to rescue medication and 88% of patients requesting rescue during the first six hours in the IV APAP group indicated that the pain was too strong to be handled by acetaminophen alone at the initial hours of study drug infusion. After the start of morphine rescue (capable of managing moderate to sever pain) treatment effect of APAP (capable of managing mild to moderate pain only) on pain reduction could no longer be shown. Therefore, neither the median time to rescue medication after the initial dose, nor the end-of-dosing pain measurements upon repeated dosing were useful in determining single and multiple-dose duration in this case. The benefit of adding IV APAP to morphine treatment appears to be mainly on the reduction of morphine use. The clinical impact of reduced morphine use in terms of reduction of morphine-related adverse events could be evaluated by large trials with safety endpoints as a primary focus.

5.3.1.4 Conclusion

Supplementing IV acetaminophen 1 g infusion to morphine analgesia has relatively small additional therapeutic benefits in treating post orthopedic surgical pain.

5.3.1.5 Appendix

Eligibility Criteria for Study 3-002

Inclusion Criteria

1. Inpatient of either gender.
2. Aged from 18 to 70 years inclusively. ***(Amended to "At least 18 years of age" in Amendment #2 dated September 27, 1999)***
3. Body weight: 50-120 kg inclusively (110 - 265 lbs inclusively).
4. Classified as ASA risk class I, II or III according to the American Society of Anesthesiologists.
5. Having provided written informed consent to participate in the study.
6. Able to understand the study procedures and the use of the pain scales, able to operate a patient controlled analgesia (PCA) device and to communicate meaningfully with the study observer and staff.
7. Patients scheduled for elective unilateral or bilateral, primary or uncomplicated secondary total replacement of hip or knee performed according to the standard technique used in each center.
8. Performed under standardized general, spinal or epidural anesthesia.
9. Patient free of any contra-indication to the study drugs, the rescue medication and to the standardized anesthesia protocol.
10. Patient free of other painful physical conditions which might confound quantifying postoperative pain resulting from total hip or knee replacement.

Exclusion Criteria

11. Pregnant woman or nursing mother and woman with a positive urine pregnancy test (minimum sensitivity 25 IU/L of P-HCG) performed on D0, before surgery, woman of child-bearing age and potential not using an effective contraceptive method (oral contraceptives, contraceptive foam, contraceptive injection or implants, intra-uterine contraceptive device, condom, diaphragm). Woman who was naturally post-menopausal within 12 months preceding the study was to be required to use a medically acceptable method of birth control during the study. Woman who had undergone hysterectomy or successful sterilization might be included.
12. Patient with known or suspected history of alcohol or drug abuse.
13. Patient with psychiatric disease or medical conditions which in the opinion of the investigator might invalidate patient ability to communicate with the investigator or to comply with the study procedures.
14. Patient having a history of complete non-response to acetaminophen, NSAIDs or morphine when seeking pain relief; patients having previously required more than usual doses of analgesics for comparable surgical procedures.
15. Patient participating in another clinical study (investigational or marketed product) within the previous 30 days.
16. Patient previously included in this study.
17. Patient who needed simultaneously any additional surgery procedures unrelated to total hip or knee replacement during the same session.
18. Patient scheduled for early re-intervention or re-instrumentation, i.e. within 30 days of the initial procedure or less.
19. Patient with abnormally high perioperative blood loss at risk of hypovolemia during the postoperative period.
20. Known hypersensitivity to- or history of serious adverse reaction to morphine, propacetamol, acetaminophen or phenacetin, drugs used for anesthesia and related compounds, or to inactive ingredients of the study medications, patients with cysteinic lithiasis.
21. Impaired liver function (transaminases > 2 x upper limit of normal range).
22. Advanced renal dysfunction (creatinine > 2.0 mg/dl) or patient at risk for renal failure due to volume depletion.
23. Respiratory insufficiency or severe cardiac insufficiency not stabilized by therapy.
24. Chronic malnutrition.
25. Patients with raised intracranial pressure or convulsions.
26. Patient who had taken NSAIDs within 8 hours before administration of the study medications or any analgesic drug within the 12 hours (48 h for long acting NSAIDs) prior to administration of the study medications except for those defined by the standardized postoperative analgesia protocol.
27. Patient who was taking any concomitant treatments (i.e. sedatives, hypnotics, anxiolytics, anti-depressant drugs, tranquilizers) which could potentially confound the quantification of analgesia. Patient requiring low oral dose of sedatives as sleep inducer was however eligible provided the doses were kept unchanged during the course of the study. A patient requiring antidepressant drug was however eligible provided this treatment had been started for at least 4 weeks, was well tolerated and doses were kept unchanged during the course of the study.
28. Patient treated with MAO inhibitors or whose treatment with these had been stopped less than 10 days prior to surgery; patient treated with corticosteroids or whose treatment with these had been stopped less than 7 days prior surgery.
29. Patient treated with microsomal enzyme inducers such as barbiturates, izoniazid, anticonvulsivants or zidovudine.
30. Patients treated with anticoagulants (except for heparin 5000 UI) ***(criterion deleted by amendment # 2,).***

Final inclusion criterion

31. Patient whose postoperative pain intensity reached moderate to severe intensity on a 4-point verbal categorical scale

5.3.2 Pain Study A-304

5.3.2.1 Protocol

The original study protocol was dated September 21, 2007 and was used when the study started on November 27, 2007. The major changes in the Amendment 1 dated March 3, 2008, included the change of baseline pain severity with the range of VAS score changed from 35-65 to 40-70 mm (moderate to severe pain on a categorical scale), and addition of an open-label extension following 24-hour treatment. These and other changes of the protocol described in Amendment 1 are noted in the description of the protocol presented below.

Study CPI-APA-304 was planned as a multiple-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose (24 hours) analgesic study of two different dosing regimens (1 g q6 hours and 650 mg q4 hours) of acetaminophen (APAP) IV infusion in hospitalized patients undergoing abdominal laparoscopic surgery.

Eligible patients were to have been adult patients undergoing abdominal laparoscopic surgery (except laparoscopic gastric bypass procedures, which was further clarified as laparoscopic bariatric procedures, including gastric bypass or gastric banding and laparoscopic exploratory procedures with no or minimal visceral dissection in Amendment 1), who had postoperative pain with severity between 35 and 65 mm on a 100 mm VAS scale (which was changed to moderate to severe pain on a categorical scale and severity between 40 and 70 mm on a 100 mm VAS scale in Amendment 1). (Refer to the complete list of the eligibility criteria attached in the Appendix of the study review).

Eligible patients were planned to be randomized to one of the four treatment groups, acetaminophen 1000 mg every six hours, acetaminophen 650 mg every four hours, and matching placebo on each of the two dosing regimens, to receive a 15-minute IV infusion of study drug for 24 hours (with open label extended use of APAP on the same dosing regimen for up to five days as added in Amendment 1).

Opioid analgesics were to have been allowed post operatively until the morning of the day after surgery (PCA opioid was to be stopped within two hours and oral opioid to be stopped within three hours before the initial dose as clarified in Amendment 1), and then allowed as rescue medication during the treatment period. The list of prohibited and restricted therapies was planned as the following: no neuraxial opioid analgesics prior to or during surgery; no continuous local anesthetic infusion (and injection as in Amendment 1) post operatively; no acetaminophen containing products, NSAIDs (including COX-2), or aspirin (except low dose aspirin for cardioprophylaxis) on surgical day and during the treatment period; no herbal supplements (such as Chapparal, Comfrey, Germander, Gin Bu Huan, Kava, Pennyroyal, Skullcap, St. John's Wort, or Valerian) during the study.

Efficacy data to be collected were to have included the measurements of pain intensity (PI, on an 100 mm visual analogue scale and on a 4-point categorical scale) at baseline and measurements of PI and pain relief (PR, on a 5-point categorical scale) hourly for up to 12 hours and every two hours from 12 to 24 hours (as well as before rescue as added in Amendment 1), time to onset of perceptible and meaningful relief, time to the first request of rescue medication and first rescue administration, amount of rescue, and patient global evaluation at 24 hours.

The planned primary efficacy endpoint was the Sum of Pain Intensity Differences (from baseline on a VAS scale) over 24 hours, or SPID24 (based on analysis through imputing data after rescue). The planned secondary efficacy endpoints included derived pain scores: SPID24 (based on analysis of actual data without imputing after rescue), TOTPAR12 (Total Pain Relief), TOTPAR24, SPI12 (Sum of Pain Intensity), SPI24; endpoints related to rescue: time to first rescue medication request and administration and total amount of rescue in 24 hours; patient global evaluation. Other efficacy endpoints were planned to include time-specific pain

measurements: PI and PID over 24 hours; derived pain scores: mean PI and PR per dosing interval, and SPID and SPRID at Hours 4, 6, 8, 12, 16, 18, 20, and 24 (with addition of SPI4, SPI6, SPI8, TOTPAR4, TOTPAR6, and TOTPAR8 in Amendment 1); rescue per dosing interval in terms of percentage taking rescue and total amount of rescue; time to onset of perceptible and meaningful relief after the initial dose.

Safety monitoring was planned to consist of reports of adverse events (AEs) during the study, where all serious AEs possibly treatment-related would have been followed until resolution or stabilization; vital signs at screening, before and after each infusion of study medication, and before study exit (or at early termination from the study); routine laboratory tests (hematology and chemistry) at screening, after surgery, 24 hours after the initial infusion, and before study exit (or at early termination from the study).

Statistical Analysis

Population for analysis

The planned modified intent-to-treat (mITT) population was to have included all treated patients with at least one dose (changed to one complete infusion in Amendment 1) of study medication.

Efficacy analysis

The planned primary efficacy parameter, SPID24 (VAS), was to be analyzed using ANCOVA with treatment, period, and site as factors and baseline PI as covariate to compare IV APAP 1 g to the combined placebo group.

Missing data management

Missing data were to have been replaced by LOCF for early discharge from the hospital and dropouts, by BOCF for dropouts due to AE or reasons other than early discharge, and by WOCF for missing score because of rescue.

Sample size

The planned sample size was 80 patients in each of the two active treatment groups and 40 in each of the two placebo groups based on an estimated effect size of treatment difference of 159.8 in SPID 24 (VAS) and estimated standard deviation of 289.3 to provide 90% power and 5% level of significance.

Protocol Amendments

There was one protocol amendment and all the amended items are noted in the protocol described above.

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

Table 5.3.2-1 Reviewer's Summary of the Protocol

Study #	CPI-APA-304
Objectives	To study single-dose and multiple-dose analgesic effects, tolerability and safety of IV acetaminophen 650 and 1000 mg in patients with postoperative pain following abdominal laparoscopic surgery
Design	Multiple-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose (24 hours in the original protocol with open label extension added in the Amendment 1), dose ranging (two different dosing regimens)
Sample population	Hospitalized adult patients undergoing abdominal laparoscopic surgery with post-operative pain (VAS scores 35-65 mm in the original protocol modified to 40-70 mm VAS and moderate to severe categorical pain in Amendment 1) in the morning of post surgical day 1
Treatment	APAP 1000 mg and matching placebo every 6 hours APAP 650 mg and matching placebo every 4 hours 15-minute IV infusion initiated in the morning of post surgical day and repeated at fixed dosing interval for one day
Rescue medication	Opioid analgesics (as rescue only and not allowed as concomitant analgesic treatment)
Efficacy data	PI (VAS & categorical) and PR (categorical) hourly for 12 hours and q2 hours in Hour 12 to 24 Rescue: time to 1st request, time to 1st administration, and amount of rescue Time to onset of perceptible and meaningful relief Patient global at 24 hours
Efficacy parameter	***Primary:*** SPID24 (with data imputation after rescue) ***Secondary:*** • Derived pain scores: SPID24 (without data imputation), TOTPAR12, TOTPAR24, SPI12, SPI24 • Rescue: o Time to 1st request of rescue o Time to 1st administration of rescue o Total amount of rescue in 24 hours • Patient global evaluation at 24 hours ***Other:*** • Time-specific PI and PID over 24 hours • Derived pain scores: o Mean PI and PR per dosing interval o SPID4, SPID6, SPID8, SPID12, SPID16, SPID18, SPID20, SPID24 o SPRID4, SPRID6, SPRID8, SPRID12, SPRID16, SPRID18, SPRID20, SPRID24 o (SPI4, SPI6, SPI8, TOTPAR4, TOTPAR6, and TOTPAR8 were added in Amendment 1) • Rescue: o Percentage taking rescue per dosing interval o Amount of rescue per dosing interval • Time to perceptible and meaningful relief after the initial dose
Safety monitoring	• Adverse events • Vital signs at screening, before and end of each infusion, and before end of study • Routine laboratory tests at screening, after surgery, 24 hours after initial infusion, and before study exit

5.3.2.2 Results

Demographic and other baseline characteristics

The study sample population consisted of 244 patients (safety sample) enrolled and received study medication, and 241 of them received a complete infusion (efficacy sample). Of the 241 patients the age range was from 18 to 78 years and mean age was 46 years, 87% were Caucasian, 10% were African American, and 81% were female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight. The group mean scores of baseline PI measured by categorical scale were similar (difference <0.2) between the treatment groups though the distribution of baseline PI among various pain categories was different. The difference in baseline PI measured by VAS scale was 5.6 to 8.2 mm between the matching groups. Using the combined placebo group as comparison baseline PI difference by VAS was still 5.0 mm between the APAP 650 mg and the combined placebo groups. The explanation for the treatment group differences in baseline PI by VAS was that a major randomization allocation error occurred when the first 109 patients were enrolled. Instead of being randomized into four study groups all 109 patients were randomized to only two treatment groups: IV APAP 1 g q6 hours and placebo q4 hours (the matching placebo for IV APAP 650 mg group) under the eligibility criteria of VAS scores 35-65 mm. As a result of correcting the mistake by changing the scheme of randomization for the remaining patients under the revised eligibility criteria of VAS scores 40-70 mm, the treatment groups IV APAP 650 mg and placebo q6 hour had higher baseline PI than the other two groups (~57 mm versus ~50 mm).

Table 5.3.2-2 Demographics and Baseline Characteristics

Study A-304 Baseline Characteristics	**Placebo q6h (n=42)**	**IV APAP 1g q6h (n=92)**	**Placebo q4h (n=66)**	**IV APAP 650mg q4h (n=41)**	**Total N=241**
Age (years)					
Mean (SD)	46.0 (11.70)	45.3 (12.26)	46.5 (13.08)	47.3 (13.04)	46.1
Median	45.0	43.0	45.0	47.0	
Minimum, Maximum	18, 72	19, 73	21, 78	21, 71	18, 78
Gender, n (%)					
Male	6 (14.3)	18 (19.6)	13 (19.7)	9 (22.0)	46 (19.1)
Female	36 (85.7)	74 (80.4)	53 (80.3)	32 (78.0)	195 (80.9)
Race, n (%)					
Caucasian	36 (85.7)	76 (82.6)	60 (90.9)	38 (92.7)	210 (87.1)
Black	5 (11.9)	15 (16.3)	3 (4.5)	1 (2.4)	24 (10.0)
Asian	0 (0.0)	1 (1.1)	2 (3.0)	1 (2.4)	4 (1.7)
Other	1 (2.4)	0 (0.0)	1 (1.5)	1 (2.4)	3 (1.2)
Height (in)					
Mean (SD)	65.2 (3.52)	65.5 (3.73)	65.7 (3.54)	64.9 (3.93)	
Median	65.0	65.0	66.0	64.0	
Minimum, Maximum	59, 72	59, 75	59, 76	60, 75	
Weight (lbs)					
Mean (SD)	176.45 (38.8)	172.48 (37.0)	177.57 (32.3)	170.48 (35.0)	
Median	171.50	173.50	175.00	159.00	
Minimum, Maximum	110.0, 284.0	103.0, 256.0	115.0, 252.0	120.0, 254.0	
Baseline PI (categorical), n (%)					
Mild	4 (9.5)	16 (17.4)	16 (24.2)	4 (9.8)	40 (16.6)
Moderate	36 (85.7)	72 (78.3)	48 (72.7)	33 (80.5)	189 (78.4)
Severe	2 (4.8)	4 (4.3)	2 (3.0)	4 (9.8)	12 (5.0)
Baseline PI (categorical)	**1.95**	**1.87**	**1.79**	**1.95**	1.88
Baseline PI (VAS)					
Mean (SD)	**57.5 (12.09)**	**51.9 (12.62)**	**49.2 (16.27)**	**57.4 (14.89)**	53.1
Median	58.5	51.0	48.5	55.0	
Minimum, Maximum	35, 89	23, 80	4, 79	23, 92	4, 92

SD = standard deviation; Min = minimum; Max = maximum; BL = baseline.
Source: Table 9 on page 43 and Table 11 on page 45 of the report for Study A-304.

Patient disposition

More than 90% patients in three of the four treatment groups completed the 24-hour double blind treatment period. Only two patients continued into the open-label extension phase of the study. Of the 14 cases of dropouts, eight were due to withdrawal of consent (four from each of the placebo groups), four were due to adverse events (three in the IV APAP 1 g group and one in the matching placebo group), two were due to early discharge from hospital, two were due to other reasons, and one was based on the Investigator's judgment.

Table 5.3.2-3 Patient Disposition

Study A-304 Patient Disposition	Placebo q6h (n=43)	IV APAP 1g q6h (n=92)	Placebo q4h (n=67)	IV APAP 650mg q4h (n=42)
Randomized population (ITT Population)	43 (100.0)	92 (100.0)	67 (100.0)	42 (100.0)
Safety population[1]	43 (100.0)	91 (98.9)[4]	67 (100.0)	43 (102.4)[4]
mITT population[2]	42 (97.7)	92 (100.0)[4]	66 (98.5)	41 (97.6)[4]
Open-label extension[3]	1 (2.3)	1 (1.1)	0	0
Completed all study medication doses in 24 hrs	36 (83.7)	88 (95.7)	62 (92.5)	39 (92.9)
Completed 24 hr double-blind period	37 (86.0)	88 (95.7)	62 (92.5)	40 (95.2)
Reasons for not Completing	6 (14.0)	4 (4.3)	5 (7.5)	2 (4.7)
AE	1 (2.3)	3 (3.3)	0	0
Withdrew consent	4 (9.3)	0	4 (6.0)	0
Investigator judgment	0	1 (1.1)	0	0
Early discharge from hospital	0	0	1 (1.5)	1 (2.4)
Other	1 (2.3)	0	0	1 (2.4)
Completed study assessments through Day 7	36 (83.7)	91 (98.9)	60 (89.6)	39 (92.9)
Reasons for not Completing				
AE	0	1 (1.1)	0	0
Withdrew consent	4 (9.3)	0	5 (7.5)	0
LTFU	3 (7.0)	0	2 (3.0)	2 (4.8)
Other	0	0	0	1 (2.4)

1 Received any portion of study medication
2 Randomized subjects who received at least one completed infusion of study medication prior to requesting rescue medication (includes subject 1501 as randomized)
3 Received at least one dose of open-label study medication (includes subject 1501 as dosed)
4 Subject 1501 was randomized to receive IV acetaminophen 1000 mg, but was administered IV acetaminophen 650 mg in error
Note: AE = Adverse Event, ITT = Intent to Treat, IV APAP = IV acetaminophen; LTFU = Lost to Follow-Up, mITT = Modified Intent-to-Treat
Source: Table 7 on page 39 of the report for Study A-304.

Protocol violations

A few patients (4%) had a major protocol deviation, defined as deviation from eligibility criteria. About 65% patients had a minor protocol deviation, which included mainly missed PI and PR assessments and not following protocol procedures. There appeared to be a much higher proportion of patients in the APAP 650 mg group who missed PI/PR assessments than the matching placebo group. With the consideration of the total amount of data collected per patient (38 PI score and 19 PR score per patient) the amount of missing PI/PR assessments was not considered as having a major differential impact on study results.

Table 5.3.2-4 Summary of Protocol Deviations

Study A-304 Number of patients with protocol deviations	Placebo q6h (n=43)	IV APAP 1g q6h (n=92)	Placebo q4h (n=67)	IV APAP 650mg q4h (n=42)	Total (n=244)
Major					9 (3.7)
Inclusion criteria	0	0	1 (1.5%)	0	1 (0.4%)
Exclusion criteria	0	1 (1.1%)	1 (1.5%)	0	2 (0.8%)
Post-surgical inclusion criteria	1 (2.3%)	4 (4.3%)	1 (1.5%)	1 (2.4%)	7 (2.9%)
Minor					158 (64.8)
Missed pain intensity assessment	7 (16.3%)	18 (19.6%)	7 (10.4%)	13 (31.0%)	45 (18.4%)
Missed pain relief assessment	5 (11.6%)	18 (19.6%)	6 (9.0%)	12 (28.6%)	41 (16.8%)
Missed global evaluation	0	2 (2.2%)	0	2 (4.8%)	4 (1.6%)

Missed protocol procedure	16 (37.2%)	36 (39.1%)	35 (52.2%)	13 (31.0%)	100 (41.0%)
Missed dose	1 (2.3%)	0	0	1 (2.4%)	2 (0.8%)
Other	8 (18.6%)	34 (37.0%)	26 (38.8%)	17 (40.5%)	85 (34.8%)

D = days

Source: Table 2 on page 152 of the report for Study A-304 and Table 2 of the submission dated June 26, 2009.

Exposure

As summarized in the table below more than 90% of all patients (patients in three of the four treatment groups specifically) received a full day of treatment. Drug exposure was about similar between the matching treatment groups.

Table 5.3.2-5 Exposure

Study A-304 Exposure	**Placebo q6h (n=43)**	**IV APAP 1g q6h (n=92)**	**Placebo q4h (n=67)**	**IV APAP 650mg q4h (n=42)**	**Total (n=244)**
#Doses, n (%)	**Distribution**				
1	2 (4.7)	1 (1.1)	1 (1.5)		
2	2 (4.7)	2 (2.2)	3 (4.5)	2 (4.8)	
3	3 (7.0)	1 (1.1)	1 (1.5)		
4	36 (83.7)	88 (95.7)			
5				1 (2.4)	
6		1 (1.1)	62 (92.5)	39 (92.9)	
24-hour dosing	36 (83.7)	88 (95.7)	62 (92.5)	39 (92.9)	225 (92.2)

Source: Listing 16.2.1.17 in Appendix 16.2.5 of the report for Study A-304.

Efficacy results

As shown in the patient disposition table (Table 5.3.2-3) above the mITT population (defined as having at least one complete infusion of study medication) had at most one patient less than the safety population (having received any treatment) per treatment group. All efficacy results in the study report were based on analysis of mITT population as summarized below. With regard to statistical issues with two separate randomization periods due to allocation error and issues with the use of pooled placebo groups of different dosing regimens, Dr. Petullo concluded that the randomization period had no significant impact on study results and that it was acceptable to use pooled placebo group based on his analyses of data.

Primary efficacy endpoint: SPID24 (IV APAP 1000 mg versus combined placebo group)

The results of primary analysis of comparison of SPID24 between IV APAP 1000 mg and combined placebo are summarized in the table below. Missing data after the first rescue medication were imputed applying WOCF in the analysis. Treatment difference was statistically significant. The results were confirmed by Dr. Petullo's re-analysis of data.

Table 5.3.2-6 Result of Protocol Defined Primary Efficacy Endpoint: SPID24

Study A-304 Primary efficacy endpoint	**Placebo Combined N = 108**	**IV APAP 1000 mg N = 92**
Mean (SD)	-45.2 (513.25)	-194.1 (593.62)
Median	0.7	-85.9
Min, Max	-1396, 1921.6	-1432, 1589.1
Analysis Results		
Treatment p-value*	0.0068	

*Analyzed using ANCOVA model with treatment group, randomization period, and study site as the fixed effect and **baseline PI VAS rest score as the covariate.**

Definitions: IV APAP = IV acetaminophen; SD = Standard Deviation; SPID = weighted sum of pain intensity difference from baseline.

Source: Table 12 on page 46 of the report for Study A-304.

Secondary and other efficacy endpoints

The review of the results of secondary and other efficacy analyses is organized under each acetaminophen dosing regimen studied (1000 mg q6 hours and 650 mg q4 hours). Time-specific pain measurements over 24 hours will be evaluated first and followed by a summary of treatment comparisons of acetaminophen with matching placebo and/or combined placebo in selected secondary and other efficacy endpoints.

Treatment comparison in time-specific measurements:
IV APAP 1000 mg versus matching placebo
The results of comparison between IV APAP 1000 mg and matching placebo in terms of differences in LSMeans of PID and PR measurements over 24 hours are summarized in the table below. Treatment differences were statistically significant at most measurement points for PR during the first three dosing intervals and at 50% of measurement points for PID in the first dosing interval only. Effect sizes of statistically significant treatment differences were small for PR (0.4-0.6) and very small for PID.

Table 5.3.2-7 Treatment Differences in LS Means of PID and PR over 24 Hours: APAP 1 g vs Placebo q6h

Dosing interval		**1st**						**2nd**						**3rd**			**4th**		
Time (hours)		1	2	3	4	5	**6**	7	8	9	10	11	**12**	14	16	**18**	20	22	**24**
PIDcat	Txn diff	0.4	0.2	0.4	0.2	0.3	0.0	0.3	0.3	0.3	0.0	0.0	-0.2	0.0	0.5	-0.1	-0.1	0.2	-0.1
	p<0.05	**x**		**x**		**x**									x				
PIDvas	Txn diff	9.7	5.3	6.6	9.9	10.9	0.3	5.0	5.5	6.8	2.6	0.7	-1.8	2.7	11.5	-3.5	-9.3	-2.4	-4.8
	p<0.05	**x**			**x**	**x**													
PR	Txn diff	0.5	0.5	0.4	0.4	0.3	0.4	0.3	0.5	0.5	0.6	0.6	0.5	0.3	0.5	0.4	0.2	0.3	0.4
	p<0.05	**x**	**x**	**x**	**x**		**x**		**x**	**x**	**x**	**x**	**x**		**x**	**x**			

Source: Table 6.6.10.1A on pages 311-319, Table 6.6.10.2A on pages 329-337, and Table 6.6.10.3A on pages 347-355 of the report for Study A-304.

Summary of treatment comparisons for selected secondary and other efficacy endpoints:
APAP 1000 mg versus placebo
The results of secondary and other efficacy analyses are summarized in the table below in terms of derived pain scores (mean scores per dosing interval, summation of scores over 24 hours, and summation of scores over the first 6 hours), percentage of patients taking rescue, and time to rescue (time for the first 25% of patients to take rescue and median time to rescue).

In terms of derived pain scores treatment differences between IV APAP 1000 mg and matching placebo were statistically significant for mean PR per dosing interval during the first three dosing intervals and for mean PI per dosing interval during the first two dosing intervals. Treatment differences were statistically significant in terms of SPID24 and TOTPAR24 using the combined placebo group for comparison and became borderline significant in SPID using the matching placebo as comparison. Treatment differences in SPID6 and TOTPAR6 were statistically significant.

In comparison of proportion of patients taking rescue per dosing interval there was a 10% difference (42% on APAP versus 52% on matching placebo) between the two treatment groups during the first dosing interval and no difference (12% taking rescue in each group) during the second dosing interval. Only two patients in the third dosing interval and none in the fourth dosing interval requested rescue. Median time to rescue after the initial dose was beyond 6 hours in both treatment groups and thus could not be used to evaluate single-dose duration. Treatment difference in time for the first 25% of patients to request for rescue was only half hour (3.3 hours for the APAP group and 2.8 hours for the placebo group).

Table 5.3.2-8 Summary of Secondary and Other Efficacy Findings: APAP 1 g versus Placebo

	Placebo comb N=108	**Placebo q6h N=42**	**APAP 1000 mg N=92**	**APAP 1000 mg vs Placebo q6h**		**APAP 1000 mg vs Placebo comb**	
Derived pain scores	**Mean (SD)**			**Difference in LS Mean**	**p value**	**Difference in LS Mean**	**p value**
Mean pain score per dosing interval							

PR							
>T0-T6		1.6 (0.79)	2.0 (0.73)	**0.5 (0.14)**	**0.0008**		
>T6-T12		1.6 (0.84)	2.1 (0.78)	**0.5 (0.15)**	**0.0013**		
>T12-T18		1.9 (0.99)	2.3 (0.87)	0.4 (0.18)	**0.0348**		
>T18-T24		2.0 (1.00)	2.4 (0.90)	0.3 (0.19)	0.1052		
PI							
>T0-T6		47.9(14.85	35.7(13.47)	-9.9 (2.48)	**0.0001**		
>T6-T12		42.0(21.67)	31.3(17.80)	-8.8 (3.57)	**0.0145**		
>T12-T18		38.2 (24.31)	30.0 (21.34)	-6.4 (4.24)	0.1311		
>T18-T24		30.7 (22.96)	25.9 (20.43)	-3.6 (4.14)	0.3819		
Summed pain score over 24 hours							
SPID24 WOCF	45.2 (513.25)	69.9 (486.63)	194.1 (593.62)	188.1 (99.69)	0.0608	178.3 (76.13)	**0.0203**
SPID24 BOCF	209.5 (336.11)	223.8 (361.61)	343.2 (422.25)	147.0 (74.62)	0.0501	138.1 (57.04)	**0.0162**
TOTPAR24	41.8 (19.60)	41.1 (18.95)	51.1 (17.28)	9.6 (3.51)	**0.0068**	9.3 (2.69)	**0.0006**
Summed pain score over 1st 6 hours (initial dose)							
SPID6	54.7 (78.69)		101.4 (89.04)			48.1 (10.68)	**<0.0001**
TOTPAR6		7.9 (3.86)	10.1 (3.89)	2.5 (0.73)	**0.0010**		
% Taking rescue per dosing interval							
		N (%)	**N (%)**	**% Difference**	**p value**		
>T0-T6		22 (52%)	39 (42%)	**-10%**	0.3031		
>T6-T12		5 (12%)	11 (12%)	0%	0.7136		
>T12-T18		0	2 (2%)	2%	0.3952		
>T18-T24		0	0		N/A		
Time to rescue (hr)							
						Difference	**p value**
Q1 (95% CI)	2.8 (1.9, 3.8)		3.3 (2.9, 4.2)			0.5 hr	
Median (95% CI)	9.3 (5.5, 17.3)		10.4 (5.2 , NA)			1.1 hr	0.5878

Source: Table 6.1.3 on page 274, Table 6.3 on page 279, Table 17 on page 50, Table 18 on pages 52 to 55 of the report for Study A-304.

Treatment comparison in time-specific measurements:
IV APAP 650 mg versus matching placebo

The results of comparison between IV APAP 650 mg and matching placebo in terms of their differences in LSMeans of PID and PR measurements over 24 hours are summarized in the table below. Treatment differences were statistically significant for PR during the second, third, and fourth dosing intervals, over most measurement points for PI based on VAS scale and half of the measurement points for PI measured by categorical scale during the first three dosing intervals. With regard to multiplicity issues with multiple comparisons of time-specific measurements multiplicity was a less of a concern because of high correlation of data and Dr. Petullo's reanalysis of data using three different methods of adjustment did not show significant impact on study results.

Effect sizes of statistically significant treatment differences were small for PR (0.4-0.6) and PID (0.3 to 0.5 on a categorical scale and 11 to 18 mm on a VAS scale).

Table 5.3.2-9 Treatment Differences in LSMeans of PID/PR over 24 Hours: APAP 650 mg vs Placebo q4h

Dosing interval		**1st**				**2nd**				**3rd**				**4th**		**5th**		**6th**	
Time (hours)		1	2	3	**4**	5	6	7	**8**	9	10	11	**12**	14	**16**	18	**20**	22	**24**
PIDcat	Txn diff	0.3	0.4	0.3	0.1	0.3	0.2	0.4	0.4	0.4	0.5	0.3	0.2	0.2	0.4	0.1	0.5	0.2	0.1
	p<0.05	**x**	**x**					**x**	**x**	**x**	**x**				x		x		
PIDvas	Txn diff	11.4	11.9	11.3	6.6	16.2	11.7	13.3	14.3	18.3	15.0	10.5	9.5	7.8	16.3	1.2	16.1	8.8	6.3
	p<0.05	**x**	**x**	**x**		**x**	**x**	**x**	**x**	**x**	**x**	**x**			x		x		
PR	Txn diff	0.3	0.2	0.3	0.3	0.4	0.4	0.6	0.5	0.5	0.6	0.5	0.5	0.5	0.6	0.4	0.6	0.4	0.5
	p<0.05					**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**		x		x

Source: Table 6.6.10.1B on pages 320-328, Table 6.6.10.2B on pages 338-346, and Table 6.6.10.3B on pages 356-364 of the report for Study A-304.

Summary of treatment comparison for selected secondary and other efficacy endpoints:
APAP 650 mg versus placebo

The results of secondary and other efficacy analyses are summarized in the table below in terms of derived pain scores (mean scores per dosing interval, summation of scores over 24 hours, and summation of scores over the first 4 hours), percentage of patients taking rescue, and time to rescue (time for the first 25% of patients to take rescue and median time to rescue).

In terms of derived pain scores treatment differences between IV APAP 650 mg and matching placebo were statistically significant for mean PR per dosing interval in five of the six dosing intervals (borderline significant for the first dosing interval) and for mean PI per dosing interval in four of the six dosing intervals (mainly the first three dosing intervals). Treatment differences were statistically significant in terms of SPID24 and TOTPAR24 using both the matching placebo and the combined placebo groups for comparison. Treatment difference was statistically significant in SPID4 and not in TOTPAR4.

In comparison of proportion of patients taking rescue per dosing interval there was a 13% difference (22% on APAP versus 35% on matching placebo) between the two treatment groups during the first dosing interval and <5% differences during the subsequent dosing intervals. Few patients in each group took rescue after the third dosing interval. Median time to rescue after the initial dose was beyond 6 hours in both treatment groups and thus could not be used to evaluate single-dose duration. Treatment difference in time for the first 25% of patients to take rescue was 3.8 hour (6.6 hours for the APAP group and 2.8 hours for the placebo group).

Table 5.3.2-10 Summary of Secondary and Other Efficacy Findings: APAP 650 mg versus Placebo

	Placebo comb N=108	Placebo q4h N=66	APAP 650 mg N=41	APAP 650 mg vs Placebo q4h		APAP 650 mg vs Placebo comb	
Derived pain scores	Mean (SD)			**Difference in LS Mean**	**p value**	**Difference in LS Mean**	**p value**
Mean pain score per dosing interval							
PR							
>T0-T4		1.6 (0.88)	1.9 (0.85)	0.3 (0.18)	0.0640		
>T4-T8		1.7 (0.88)	2.2 (0.82)	**0.5 (0.18)**	**0.0040**		
>T8-T12		1.8 (0.90)	2.3 (0.80)	**0.6 (0.18)**	**0.0010**		
>T12-T16		1.7 (1.01)	2.2 (0.88)	**0.6 (0.21)**	**0.0054**		
>T16-T20		1.9 (1.07)	2.4 (1.07)	**0.6 (0.24)**	**0.0144**		
>T20-T24		1.9 (1.09)	2.5 (1.05)	**0.6 (0.23)**	**0.0104**		
PI							
>T0-T4		41.7 (16.91)	41.0 (17.21)	-6.4 (2.67)	**0.0177**		
>T4-T8		40.1 (20.74)	35.7 (22.00)	-8.9 (3.98)	**0.0268**		
>T8-T12		40.3 (20.69)	33.7 (22.08)	-10.6 (4.10)	**0.0108**		
>T12-T16		36.1 (22.65)	34.9 (25.17)	-5.3 (4.75)	0.2680		
>T16-T20		33.3 (25.16)	27.6 (24.13)	-9.3 (5.05)	0.0680		
>T20-T24		27.1(20.40)	21.0(19.48)	-9.0 (4.10)	**0.0307**		
Summed pain score over 24 hours							
SPID24 WOCF	45.2 (513.25)	29.4 (532.56)	323.1 (619.27)	250.8 (107.83)	**0.0216**	234.0 (97.94)	**0.0183**
SPID24 BOCF	209.5 (336.11)	200.4 (321.34)	434.2 (500.74)	192.9 (80.36)	**0.0171**	192.9 (80.36)	**0.0067**
TOTPAR24	41.8 (19.60)	42.3 (20.14)	51.8 (18.96)	10.2 (3.78)	**0.0078**	10.4 (3.47)	**0.0029**
Summed pain score over 1st 6 hours (initial dose)							
SPID4	35.4 (51.29)		65.4 (60.28)			23.9 (9.42)	**0.0124**
TOTPAR4		4.9 (2.95)	5.6 (2.96)	0.9 (0.61)	0.1436		
% Taking rescue per dosing interval							
		N (%)	**N (%)**	**% Difference**	**p value**		
>T0-T4		23 (34.8%)	9 (22.0%)	**-13%**	0.1406		
>T4-T8		2 (3.0%)	3 (7.3%)	4%	0.4196		
>T8-T12		9 (13.6%)	5 (12.2%)	-1%	0.6103		
>T12-T16		1 (1.5%)	1 (2.4%)	1%	0.8264		
>T16-T20		1 (1.5%)	2 (4.9%)	3%	0.3762		

>T20-T24		0	0		N/A		
Time to rescue (hr)							
						Difference	**p value**
Q1 (95% CI)	2.8 (1.9, 3.8)		6.6 (2.8, 11.8)			3.8 hrs	
Median (95% CI)	9.3 (5.5, 17.3)		16.4 (10.2, NA)			7.1 hrs	0.1629

Source: Table 6.1.2 on page 273, Table 6.3 on page 279, Table 17 on page 50, Table 18 on pages 52 to 55 of the report for Study A-304.

The results in SPID24 and TOPPAR24 were consistent to the results of Dr. Petullo's analyses of data from the ITT population.

5.3.2.3 Summary of Findings and Discussion

Study conduct
The treatment groups in Study A-304 were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight. Mean baseline PI by categorical scale was similar between the treatment groups and was less than 2.0 for all treatment groups. There were noticeably differences in mean baseline PI by VAS scale between the matching groups (5.6 mm between IV APAP 1 g and placebo q6 hours and 8.2 mm between IV APAP 650 mg and placebo q4 hours) due to change of randomization scheme and baseline PI eligibility criteria when randomization allocation error was identified after enrollment of 109 patients as explained in the review section 5.3.2.2. VAS pain scores were used in efficacy analyses of primary and secondary endpoints involving PI, where baseline PI VAS rest scores were incorporated as covariate in all these analyses (pending statistical review of interaction between treatment and baseline PI).

Dropouts accounted for less than 7% (17/244) of the study population, mainly due to withdrawal of consent (eight cases) and AEs (four cases). A total of four patients dropped out of the IV APAP 1 g group and two out of the IV APAP 650 mg group in comparison to 11 dropped out of the combined placebo group.

Major and minor protocol deviations were 4% and 65%, respectively. Protocol deviations were approximately balanced between the IV APAP 1 g and the matching placebo group. The higher proportion of patients missing PI/PR assessments in the APAP 650 mg group than the matching placebo group was not considered as having a major impact on study outcomes when the total amount of data was considered (38 PI score and 19 PR score per patient).

Efficacy
The efficacy results are summarized for each dosing regimen in the tables below in terms of statistically significant treatment differences between IV APAP and placebo during each dosing interval and over the 24-hour period. The effect sizes of the treatment differences were relatively small in general as discussed above.

IV APAP 1g
Treatment difference between IV APAP and placebo (the combined placebo group) was statistically significant in SDID24, the primary efficacy endpoint and the result was confirmed by Dr. Petullo's re-analysis of data. Statistically significant treatment differences between IV APAP 1 g and placebo were also shown in summation of pain scores, SPID (secondary analyses) and TOTPAR over 24 hours and over first dosing interval and in time-specific PR and mean PR per dosing interval during the first three dosing intervals and mean PI per dosing interval during the first two dosing intervals.

Table 5.3.2-11 Summary of Efficacy Findings in Support of IV APAP 1 g

Study A-304 Efficacy summary	Statistically significant treatment differences: APAP 1 g versus placebo				
Efficacy endpoint	24 hours	Dosing interval			
		1st	2nd	3rd	4th
Primary efficacy endpoint					
SPID24 WOCF	x				
Secondary and other efficacy endpoint					
SPID24 BOCF	x				
TOTPAR24	x				
SPID6		x			
TOTPAR6		x			
Time-specific PR		x	x	x	
Time-specific PI					
Mean PR/dosing interval		x	x	x	
Mean PI/dosing interval		x	x		

Noticeable treatment difference in proportion of patients taking rescue per dosing interval (10% difference with 42% on APAP versus 52% on matching placebo) was only shown during the first dosing interval. Median time to rescue after the initial dose could not be determined because it was beyond 6 hours in both treatment groups.

IV APAP 650 mg

Statistically significant treatment differences between IV APAP 650 mg and placebo were shown in summation of pain scores, SPID and TOTPAR over 24 hours and SPID over first dosing interval, in time-specific PR from 2nd to 4th dosing interval, in mean PR per dosing interval from 2nd to 6th dosing interval, and in time-specific PI and mean PI per dosing interval from 1st to 3rd dosing interval.

Table 5.3.2-12 Summary of Efficacy Findings in Support of IV APAP 650 mg

Study A-304 Efficacy summary	Statistically significant treatment differences: APAP 650 mg versus placebo						
Efficacy endpoint	24 hours	Dosing interval					
		1st	2nd	3rd	4th	5th	6th
SPID24 WOCF	x						
SPID24 BOCF	x						
TOTPAR24	x						
SPID4		x					
TOTPAR4							
Time-specific PR			x	x	x		
Time-specific PI		x	x	x			
Mean PR/dosing interval			x	x	x	x	x
Mean PI/dosing interval		x	x	x			x

Noticeable treatment difference in proportion of patients taking rescue per dosing interval (13% difference with 22% on APAP versus 35% on matching placebo) was only shown during the first dosing interval. Median time to rescue after the initial dose could not be determined because it was beyond 6 hours in both treatment groups.

The potential issues with randomization period and pooling placebo group were addressed by Dr. Petullo. Statistical significance of treatment difference in primary efficacy endpoint and in selected secondary efficacy endpoints were confirmed by Dr. Petullo's reanalysis of data.

Discussion

Baseline pain experienced by patients in the morning of the day following abdominal laparoscopic surgery in this study was not that strong (less than moderate by categorical scale on the average) and very few patients had severe pain even after the change of eligibility criteria to a higher range of VAS scores. About 50% or less of patients, including those on placebo, requested rescue during the first dosing interval indicated that the pain was not sufficiently severe to allow adequate assessment of single-dose duration. The size of the treatment differences in time-specific pain scores suggested that treatment effects could best be shown for 12 hours due to milder pain associated with the pain model.

5.3.2.4 Conclusion

IV acetaminophen regimens, 1000 mg given every six hours and 650 mg given every four hours, are considered effective in treating milder pain in hospitalized patients undergoing abdominal laparoscopic surgery based on the demonstration of statistically significant and clinically noticeable treatment differences in Study A-314.

5.3.2.5 Appendix

Eligibility Criteria for Study A-304

Inclusion Criteria (Screening)

1. Provided **signed (added in Amendment 1)** written Informed Consent prior to participation in the study
2. Was scheduled to undergo abdominal laparoscopic surgery **under general anesthesia. Exceptions were expanded from laparoscopic gastric bypass procedures to the following in Amendment 1: laparoscopic bariatric procedures, including gastric bypass or gastric banding, laparoscopic exploratory procedures in which no visceral dissection was performed, and laparoscopic procedures with minimal visceral dissection, such as laparoscopic sterilization**
3. Had a negative pregnancy test within 21 days of surgery (for female of childbearing potential)
4. Was at least 18, but not more than 80 years of age
5. Had a Body Mass Index (BMI) ≥ 19 and ≤ 45 lb/in^2 (**changed to 40 lb/in^2 in Amendment 1**)
6. Had an ASA risk class of I, II, or III according to the American Society of Anesthesiologists
7. Had the ability to read and understand the study procedures and the use of the pain scales and had the ability to communicate meaningfully with the Investigator and staff
8. Was free of other physical, mental, or medical conditions which, in the opinion of the Investigator, made study participation inadvisable

Exclusion Criteria (Screening)

1. Used opioids or tramadol daily for greater than 7 days prior to study medication administration, or had or was developing opioid tolerance in the Investigator's opinion
2. Had been treated with Chapparal, Comfrey, Germander, Gin Bu Huan, Kava, Pennyroyal, Skullcap, St. John's Wort, or Valerian within 14 days prior to surgery
3. Had **a chronic pain condition or any (added in Amendment 1)** significant medical disease(s), laboratory abnormalities or condition(s) that in the Investigator's judgment could have compromised the subject's welfare, ability to communicate with the study staff, complete study activities, or otherwise contraindicated study participation
4. Had known hypersensitivity to opioids, acetaminophen, or the inactive ingredients (excipients) of the study medication
5. Had known or suspected history of alcohol or drug abuse or dependence within the previous 2 years
6. Had impaired liver function, e.g., AST/ALT/bilirubin greater than or equal to 3.0 times the upper limit of normal, active hepatic disease, evidence of clinically significant liver disease, or other condition (e.g., alcoholism, cirrhosis, or hepatitis) that suggested the potential for an increased susceptibility to hepatic toxicity with study medication exposure
7. Had been treated with monoamine oxidase inhibitors (MAOIs) within 7 days prior to surgery
8. Had participated in another clinical study (investigational or marketed product) within 30 days of surgery

Post Operative Exclusion Criteria

1. Had any other surgery than the planned laparoscopic surgery or had intra operative or post operative complications which in the view of the Investigator, made study participation inadvisable
2. Had taken non steroidal anti-inflammatory drugs (NSAIDs), steroids or MAOIs during the day after surgery, except the use of low-dose aspirin, e.g., 81 mg/day, for cardioprophylaxis, and **limited use of (added in Amendment 1)** topical or inhaled steroids
3. Had any neuraxial opioids or continuous local anesthetic infusions via percutaneous catheters administered as part of the anesthetic or post operative analgesic management (local anesthetic infiltration of surgical wounds at the time of closure was acceptable if done as a single injection) (**rephrased in Amendment 1 as the following: Had any neuraxial (spinal or epidural) opioid injected perioperatively; Had a local anesthetic agent injection (including into the surgical wound at closure) or continuous infusion by any route; Had an epidural, regional, or percutaneous (intrawound) catheter with continuous local anesthetic infusion used for post operative analgesic management)**
4. Had a fever (greater than 38.6oC or 101.5oF) requiring treatment **with antipyretics (added in Amendment 1)**

Post Operative Day 1 Randomization Criterion

- Had a **PI categorical score of moderate or severe and a visual analog scale (VAS) (added in Amendment 1)** score ≥35 mm, but ≤65 mm **(changed to ≥40 mm, but ≤70 mm in Amendment 1)** at rest on a 100 mm Visual Analogue Scale (VAS) on the morning of post operation Day 1

5.3.3 Adult Fever Study F-302

5.3.3.1 Protocol

Study CPI-APF-302 was planned as a randomized, double-blind, placebo-controlled, parallel, single-dose study of acetaminophen (APAP) IV infusion of 1000 mg for the treatment of endotoxin-induced fever in healthy adult males.

Eligible patients were to have been adult healthy male subjects with an average baseline core temperature ≤37°C (98.6°F) with no variation of more than 0.4°C (0.7°F) from lowest to highest on three assessments performed during a 30-minute period and with no allergic or exaggerated systemic response to a test dose of endotoxin, who had a fever response to a standard dose of endotoxin with a core temperature elevation to at least 38.6°C (101.5°F) and near peak temperature by two consecutive temperature assessments 5 minutes apart that were within 0.2°C (0.4°F) of each other.

Eligible subjects who tolerated the IV endotoxin test dose of 1 ng/kg with no more than a moderate (e.g., more than 20%) cardiovascular response (elevated cardiac index, elevated heart rate, and decreased mean arterial pressure) within the first hour, were to have been receiving a standard dose of endotoxin of 4 ng/kg (2 ng/kg for the hyperresponders defined by a > 0.5°C (0.9°F) temperature increase within 30 minutes after the test dose). Subjects with a temperature elevation to ≥38.6°C (101.5°F) within 4 hours of 4 ng/kg endotoxin dose (or 2 ng/kg dose in hyperresponders) were planned to be randomized to receive a 15-minute IV infusion of either acetaminophen 1 g or matching placebo.

Rescue treatments were to have been allowed for severe fever-associated symptoms. Ibuprofen 600 mg and aspirin 650 mg were planned rescue antipyretics by oral route with ketorolac 30 mg IV available as an alternative for those unable to take PO medication.

Efficacy data to be collected were to have included measurements of core temperature at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, 300, 330, and 360 minutes after the start of IV infusion using the VitalSense Integrated Physiological Monitoring System, time to rescue, and patient global.

The planned primary efficacy endpoint was WSTD6 (weighted sum of temperature differences through 6 hours from baseline). The planned secondary efficacy endpoints included WSTD3, maximum temperature reduction during 6 hours, Subject's Global Evaluation at 6 hours, and percentage of subjects with temperature reaching <38°C (100.4°F) at any time during the 6-hour evaluation period. Other efficacy endpoints were to have included change in temperature at each scheduled assessment time point from baseline, time to request of rescue, and percentage of subjects requesting and receiving rescue medication during 6 hours.

Safety monitoring was planned to consist of reports of adverse events (AEs) during the study and serious AEs within 30 days after dosing; vital signs every 15 minutes after RSE test dose, every 30 minutes after RSE dose at 4 ng/kg, immediately before and after IV infusion, and at study completion; physical examination and liver function tests (bilirubin, ALT, AST, alkaline phosphatase, and GGT) before treatment and at study completion.

Statistical Analysis (refer to statistical review for detail)

Population for analysis

The planned modified intent-to-treat (mITT) population was to have included all treated patients with at least one dose of study medication.

Efficacy analysis

The planned primary efficacy parameter, the weighted sum of temperature differences through 6 hours from baseline, or WSTD6, was to have been analyzed using the analysis of covariance (ANCOVA) with the treatment group as the fixed effect and baseline temperature as covariate.

Missing data management

Missing data were to have been imputed by WOCF for discontinuation due to rescue and by LOCF for discontinuation due to other reasons.

Sample size

The planned sample size was 30 patients per treatment group based on 19 per group calculated from an estimated effect size of treatment difference of 4°C (7.2°F) x h in WSTD6 with standard deviation of 3.8ºC (6.8ºF) x h to provide 90% power at the 5% level of significance.

Protocol Amendments

There were no protocol amendments.

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

Table 5.3.3-1 Reviewer's Summary of the Protocol

Study #	CPI-APF-302
Objectives	To study antipyretic efficacy, tolerance, and safety of a single dose of IV acetaminophen 1 g, in comparison to placebo, in treating fever induced by a standard dose of endotoxin.
Design	Randomized, double-blind, placebo-controlled, parallel, single-dose, single-center
Sample population	Adult healthy male with stable baseline temperature in normal range [≤37°C (98.6°F)], reasonable tolerance to a test dose of endotoxin, and a fever response to a standard dose of endotoxin as shown by a temperature elevation to near peak of at least 38.6°C (101.5°F), which would persist for at least 5 minutes in duration
Treatment	A single dose of 15-minute IV infusion of either acetaminophen 1 g or matching placebo
Rescue medication	Ibuprofen 600 mg and aspirin 650 mg orally and ketorolac 30 mg IV (rescue based only on intolerance of fever-associated symptoms not on degrees of temperature elevation)
Efficacy data	Temperature at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, 300, 330, and 360 minutes after the start of IV infusion, time to rescue, and patient global
Efficacy parameter	***Primary:*** WSTD6 (weighted sum of temperature differences from baseline) ***Secondary:*** • WSTD3 • Maximum temperature reduction in 6 hours • Subject's Global Evaluation at Hour 6 • Percentage with temperature <38°C (100.4°F) at any time during 6-hour period ***Other efficacy endpoints:*** • Change in temperature at each assessment time point from baseline • Time to subject's request of rescue medication during 6-hour period • Percentage of subjects requesting and receiving rescue medication during 6-hour period
Safety monitoring	• Adverse events • Vital signs every 15 minutes after RSE test dose, every 30 minutes after RSE dose of 4 ng/kg, immediately before and after IV infusion, and at study completion • PE before treatment and at study completion • Liver function tests (bilirubin, ALT, AST, alkaline phosphatase, and GGT) before treatment and at study completion

5.3.3.2 Results

Demographic and other baseline characteristics

The sample population consisted of 60 subjects enrolled who received the study medication, with an age range of 18 to 55 years and a mean of 30 years. Of the 60 subjects, 75% were Caucasian, 22% were African American, and all were male. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight and with regard to baseline temperature. Mean temperature at baseline was about 39.3 ºC (102.8 ºF).

Table 5.3.3-2 Demographics and Baseline Characteristics

Study F-302 Baseline Characteristics	**Placebo (n=29)**	**IV APAP 1g (n=31)**	**Total (n=60)**
Age (years)			
Mean (SD)	30.0 (10.02)	29.7 (7.35)	29.9 (8.67)
Median	29.0	28.0	28.0
Minimum, Maximum	18, 55	18, 49	18, 55
Gender, n (%)			
Male	29 (100%)	31 (100%)	60 (100%)
Female	0	0	0
Race, n (%)			
Caucasian	22 (75.9)	23 (74.2)	45 (75.0)
Black	6 (20.7)	7 (22.6)	13 (21.7)
Asian	1 (3.4)	0 (0.0)	1 (1.7)
Other	0 (0.0)	1 (3.2)	1 (1.7)
Height (in)			
Mean (SD)	70.5 (2.21)	69.0 (3.17)	69.8 (2.83)
Median	70.0	70.0	70.0
Minimum, Maximum	66, 76	61, 75	61, 76
Weight (lbs)			
Mean (SD)	172.2 (23.69)	179.2 (26.54)	175.8 (25.24)
Median	169.0	180.0	177.5
Minimum, Maximum	130, 219	126, 232	126, 232
Temperature prior to study drug administration (ºC)			
Mean (SD)	39.29 (0.55)	39.39 (0.49)	39.34 (0.52)
Median	39.3	39.3	39.3
Minimum, Maximum	38.2, 41.1	38.6, 40.4	38.2, 41.1
Mean baseline temperature in ºF	102.7	102.9	102.8

SD = standard deviation; Min = minimum; Max = maximum

Source: Table 5 on page 31 and Table 3 on pages 62 to 67 of the report for Study F-302.

Patient disposition

Only four of 60 subjects, two from each treatment group, discontinued because of taking rescue medication.

Table 5.3.3-3 Patient Disposition

Study F-302 Patient Disposition	**Placebo (n=29)**	**IV APAP 1g (n=31)**	**Total (n=60)**
All Treated Patients			
***Discontinued* n (%)**	**2 (6.9%)**	**2 (6.5%)**	**4 (6.7%)**
Reason for discontinuation			
Need for rescue	2 (6.9%)	2 (6.5%)	4 (6.7%)

Source: Table 1 on pages 60 to 61 of the report for Study F-302.

Protocol violations

Protocol deviations were reported in a quarter of subjects, mainly as miss-timed measurements of temperature and vital signs, and were not considered as having a major differential impact on study outcome.

Table 5.3.3-4 Summary of Protocol Deviations

Study 302 Protocol deviations	Placebo (n=29)	IV APAP 1g (n=31)	Total (n=60)
Total number of patients with protocol deviations	8 (27.6%)	7 (22.6%)	15 (25%)
Miss timed temperature measurements	2 (6.9%)	6 (19.4%)	
Missing temperature measurements	0	1 (3.2%)	
Miss timed vital signs	4 (13.8%)	0	
Miss timed peak temperature measurements	2 (6.9%)	0	
Endotoxin dosing error (half dose)	1 (3.4%)	0	

Source: Table 4 on page 29 of the report for Study F-302.

Exposure

All 60 subjects received a full volume of infusion of the study medication.

Efficacy results

Primary efficacy endpoint: accumulative temperature differences from baseline through 6 hours

The results of analyses of primary efficacy measurements are summarized in terms of weighted sum of temperature differences from baseline over six hours, or WSTD6 in the table below. The analysis with and without imputation of data for taking rescue had the same results because of a small proportion of subjects taking rescue (two subjects per treatment group). The treatment difference was statistically significant.

Table 5.3.3-6 Weighted Sum of Temperature Differences from Baseline through 6 Hours

Study F-302 Primary efficacy endpoint	Placebo (n=29)	IV APAP 1g (n=31)	Placebo (n=29)	IV APAP 1g (n=31)
Summary Statistics	°C		°F	
Mean (SD)	-0.7 (3.32)	-3.7 (3.58)	-1.26 (5.98)	-6.66 (6.44)
Median	-1.2	-3.7	-2.16	-6.66
Min, Max	-10.0, 8.2	-9.8, 5.5	-18.0, 14.76	-17.64, 9.9
Analysis Results				
Least-Squares Mean Difference (SE)	-2.5 (0.61)		-4.5 (1.10)	
ANCOVA[1] p-value	0.0001			

1. Analyzed using treatment group as the fixed effect and temperature score at T0 as the covariate

Definitions: SD = Standard Deviation; SE =Standard Error

Source: Tables 6 on page 34 of the report for Study F-302.

Secondary and other efficacy endpoints:

Time-specific measurements of temperature in six hours

The mean temperature measurements, mean changes from baseline temperature, differences in mean changes from baseline, and differences in LSMeans are summarized in Table 5.3.3-7 in terms of °C and converted to °F in Table 5.3.3-8. Treatment differences were statistically significant from 0.5 to 5.5 hours. Effect sizes of the statistically significant treatment differences in mean changes from baseline were mostly between 0.8 and 1.3 ºF from 40 minutes to 5.5 hours and were considered clinically meaningful.

Table 5.3.3-7 Time-Specific Temperature Measurements (°C) and Treatment Differences in 6 Hours

Time (min)	0	5	10	15	20	25	30	40	50	60	75	90	105
Temperature (°C)													
Mean temperature													
APAP 1g	39.39	39.52	39.63	39.68	38.67	38.68	39.63	38.38	38.35	39.25	38.17	39.11	38.96
Placebo	39.29	39.36	39.58	39.68	39.76	39.73	39.82	39.82	38.90	39.79	38.74	39.67	39.61
Mean Change from baseline													
APAP 1g		0.12	0.24	0.29	0.27	0.29	0.24	-0.02	-0.04	-0.14	-0.22	-0.28	-0.43
Placebo		0.07	0.28	0.39	0.47	0.44	0.52	0.53	0.60	0.50	0.45	0.38	0.31
Difference in mean change													
		0.05	-0.04	-0.1	-0.2	-0.15	-0.28	-0.55	-0.64	-0.64	-0.67	-0.66	-0.74

Difference in LSMean													
		0.07	-0.03	-0.08	-0.17	-0.12	-0.25	-0.51	-0.60	-0.58	-0.61	-0.59	-0.67
P<0.05							x	x	x	x	x	x	x

Table 5.3.3-7 continued

Time (hr)	2	2.5	3	3.5	4	4.5	5	5.5	6
Temperature (°C)									
Mean temperature									
APAP 1g	38.93	38.83	38.71	38.59	38.47	38.39	38.36	38.35	38.35
Placebo	39.51	39.31	39.17	39.03	38.93	38.85	38.69	38.69	38.62
Mean Change from baseline									
APAP 1g	-0.46	-0.56	-0.69	-0.81	-0.92	-1.00	-1.03	-1.05	-1.05
Placebo	0.22	0.02	-0.12	-0.27	-0.36	-0.44	-0.60	-0.60	-0.67
Difference in mean change									
	-0.68	-0.58	-0.57	-0.54	-0.56	-0.56	-0.43	-0.45	-0.38
Difference in LSMean									
	-0.60	-0.49	-0.47	-0.45	-0.46	-0.46	-0.33	-0.34	-0.27
P<0.05	x	x	x	x	x	x	x	x	

Source: Table 6.3 on pages 81 to 101 of the report for Study F-302.

Table 5.3.3-8 Time-Specific Temperature Measurements (°F) and Treatment Differences in 6 Hours

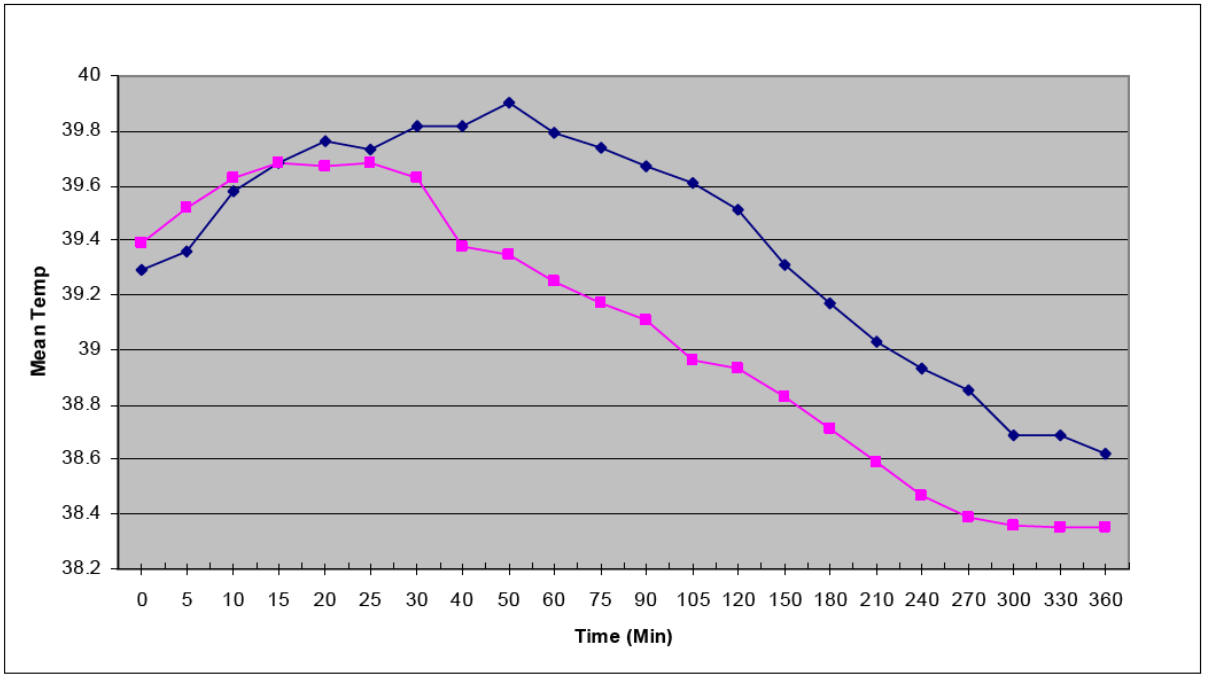
Time (min)	0	5	10	15	20	25	30	40	50	60	75	90	105
Temperature (°F)													
Mean temperature													
APAP 1g	102.9	103.1	103.3	103.4	101.6	101.6	103.3	101.1	101.0	102.7	100.7	102.4	102.1
Placebo	102.7	102.8	103.2	103.4	103.6	103.5	103.7	103.7	102.0	103.6	101.7	103.4	103.3
Mean Change from baseline													
APAP 1g		0.22	0.43	0.52	0.49	0.52	0.43	-0.04	-0.07	-0.25	-0.40	-0.50	-0.77
Placebo		0.13	0.50	0.70	0.85	0.79	0.94	0.95	1.08	0.90	0.81	0.68	0.56
Difference in mean change													
		0.09	-0.07	-0.18	-0.36	-0.27	-0.50	**-0.99**	**-1.15**	**-1.15**	**-1.21**	**-1.19**	**-1.33**
Difference in LSMean													
		0.13	-0.05	-0.14	-0.31	-0.22	-0.45	**-0.92**	**-1.08**	**-1.04**	**-1.10**	**-1.06**	**-1.21**
P<0.05							**x**	**x**	**x**	**x**	**x**	**x**	**x**

Table 5.3.3-8 continued

Time (hr)	2	2.5	3	3.5	4	4.5	5	5.5	6
Temperature (°F)									
Mean temperature									
APAP 1g	102.1	101.9	101.7	101.5	101.2	101.1	101.0	101.0	101.0
Placebo	103.1	102.8	102.5	102.3	102.1	101.9	101.6	101.6	101.5
Mean Change from baseline									
APAP 1g	-0.83	-1.01	-1.24	-1.46	-1.66	-1.80	-1.85	-1.89	-1.89
Placebo	0.40	0.04	-0.22	-0.49	-0.65	-0.79	-1.08	-1.08	-1.21
Difference in mean change									
	-1.22	**-1.04**	**-1.03**	**-0.97**	**-1.01**	**-1.01**	**-0.77**	**-0.81**	-0.68
Difference in LSMean									
	-1.08	**-0.88**	**-0.85**	**-0.81**	**-0.83**	**-0.83**	-0.59	-0.61	-0.49
P<0.05	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	

Source: by conversion of temperature measured in °C to temperature in °F

Figure 5.3.3-1 Time-Specific Mean Temperature Curves



Source: Figure 1 on page 40 of the report for Study F-302.

Secondary and other efficacy endpoints:

Percentage of subjects with temperature <38ºC at any time during six hours

As shown in the table below there was a statistically significant difference of 32 % (about 42% in the APAP group versus about 10% in the placebo group) of subjects with temperature reduced to <38ºC (100.4ºF) during the 6-hour evaluation time period. The effect size of the treatment difference is considered clinically meaningful.

Table 5.3.3-9 Percentage of Subjects with Temperature <38ºC at any Time during Six Hours

Study F-302 Secondary efficacy endpoint	**Placebo (n=29)**	**IV APAP 1g (n=31)**
# subjects (%) with temperature <38ºC during 6 hours	3 (10.3%)	13 (41.9%)
Chi-square p-value	0.006*	

Source: Table 11 on page 37 of the report for Study F-302.

The remaining secondary efficacy endpoints such as WSTD3, the maximum temperature reduction in six hours, and subject global assessment, will not be reviewed in detail for the reasons that WSTD3 represents cumulative effect during only the first half of the dosing interval, maximum temperature reduction indicates only the peak effect, and no expectation of additional value by subject global because objective measures of treatment effects are already available.

5.3.3.3 Summary of Findings and Discussions

Study conduct
The treatment groups in Study F-302 were balanced with regard to demographic characteristics such as age, gender, race, height, and weight and with regard to mean temperature at baseline, which was about 39.3 ºC (102.8 ºF). There were no dropouts from the study. Protocol deviations were relatively small and were not considered as having differential impact on study outcomes.

Efficacy
The efficacy results are summarized in the table below in terms of treatment differences from placebo evaluated by statistical significance and effect sizes for clinical interpretation of the findings. The treatment differences were statistically significant for the primary and the key secondary efficacy endpoints. The effect sizes of treatment differences of 0.8 to 1.3 °F in mean temperature reduction from baseline up to 5.5 hours and 32% more subjects in the IV APAP group than the placebo group with temperature reduced to <38ºC (100.4ºF), are all considered clinically meaningful.

Table 5.3.3-10 Efficacy Summary for Study F-302

Study F-302	**Treatment differences from placebo**	
Efficacy summary	**p<0.05**	**Effect size**
Primary efficacy endpoint, WSTD6		
Difference in LSMeans	x	-4.5 °F
Secondary efficacy endpoints		
Mean changes from baseline in time-specific temperature measurements	0.5 to 5.5 hours	0.8 to 1.3 °F
% of subjects with temperature <38ºC during 6 hours	x	31.6%

Refer to all the efficacy tables in this section.

5.3.3.4 Conclusion

IV APAP 1 g is effective in treating fever induced by endotoxin based on the demonstration of statistically significant and clinically meaningful treatment differences in Study F-302.

5.3.3.5 Appendix

Eligibility criteria for Study F-302

Inclusion Criteria (Screening)

1. Provided written Informed Consent prior to participation in the Study
2. Was a healthy male between the ages of 18 and 75 years of age, inclusive, at randomization
3. Had a Body Mass Index (BMI) ≥ 9 and ≤ 45 lbs/in^2
4. Had the ability to read and understand the Study procedures and had the ability to communicate meaningfully with the Study Investigator and staff
5. Was free of physical, mental, or medical conditions which, in the opinion of the Investigator, might confound quantifying assessments for the Study
6. Was willing to abstain from smoking cigarettes or using nicotine products from the time of admission to Clinic until Study Completion

Inclusion Criteria (Pre-Randomization)

1. Was free of evidence of infection based upon clinical assessment and blood (CBC) and urine testing
2. Had an average baseline oral temperature that was equal to or below 37°C (98.6°F) with no variation of more than 0.4°C (0.7°F) from lowest to highest on three assessments performed during a 30-minute period
3. Had not developed a medically significant allergic or exaggerated systemic response to administration of a test dose of reference standard endotoxin
4. Developed a core temperature of at least 38.6°C (101.5°F) after IV reference standard endotoxin dosed per Study guidelines and had a fever response to endotoxin that is at or near the peak temperature by virtue of two consecutive temperature assessments 5 minutes apart that were within 0.2°C (0.4°F) of each other

Exclusion Criteria (Screening)

1. Had been treated with any medication having antipyretic effects (e.g., corticosteroid, NSAID, aspirin, or acetaminophen) within 2 days of clinic admission (aspirin at low dose for cardiac prophylaxis is allowed, but should not have been taken on the day of the Study)
2. Had significant medical disease(s), laboratory abnormalities, or condition(s) that in the Investigator's judgment could compromise the Subject's welfare, ability to communicate with the Study staff, complete Study activities, or would otherwise contraindicate Study participation
3. Had known hypersensitivity or contraindication to receiving endotoxin that in the Investigator's clinical judgment merited discontinuation from further Study participation
4. Had known hypersensitivity to acetaminophen, the inactive ingredients (excipients) of the IV or PO acetaminophen formulation or the Rescue Medications (ibuprofen, aspirin, and ketorolac)
5. Had known or suspected recent history of alcohol or drug abuse or dependence (as defined by DSM-IV criteria)
6. Had a history of nasal polyps, angioedema, significant or actively treated bronchospastic disease, or any other significant medical condition that contraindicated participation in the Study or receiving endotoxin, Study Medication, or Rescue Medication
7. Had an active infection or other disease or condition that might cause abnormal alterations in body temperature
8. Had impaired liver function, e.g., ALT greater than or equal to 3 times the upper limit of normal, bilirubin greater than 3.0, active hepatic disease, or evidence of clinically significant liver disease (e.g., cirrhosis or hepatitis)
9. Had participated in another clinical Study (investigational or marketed product) within 30 days of Screening

5.3.4 Other efficacy studies

5.3.4.1 Additional analgesic studies

Study CPI-APA-301
Study CPI-APA-301 was planned as a multiple-center (27 sites), randomized, double-blind, placebo-controlled, parallel, multiple-dose (8 doses in 48 hours with open-label use for up to 5 days), analgesic study of acetaminophen (APAP) IV infusion of 1 g in hospitalized patients undergoing abdominal gynecological surgery. Study drug infusion was to be started at the time of post operative recovery. Opioid analgesics were allowed as rescue and concomitant analgesic during the study. Efficacy data in the study were to have included pain intensity (PI) and pain relief (PR) scores at each mid dosing interval and end of dosing interval, information on rescue, and patient global evaluation.

A total of 131 patients, 166 in the IV APAP 1 g group and 165 in the placebo group, received treatment. Mean baseline pain intensity (PI) was 81 mm by VAS scale for pain with activity, 72 mm for pain at rest, and 2.4 on a 4-point categorical scale and was balanced between the treatment groups. Treatment differences were not statistically significant in time-specific pain scores measured at mid and end of dosing interval at most time points during 48 hours and not statistically significant in all derived PI scores, which counted for the primary (SPI24rest and SPI48rest) and most of the secondary efficacy endpoints (SPI24activity, SPI48activity, mean PI per dosing interval). Additional efficacy analyses revealed median time to rescue was 1.1 hours for the APAP group and 0.8 hours for the placebo group and percentage of rescue was 91% (APAP) versus 96% (placebo) during the first 6 hours.

Study RC210 3 001
Study RC210 3 001 was planned as a single-center, randomized, double-blind, active- and placebo-controlled, parallel, single-dose analgesic study of acetaminophen (APAP) IV infusion of 1 g in comparison to propacetamol (PPA) 2g and placebo in subjects undergoing outpatient dental surgery for third molar extraction.

A total of 152 patients, 51 in the IV APAP 1 g group, 51 in the IV PPA 2 g group, and 50 in the placebo group, received a single dose of IV infusion. Mean baseline pain intensity (PI) was 52 mm by VAS scale and 2.0 on a 4-point categorical scale and was balanced between the treatment groups. Treatment differences were statistically significant in time-specific PR, the primary efficacy endpoint, and time-specific PID and summation of pain scores. Median time to rescue was 2.1 hours for the IV APAP 1 g group and 0.7 hours for the placebo group and percentage of rescue was 82% (APAP) versus 98% (placebo) during the 6-hour evaluation period.

Study CN145-004
Study CN145-004 was planned as a single-center, randomized, double-blind, placebo-controlled, parallel, single-dose, dose ranging analgesic study of acetaminophen (APAP) IV infusion 1 g and 2 g in subjects undergoing outpatient dental surgery for third molar extraction.

A total of 297 patients, 132 in the IV APAP 1 g group, 132 in the IV APAP 2 g group, and 33 in the placebo group, received a single dose of IV infusion. Mean baseline pain intensity (PI) was 47 mm by VAS scale and 2.0 on a 4-point categorical scale and was balanced between the treatment groups. Treatment differences were statistically significant in TOTPAR6, the primary efficacy endpoint, and time-specific measurements of PR and PID and summation of pain scores. Median time to rescue was 3.2 hours for the IV APAP 1 g group and 1.0 hour for the placebo group and percentage of rescue was 91% (APAP) versus 97% (placebo) during the 8-hour evaluation period.

Study 136-01-03
Study 136-01-03 was planned as a multiple-center (11 sites), randomized, double-blind, placebo-controlled, parallel, single-dose, analgesic study of acetaminophen (APAP) IV infusion of 1 g in hospitalized patients undergoing total hip arthroplastic surgery. The planned sample size was 60 patients per treatment group.

The study was terminated early due to particulates detected in the placebo injection. A total of 69 (of the 120 to be enrolled) patients received treatment including 35 patients in the IV APAP 1 g group and 34 in the placebo group. Median time to rescue was 4.7 hours for the APAP group and 1.4 hours for the placebo group and percentage of rescue was 57% (APAP) versus 85% (placebo) during the first 6 hours.

Study 136-02-03
Study 136-02-03 was planned as a multiple-center (16 sites), randomized, double-blind, placebo-controlled, parallel, multiple-dose (4 doses at 0, 4, 10, and 16 hours), analgesic study of acetaminophen (APAP) IV infusion of 1 g in hospitalized patients undergoing total hip arthroplastic surgery. The planned sample size was 100 patients per treatment group.

The study was terminated early due to particulates detected in the placebo injection. A total of 61 (of the 200 to be enrolled) patients received treatment including 30 patients in the IV APAP 1 g group and 31 in the placebo group. Median time to rescue was >4 hours for the APAP group and 1.3 hours for the placebo group and percentage of rescue was 50% (APAP) versus 81% (placebo) during the first 4 hours.

Study 136-03-03
Study 136-03-03 was planned as a multiple-center (14 sites), randomized, double-blind, placebo-controlled, parallel, multiple-dose (4 doses at 0, 4, 10, and 16 hours), analgesic study of acetaminophen (APAP) IV infusion of 1 g in hospitalized patients undergoing vaginal hysterectomy surgery. The planned sample size was 100 patients per treatment group.

The study was terminated early due to particulates detected in the placebo injection. A total of 44 (of the 200 to be enrolled) patients received treatment including 23 patients in the IV APAP 1 g group and 21 in the placebo group. Median time to rescue was >4 hours for the APAP group and 0.9 hours for the placebo group and percentage of rescue was 39% (APAP) versus 81% (placebo) during the first 4 hours.

Study CPI-APA-351
Study CPI-APA-351was planned as a multiple-center (15 sites), randomized, open-label, standard of care-controlled, parallel, multiple-dose study of acetaminophen (APAP) IV infusion dosing regimen of 1000 mg q6 hours and 650 mg q4 hours to be given for five days in patients with pain or fever who were in need of IV treatment.

5.3.4.2 Additional antipyretic study

Study CPI-APF-303 was planned as a randomized, double-blind, active-controlled, parallel, single-dose study of acetaminophen (APAP) 1 g by IV infusion in comparison to the same dose given by oral route for the treatment of endotoxin-induced fever in healthy adult males.

A total of 105 subjects, 54 in the IV APAP 1 g group and 51 in the oral APAP 1 g group, received treatment. Mean baseline temperature was 38.8 ºC (101.8 ºF) in both treatment groups. The mean change of temperature from baseline was 0.7 ºC (1.26 ºF) for the IV APAP group and 1.0 ºC (1.80 ºF) for the oral APAP group at the end of 6-hour evaluation period. Without placebo as a comparison treatment effects could not be determined. Treatment differences in time-specific measurements of mean change of temperature from baseline showed 0.2-0.3 ºC (0.36-0.54 ºF) more temperature reduction during the Hours 0.5 to 1.5 and 0.2-0.3 ºC (0.36-0.54 ºF) less temperature reduction during the Hours 4.5 to 6 in the IV APAP group than the oral APAP group. However,

there were no statistically significant difference in WSTD3 and WSTD6 (weighted sum of temperature differences from baseline over three and six hours, respectively). The protocol defined primary efficacy endpoint WSTD2 was not appropriate because it did not address the main issue whether the antipyretic effects of IV APAP could last for approximately the entire dosing interval.

5.3.4.3 Pediatric studies

There were three pediatric studies, Study RC210 3 006, CN145-001, and CPI-APA-352. None could be used to support efficacy for the reasons that Study RC210 3 006 and CN145-001 were active-controlled studies using unapproved drug (b) (4) as a control and had a non inferiority design, and that Study CPI-APA-352 was an open-label study without controls. (Refer to Dr. Spaulding's review for safety assessment of pediatric studies.)

5.3.4.4 Conclusion

The results of these studies presented above could not be used to support efficacy for various reasons: no demonstration of statistically significant and clinically meaningful treatment differences as in Study CPI-APA-301; single-dose evaluation in non target population as in Study RC210 3 001 and Study CN145-004; incomplete studies due to particulates in placebo infusion for Studies 136-01-03, 136-02-03, and 136-03-03; open-label studies designed to evaluate safety as in Study CPI-APA-351 and CPI-APA-352; active-controlled studies with no demonstration of superiority on key efficacy parameters as in Study CPI-APF-303, RC210 3 006, and CN145-001.

6. INTEGRATED REVIEW OF EFFICACY

Summary of Efficacy Results and Conclusions

Three Phase 3 efficacy studies have been reviewed in detail, two analgesic studies (Study 3-002 and Study A-304) and one antipyretic study (Study F-302). All three studies had a randomized, double-blind, placebo-controlled design. The analgesic studies were multiple-dose studies of IV APAP 1 g dosed every 6 hours (both studies) and 650 mg dosed every 4 hours (Study A-304 only) in hospitalized patients with post operative pain associated with orthopedic surgery in Study 3-002 and with abdominal laparoscopic surgery in Study A-304. The antipyretic study was a single-dose study of IV APAP 1 g in treating endotoxin-induced fever in healthy adult males.

The studies enrolled representative sample populations with the treatment groups approximately balanced in demographic characteristics. Only a very small proportion of patients (<10%) dropped out from the studies, mainly due to withdrawal of consent and adverse events (AEs).

The key evidence in support of analgesic efficacy for acetaminophen IV 1 g in Study 3-002 is the demonstration of statistically significant and clinically meaningful treatment differences in time-specific pain measurements for six hours in the first dosing interval supported by a 33% (~20mg) more reduction of morphine consumption (38 mg versus 57 mg) and significantly lower pain intensity adjusted for morphine consumption over 24 hours in comparison to placebo. The key evidences in support of analgesic efficacy for acetaminophen IV 1 g and 650 mg in Study A-304 are the demonstrations of statistically significant treatment differences in SPID over 24 hours supported by significant treatment differences in time-specific pain measurements and in derived mean pain scores per dosing interval.

The key evidence in support of antipyretic efficacy for acetaminophen IV 1 g in Study F-3002 is the demonstration of statistically significant and clinically meaningful treatment difference in summation of temperature reduction over 6 hours supported by a 0.8 to 1.3°F more temperature reduction than placebo in the time interval of 40 minutes to 5.5 hours based on time-specific temperature measurements and 32% more subjects with temperature reduced to <38ºC (100.4ºF) than placebo.

The sample sizes of subpopulations were too small to allow subpopulation analyses with regard to age, gender, or race. Treatment differences in end-of-dosing assessments of PR in Study A-304 provided support for every 6-hour dosing of APAP 1 g and every 4-hour dosing of APAP 650 mg for the pain indication. Treatment differences in summation of temperature reduction over 6 hours supported by clinically meaningful further temperature reduction by time-specific measurement provided support for every 6-hour dosing of APAP 1 g for the fever indication.

Acetaminophen IV treatments have been shown to be efficacious in treating fever and is considered beneficial in treating mild to moderate pain and in supplementing opioid analgesia in treating moderate to moderately severe post-surgical pain in a hospital setting based on the results of the three efficacy studies.

6.1 Proposed Indication

The proposed indication for acetaminophen IV injection is for the treatment of acute pain and fever.

6.2 Methods/Study Design

The three pivotal Phase 3 studies reviewed in detail were randomized, double-blind, placebo-controlled efficacy studies of pain (Study 3-002 and A-304) and fever (Study F-002). Study 3-002 was a multiple-center,

randomized, double-blind, active- and placebo-controlled, parallel, multiple-dose (4 doses in 24 hours) analgesic study of acetaminophen (APAP) 1 g IV infusion in hospitalized patients undergoing orthopedic surgery. Study A-304 was a multiple-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose (24 hours) analgesic study of two different dosing regimens (1 g q6 hours and 650 mg q4 hours) of acetaminophen (APAP) IV infusion in hospitalized patients undergoing abdominal laparoscopic surgery. Study CPI-APF-302 was a randomized, double-blind, placebo-controlled, parallel, single-dose study of acetaminophen (APAP) 1 g IV infusion for the treatment of endotoxin-induced fever in healthy adult males.

The primary efficacy parameter was time-specific measurements of PR during the first six hours after the initial dose in Study 3-002, SPID24 (the Sum of Pain Intensity Differences from baseline over 24 hours) in Study A-304, and was WSTD6 (weighted sum of temperature differences from baseline through 6 hours) in Study F-302.

The secondary and other efficacy parameters reviewed were basically time-specific pain measurements, derived pain scores (including summation of pain scores and mean score per dosing interval), and endpoints related to taking rescue medication (time to rescue, percent of rescue, and amount of rescue) in analgesic studies, and time-specific temperature reduction from baseline and percentage of subjects with temperature reduced to <38°C (100.4°F) during the 6-hour period. The main focus was the duration of effects of the initial dose and of the repeated dosing.

6.3 Demographics

Demographic and baseline characteristics of the sample population in each study are tabulated and described in detail in the individual study reviews in Section 5.3. The study of post orthopedic surgical pain (Study 3-002) had more elderly patients, about half male and half female patient populations, and three quarters of patients with moderate pain and one quarter with severe pain at baseline (mean baseline PI of 2.2 on a categorical scale and 58 mm on a VAS scale). The study of post abdominal laparoscopic surgical pain (Study A-304) had more female patients (80%) and relatively low pain severity at baseline (mean baseline PI of 1.9 on a categorical scale and 53 mm on a VAS scale). The study of endotoxin induced fever (Study F-302) was conducted in non elderly male healthy volunteers who had mean temperature increase to 39.3 ºC (102.8 ºF) at baseline. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight in all of the studies.

6.4 Patient Disposition

Patient disposition in each study is presented and discussed in detail in Section 5.3. Dropouts accounted for a relatively small proportion of the study population in each of the studies (9% in Study 3-002 and 7% each in Study A-304 and Study F-302). The most common reasons for dropouts were withdrawal of consent (14/31 dropout cases) and adverse events (8/31 dropout cases) in the two analgesic studies (refer to Dr. Spaulding's safety review for dropouts due to AEs). The reason for dropouts in the fever study was the need for rescue (all four dropout cases).

6.5 Analysis of the Primary Endpoint(s)

Analgesic effects
The primary efficacy endpoint in Study 3-002 was time-specific pain relief scores measured sequentially during the first six hours after the initial dose. Treatment differences between IV APAP 1 g and placebo were statistically significant during the entire six-hour period. The results were confirmed by Dr. Petullo's analyses with various methods of adjustment for multiplicity and sensitivity analyses using different ways of missing data management.

The primary efficacy endpoint in Study A-304 was SPID24, or the summation of PID over 24 hours of treatment. Treatment differences between IV APAP 1 g and placebo were statistically significant based on

analyses with and without randomization period included in the statistical model and based on sensitivity analysis. The results were confirmed by Dr. Petullo based on his analyses of data of the ITT population. He concluded that randomization period had no impact on study results and it was acceptable to use pooled placebo group as a comparison to active treatments.

Antipyretic effects
The primary efficacy endpoint in Study F-302 was WSTD6, or weighted sum of temperature differences from baseline through 6 hours. Treatment differences between IV APAP 1 g and placebo were statistically significant based on analyses with and without imputation of data after rescue. Statistical reviewer, Dr. Feng Li agreed with the results of the Applicant's analyses.

6.6 Secondary Endpoint(s)

Analgesic effects
The key secondary efficacy endpoints in Study 3-002 included single-dose measurements such as time-specific PID during the first six hours, derived pain scores (TOTPAR6, SPID6, and SPRID6) over six hours, and time to rescue and percentage of patients taking rescue, as well as multiple-dose measurements such as amount of rescue medication, average PI in 24 hours, and average PI in 24 hours adjusted for the amount of rescue. As reviewed in detail in section 5.3 and summarized in the table below, single-dose effects of IV APAP 1 g were supported by statistically significant treatment differences in time-specific pain measurements and derived pain scores. Multiple-dose effects of IV APAP 1 g were supported by statistically significant treatment differences (33% more than placebo) in reduction of morphine consumption (38 mg versus 57 mg) and in the average pain intensity adjusted for morphine consumption over 24 hours.

The observations that most patients (88%) requested rescue with median time to rescue being three hours (versus 0.8 hours in placebo) during the first dosing interval suggested that the pain could not be managed by the use of acetaminophen alone for more than a few hours. After the start of morphine treatment (a relatively strong analgesic) it was difficult to show additional pain reduction by the use of APAP (a relatively weak analgesic) as compared to placebo as shown in PI measured at 18, 20, and 24 hours. The clinical impact of reduced morphine use could not be evaluated because of the small amount of morphine consumption and limited sample size.

Table 6.1 Summary of Results of Secondary Efficacy Measurements in Study 3-002

Study 3-002 Efficacy summary	Statistically significant treatment differences: APAP 1 g versus placebo				
Efficacy endpoint	24 hours	Dosing interval			
		1st	2nd	3rd	4th
Time-specific PID (VAS)		x (15-30mm)	*N/A	*	*
Time-specific PID (categorical)		x (0.5-0.7)	*N/A	*	*
TOTPAR6		x			
SPID6 (VAS)		x			
SPID6 (categorical)		x			
SPRID6		x			
MPI (average PI by VAS)	x				
MPI (average PI by categorical)	x				
MPI (VAS) adjusted for rescue	x				
MPI (categorical) adjusted for rescue	x				
Median time to 1st rescue	2.2 (3 vs 0.8) hr	2.2 (3 vs 0.8) hr			
% of patients taking rescue	0 (100% in both)	-12% (88 vs 100%)			
Amount of rescue: morphine (mg)	-19.1 (33%↓)	-8.2 (46%↓)	-2.7 (18%↓)	-3.8 (31%↓)	-4.3 (34%↓)

*Note: Pain was not measured during the second dosing interval and was measured only at 18 hours (the end of third dosing interval) and 20 and 24 hours (the 2-hour after and end of fourth dosing interval).

The key secondary efficacy endpoints in Study A-304 included 24-hour evaluation of time-specific pain scores (PR and PI), derived pain scores (TOTPAR24 and SPID24-sensitivity analysis), mean pain scores per dosing interval, and percentage of patients taking rescue per dosing interval and median time to the first rescue. As reviewed in detail in section 5.3 and summarized in the table below, effects of IV APAP 1 g and 650 mg were supported by statistically significant treatment differences in summation of pain scores over 24 hours and in time-specific pain measurements as well as the derived mean pain scores per dosing interval, especially during the first few dosing intervals.

The average baseline pain intensity of less than moderate and relatively small proportions of patients requesting rescue (e.g., <50% in the first dosing interval and ≤12% in the other dosing intervals for the APAP groups) with median time to rescue beyond the end of first dosing interval in both treatment groups, suggested that the pain associated with abdominal laparoscopic surgery in the morning of the day after surgery was not sufficiently strong to allow for 24-hour assessment.

Table 6.2 Summary of Results of Secondary Efficacy Measurements in Study A-304

Study A-304	Statistically significant treatment differences											
Efficacy summary	APAP 1 g versus placebo					APAP 650 mg versus placebo						
Efficacy endpoint	24 hours	Dosing interval				24 hours	Dosing interval					
		1st	2nd	3rd	4th		1st	2nd	3rd	4th	5th	6th
SPID24 WOCF	x					x						
SPID24 BOCF	x					x						
TOTPAR24	x					x						
SPID (1st dosing interval)		x					x					
TOTPAR (1st dosing interval)		x										
Time-specific PR		x	x	x				x	x	x		
Time-specific PI							x	x	x			
Mean PR/dosing interval		x	x	x				x	x	x	x	x
Mean PI/dosing interval		x	x				x	x	x			x
Median time to 1st rescue (hours)	1.1 (10.4 vs 9.3)					7.1 (16.4 vs 9.3)						
% of patients taking rescue		-10%	0%	2%	n/a		-13%	4%	-1%	1%	3%	n/a

Antipyretic effects

The key secondary and other endpoints were temperature reductions from baseline based on time-specific sequential measurements of temperature over six hours and percentage of subjects with temperature reduced to <38ºC (100.4ºF) during six hours. Treatment differences in time-specific temperature changes from baseline were statistically significant from 0.5 to 5.5 hours and there were 0.8 to 1.3°F more temperature reduction in the APAP 1 g group in comparison to placebo during the time interval of 40 minutes to 5.5 hours. The treatment difference of 32% more subjects in the IV APAP group than the placebo group with temperature reduced to <38ºC (100.4ºF) was also statistically significant. The effect sizes of the statistically significant treatment differences are considered clinically meaningful.

6.7 Subpopulations

Subpopulation analyses of efficacy are not applicable because of the very small subpopulation size of the study groups divided by age, gender or race. For example, there were basically less than 30 patients (sample size cut into half) in the subgroups characterized by gender and elderly status in Study 3-002, small subgroups of elderly, male, or non-Caucasian in Study A-304, and no elderly or female in Study F-302.

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

It is a challenge to use median time to rescue as a measure of single-dose duration in case of too much pain that majority of patients would request rescue early or in case of not enough pain that less than 50% of the study population would need rescue. As shown in Study 3-002, Study A-301, and the two single-dose dental studies (refer to the Review Section 5.3.4.1 for detail) median time to rescue was about 2 to 3 hours when >80% patients in the APAP group requested rescue after the initial dose due to too much pain. On the other hand, with less than moderate baseline PI as in Study A-304, median time to rescue were beyond first dosing interval in both APAP and placebo groups when there were ≤50% study population in the two groups requested rescue during the initial dosing interval. In the three incomplete studies the pain level appeared to be in the right range for using median time to recue to define single-dose duration. The median time to rescue was 4.7 hours (versus 1.4 hours for placebo) in Study 01-03 and >4 hours (versus 0.9-1.3 hours for placebo) in Studies 02-03 and 03-03 when the percentage requesting rescue was 40 to 60% in the APAP group and >80% in the placebo group.

There were no end-of-dosing assessments planned for evaluation of multiple-dose effects in Study 3-002. Pain intensity was not measured in the second dosing interval. Comparison of PI at the end of third and fourth dosing interval showed basically no treatment difference. The results of analyses of end-of-dosing assessments in Study A-304 showed treatment differences in PR at the end of first three dosing intervals in support of the 6-hour dosing interval for APAP 1 g and at the end of dosing intervals 2 to 6 in support of the 4-hour dosing interval for APAP 650 mg for the pain indication.

The evidence in support of every 6-hour dosing for APAP 1 g is the demonstration of statistically significant and clinically meaningful treatment difference in summation of temperature reduction over 6 hours in Study A-304 and supported by significantly more temperature reduction of 0.8 to 1.3°F up to 5.5 hours by using APAP than placebo based on time-specific measurements.

6.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance effects for either fever or acute pain could not be adequately evaluated because of the rapid resolution of these signs/symptoms in a relatively short period that leaves only a small window of opportunity for demonstration of treatment effects.

6.10 Additional Efficacy Issues/Analyses

None.

7. INTEGRATED REVIEW OF SAFETY

Refer to Dr. Spaulding's safety review for information in detail.

8. POSTMARKETING EXPERIENCE

Refer to Dr. Spaulding's safety review for information in detail.

9. APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

Refer to Dr. Spaulding's safety review for information in detail.

9.2 Labeling Recommendations

Labeling will be reviewed separately.

9.3 Advisory Committee Meeting

There is no Advisory Committee Meeting planned for IV acetaminophen. Refer to Dr. Spaulding's safety review for summary information on previous Advisory Committee's recommendations with regard to safe use of acetaminophen containing products.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	ACETAMINOPHEN FOR INJECTION FOR IV USE

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/s/

CHRISTINA L FANG
10/23/2009

ELLEN W FIELDS
10/24/2009

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022450
Priority or Standard	Priority
Submit Date(s)	13 May 2009
Received Date(s)	15 May 2009
PDUFA Goal Date	13 November 2009
Division / Office	Anesthesia, Analgesia & Rheumatology Products
Reviewer Name(s)	Jacqueline A. Spaulding, M.D.
Review Completion Date	06 October 09
Established Name	Acetaminophen injection for intravenous use
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Non-opioid analgesic
Applicant	Cadence
Formulation(s)	Intravenous
Dosing Regimen	**Adults and adolescents weighing 50 kg and over:** 650 to 1000 mg every 4-6 hours **Adults and adolescents weighing under 50 kg and all children::** 12.5 to 15 mg/kg every 4-6 hours (b) (4)

Indication(s)	Acute pain and fever
Intended Population(s)	Adult and Pediatric

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the context of the finding of efficacy, based on my review of the safety data submitted in this application, I recommend the approval of intravenous acetaminophen for the indications of the treatment of acute pain and fever in adult and pediatric patients.

1.2 Risk Benefit Assessment

The assessment of efficacy was conducted by Christina Fang, M.D. with a secondary review by Ellen Fields, M.D., MPH. Dr. Fang found that IV acetaminophen was efficacious for the indications of fever and pain in adults based on the results of three adequate and well-controlled Phase 3 efficacy trials. Pediatric efficacy was extrapolated from the adequate and well-controlled studies of IV acetaminophen in adults and the use of oral acetaminophen in pediatric patients.

No new or unexpected safety signals were detected upon my review of the safety database. As with oral acetaminophen, the use of IV acetaminophen requires caution when administered to patients with pre-existing hepatic disease, hepatic dysfunction or when other hepatic risk factors are present including: alcoholism, malnutrition, or hypovolemia.

Across the 19 clinical studies, safety data was derived from a variety of medical and surgical conditions in adult and pediatric populations in the hospital setting. . In addition, the Applicant has fulfilled the Division's requirement that the safety database include a minimum of 300 adult and 300 pediatric exposures; and a minimum of 50 adult and 50 pediatric patients treated with IV acetaminophen for five days.

The risk benefit assessment of IV acetaminophen is adequate for the treatment of acute pain and fever in adults and pediatric patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Please see Dr. Fang's review for this information.

2.2 Tables of Currently Available Treatments for Proposed Indications

Please see Dr. Fang's review for this information.

2.3 Availability of Proposed Active Ingredient in the United States

Please see Dr. Fang's review for this information.

2.4 Important Safety Issues With Consideration to Related Drugs

The key safety issue related to the use of acetaminophen containing products is drug-induced hepatotoxicity. Acetaminophen hepatotoxicity is believed to be most closely related to dose and, in overdose, the mechanism of hepatic injury is well studied and understood. However, acetaminophen hepatotoxicity has been observed at doses that are at or below recommended dose of 4 grams per day. In these latter cases factors such as alcohol, starvation, use of drugs that induce CYP2E1 and genetics are believed to enhance the hepatotoxic effect of acetaminophen.

Acetaminophen is one of the most commonly used medications. The moiety is available as a single agent as an over-the-counter product or in combination with other medications like opioids and antihistamines as either prescription of over-the-counter products. Acetaminophen is classified as safe and effective when used within the recommended daily dose of 4 g in adults. More importantly, the acetaminophen monograph instructs that the use of acetaminophen in doses higher than the recommended dose, or in patients with hepatic impairment, hepatic disease, alcoholism, malnutrition, and renal disease may result in hepatic injury including hepatotoxicity and death

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Please see Dr. Fang's review for this information.

2.6 Other Relevant Background Information

Please see Dr. Fang's review for this information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Please see Dr. Fang's review for this information.

3.2 Compliance with Good Clinical Practices

Please see Dr. Fang's review for this information.

3.3 Financial Disclosures

Please see Dr. Fang's review for this information.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see Dr. Fang's review for this information.

4.2 Clinical Microbiology

Please see Dr. Fang's review for this information.

4.3 Preclinical Pharmacology/Toxicology

Please see Dr. Fang's review for this information.

4.4 Clinical Pharmacology

Please see Dr. Ji's review for this information

5 Sources of Clinical Data

Please see Dr. Fang's review for this information.

6 Review of Efficacy

Please see Dr. Fang's review for this information.

7 Review of Safety

Safety Summary

The emphasis in the safety review of this application was to assess whether the safety profile of IV acetaminophen differed from that of established oral acetaminophen. In general, there were no unexpected on unusual findings in either the adult or pediatric clinical programs. As per the End-of-Phase 2 meeting requirements set forth by the Division, the Applicant has exposed adequate numbers of patients to IV acetaminophen A total of 1020 adult patients have received IV acetaminophen in clinical trials including 37.3% (n=380) who received 5 or more doses and 17.0 % (n=173) who received more than 10 doses. A total of 355 pediatric patients have received IV acetaminophen in clinical trials including 59.7% (n=212) who received 5 or more doses and 43.1 % (n=153) who received more than 10 doses.

In adult clinical trials, a total of 8 deaths occurred. None of the deaths were related to IV acetaminophen treatment. There were no significant differences in the incidence of serious adverse events between treatment groups [IV acetaminophen (5.6%) and placebo (5.7%)]. The overall incidence of adverse events leading to discontinuation was both low and similar in patients who received IV acetaminophen (3%) and in patients who received placebo (4%). The most common adverse events in adult patients treated with IV acetaminophen (incidence ≥ 5% and greater than placebo) were nausea, vomiting, headache, and insomnia. No new safety information related to hepatic laboratory analyses and hepatic related adverse events were identified.

In the pediatric population, there were no placebo-controlled trials. There were no deaths. The incidence of serious adverse events was 8.5% in pediatric clinical trials with the children's (2-12 years old) age stratum experiencing the highest proportion (10.5%) of SAEs as compared to neonates, infants and adolescents. There was no evidence these SAEs were associated with IV acetaminophen but were consistent with the underlying disease processes. In pediatric patients, the overall incidence of adverse events leading to discontinuation was low (n=5/355, 1.4%), however all 5 of these discontinuations were secondary to liver function test elevations. These five cases had confounding factors (concomitant hepatotoxic medications, posterior spinal fusion surgery) that may have contributed to hepatic enzyme elevations. The most common

adverse events in pediatric patients treated with IV acetaminophen (incidence ≥ 5%) were nausea, vomiting, constipation, pruritus, agitation and atelectasis. No new safety information related to hepatic laboratory analyses and hepatic related adverse events were identified.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from a total of fourteen adult clinical trials are included in this submission, three studies which enrolled healthy subjects and eleven studies which enrolled patients. An overview of the fourteen studies is presented in Table 1.

Table 1: Overview of Clinical Studies of IV Acetaminophen in Adults

Protocol	Phase	Population	Indication	Study Design	Single (S) Repeated (R) dose/ Duration	IV APAP	Control	Total
116-01-03	1	Healthy males	N/A	Randomized, O/L, 2 way, crossover PK, safety	S/6h	21	PO APAP n=22	22
98051C-CIS	1	Healthy males	N/A	Randomized, O/L, 3 way, crossover PK, safety	S/6h	26	IV PPA n=25	27
CPI-APA-101	1	Healthy males	N/A	Randomized, O/L, 4 way, crossover PK, safety	R/48h	34	PO APAP n=36	38
CPI-APF-302	3	Healthy males	Fever	Randomized, ,DB, PC, endotoxin-induced fever, efficacy, safety	S/6h	31	Placebo n=29	60
CPI-APF-303	3	Healthy males	Fever	Randomized, DB, PC, endotoxin-induced fever, efficacy, safety	S/6h	54	PO APAP N=51	105
CPI-APA-304	3	Inpatient	Pain	Randomized, DB, PC, abdominal laparoscopic surgery, efficacy safety	R/24h	134	Placebo N=110	244
CN 145-004	3	Outpatient	Pain	Randomized, DB, PC, 3rd molar extraction, efficacy, safety	S/6h	264	Placebo N=33	297
RC 210 3 001	3	Outpatient	Pain	Randomized, DB, PC, hip arthroplasty, PK efficacy, safety	S/6h	51	IV PPA n=51 Placebo N=50	152

Protocol	Phase	Population	Indication	Study Design	Single (S) Repeated (R) dose/ Duration	IV APAP	Control	Total
RC 210 3 002	3	Inpatient	Pain	Randomized, DB, PC, hip or knee arthroplasty, efficacy, safety	R/24h	49	IV PPA N=50 Placebo N=52	151
136-02-03	3	Inpatient	Pain	Randomized, DB, PC hip arthroplasty, efficacy, safety	R/24h	30	Placebo N=31	61
136-03-03	3	Inpatient	Pain	Randomized, DB, PC, vaginal hysterectomy, efficacy, safety	R/24h	23	Placebo N=21	44

Source: Applicant's submission (Adult ISS, pp.17-18)

Of the fourteen studies, three were phase 1 pharmacokinetic (PK) studies that involved single and repeat-dosing. There were eleven phase 3 adult clinical studies, and 10/11 of these studies can be classified as adequate and well controlled clinical studies. Furthermore, five out of the ten randomized, double-blind, placebo-controlled studies involved repeat dose testing. One phase three study was an open-label study.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MEDDRA, Version 10.0) system. The appropriateness of the applicant's coding was assessed by comparing the preferred terms to the verbatim terms recorded by investigators within a sampling of case report forms. The coding was found to be accurate.

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

The Applicant pooled the safety data across studies based on the following: population enrolled, study design and dosing regimen as displayed in Table 2.

Table 2: Study Pools for Analysis of Safety Data in Adults

	Study Pools (Number Dosed with IV APAP)					
Protocol Identifier	**Studies involving patients**	**Studies involving healthy adults**	**Single dose studies**	**Repeat dose studies**	**Single dose PK studies**	**Repeat dose PK studies**
116-01-03		21	21		21	
98051C-CIS		50	50		25	
CPI-APA-101		34		34		34
CPI-APF-302	31		31			
CPI-APF-303	54		54			
CPI-APA-301	166			166		
CPI-APA-304	134			134		
CPI-APA-351	183			183		
CN 145-004	264		264			
RC 210 3 001	51		52			
136-01-03	35		35		35	
RC 210 3 002	49			49		
136-02-03	30			30		
136-03-03	23			23		
Total IV APAP	**1020**	**81**	**482**	**619**	**81**	**34**
Total in Group	**1727**	**163**	**776**	**1078**	**115**	**70**

Source: Applicant's submission (Adult – ISS, pg. 25)

The Applicant submitted safety data pooled as follows:

1. studies involving patients
2. studies involving healthy adults
3. single-dose studies
4. repeat-dose studies
5. single-dose PK studies and
6. repeat-dose PK study

The initial submission did not contain the subset of patients enrolled in randomized, double-blind, placebo-controlled studies. Therefore, the Applicant was asked to reanalyze the safety population to include the complete adverse event data and summary statistics for the pools below:

1. all adults in randomized, double-blind, placebo –controlled studies
2. all adult patients
3. all patients in repeat-dose studies and

4. all patients in single-dose studies

7.2 Adequacy of Safety Assessments

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

Drug Dose and Duration Exposure

A summary of exposure for the all adult patient pool is displayed in Table 3.

Table 3: Exposure to IV Acetaminophen and Placebo – All Adult Patients

Parameter:	IV APAP[1] (N = 1020)	Placebo (N = 525)
Number of doses received, n (%)		
1	440 (43.1)	158 (30.1)
2 to 4	200 (19.6)	147 (28.0)
5 to 6	53 (5.2)	70 (13.3)
7 to 10	154 (15.1)	150 (28.6)
> 10	173 (17.0)[3]	0
Number of doses received		
Mean (SD)	6.5 (7.97)	4.4 (2.76)
Median	4.0	4.0
Minimum, Maximum	1, 30	1, 8
Duration of treatment (days)		
Mean (SD)	1.45 (1.560)	1.06 (0.683)
Median	1.01	1.01
Minimum, Maximum	0.3, 5.4	0.2, 2.3
Total dose received (g)		
Mean (SD)	5.7 (6.03)	NA
Median	3.96	
Minimum, Maximum	1.0, 21.0	
Average Daily Dose (g), Repeated-dose Studies[2]		
Mean (SD)	3.95 (0.180)	NA
Median	3.96	
Minimum, Maximum	2.8, 5.2	

Source: Applicant's submission (Adult ISS, pg.. 42)

In the IV acetaminophen group, 37% of adult patients received ≥ 5 doses of study drug and 17% received > 10 doses of IV acetaminophen.

Demographics

In response to a request for additional information, the applicant submitted demographic data for all adults enrolled in randomized, double-blind, placebo-controlled studies as shown in Table 4.

Table 4: Demographics Study Group: All Randomized, Double-blind, Placebo-controlled Adult Patient Studies Safety Population

Parameter	IV APAP[2] (N=783)	Placebo (N=525)
Gender		
Male	238 (30.4%)	137 (26.1%)
Female	545 (69.6%)	388 (73.9%)
Age (years)		
N	783	525
Mean (SD)	38.2 (16.06)	44.5 (15.29)
Median	35.0	44.0
Min-Max	18-87	18-86
Age (years)		
18 to 39	455 (58.1%)	190 (36.2%)
40 to 64	253 (32.3%)	270 (51.4%)
65 to 75	54 (6.9%)	53 (10.1%)
> 75	21 (2.7%)	12 (2.3%)
Race		
American-Indian/Alaska Native	0	0
Asian	11 (1.4%)	13 (2.5%)
Black or African-American	77 (9.8%)	64 (12.2%)
Hispanic	3 (0.4%)	1 (0.2%)
Native Hawaiian/Pacific Islander	1 (0.1%)	2 (0.4%)
Caucasian	676 (86.3%)	432 (82.3%)
Other	15 (1.9%)	13 (2.5%)
Ethnicity		
Hispanic/Latino	75 (9.6%)	61 (11.6%)
Non-Hispanic/Latino	256 (32.7%)	243 (46.3%)
Unknown	452 (57.7%)	221 (42.1%)
BMI (kg/m2)		
< 25	395 (50.4%)	198 (37.7%)
25-< 30	210 (26.8%)	171 (32.6%)
30-< 40	168 (21.5%)	133 (25.3%)
>= 40	10 (1.3%)	23 (4.4%)
BMI (kg/m2)		
N	783	525
Mean (SD)	26.0 (5.21)	27.5 (5.75)
Median	24.9	26.5
Min-Max	17-44	17-45
Body Weight (kg)		
< 50	8 (1.0%)	6 (1.1%)
>= 50	775 (99.0%)	519 (98.9%)

[1] Defined as all 9 studies in adult patients: CPI-APF-302, CN145-004, RC 210 3 001, 136-01-03, RC 210 3 002, 136-02-03 136-03-03, CPI-APA-301, CPI-APA-304
[2] Defined as 1g, 2g and 650 mg.

Source: Applicant's submission (Amendment 8- Response to Clinical Information Request, pp. 4-5)

In general, there were more females than males in both the IV acetaminophen and placebo groups. The IV acetaminophen group was younger than the placebo group with a mean age of 38.4 years vs. 44.5 years respectively. Across racial groups, Caucasians represented the majority and the proportion was comparable in both IV

acetaminophen and placebo groups (86.3% vs. 82.3%) respectively. Similarly, other races (Blacks, Hispanics, Asians, and Native Hawaiian/Pacific Islander) had comparable proportions in both groups.

7.2.2 Explorations for Dose Response

The incidence of TEAES by system organ class in repeat-dose, randomized, double-blind, placebo-controlled adult patient studies is illustrated in Table 5.

Table 5: Incidence of TEAEs by System Organ Class: Repeat-Dose, Randomized, Double-Blind, Placebo-Controlled Adult Patient Studies Safety Population

	IV APAP			
System Organ Class	**650 mg (N=43)**	**1g (N=359)**	**Total (N=402)**	**Placebo (N=379)**
# of Pts with any Event	28 (65.1%)	278 (77.4%)	306 (76.1%)	293 (77.3%)
Gastrointestinal disorders	17 (39.5%)	208 (57.9%)	225 (56.0%)	206 (54.4%)
General disorders and Administration site conditions	5 (11.6%)	57 (15.9%)	62 (15.4%)	78 (20.6%)
Nervous system disorders	3 (7.0%)	50 (13.9%)	53 (13.2%)	54 (14.2%)
Skin and subcutaneous tissue disorders	2 (4.7%)	43 (12.0%)	45 (11.2%)	57 (15.0%)
Psychiatric disorders	4 (9.3%)	29 (8.1%)	33 (8.2%)	28 (7.4%)
Blood and lymphatic disorders	0	25 (7.0%)	25 (6.2%)	24 (6.3%)
Investigations	2 (4.7%)	22 (6.1%)	24 (6.0%)	37 (9.8%)
Respiratory, thoracic and mediastinal disorders	6 (14.0%)	15 (4.2%)	21 (5.2%)	18 (4.7%)

Source: Applicant's submission (Amendment 8-Response to Information Request, ISS, pp 83-95)

Across the 5 repeat-dose, randomized, double-blind placebo-controlled trials, overall TEAE rates were 77.4% in the 1 g IV acetaminophen group and 77.3 % in the placebo group. The 650 mg IV acetaminophen group (N=43) had far fewer patients compared to the 1 gm IV acetaminophen group (N=359) and placebo (379). The system organ class with the highest incidence of TEAEs involved gastrointestinal disorders.. Overall, there were no clinically meaningful differences in the frequency of TEAEs between the 1 gm of IV acetaminophen and placebo group.

7.2.3 Special Animal and/or In Vitro Testing

Please see pharmacology/toxicology review for details on this section.

7.2.4 Routine Clinical Testing

Safety assessments performed in adult clinical trials included: vital signs, physical examination, hematology and chemistry laboratory investigations (including liver function tests), urinalysis, and evaluation for adverse events. Because a primary safety concern for IV acetaminophen involves hepatic events, the LFT monitoring was reviewed and it included laboratory evaluations at screening, daily, and end of study/early termination. Overall, the safety testing for the adult clinical development program appears to be adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new pre-clinical information was submitted in this NDA.

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

Adverse events associated with the use oral acetaminophen are well described in the literature and include, most prominently, hepatotoxicity. These potential adverse events are described in the IV acetaminophen label.

7.3 Major Safety Results

7.3.1 Deaths

A total of 8 deaths occurred in adult controlled and uncontrolled studies. All of the eight deaths occurred in the IV acetaminophen group. Of the eight deaths, seven occurred in the open-label study (CPI-APA-351) and one death occurred in the placebo-controlled post-orthopedic surgery study (RC 210 3 002). Information including narrative, case report forms and data listings for each death was reviewed. None of the deaths appear to be related to IV acetaminophen. Narratives for each death are immediately following:

Patient 001-12 (Study CPI-APA-351)

This 59-year-old male received his first dose of IV acetaminophen 1 gm q6h for pain on 27 June 08 and received his last dose of IV APAP on 02 July 08 for a total of 19 doses. At the time of study entry, the patient's medical history included diabetes mellitus, myocardial infarction, gastric cancer, hypertension, hyperlipidemia, gastric reflux disease and allergy to contrast media. Prior surgical procedures included cholesystectomy, disectomy L4/5, total gastrectomy, distal esophagectomy with Roux-en-Y esophagojejunostomy. Concomitant medications included: metformin, carvedilol, atorvostatin, clopidrogel, bisulfate, glyburide and sucralfate.

The patient underwent distal esophagectomy with Roux-en-Y esophagojejunostomy on (b) (6) a single contrast upper gastrointestinal study showed no evidence of leaking and the patient was started on a clear liquid diet. (b) (6), the patient complained of left-sided chest pain and shortness of breath. A chest CT with contrast was performed which appeared to show evidence of a leak at the anastomosis, left-sided pleural effusion, and left–sided empyema with infectious changes. The patient was subsequently transferred to the surgical intensive case unit (SICU) where a chest tube was placed and the patient was started on broad spectrum antibiotics with response followed by serial chest x-rays. (b) (6), the patient developed increased shortness and breath and hemoptysis and was subsequently intubated due to increased bleeding. The hemoglobin level at that time was 6.0 g/d and the patient was taken to the operating room for an emergency procedure. During this procedure, blood loss continued (approximately 6 liters), the patient experienced cardiac arrest, and despite resuscitative efforts, he died in the operating room.

This death was not related to IV acetaminophen treatment.

Patient 003-06 (Study CPI-APA-351)

This 69-year-old male received his first dose of IV APAP 1 gm q6h for pain on 13 April 2008 and received his last dose on 18 April 2008 for a total of 20 doses

At the time of study entry, the patient's medical history included chronic renal insufficiency, renal failure, rectal bleeding, chronic anemia, hypertension, elevated cholesterol, and emphysema. Prior surgical history included colonoscopy, aortic valve replacement, and right hemicolectomy. Concomitant medications included tamsulosin, simvastatin, furosemide,bupropion, metoprolol XL,pantoprazole,piperacillin/tazobactam, morphine, fondaparinux,albuterol, ipratropium, epoetin alfa, intravenous fat emulsion, ondansetron, neomycin,erythromycin, propoxyphene/acetaminophen, ferrous sulfate, enoxaparin, oxycodone, bisacodyl, magnesium sulfate, hydrocodone/acetaminophen, and enalapril, iron sucrose injection, and acetaminophen.

(b) (6), the patient underwent a right hemicolectomy for stage III colon cancer and appeared to have a normal postoperative course. On 22 April 2008, the patient developed a fever and had positive blood cultures for Enterococcus faecalis and was started on piperacillin/tazobactam and vancomycin. A second blood culture on 27April 2008 was also positive for enterococcus. Because of the subject's guarded renal status, a CT with contrast was not done. A transesophageal echocardiogram was negative for vegetations. The patient was diagnosed with abdominal peritonitis and continued on antibiotics. On (b) (6) a blood culture was negative and the subject was discharged home with a follow-up 21 day course of oral antibiotics.

On (b) (6) the patient was found by his wife to be unresponsive. He was transferred to the hospital by ambulance and admitted with aphasia and hemiparesis consistent with a cerebrovascular accident. The patient was started on aspirin and remained stable except for a single episode of ventricular tachycardia, which was felt to be due to a low magnesium level. During the resuscitation for the ventricular tachycardia, the patient was defibrillated back into a normal sinus rhythm and started on magnesium, amiodarone, and metoprolol. The patient remained stable and was discharged to a rehabilitation facility (b) (6) and then to home the following day. The patient died at home (b) (6)

This death was not related to IV acetaminophen treatment.

Patient 003-22 (Study CPI-APA-351)

This 86-year-old male received his first dose of IV acetaminophen 1 gm q6h for pain beginning on 20 June 2008 and received his last dose on 25 June 2008 for a total of 20 doses.

At the time of study entry, the patient's medical history included colon cancer, anemia, heart murmur, confusion (sundown syndrome), cerebrovascular accident, osteoporosis, hypertension and abdominal aortic aneurysm. Concomitant medications included cefuroxime, famotidine, enoxaparin, morphine, labetalol, tinzaparin, systemic phosphates and haloperidol.

The patient underwent a sigmoid colectomy for cancer (b) (6) and appeared to have a normal postoperative course. Due to postoperative weakness, he was transferred to a facility (b) (6). The patient progressively weakened and refused to eat (b) (6), the decision was made to transfer him to home under hospice care. Later that day, the patient became comatose and experienced a rapid weak pulse, rapid shallow breathing, and severe hypotension. He died later that day.

This death was not related to IV acetaminophen treatment.

Patient 008-05 (Study CPI-APA-351)

This 69–year-old female received her first dose of IV acetaminophen 650 mg q4h for fever beginning on 28 March 08 and received her last dose on 02 April 08 for a total of 30 doses.

At the time of study entry, the patient's medical history included gliobastoma multiforme diagnosed in January 2008 and treated with chemotherapy and radiation therapy, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, stomach ulcers, back surgery for disc rupture, hysterectomy, appendectomy, prior dental implants and heart catherization in 1994 that was reportedly negative, elevated liver enzymes and thrush. Concomitant medications induded losartan, amlodipine, dexamethsone, novulin regular insulin, azithromcyin, clindamycin , piperacillin-tazobactan, metoclopramide, pantoprazole, sertraline, conjugated estrogens, glipizide, alprazolam, propoxyphene/acetaminophen, hydrocodone/acemtaminophen, tramadol and phenytoin.

The patient was admitted to the hospital (b) (6) for treatment of intermittent fever to 103 °F. Prior to admission, she had been treated with levofloxacin for 7 days for a diagnosis that was not specified in either the submission or case report form. The course of levofloxacin was then followed with a course of fluconazole , then another course of levofloxacin and finally a course of amoxicillin/clvulanate. She also experienced watery diarrhea for 2 days prior to admission.

On admission, the patient's vitals were significant for a respiratory rate of 22/iminute and oxygen saturation of 88% on room air; other vitals appeared to be within normal limits (heart rate of 90 beats/minute and temperature of 98.1° F. Her physical examination was significant for slight abdominal distention, otherwise unremarkable. Chest X-ray showed changes consistent with left upper lobe pneumonia. ECG and urinalysis were reported as unremarkable. Treatment was initiated for presumed infection, possibly sepsis, thought to be related to pneumonia or the gastrointestinal process manifesting as diarrhea. She was also treated with supplemental oxygen.

Over her hospital course, a diagnostic workup indicated multiple organ failure as a result of complications from her glioblastoma multiforme, pneumocystis carinii pneumonia, acute cerebrovascular accident, anemia, hypoalbuminemia, sepsis and elevated liver enzymes. The patient received appropriate supportive care, intravenous antibiotics, and steroids, but she continued to deteriorate ultimately requiring mechanical ventilation support. She died of multi-organ failure (b) (6)

This death was not related to IV acetaminophen treatment.

Patient 008-14 (Study CPI-APA-351)

This 70-year-old female received her first dose of IV acetaminophen 1gm q6h for pain on (b) (6) and received her last dose on (b) (6) for a total of 7 doses.

At the time of study entry, the patient's medical history included hypertension, hypothyroidism, diabetes mellitus, hypercholesterolemia, coronary artery disease, myocardial infarction, gastroesophageal reflux disease and slightly elevated AST levels. Prior surgical procedures included hysterectomy and appendectomy. Concomitant medications included diazepam, furosemide, metoprolol, hydroxyzine, famotidine, enoxaparin, cefuroxime, ketorolac, calcium chloride, magnesium sulfate, insulin, morphine, heparin, albumin, and diazepam.

The patient was admitted to the hospital (b) (6) because of chest pain resulting from a myocardial infarction. She underwent coronary bypass graft (b) (6) and her initial post –operative course was stable including labs through (b) (6) she developed severe hypertension with a blood pressure of 60/40. Her hypotension was corrected over several hours with norepinephrine and phenylephrine intravenous drips however, she subsequently developed acute renal failure followed by acute liver failure. That evening the labs associated with her acute renal failure were BUN of 29 and creatinine of 2.6. (b) (6) her liver function tests were elevated with AST or 5204, ALT of 2862, GGT of 52, total bilirubin of 6.4 with direct bilirubin of 3.7. (b) (6) the patient become acidotic, suffered cardiac arrest and died.

This death was not related to IV acetaminophen treatment.

Patient 011-02 (Study CPI-APA-351)

This 87-year-old female received her first dose of IV acetaminophen 1 gm q6h for pain on (b) (6) and received her last dose on (b) (6) for a total of 20 doses.

At the time of study entry, the patient's medical history included congestive heart failure, hypertension, hypokalemia, coronary artery disease, myocardial infarction, paroxysmal atrial fibrillation, metabolic acidosis, urinary tract infection, acute renal failure, intracranial hemorrhage, anorexia, pneumonia, cough, lymphocytopenia, elevated thyroid stimulating hormone, macular degeneration, glaucoma and active T12 and T6 compression fractures. Concomitant medications included nitroglycerin, amiodarone, diltiazem, sodium polystyrene, cholestyramine, piperacillin/tazobactam, latanoprost, dorzolamide hydrochloride ophthalmic solution, timolol, carvedilol, partially hydrolyzed guar gum, dronabinol, furosemide, diltiazem, levalbuterol, levothyroxine, potassium supplementation, bisacodyl, metronidazole, vancomycin,guaifenesin and fluconazole.

After completion of the course of study medication, the patient remained in the hospital for treatment of her multiple disease conditions and eventually was discharged to hospice care (b) (6) the patient developed complications and died.

This death was not related to IV acetaminophen treatment.

Patient 011-03 (Study CPI-APA-351)

This 82-year-old male received his first dose of IV acetaminophen 1 g q6h for pain on (b) (6) and received his last dose on (b) (6) for a total of 20 doses.

At the time of study entry, the patient's medical history included ischemic heart disease, atrial flutter, dyslipidemia, asthma and reactive airway disease, diabetes mellitus, bilateral lower extremity thrombosis, anemia, hypothyroidism, acute renal failure, left renal transitional cell cancer, retroperitoneal fibrosis, right leg lymphedema, gout, urethral obstruction, gastroesophageal reflux disease, right heel pressure sore and spinal stenosis with pseudoclaudication radiculopathy. Concomitant medications included: levothyroxine, pantoprazole, simvastatin, gabapentin, montelukast, metoprolol, nitroglycerin, ocodone/acetaminophen, metronidazole, vancomycin, ondansetron, furosemide, amiodarone, prednisone and castor oil.

The patient was admitted to the hospital (b) (6) for a left nephrectomy scheduled for the following day. During the surgery, it was decided not to proceed as a result of the extensive degree of cancer that was discovered. . On the morning of (b) (6) the subject experienced shortness of breath and was started on oxygen. Later that morning, the patient suffered continued oxygen desaturation and was found to have diffuse rhonchi and bilateral 3+ pitting edema. He suffered a cardiac arrest with his cardiac monitor showing asystole and, after extensive and unsuccessful resuscitative efforts, was pronounced dead.

This death was not related to IV acetaminophen treatment.

Patient 07-123 (Study RC 210 3 002)

This 81-year-old male received his first dose of IV acetaminophen on 1 g q6h for pain on (b) (6) and received his last dose on (b) (6) for a total of 4 doses.

At the time of study entry, the patient's medical history included hypertension, mild tricuspid regurgitation, mild aortic regurgitation, mild mitral regurgitation, moderate aortic stenosis, left hip osteoarthritis, gastroesophageal reflux and hearing deficit. Prior surgical history included hernia repair, bilateral cataract removal, transurethral resection of prostate, and amputation of left 4th digit. Concomitant medications included: lovenox,

cefazolin, morphine sulfate patient controlled analgesia, ondansetron, triamterene, metoprolol, norvac, captopril, senokot, and colace.

(b) (6) the patient underwent a uncomplicated left total hip arthroplasty under spinal anesthesia with midazolam premedication, bupivacaine in the spinal and morphine induction and fentanyl and profopofol for conscious sedation.

(b) (6) the patient was found unresponsive and resuscitated for 30 minutes prior to establishment of a pulse during which time he was intubated and transferred to the critical care unit in 2nd degree atrioventricular block. He was placed on a ventilator and received vasopressor support for persistent hypotension. After suffering a prolonged course of ventricular ectopy, he was pronounced dead later that day.

This death was not related to treatment with IV acetaminophen.

7.3.2 Nonfatal Serious Adverse Events

In the all adult patient study pool a total of 57 patients in the IV acetaminophen group experienced a serious treatment emergent adverse event (TEAE). The overall incidence of serious TEAEs in the IV acetaminophen group (5.6%) was comparable to the placebo group (5.7%). I selected serious adverse events (SAEs) that occurred at higher frequencies and SAEs that I believed were uniquely relevant to the safety of IV APAP. Subsequently, I reviewed case narratives and case report forms for 25 out of the 57 patients in the IV acetaminophen group that met my selection criteria. The case narratives for these patients are included below:

Accidental overdose
Accidental overdose defined as greater that 4g of acetaminophen in a 24 hour period was the most commonly reported serious TEAE both in the IV acetaminophen group and placebo groups. The majority of the cases of accidental overdose involved concomitant dosing with a combination opioid/acetaminophen medication. Although I believe that receiving greater than the recommended dose of acetaminophen in a clinical trial was concerning, there were no medical consequences as a result of these errors.

Patient 05-0004, a 56-year-old female enrolled in Study 136-01-03 (randomized, placebo-controlled, hip arthroplasty), was reported to have received an acetaminophen overdose on 30 March 2004. The patient was randomized to and received the planned single dose of 1000 mg IV acetaminophen at 5:15 on 30 Mar 2004. Over the course of the next 15 hours, the patient received 3 PO doses of acetaminophen 650 mg for control of fever. No further doses were administered that day; thus the total acetaminophen dose in 24 hours was 2950 mg. A final dose of PO acetaminophen 650

mg was administered the following day (31 March 2004), more than 24 hours after the IV dose. The only other adverse event reported in this patient was fever. Screening ALT and TBL were 22 U/L and 5 µmol/L, respectively (ULN of 47 U/L and 19 µmol/L, respectively). At the 24-hour post-treatment assessment ALT and TBL remained in the normal range at 17 U/L and 7 µmol/L, respectively. There were no clinical signs of acetaminophen-based toxicity and the event of accidental overdose was considered resolved on the same day. This patient does not appear to have been overdosed with acetaminophen in that the total amount of APAP received over the 24 hour time period was 2.95 g (< 4 grams, the maximum daily dose for APAP).

Patient 11-0003, a 49-year-old female enrolled in Study 136-02-03 (randomized, placebo-controlled hip arthroplasty), was reported to have received an acetaminophen overdose on (b) (6) The patient was randomized to IV acetaminophen and received 4 doses of 1000 mg on (b) (6) at T0 (7:19), 4 (11:20), 10 (17:20) and 16 (23:20) hours. The patient received hydrocodone with acetaminophen 500 mg the following day at 7:00; thus receiving 4500 mg acetaminophen within a 24-hour period. Acetaminophen 650 mg PO was administered at 16:30 on (b) (6) and hydrocodone with acetaminophen 650 mg was administered on (b) (6) No other TEAEs were reported in this patient. Liver function tests performed on 26 May 2004 after the event were within normal limits with a ALT of 23 U/L, AST of 37 U/L and total bilirubin of 0.4. . There were no clinical signs of acetaminophen-based toxicity and the event of accidental overdose was considered resolved on the same day.

Patient 17-0003, a 32-year-old female enrolled in Study 136-03-03 (randomized, placebo-controlled, vaginal hysterectomy), was reported to have received an acetaminophen overdose on 08 May 2004. The patient was randomized to IV acetaminophen and received 4 doses of 1000 mg between 07 and 08 May 2004 at T0 (16:30), 4 (20:30), 10 (2:41) and 16 (8:39) hours. The patient received a single dose of 650 mg acetaminophen plus hydrocodone at 11:20 on 08 May 2004, thus receiving a total of 4650 mg acetaminophen within a 24-hour period. No other adverse events were reported in this patient. Per the applicant predose ALT and TBL were 18 U/L and 3 µmol/L, respectively (ULN 47 U/L and 19 µmol/L, respectively); at the 24-hour post-treatment assessment ALT and TBL remained in the normal range at 15 U/L and 5 µmol/L, respectively. There were no clinical signs of acetaminophen-based toxicity and the event of accidental overdose was considered resolved on the same day. Review of chemistry lab reports for this patient shows ALT, AST and TBLvalues were normal throughout this event and on follow-up.

Patient 17-0004, a 31-year-old female enrolled in Study 136-03-03 (randomized, placebo-controlled, vaginal hysterectomy), was reported to have received an acetaminophen overdose on 03 June 2004. The patient was randomized to IV acetaminophen and received 4 doses of 1000 mg between 02 and 03 Jun 2004 at T0 (16:12), 4 (20:22), 10 (2:12) and 16 (8:13) hours. The patient received a single dose of 650 mg acetaminophen plus hydrocodone at 14:19 on 03 Jun 2004, thus receiving a

total of 4650 mg acetaminophen within a 24-hour period. Review of chemistry lab reports shows her screening LFTs were normal (ALT 8 U/L, AST 17 U/L, TBL 0.1 mg/dL) At the 24-hour post-treatment assessment ALT, AST and TBL remained in the normal range at 7 U/L, 15 U/L and 0.1 mg/dL respectively. On trial follow-up LFTs continued to be normal with a ALT of 11 U/L, AST of 16 U/L and TBL of 0.1 mg/dL. There were no reported clinical signs of acetaminophen-based toxicity and the event was considered resolved on the same day.

Post-operative infection

Post-operative wound infection was also reported as a serious TEAE for 4 patients in the all adult patient pool of which all of these patients had received study drug IV acetaminophen group. In addition, these patients were enrolled at the same site in the open-label safety trial (CPI-APA-351), and had undergone abdominal surgical procedures. No patients in the placebo group had a serious adverse event of postoperative wound infection. Despite this finding, my review of these cases reveals no direct relationship between post operative wound infection and IV acetaminophen. More likely, these events are a result of their surgical procedures. The narratives for these four patients are included below.

Patient 012-09, a 73-year-old male with colon cancer, received a total of 16 doses of IV APAP 650 mg Q4h for pain between (b) (6) following left open colon resection (b) (6). The patient completed the study and was discharged home uneventfully. At a follow up visit (b) (6), a surgical site infection with wound dehiscence was discovered and the patient was readmitted for appropriate treatment and discharged uneventfully.

This serious adverse event involving post-operative infection was not related to IV acetaminophen treatment.

Patient 012-12, a 46-year-old male with ulcerative colitis, received a total of 30 doses of IV APAP 650 mg Q4h for pain between (b) (6) following open restorative proctocolectomy (b) (6) after an exacerbation of his ulcerative colitis with rectal bleeding and worsening abdominal pain. (b) (6) the patient developed fever and leukocytosis. The left lower quadrant abdominal drain was noted to have purulent drainage. A bedside incision and drainage procedure was performed and the patient was started on ampicillin/sulbactam. CT scan showed no interval changes. The following day, the drainage site was improving and the patient was discharged. On (b) (6) the patient presented to the emergency department with complaints of decreased ostomy output, crampy abdominal pain, nausea, and what appeared to be a recurrence of a wound infection. His leukocyte count was approximately 24,000; however, he remained afebrile. He was admitted and started on intravenous

vancomycin and piperacillin/tazobactam, and by Day 3, his leukocyte count had normalized and he was discharged to home.

This serious adverse event involving post-operative infection was not related to IV acetaminophen treatment.

Patient 012-13, a 47-year-old male with diverticulitis, received a total of 20 doses IV acetaminophen 1000 mg Q6h for pain between (b) (6) following laparoscopic sigmoid resection (b) (6) the patient reported increased abdominal pain and on the following day chills, diaphoresis and fever. Wound cultures revealed light growth of Enterococcus faecium and moderate growth of Bacteroides fragilis. The subject responded well to treatment and was discharged home (b) (6) on continued amoxicillin/clavulanate.

This serious adverse event involving post-operative infection was not related to IV acetaminophen treatment.

Patient 012-14, a 64-year-old male with colon cancer, received a total of 20 doses IV acetaminophen 1000 mg Q6h for pain between (b) (6) following lower anterior resection and diverting colostomy (b) (6) On postoperative Day 4, the surgical wound showed erythema and clear discharge. The wound was opened and a small amount of purulent drainage was found. Papain/urea was started and a vac-dressing was placed. Wound dehiscence occurred on postoperative day 9. The wound responded gradually to continued treatment and (b) (6) the patient was discharged home.

This serious adverse event involving post-operative infection was not related to IV acetaminophen treatment.

Hepatic Enzyme Elevation

Four IV acetaminophen patients in the all adult patient safety pool had hepatic events, specifically liver function tests elevations that were assessed as serious adverse events. Three of these patients were enrolled in the open-label study (CPI-APA-351) and were receiving IV acetaminophen 650 mg q4h. One patient was enrolled in the randomized, active/placebo controlled, 24 hour study (RC 210 3 002) and was receiving IV acetaminophen 1000 mg q6h. All 4 of these patients had undergone surgery and were receiving IV acetaminophen for pain post-operatively. Three of the four patients had elevations in ALT and/or AST > 3x ULN and 1 patient had ALT/AST elevation 2x ULN with a normal total bilirubin in all four patients. A summary of each patient's LFT value of the course of the trials is provided in Table 6. Case narratives for these patients follow this summary.

Table 6: Quantitative LFT Values for Patients with Hepatic Events Assessed as a Serious Event (All Adult Patient Study Pool)

Study Patient ID	LFT[1] Value	Visit								
		Screen	Prior to T0/Day 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7-10[4]
CPI-APA-351 004-08[2]	ALT	36	18	38	37	62 H	236 H	262 H	ND	89 H
	AST	ND	25	68 H	46 H	83 H	279 H	221 H	ND	25
	TBL	0.8	1.1	0.4	0.2 L	0.7	0.5	0.4	ND	0.4
	ALP	48	25 L	23 L	28 L	29 L	36 L	38	ND	48
CPI-APA-351 010-35[2]	ALT	56 H	71 H	85 H	217 H	ND	ND	ND	ND	45
	AST	59 H	88 H	150 H	566 H	ND	ND	ND	ND	32
	TBL	0.6	0.8	0.8	1.3	ND	ND	ND	ND	0.2 L
	ALP	113	72	77	70	ND	ND	ND	ND	97
CPI-APA-351 011-32[2]	ALT	20	ND	16	17	20	25	59 H	123 H[5]	130 H
	AST	15		16	18	23	30	77 H	117 H[5]	105 H
	TBL	0.5	ND	0.6	0.5	0.4	0.4	0.4	NR	0.3
	ALP	64	ND	56	58	60	69	82	NR	79
RC 210 3 002 07-123[3]	ALT	12	ND	137 H	N/A	N/A	N/A	N/A	N/A	N/A
	AST	25	ND	360 H	N/A	N/A	N/A	N/A	N/A	N/A
	TBL	0.5	ND	0.5	N/A	N/A	N/A	N/A	N/A	N/A
	ALP	85	ND	79	N/A	N/A	N/A	N/A	N/A	N/A

KEY ALT=alanine amintransferase, ALP=alkaline phosphatase, TBL=total bilirubin H- high (value >ULN) , N/A= non-applicable, ND=not done, NR=not reported T0-start of IV infusion
Source: Applicant's submission (Adult ISS, Table 33, pg. 77))

Patient 004-08, a 51-year-old male, enrolled in Study CPI-APA-351, who underwent a radical cystectomy, and pelvic lymph node dissection received a total of 25 doses of IV acetaminophen 650 mg q4h for pain between [redacted](b) (6). .At the time of study entry, his medical history included multifocal urothelial carcinoma, prostate cancer, urinary frequency, and joint pain. His prior surgical and procedure history included a cystoscopy, transrectal ultrasound guided biopsy, bilateral retrograde pyelograms, bilateral ureteroscopy, multiple bladder biopsies, urethral dilation, radical cystoprostatectomy, extended pelvic/iliac/retroperitoneal lymph node dissection and continent cutaneous diversion. Concomitant medications included glucagon, heparin, insulin, morphine, nalbuphine, naloxone, ondansetron, cefoxitin, metronidazole, ranitidine, oxycodone, promethazine, ranitidine, and epidural ropivacaine/ hydromorphone. The patient's baseline AST and ALT values were normal at 25 and 36 U/L (AST ULN of 45 and AST ULN 55 U/L) respectively. On Day 3 of IV acetaminophen administration the AST was 83 U/L and ALT was 62 U/L. On Day 4 of treatment AST and ALT had increased to 279 and 236 U/L, respectively (approximately 6×ULN and 4×ULN, respectively); TBL remained normal throughout treatment. The patient was discontinued from treatment due to the increased hepatic enzymes. At the time of his hospital discharge on Day 7 (2 days after the last dose of IV acetaminophen), he was taking oral acetaminophen for pain. On Day 10 (5 days post-treatment), follow-up laboratory assessments showed a normal AST and a resolving ALT (25 and 89 U/L,

respectively). On Day 22, the ALT was normal as well. This adverse event was deemed serious due to prolongation in the patient's hospitalization. Although likely etiologies for this patient's hepatic enzyme elevation include his extensivie surgery and concomitant medications (ranitidine and ondanestron), I can not completely rule out acetaminophen as an etiology as well.

This serious event of hepatic enzyme elevation was possibly related to treatment with IV acetaminophen.

Patient 010-35, a 46-year-old male enrolled in Study CPI-APA-351, who underwent left knee arthroplasty, received a total of 12 doses of IV acetaminophen 650 mg q4h for pain between 21 July 2008 and 23 July 2008. At the time of study entry, his medical history included fatty liver disease, morbid obesity (wt. 165. 5 kg, ht 185 cm, BMI), hypertension, presumptive avascular necrosis of left hip, anxiety, insomnia,low back pain, prior left hip fracture with left hip pain and osteoarthritis. His surgical history included right total hip arthroplasty, left hip resection arthroplasty (and multipleother left hip procedures) and left total knee arthroplasty. Concomitant medications included aspirin, celecoxib, docusate, iron supplementation, ketorolac, levofloxacin, metoprolol, venlafaxine, zolpidem, ondansetron, oxycodone, morphine, ranitidine, and vancomycin. Prior to the first dose, his AST and ALT were mildly elevated (88 and 71 U/L; with ULN of 45 and 55 U/L, respectively). Following the first dose, the AST and ALT increased to 150 and 85 U/L and on Day 2 were 566 and 217 U/L, respectively, (12 × and 4 × ULN, respectively); TBL remained normal throughout treatment (1.3 mg/dL on Day 2) however treatment was discontinued on Day 2 due to the elevations in aminotransferases (ATs). Eight days post-treatment, AST and ALT were normal. The event was deemed to be serious due to a prolongation of the patient's hospitalization. While IV acetaminophen cannot be completed ruled out as an etiology in this event, the patient's known hepatic steatosis and concomitant medications (randtidine and ondnestron) offer additional etiologies as well.

This serious adverse event of hepatic enzyme elevation was possibly related to IV acetaminophen treatment.

Patient 011-32, a 48-year-old male in Study CPI-APA-351, received a total of 30 doses of IV acetaminophen 650 mg q4h for pain between (b) (6) following a rattle snake bite to the left index finger. Prior to his hospital admission for treatment of the snake bite, his medical history was negative and he was on no regular medications. His surgical history included appendectomy and knee surgery. Concomitant medications included hydrocodone/acetaminophen, Crotalidae polyvalent immune Fab ovine antivenom (antivenom for the snake bite), oxycodone hydromorphone, alprazolam, morphine, diphenhydramine, mineral oil enema, bisacodyl, magnesium hydroxide in water, polyethylene glycol, ampicillin/sulbactam, pantoprazole, docusate sodium, oxycodone, amoxicillin/clavulanate, mafenide, ondansetron, insulin

and famotidine. The patient was admitted to the hospital for a snake bite to the left index finger and was treated with a total of 16 vials of antivenom. The patient's baseline AST and ALT values were normal at 16 and 16 U/L respectively (ULN of 45 and 55 U/L, respectively). On Day 2 of treatment, he underwent a fasciotomy due to compartment syndrome. On Day 4, he was found to have low fibrinogen and high fibrinogen degradation products that continued through to Day 7 (2 days after completion of IV acetaminophen treatment). After Day 5, the last day of treatment, AST and ALT had increased to 59 and 77 U/L,respectively. On Day 6, the AST was 117 U/L and ALT was 123 U/L, each approximately 2 × ULN. For unclear reasons, the subject received prophylactic N-acetylcysteine on Days 6 and 7. No acetaminophen levels were obtained. On Day 7, the subject was discharged home with AST and ALT: 105 U/L and 130 U/L, respectively. The TBL remained normal throughout treatment and was 0.3 mg/dL on Day 7. No follow-up LFT values were reported. This adverse event was deemed serious due to prolongation of the patient's hospitalization.

The serious event of hepatic enzyme elevation was possibly related to treatment with IV acetaminophen.

Patient 07-123, an 81-year-old male, in Study RC 210 3 002, received a total of 4 doses of IV acetaminophen 1000 mg Q6h for pain between (b) (6) following a left total hip arthrooplasty (b) (6). At the time of study entry, the patient's medical history included hypertension, mild tricuspid regurgitation, mild aortic regurgitation, mild mitral regurgitation, moderate aortic stenosis, left hip osteoarthritis, gastroesophageal reflux and hearing deficit. Prior surgical history included hernia repair, bilateral cataract removal, transurethral resection of prostate, and amputation of left 4th digit. Concomitant medications included: lovenox, cefazolin, morphine sulfate patient controlled analgesia, ondansetron, triamterene, metoprolol, norvac, captopril, senokot, and colace. Baseline (just prior to surgery) AST and ALT were normal at 25 and 12 U/L respectively (ULN of 45 and 48 U/L, respectively). (b) (6) after (b) (6) dose of IV acetaminophen a routine check revealed an absent pulse was obtained at which time resuscitative efforts began. The patient was intubated and subsequently transferred to the critical care unit in 2nd degree atrioventricular block. A cardiac arrest was suspected and was felt likely related to either a pulmonary embolus or myocardial infarction. He was placed on a ventilator and received vasopressor support for persistent hypotension. After suffering a prolonged bout of ventricular ectopy, he was pronounced dead. (b) (6) of IV acetaminophen, (b) (6) after the cardiac event AST and ALT values were 360 and 137 U/L, respectively (8x and 3x ULN, respectively). No further measurements were obtained prior to the patient's death. This adverse event was deemed serious due to the death of the patient.

The serious events of increased AST and ALT were not related to IV acetaminophen treatment.

Other Serious Adverse Events

Patient 030-01, a 40–year-old female in Study CPI-APA-301, who underwent exploratory laparatomy, left salpinogoopherectomy, lysis of ovarian adhesions and enterorraphy (b) (6) received a total of 8 doses of IV acetaminophen 1000mg q6h for pain between (b) (6) At the time of study entry, the patient's medical history included pelvic inflammatory disease, menomenorrghia, chronic cervicitis, cervical dysplasia, ovarian cyst, diverticulosis, left lower quandrant pain and depression. Her prior surgical history included total abdominal hysterectomy, lumbar lamincetomy, cervical spine surgery and repair of torn anterior cruciate lligament. Concomitant medications included morphine, promethazine hydrochloride and cefazolin sodium injection. Preoperative and intraoperative medications included vecuronium bromide, morphine, fentanyl citrate injection, propoful, lidocaine, ondansetron, metoclopramide, robinol, cefazolin, neostigmine, sevoflovane (b) (6) the patient developed abdominal pain, requiring evaluation by CT scan. A presumptive diagnosis of ileus was given which was reported as being resolved (b) (6)
This adverse event was considered serious due to prolongation of the patient's hospitalization.

The serious adverse event of ileus was most likely due to the patient's post-operative state and medications and not related to IV acetaminophen.

Patient 032-08, a 46-year-old female in Study CPA-APA-301, who underwent a supracervical hysterectomy, bilateral salpingoophorectomy, cystocopy, and retrograde pylelogram (b) (6), received a total of 8 doses of IV acetaminophen 1000 mg q6h for pain between (b) (6). At the time of study entry, the patient's medical history included uterine fibroids, endometrioma of the right ovary, hypertension, anxiety, depression and seasonal allergies with no record of any prior surgical history. Medications prior to surgery included cetirizine, fluoxetine, mometasone furoate monohydrate spray, diltiazem hydrochloride, and lorazepam. Concomitant medications included hydromorphone, clindamycin, and gentamycin. The applicant reported an SAE of neutropenia that occurred a few days after completion of IV acetaminophen. Screening complete blood count with differential (CBC/diff) showed a normal WBC count of 7.1 and high neutrophils of 76.7% (normal range 40-70). On the last day of IV acetaminophen treatment, the patient WBC was low at 3.8 (normal range 4.5 – 11.0) with a high neutrophil count of 85.3 %. On follow-up, the patient's WBC had returned within normal range at 5.1 with a neutrophil count of 75.1%. This event does not meet the definition of neutropenia which is an absolute neutrophil count (ANC) of <1500/mm3 but rather a mild leukopenia. The applicant classified the patient's "neutropenia" as serious due to prolongation of the patient's hospitalization. This patient's transient leukopenia is was likely due to gentamicin and clindamycin as the leukopenia improved after discontinuation of these concomitant medications.

This serious adverse event of neutropenia was not related to IV acetaminophen treatment.

Patient 003-28, a 30-year-old female in Study CPA-APA-301, who underwent an abdominal myomectomy (b) (6), received a total of 8 doses of IV acetaminophen 1000mg q6h for pain between (b) (6) At the time of study entry, the patient's medical history included uterine fibroids. Her prior surgical history included cervix cauterization and ceasearan section. Concomitant medications included morphine, ondansetron, lorazepam, mylicon, and surfak.

On (b) (6) the day of her last dose of IV acetaminophen, the patient was diagnosed with a pulmonary embolism despite a normal physical exam with no pulmonary symptoms that required treatment with coumadin and enoxaparin. Review of her vital signs around the time of this adverse event revealed tachycardia (pulse of 126) and upper limit of normal respiratory rate (RR 20). On (b) (6) day of discharge, vital signs including heart rate, respirations and blood pressure were normal and the adverse event of pulmonary embolism was documented as resolved.
This adverse event was considered serious due to prolongation of the patient's hospitalization.

This serious adverse event of pulmonary embolism was not related to IV acetaminophen

Patient 010-22, a 44-year-old female in Study CPI-APA-304, who underwent an abdominal hysterectomy and cystoscopy (b) (6) received a total of 4 doses of IV acetaminophen 1000 mg Q6h for pain between (b) (6) At the time of study entry, the patient's medical history included uterine leiomyomata, menorrhagia, adenomyosis, right side endometrioma, anemia, and chipped tooth with no record of prior surgical history. Post-operative medications before start of trial included morphine sulfate, hydromorphone patient controlled analgesia, promethazine, ondansetron Concomitant medications included meperidine/promethazine, ondansetron, promethazine, ducolax, and mylanta.

(b) (6) the patient had intermittent nausea requiring treatment with promethazine and odansetron. (b) (6) after her last dose of IV acetaminophen (b) (6) the patient developed moderate vomiting in addition to her symptoms of intermittent nausea for which she received phenergan. Her vomiting was reported to have resolved (b) (6). This adverse event was considered serious due to prolongation of the patient's hospitalization.

This serious adverse of vomiting was not related to IV acetaminophen.

Patient 001-20, a 38-year-old female in Study CPI-APA-304, who underwent an abdominal hysterectomy (b) (6) received a total of 6 doses of IV acetaminophen 650 mg q4h for pain between (b) (6). At the time of study entry, the patient had an extensive medical history including type 1 diabetes mellitus, hypertension, hypercholesteremia, peripheral neuropathy, uterine fibroids, menorrhagia, dysmenorrheal, gastroesophageal reflux, anemia, spleen cyst, back and knee pain, and pelvic pain. Her prior surgical history included splenectomy, appendectomy, bilateral tubal ligation, left eye lens implant, and partial patella repair. Concomitant medications included novolog insulin, lantus insulin, pravastatin, gabapentin, naproxen, diovan, metoprolol, norvasc, ferrous sulfate., morphine, ondansetron, (b) (6) , 24 hours after completion of trial drug, the patient developed gastroparesis which resolved 10 days later (b) (6).
This adverse event was considered serious due to prolongation of this patient's hospitalization however her diagnosis of gastroparesis is most likely due to her underlying diabetic neuropathic condition.

This serious adverse event of gastroparesis was not related to IV acetaminophen.

Patient 014-19, a 59-year-old male in Study CPI-APA-304, who underwent an hernia repair (b) (6), received a total of 6 doses of IV acetaminophen 650 mg q4h for pain between (b) (6). At the time of study entry, this patient's extensive medical history included coronary artery disease, ischemic heart disease, chronic obstructive pulmonary disease, hypertension, hypercholesterolemia, hepatics c, ventral hernia, gastroesophageal reflux disease, anxiety and multiple tattoos. His prior surgical history included coronary artery bypass graft, percutaneous transluminal coronary angioplasty, bowel surgery, bilateral forearm surgery, and left elbow surgery. Post-operative medications before start of trial entry included morphine, odansetron, meperidine, and oxycodone. Concomitant medications included oxycodone, clonidine, metoprolol, omeprazole, simvastatin, nifedepine, benzapril, ketorolac, and morphine.

(b) (6) the patient developed nausea and (b) (6) he was diagnosed with a post-operative ileus requiring treatment biscodyl and this event was reported to have resolved (b) (6). This adverse event was considered serious due to prolongation of this patient's hospitalization. The SAE of post operative ileus was most likely due her post-operative status and medications.

This serious adverse advent of post-operative ileus was not related to IV acetaminophen.

Patient 017-02, a 48-year-old female, in Study CPI-APA-304 who underwent a sigmoid colon resection (b) (6) and received a total of 6 doses of IV acetaminophen q4h for pain between (b) (6). At the time of study entry, the

patient's medical history included mitral valve prolapse, diverticulitis, hyperplastic polyps, history of renal cell carcinoma, osteoarthritis, gastroesophageal reflux disease, nausea, vomiting, hemmorhoids, chronic bronchits, and environmental allergies. Her prior surgical history included left partial nephrectomy. Standard preoperative and intraoperative medications included fentanyl, lidocaine, neostigmine, glycopyrrolate, midazolam, ondanestron, propofol, isoflurance and cefotatan. Concomitant medications included morphine, famotidine, omeprazole, metoprolol tartrate, and metoclopramide.

This patient's hospital course was complicated by worsening nausea and vomiting and (b) (6) days after that last dose of IV acetaminophen she was diagnosed with a post-operative ileus. This adverse event was considered serious due to prolongation of the patient's hospitalization and was most likely due to her underlying condition and post-operative status.

This serious adverse event of post - operative ileus was not related to IV acetaminophen.

Patient 003-01, a 77-year-old female in Study CPI-APA-351, who underwent a laproscopic-assisted left colon resection (b) (6), received a total 21 doses of IV acetaminophen 1000 mg q6h for pain between (b) (6). At the time of study entry, the patient's medical history included diverticulitis, mild emphysema, hypercholesterolemia, left adrenal gland nodule, and gastroesophageal reflux disease with no prior surgical history. Concomitant medications included famotidine, morphine, odansetron, metoclopramide, enalapril, and marcaine.

(b) (6), 5 days after her last dose of IV acetaminophen, the patient developed altered mental status that resolved (b) (6). This adverse event was considered serious due to prolongation of the patient's hospitalization. Although the etiology of her altered mental status was not determined, the timing of the event days after her last dose of IV acetaminophen makes this association less likely.

This serious adverse event of altered mental status was not related to IV acetaminophen.

Patient 011-21, a 73-year-old female in Study CPI-APA-351 underwent open reduction and internal fixation of a left wrist fracture (b) (6) and received a total of 20 doses of IV acetaminophen 1000 mg q6h for pain between 21 May 2008 and 26 May 2008. At the time of study entry, the patient's medical history included history of left wrist fracture, chronic atrial fibrillation, hypertension, tachycardia, hyperglycemia, hypothyroidism, osteoarthritis, degenerative disk disorder, history of transient ischemic attack, history of pneumonia, seasonal allergies and constipation. Her prior surgical history included left total knee arthroplasty and fusion of cervical vertebrae C5-C6.

Concomitant medications included metoprolol, oxycodone, ambien, cordarone, valsartan, aspirin, ferrous sulfate, vitamin C, pantoprazole, diltiazem hydrochloride and alprazolam.

(b) (6) after receiving her last dose of IV acetaminophen, the patient suffered a myocardial infarction with non st elevation on electrocardiogram requiring cardiac catherization and therapy with nitroglycerin and heparin. This event was documented as resolving (b) (6). This adverse event was considered serious due to prolongation of the patient's hospitalization.

This patient's SAE, myocardial infarction, was not related to IV acetaminophen treatment.

Patient 010-39, a 75-year-old female in Study CPI-APA-351 who underwent total knee replacement (b) (6) received a total of 30 doses of IV acetaminophen 650 mg q4h for pain between (b) (6). The patient's medical history included hypertension, renal insufficiency, anemia, arthritis, right knee pain, gastroesophageal reflux disease and history of back injury. Her prior surgical history included appendectomy, hysterectomy, and hemorrhoidectomy. Concomitant medications included morphine patient controlled analgesia, ketorolac, metoprolol, oxycodone, pantoprazole, enoxaparin, docusate, ferrous sulfate, furosemide, hydrochlorothiazide, naloxone, ondansetron, telmisartan, reglan, celebrex, diphenhydramine, randitidine, and tramadol.

During the patient's early post-operative course (b) (6), she experienced hypotension with a blood pressure of 97/48 requiring fluid resuscitation (maintenance fluids, albumin). Between (b) (6) this patient also received 4 units of packed red blood cells for anemia due to blood loss. Her last documented blood pressure was 131/65 (b) (6) with resolution of hypotension documented (b) (6). Her hypotension developed before starting IV acetaminophen. This adverse event was considered serious due to prolongation of the patient's hospitalization.

This serious adverse event of hypotension was not likely related to IV acetaminophen treatment.

Patient 011-10, a 64-year-old male in Study CPI-APA-351 underwent a radical cystectomy (b) (6) and received a total of 16 doses of IV acetaminophen 1000 mg q6h for pain between (b) (6). The patient's medical history included bladder adenocarcinoma, right hydronephrosis, renal insufficiency, anemia, asthma, bronchitis, low back strain and leukocytosis. His prior surgical history included

bladder biopsy, and resection of bladder tumor. Concomitant medications included famotidine, fentanyl, cefazolin, and oxycodone.

The patient's baseline creatinine was 1.55 mg/dl (ULN 1.1 mg/dl). On day 2 ((b) (6) of IV acetaminophen per the CRF moderate acute renal failure was reported as a serious TEAE and the Cr at that time was reported as 2.97 mg/dl, although dosing continued through Day 4 (b) (6) of IV acetaminophen treatment at which time the patient was discontinued from the trial with a Cr of 2.75 mg/dl. The Cr value one day post discontinuation (b) (6) was 1.72 mg/dL The acute renal failure was reported as resolved 3 days (b) (6) post discontinuation with a Cr level of 1.0 mg/dl. This adverse event was considered serious due to prolongation of the patient's hospitalization. Although the concurrent use of cefazolin is a possible etiology of this patient's acute renal failure, the CRF reveals that the cefazolin medication was continued until (b) (6) (3 days after IV acetaminophen discontinuation) when the Cr was normal.

This serious adverse event of acute renal failure was possibly related to IV acetaminophen treatment.

Patient 05-074, a 75-year-old male in Study RC 210 3 002 underwent a right hip arthroplasty (b) (6) and received a total of 4 doses of IV acetaminophen 1000 mg q6h for pain between (b) (6). The patient's medical history included benign prostatic hyperplasia, degenerative joint disease of right hip, arthritis, sarcoidosis, hypertension, gastroesophageal reflux disease, hx of small bowel obstruction, and insomnia. Prior surgical history included removal of facial skin cancer. Pre-operative and intraoperative medications included midazolam, propofol, thiopental, rocuronium, fenanyl, morphine, neostigmine, and glycopyrrolate. Concomitant medications included morphine patient controlled analgesia, lisinopril, zinc, vitamin a, vitamin c, colace, lansoprazole, coumadin, terazosin, elavil

(b) (6), over 24 hours after the last dose of IV acetaminophen the patent developed abdominal distension and tenderness and was subsequently diagnosed with an ileus and received nothing by mouth as well as a nasogastric tube placement, laxatives and Fleet's enemas. The ileus was reported as resolved (b) (6). This adverse event was considered serious due to prolongation of the patient's hospitalization.

This serious adverse event, ileus, was not related to IV acetaminophen treatment.

Patient 008-17, a 71–year-old-female in Study CPI-APA-351 underwent total colectomy (b) (6) and received a total of 20 doses of IV acetaminophen 1000 mg Q6h for pain between (b) (6). The patient's medical history

included colon cancer, Merkel cell carcinoma, splenic flexure cancer, pulmonary embolus, heart murmur, hypertension, anemia, hypercholesterolemia, hypoxemia, urinary tract infection and history of deep vein thrombosis. Prior surgical history included hip replacement, ligation of varicose veins and removal of right arm carcinoma. Concomitant medications included atorvastatin, enoxaparin, valsartan, clindamycin, ciprofloxacin, furosemide, potassium chloride, ondansetron, ketorolac, promethazine, pantoprazole, calcium carbonate, glucosamine, and acetaminophen-propoxyphene. The patient was diagnosed with an ileus (b) (6) before her first dose of IV acetaminophen and was documented as resolving on (b) (6).
This adverse event was considered serious due to prolongation of the patient's hospitalization.

This serious adverse event, ileus, was not related to IV acetaminophen treatment.

7.3.3 Dropouts and/or Discontinuations

In the all adult patient pool 3% (32 of 1020) of patients were discontinued from trials in comparison to 4% (20 of 525) of patients in the placebo group that were discontinued from trials. The treatment emergent adverse events leading to discontinuation in the IV acetaminophen group that will be discussed in this review are hepatic enzyme or transaminases increases, infusion site pain, nausea and vomiting, headache and skin disorders. Narratives for each of these patients are included below.

Patient 009-02, an 81-year-old male in Study CPI-APA-351 received a total of 7 doses of IV acetaminophen 1000 mg q6h for pain between 7 May 2008 and 9 May 2008 following left total hip arthroplasty. His medical history included coronary artery disease with angina, hypertension, chronic obstructive pulmonary disease, colon cancer, carpal tunnel symptoms, history of ankle fracture, history of deep venous thrombosis, osteoarthritis, dyspepsia, hypercholesterolemia, insomnia, and an abdominal hernia. His prior surgical history included cataract surgery, tonsillectomy, cardiac stent, cervical spine surgery, lumbar laminectomy, knee arthroscopy, bilateral rotator cuff repairs, bilateral total knee arthroplasties, appendectomy, cholecystectomy, prostatectomy, and right total hip arthroplasty. His concomitant medications included rabeprazole, diltiazem, digoxin, simvastatin, fluticasone, aspirin, cefazolin, metoclopramide, ondansetron, ketorolac, morphine, docusate, magnesium hydroxide, nitroglycerin, and zolpidem. All screening LFTs (prior to surgery) for this patient were normal with ALT of 20 U/L, AST 22 U/L and total bilirubin of 1.1 mg/dL. Prior to T0/Day 1 (before IV acetaminophen dosing), his AST (74 U/L; ULN of 45) and TBL (1.9 mg/dL; ULN of 1.5 mg/dL) were elevated. The patient's ALT and GGT were normal (36 U/L, ULN 55 U/L; and 40 U/L, ULN 50 U/L respectively). Following Day 1 of IV acetaminophen, ALT, ALP, AST, TBL, and GGT were 76 U/L, 69 U/L, 100 U/L, 2.9 mg/dL, and 87 U/L (all < 2 × ULN), respectively, and after Day 2, ALT ALP, AST, TBL and GGT values were 50 U/L, 72

U/L, 47 U/L, 2.4 mg/dL, and 79 U/L, respectively. On day 2 of IV acetaminophen was discontinued due to the elevations in LFTs, even though all LFTs except for ALP were decreasing on treatment. On Day 3, at the time of early discontinuation, ALT, ALP, AST, TBL and GGT values were 34 U/L, 67 U/L, 29 U/L, 1.9 mg/dL, and 64 U/L, respectively. On Day 8, all values were normal) except for the GGT at 80 U/L. While I cannot rule out acetaminophen as an etiology in this adverse event, there were other factors that could have caused the elevation in LFTs including concomitant medications, and the patient's post- surgical status.

The adverse event of elevated liver enzymes leading to this patient's discontinuation was possibly related to IV acetaminophen treatment.

Patient 010-15, a 55-year-old female in Study CPI-APA-351 received a total of 12 doses of IV acetaminophen 1000 mg q6h for pain between 4 June 2008 and 7 June 2008 following right total knee revision. Her medical history included hypertension, prior upper respiratory infection, muscle spasms, prior closed head injury, constipation, gastroesophageal reflux, right knee pain, iodine allergy, osteoarthritis, systemic lupus erythematosus, Sjögren's syndrome, and rheumatoid arthritis. Her prior surgical history included bilateral parotid gland removal, bilateral knee arthroscopies, right total knee arthroplasty, left wrist surgery, cholecystectomy, hysterectomy and tubal ligation. Concomitant medications. included cefazolin, duramorph (epidural morphine), morphine, levofloxacin, fentanyl, ketorolac, ranitidine, diphenhydramine, cevimeline, docusate, enoxaparin, magnesium hydroxide, ondansetron, oxycodone, pantoprazole, prochlorperazine, folic acid, hydroxychloroquine, naproxen, and zolpidem.. At screening, ALT 62 U/L (ULN 55), AST 47 U/L (ULN 45) and GGT 92 U/L (ULN 50) were all elevated with a normal TBL (0.6 mg/dL). On Day 1, prior to start of IV acetaminophen, all LFTs were normal except for GGT at 64 U/L. On Day 2, GGT increased to 89 U/L and the other LFTs remained normal. Patient was discontinued from trial after dose 4 on Day 3. GGT increased to 215 U/L (4 × ULN) on Day 4, and other LFTs remained normal. Four days post-IV acetaminophen, GGT was 157 U/L; AST and ALT were slightly elevated to 51 and 59 U/L, respectively, and TBL and ALP were normal. With GGT being nonspecific I believe there are other potential etiologies (history of Sjorgren's syndrome and concomitant mediations) for this patient's elevated GGT

The adverse event of isolated gamma-glutamyltransferase elevation leading to this patient's discontinuation was not likely related to IV acetaminophen treatment.

Patient 011-15, a 51-year-old female in Study CPI-APA-351 received a total of 12 doses of IV acetaminophen 1000 mg q6h between 29 April 2008 and 2 May 2008 for pain due to right groin cellulitis. Her medical history included bronchitis, rheumatoid arthritis, psoriasis, nausea and vomiting, morbid obesity, history of urinary tract infection, mild renal insufficiency, diabetic peripheral neuropathy, type I diabetes, anxiety, depression and anemia. Her prior surgical history included a neurostimulator

implant. Concomitant medications included ceftriaxone, insulin, glopizide metformin, sertraline, morphine, silvadene/nystatin topical, vancomycin, voriconazole, pantoprazole, salbutamol inhaler, lorazepam, fentanyl patch, iron supplementation, bisacodyl, duloxetine, senna supplement, phenazopyridine, fluconazole topical, gabapentin, and filgrastim. At screening, T0 (predosing), Day 1 and Day 2, all LFTs including TBL were normal. On Day 3, AST and GGT were mildly elevated to 55 and 114 U/L (approximately 1.2x and 2.3 x ULN, respectively) and ALT and TBL remained normal. Treatment was discontinued after dosing on day 3 due to the increased hepatic enzymes, but per the case report forms no repeat assessments were performed at that time. Three days post-treatment on 5 May 2008, AST, ALP and GGT were elevated at 87 U/L (1.9x ULN), 202 U/L (1.4x ULN), and 323 U/L (6.5x ULN), respectively with ALT and TBL normal. Given the patient's morbid obesity status, active infection, concomitant medications, and the timing of AST and GGT elevations without ALT elevation it does not appear that IV acetaminophen played a role.

The adverse event of hepatic enzyme elevation leading to this patient's discontinuation was not likely related to IV acetaminophen.

Patient 011-26, a 52-year-old female in Study CPI-APA-351 received a total of 16 doses of IV acetaminophen 1000 mg q6h for pain between 19 June 2008 and 23 June 2008 following total knee arthroplasty. Her medical history included chronic back pain, gastroesophageal reflux disease, constipation, postmenopausal status, hypothyroidism, hypopituitarism, anxiety, depression, insomnia, osteopenia, osteoarthritis, and Cushing's syndrome, ischemic heart disease, hypertension, palpitations, obesity, asthma, and irritable bowel syndrome. Her prior surgical history included bilateral shoulder arthroplasty, total knee and hip replacement, and hysterectomy. Her concomitant medications included iron supplementation, diphenhydramine, celecoxib, tramadol, oxycodone, docusate, morphine, enoxaparin, triamterene/hydrochlorothiazide, temazepam, famotidine, lisinopril, fentanyl patch, lactulose, senna, ketorolac, ondansetron, metoclopramide, metaxalone, hydrocortisone, clindamycin, and packed red blood cell transfusions. At screening, ALP was elevated at 193 U/L, but on repeat was normal at 132. At T0 prior to the first dose, AST, ALT, and TBL were normal (18 and 29 U/L, and 0.2 mg/dL, respectively) but the GGT was elevated at 77 U/L (ULN 50) and GGT remained elevated on Day 1 and 2: 64 and 76 U/L, respectively. On Day 3, ALT 73 U/L (ULN 55), ALP 201 U/L (ULN 147), AST 50 U/L (ULN 45) and GGT 127 U/L were all elevated, but TBL was normal. On Day 4, ALT 63 U/L (1.1x ULN), ALP 307 U/L (2.1x ULN), and GGT 158 U/L (3.2x ULN) were elevated. The patient was discontinued from study treatment, and at that time, ALT was 72 U/L, ALP 349 U/L and GGT 158 U/L. At Day 7-10 follow up, the following values were still elevated: ALT 112 U/L, alkaline phosphatase 517 U/L and GGT 268 U/L. On 10 July 2008 (16 days post last dose of IV APAP, LFTs had returned to normal except for ALP (193 U/L). The pattern of LFT elevations suggests several possible etiologies including thyroid status, obesity status, concomitant medications as well as IV acetaminophen administration.

The adverse event of transaminitis leading to this patient's discontinuation was possibly related to treatment with IV acetaminophen.

Patient 010-35, a 46-year-old male in Study CPI-APA-351 received a total of 12 doses of IV acetaminophen 650 mg q4h for pain between 21 July 2008 and 23 July 2008 following left total hip arthroplasty. His medical history included fatty liver disease, morbid obesity (wt. 165. 5 kg, ht 185 cm, BMI), hypertension, presumptive avascular necrosis of left hip, anxiety, insomnia, low back pain, prior left hip fracture with left hip pain and osteoarthritis. His prior surgical history included right total hip arthroplasty, left hip resection arthroplasty (and multiple other left hip procedures) and left total knee arthroplasty. Concomitant medications included aspirin, celecoxib, docusate, iron supplementation, ketorolac, levofloxacin, metoprolol, venlafaxine, zolpidem, ondansetron, oxycodone, morphine, ranitidine, and vancomycin. At screening his AST and ALT, were mild elevated (59 U/L, 56 U/L, with ULN of 45 U/L and 55 ULN respectively and GG T was elevated at 356 U/L (7x ULN). Prior to the first dose (T0), his AST and ALT were continued to be mildly elevated (88 and 71 U/L; respectively). On day 1 following the first dose, the AST and ALT increased to 150 and 85 U/L respectively with AST 3x ULN; GGT remained elevated at 285 U/L (5x ULN). On Day two AST, ALT and GGT were 566 U/L, 217 U/L, and 224 U/L respectively, (with AST 12x ULN, ALT 4 x ULN and GGT 4x ULN); TBL remained normal throughout treatment. Study drug treatment was discontinued after dosing on day 2 due to the elevations in aminotransferases (ATs). Eight days post-treatment, AST and ALT were normal (32 U/L and 45 U/L respectively) however GGT level remained elevated at 152 U/L (3x ULN). TBL was normal at 0.2.

While IV acetaminophen cannot be completed ruled out as an etiology in this event, the patient's known hepatic steatosis, morbid obesity and numerous concomitant medications (randtidine and ondanestron) that cause hepatotoxicity and LFT elevations respectively offer additional etiologies as well.

The adverse event of transaminitis leading to this patient's discontinuation was possibly related to IV acetaminophen treatment.

Patient 004-08, a 51-year-old male in Study CPI-APA-351 received a total of 25 doses of IV acetaminophen 650 mg q4h for pain between 22 July 2008 and 26 July 2008 following radical cystectomy and pelvic lymph node dissection. His medical history included multifocal urothelial carcinoma, prostate cancer, urinary frequency, and joint pain. His prior surgical and procedure history included a cystoscopy, transrectal ultrasound guided biopsy, bilateral retrograde pyelograms, bilateral ureteroscopy, multiple bladder biopsies, urethral dilation, radical cystoprostatectomy, extended pelvic/iliac/retroperitoneal lymph node dissection and continent cutaneous diversion. Concomitant medications included glucagon, heparin, insulin, morphine, nalbuphine,

naloxone, ondansetron, cefoxitin, metronidazole, ranitidine, oxycodone, promethazine, ranitidine, and epidural ropivacaine/ hydromorphone. The patient's screening and T0 (predose) ALT, GGT, ALP and TBL were all normal. AST was not performed at screening. On day 1 of treatment AST was mildly elevated at 68 U/L (45 ULN). On day 2 of treatment, AST had returned to normal at 46 U/L and ALT, ALP, GGT and TBL continued to remain normal. On day 3 of IV acetaminophen administration the AST was 83 U/L and ALT was 62 U/L. On day 4 of treatment AST and ALT had increased to 279 and 236 U/L, respectively (approximately 6×ULN and 4×ULN, respectively); TBL remained normal throughout treatment. The patient was discontinued from treatment after the first dose on day 5 due to the increased hepatic enzymes. At the time of his hospital discharge on day 7 (2 days after the last dose of IV acetaminophen), he was taking oral acetaminophen for pain. On day 10 (5 days post-treatment), follow-up laboratory assessments showed a normal AST and a resolving ALT (25 and 89 U/L, respectively). On trial follow-up (~ 14 post drug treatment) both AST and ALT had returned to normal baseline (22 U/L and 47 U/L) respectively.

Although the likely etiologies for this patient's hepatic enzyme elevation include his extensivie surgery and concomitant medications (rantidine and ondanestron), I can't completely rule out IV acetaminophen as an etiology.

The adverse event of hepatic enzyme elevation leading to this patient's discontinuation was possibly related to treatment with IV acetaminophen.

Patient 010-17, a 36-year-old female in Study CPI-APA-301 received a total of 5 out of 8 planned doses of IV acetaminophen 1000 mg q6h for pain relief between 4 May 2007 and 5 May 2007 following uterine myomectomy and chromo-pertubation. Her medical history included uterine fibroids, menorrhagia, infertility and back pain. Her prior surgical history included choleystecomy. Concomitant medications included dilaudid and diphenhydramine. After receiving 5 doses of IV acetaminophen, the patient complained of pain at the infusion site and was subsequently discontinued from the study.

The adverse event of pain at the infusion site leading to this patient's discontinuation was probably related to IV acetaminophen.

Patient 001-09, a 39-year-old female in Study CPI-APA-304 received a total of 1.5 out of four planned doses of IV acetaminophen 1000 mg q6h for pain on 20 February 2008 following a abdominal hysterectomy and cystoscopy (b) (6). Her medical history included uterine fibroids, menorrhagia, dysmenorhea, asthma, hypothyroidism, hyperchosterolemia, gastroesophageal reflux disease, dermatofibroma and bilateral knee pain. Concomitant medications included morphine sulfate and simvastatin. During infusion of her second dose of IV acetaminophen, the patient development pain and it

was subsequently discovered that the intravenous site had infiltrated and the patient withdrew consent so she was discontinued from the trial.

The adverse event of pain at the infusion site leading to this patient's discontinuation was not likely related to IV acetaminophen treatment.

Patient 015-05, a 31-year-old female in Study CPI-APA-304 received a total of 2 out of 4 planned doses of IV acetaminophen 1000 mg q6h for pain on 28 December 2007 following a diagnostic laparoscopy with carbon dioxide vaporization of endometrial implants (b) (6). Her medical history included endometriosis, dysmenorrheal, urinary incontinence, kidney stones, migraine headaches, hypercholesterolemia, gastroesophageal reflux disease, seasonal allergies and myopia. Her prior surgical history includes ceasaran section, umbilical hernia repair, hemorrhoid removal, and left eye surgery. Concomitant medications included aluterol, simvastatin, rabeprazole, fexofenadine, tolterodine tartrate, and ethinyl estradiol levoorgestrel. After the second dose of IV acetaminophen, the patient reported pain at the IV site, and it was subsequently discovered that the site had infiltrated and she refused replacement of the intravenous line so she was discontinued from the trial.

The adverse event of pain at the infusion site leading to this patient's discontinuation was not likely related to IV acetaminophen treatment.

Patient 011-28, a 54-year-old-female in Study CPI-APA-351 received a total of 8 out of 20 planned doses of IV acetaminophen 1000 mg q6h for pain between 19 June 2008 and 21 June 2008 following revision of total knee arthroplasty (b) (6). Her medical history included arthritis, right paraprosthetic femur fracture, hypertension, hypothyroidism, anemia, seasonal allergies and history of varicella. Her prior surgical history included total bilateral knee arthroplasty, bariatric surgery, hernia repair, and tonsillectomy. Concomitant medications included ketorolac, hydromorphone, enoxaparin, metoclopramide, oxycodone, On day 2 of IV acetaminophen the patient's intravenous line infiltrated and she was subsequently discontinued from the trial.

The adverse event of intravenous line infiltration leading to this patient's discontinuation was not likely related to IV acetaminophen treatment.

Patient 013-04, a 60-year-old male in Study CPI-APA-351 received a total of 4 out of 30 planned doses of IV acetaminophen 650 mg q4h for pain on 11 July 2008 following left hip arthroplasty revision (b) (6). His medical history included left hip osteoarthritis, left hip abscess, chronic osteomyelitis, left thigh anterior abscess, staphylococcus aureus infection, chronic low back pain, septic arthritis, hypertension, history of bradycardia and history of bacteremia. His prior surgical history included left total hip arthroplasty, and incision and drainage of left thigh abscess. Preoperative and intraoperative medications included midazolam, fentanyl, ceruroxime, propofol,

rocuronium, hydromorphone, phenylephrine, ondansetron, neostigmine, glycopyrrolate, sevoflurane, marcaine, bupivacaine, and hydrocodone. Concomitant medications included vancomycin, cefazolin, and dilaudid.. On 11 July 2008 @ 21:00 the patient was reported to have moderate vomiting and he was subsequently discontinued from the trial.

The adverse event of vomiting leading to this patient's discontinuation was not likely related to IV acetaminophen treatment.

Patient 01-0016, an 80-year-old female in Study 136-02-03 received a total of 2 out of 4 doses of IV acetaminophen 650 mg q4h for pain on 30 March 2004 following left hip arthroplasty (b) (6). Her medical history included left hip osteoarthritis, Meniere's disease, bilateral foot neuropathy, borderline diabetes mellitus, Grave's disease, hypothyroidism, obesity, ulcerative colitis, hiatal hernia, and history of pulmonary embolism. Prior surgical history included right hip arthroplasty, radioactive thyroidectomy and tonsillectomy. Concomitant medication included morphine patient controlled analgesia. On 30 March, approximately 3.5 hours after her first dose of IV acetaminophen the patient developed nausea. Approximately 2 hours after receiving her second dose of IV acetaminophen and the patient was reported to have nausea and severe vomiting and she was subsequently discontinued from the trial.
While the morphine patient controlled analgesia medication is a more plausible etiology of the patient's vomiting, I cannot rule out IV acetaminophen as an possible etiology as well.

The adverse event of vomiting leading to this patient's discontinuation was possibly related to IV acetaminophen treatment.

Patient 010-39, a 22-year-old female in Study CPI-APA-301 received a total of 6 out of 8 planned doses of IV acetaminophen 1000 mg q6h for pain between 16 July 2008 and 17 July 2007 following excision of right dermoid cyst and salpingo-oophorectomy via laparotomy (b) (6). Her medical history included right adrenal mass, intermittent diarrhea, abdominal discomfort and low back pain. There was no prior surgical history. Concomitant medications included hydromorphone , oxycodone, and colace. On day 2 of IV acetaminophen treatment the patient developed a truncal rash at which time trial drug treatment was discontinued. The truncal rash was reported as resolved 2 days after discontinuation from IV acetaminophen.

The adverse event of truncal rash leading to this patient's discontinuation was possibly related to IV acetaminophen treatment.

Patient 015-07, a 47-year-old female in Study CPI-APA-301 received a total of 5 out of 8 planned doses of IV acetaminophen 1000 mg q6h for pain between 16 April 2007 and 17 April 2007 following a total abdominal hysterectomy (b) (6). Her medical history included uterine fibroids, endometriosis, pelvic pain, hypertension, asthma, vision deficit and depression. There was no prior surgical history. Concomitant medications included hydromorphone, albuterol inhaler, fluticasone propionate/salmetorol diskus, fluticasone priopionase spray, lisonipril, and fluoxetine On 17 April 2007 the patient was reported as having an adverse event, a severe headache, for which medication (ketrolac) was required and she was subsequently discontinued from the trial. Her headache was reported to have resolved on 19 April 2007 2 days after IV acetaminophen was stopped.

The adverse event of headache leading to this patient's discontinuation was not likely related to IV acetaminophen treatment.

Patient 010-33, a 63-year-old female in Study CPI-APA-351 received a total of 15 out of 30 planned doses of IV acetaminophen 650 mg q4h for pain between 15 July 2008 and 18 July 2008 following spinal lumbar 3 -4 fusion (b) (6). Her medical history included spinal stenosis, lumbar 3-4 herniated disc, scoliosis, back pain, kidney stones, asthma, migraine headaches, obesity, bilateral carpel tunnel syndrome, history of bleeding gastrointestinal ulcers, nocturia, hypothyroidism and depression. Her prior surgical history included gastric bypass, hysterectomy, carpal tunnel repair, and bilateral breast biopsies. Concomitant medications include morphine patient controlled analgesia, levothroxine, ketorolac, paroxetine, cefazolin, docusate, benzoaine-cetylpyridinium, prochlorperazine, sumatriptan, zolpidem, baclofen and ondastrenon,

On day 3 of IV acetaminophen the patient developed nausea and vomiting and hematemesis for which medications (hydroxyzine, metoclopramide,) were required and was she was subsequently discontinued from the trial. These symptoms resolved approximately 8 hours after IV acetaminophen was stopped. This patient's history of bleeding ulcers as well as concomitant use of ketorolac are the most likely etiologies of these adverse events..

The adverse events of nausea, vomiting and hematemesis leading to this patient's discontinuation are were not likely related to IV acetaminophen

7.3.4 Significant Adverse Events

Please see section 7.3.5

7.3.5 Submission Specific Primary Safety Concerns

This section addresses significant adverse events observed in the adult clinical trial program including: accidental acetaminophen overdose and drug-related hepatic events.

Accidental overdose
Accidental overdose (exceeding the 4000 mg acetaminophen daily limit) was the most commonly reported serious TEAE in patients in the IV acetaminophen group (n=4, 0.4%) and the placebo group (n=8, 1.5%) These "overdoses" included theoretical overdoses since the patients treated with placebo did not receive APAP. However, since they could have received APAP, the Applicant treated the cases as legitimate overdoses.

In actuality, four patients (1 – IV APAP, 3, - placebo) did not receive acetaminophen doses in excess of the daily limit. Of the 8 "actual" accidental overdose cases, 3 patients were enrolled in trial 136-02-03 (24 hour, repeat-dose, adult hip trial) and 5 patients were enrolled in trial 136-03-03 (24 hr, repeat-dose, vaginal hysterectomy trial). These cases of accidental overdose were associated with concomitant dosing with an oral acetaminophen-containing product, nearly always with a combination opioid/acetaminophen medication. None of these 8 cases were associated with adverse reactions or LFT elevations. However, these events involving accidental overdose in a clinical trial setting underscores the potential risk pending approval and marketing of the IV acetaminophen within the United States

This drug is currently approved in nearly 80 countries. The Applicant estimated that approximately 53.6 million patients have been exposed to IV acetaminophen since 2001. There have been a total of 50 cases (13 – adult, 37-pediatrics) of overdose (defined as >4 g of oral and/or IV acetaminophen in 24 hrs) as reported in the post-marketing summary. Per the applicant, there were no reported fatalities associated with acetaminophen overdose. The most common sequelae of overdose involved mild to moderate LFT elevations that were reversed with medical therapy including in some cases the administration of N-acetyl-cysteine.

The draft label for IV acetaminophen contains a section on "overdosage" that addresses part of this issue. The section on "overdosage" states that serious potential consequences can result from overdosing with acetaminophen- containing products including hepatic failure leading to death with an additional reference to the warning and precautions section of the label. In addition, the overdose section of the label provides recommendations in cases of acetaminophen overdose. The applicant has also submitted a risk management plan that it hopes will be consistent with the IV acetaminophen label.

Drug-Related Hepatic Events

The MedDRA category of hepatic disorders was used to assess the incidence, severity, seriousness, and baseline characteristics of all adult patients who experienced a hepatic event. Overall, the incidence of hepatic events was similar in the IV acetaminophen group (4.4%) as compared to the placebo group (5.8%). There were no deaths while on study in either group that were related to hepatic TEAE. The incidence of serious hepatic TEAEs was higher in the IV acetaminophen group (0.4%) as compared to the placebo group (0 %). Also, the incidence of hepatic TEAEs leading to discontinuations was higher in the IV acetaminophen group (0.6%) as compared to the placebo group (0%).

Four IV acetaminophen patients had hepatic events that were assessed as serious adverse events. The case narrative and case report forms were reviewed. All 4 cases involved post-surgical procedures. Three of the four patients had elevations in AST and/or ALT > 3x ULN and 1 patient had a maximum elevation of 2x ULN; total bilirubin was normal in all 4 patients.

Six IV acetaminophen patients had hepatic events that led to discontinuation, including two of the six patients assessed with serious TEAEs. The case narratives and case report forms for all the involved patients were reviewed. Five out of the six cases were enrolled into the study post-surgical procedures (hip or knee arthroplasty) and the remaining case involved a groin cellulitus. Three of the six discontinued IV study drug patients had elevations in GGT> 3x ULN with normal to mildly elevated ALT values and normal TBL values. The remaining three patients had elevations in AST and/or ALT > 3x ULN with normal TBL values. All six patients had complicated medical histories, with confounding factors including concomitant hepatotoxic medications that may have been possible etiologies of their LFT elevations, however I could not completely rule out IV acetaminophen as a factor in LFT elevations leading to discontinuation from the trials.

There were 2 cases that met laboratory criteria for Hy's Law (concurrent elevation in AST/ALT > 3x ULN with TNL > 2x ULN). The first patient was a 70 year old female with a significant cardiac history who received IV acetaminophen status post coronary bypass graft procedure. Post-operatively she suffered experienced severe, prolonged hypotension that resulted in multi-organ failure around which time her LFT values were elevated. This case represents LFT elevation as a result of severe hemodynamic compromise (shock). Because there was another reason for her elevations in LFTs, this does not represent a case of Hy's Law.

The 2nd patient was a 39 year old male with a significant spinal orthopedic history and social history of 18 alcoholic drinks per week who received IV acetaminophen status post an orthopedic procedure. His pre-treatment LFT values were elevated (AST > ALT) consistent with excessive alcohol use. His LFT values peaked on day five of IV acetaminophen treatment with an ALT of 3.8x ULN, AST 14.9x ULN and TBL 2.6x ULN.

This second case represents acetaminophen toxicity in a patient with a hepatic risk factor (excessive alcohol use).

The clinical database for acetaminophen IV contained a few cases of drug-related elevations in LFTs. The draft label for IV acetaminophen contains a precaution on the use of IV acetaminophen in patients with pre-existing hepatic dysfunction or when other hepatic risk factors are present such as alcoholism, chronic malnutrition, severe hypovolemia or severe renal impairment. The label also states that in these situations a reduced total daily dose of acetaminophen may be warranted.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Using the dataset files provided by the applicant in the 28 July 2009 submission, I verified the counts for common adverse events occurring at a rate of ≥ 1% in the randomized double blind placebo controlled adult patient studies as seen in Table 7.

Table 7: Common (≥1%) Incidence of Treatment-Emergent Adverse Events by Frequency in IV APAP Study Group: All Randomized, DB, PC Adult Patient Studies Safety Population

Preferred Term	IV APAP[a] (N=783)	Placebo (N=525)
Nausea	151 (19.3%)	131 (25.0%)
Constipation	93 (11.9%)	95 (18.1%)
Headache	73 (9.3%)	45 (8.6%)
Vomiting	69 (8.8%)	46 (8.8%)
Procedural pain	67 (8.6%)	9 (1.7%)
Fatigue	42 (5.4%)	9 (1.7%)
Flatulence	39 (5.0%)	39 (7.4%)
Pyrexia	35 (4.5%)	57 (10.9%)
Pruritus	34 (4.3%)	37 (7.0%)
Insomnia	34 (4.3%)	28 (5.3%)
Anaemia	28 (3.6%)	23 (4.4%)
Dizziness	27 (3.4%)	25 (4.8%)
Abdominal distension	19 (2.4%)	14 (2.7%)
Post procedural haemorrhage	17 (2.2%)	4 (0.8%)
Tachycardia	15 (1.9%)	18 (3.4%)
Alveolar osteitis	15 (1.9%)	4 (0.8%)
Aspartate aminotransferase increased	14 (1.8%)	8 (1.5%)
Trismus	14 (1.8%)	1 (0.2%)
Diarrhoea	11 (1.4%)	18 (3.4%)
Injection site extravasation	11 (1.4%)	10 (1.9%)
Infusion site pain	11 (1.4%)	4 (0.8%)
Gamma-glutamyltransferase increased	10 (1.3%)	11 (2.1%)
Alanine aminotransferase increased	10 (1.3%)	8 (1.5%)
Abdominal pain	10 (1.3%)	7 (1.3%)

Table 8: Common (≥1%) Incidence of Treatment-Emergent Adverse Events by Frequency in IV APAP Study Group: All Randomized, DB, PC Adult Patient Studies Safety Population

Preferred Term	IV APAP[2] (N=783)	Placebo (N=525)
Dysuria	10 (1.3%)	7 (1.3%)
Post procedural infection	10 (1.3%)	2 (0.4%)
Haemorrhage	9 (1.1%)	5 (1.0%)
Hypotension	9 (1.1%)	2 (0.4%)
Paraesthesia oral	9 (1.1%)	0
Dyspepsia	8 (1.0%)	7 (1.3%)
Oedema peripheral	8 (1.0%)	5 (1.0%)
Abdominal pain upper	8 (1.0%)	3 (0.6%)
Pain	8 (1.0%)	1 (0.2%)
Hypokalaemia	7 (0.9%)	9 (1.7%)
Back pain	6 (0.8%)	17 (3.2%)
Postoperative fever	5 (0.6%)	7 (1.3%)
Prothrombin time prolonged	5 (0.6%)	6 (1.1%)
Urinary retention	5 (0.6%)	6 (1.1%)
Accidental overdose	4 (0.5%)	8 (1.5%)
Anaemia postoperative	4 (0.5%)	7 (1.3%)
Rash	4 (0.5%)	6 (1.1%)
Body temperature increased	1 (0.1%)	7 (1.3%)

[1] Defined as all 9 studies in adult patients: CPI-APF-302, CN145-004, RC 210 3 001, 136-01-03, RC 210 3 002, 136-02-03 136-03-03, CPI-APA-301, CPI-APA-304
[2] Defined as 1g, 2g and 650 mg.

Source: Applicant's submission (Amendment 8, Response to Clinical Information Request- Adult ISS, pp. 27-28)

The most common adverse events were nausea, constipation, headache, vomiting, and procedure pain. The incidence rates of common adverse events between IV acetaminophen and placebo were generally comparable except for clinically meaningful events where IV acetaminophen rates were higher than placebo including: procedural pain (8.6 % vs. 1.7 %), post procedural hemorrhage (2.2 % vs. 0.8%), hypotension (1.1 % vs. 0.4%, trismus (1.8%) vs.0.2%) and pain (1.0% vs. 0.2%) respectively.

7.4.2 Laboratory Findings

In the clinical development program, the laboratory evaluation of safety was conducted using standard hematology and chemistry (including liver function tests) investigations. At times the analysis of laboratory safety data was confounded by

1. lack of comparator group in the five day open - label trial and;
2. use of concomitant medications known to be related to adverse events such as hepatic enzyme elevation, and renal function test elevations

In the adequate and well–controlled trials, lab investigations including hematology, chemistry and urinalysis were drawn at screening, daily, and end of trial/ early termination.In the open–label day trial (CPI-APA-351), lab investigations including hematology, chemistry ad urinalysis were drawn at screening, study completion or early termination (if applicable). Liver function tests were drawn at screening, daily during treatment, and at end of study/ early termination.

7.4.2.1 Hematology analysis

Analysis focused on measures of central tendency

A summary of mean hematology values at baseline and changes from baseline to the last visit is provided in Table 8 for the IV acetaminophen and placebo groups in the seven repeat dose trials (RC 210 2 002, 136-02-03, 136-03-03, CPI-APA-101, CPI-APA-201, CPI-APA-304 and CPI-APA-351). I analyzed the repeated- dose trials rather than the single dose trials to evaluate for any changes in hematological values over multiple doses.

Table 9: Mean (SD) Hematology Values at Baseline and Change from Baseline to Last Value on Study: All Repeat-dose Studies (Safety Population)

Parameter	IV APAP							
	650 mg (N = 134)		1000 mg (N = 485)		Total (N = 619)		Placebo (N = 379)	
Timepoint	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Hemoglobin (g/dL)								
Baseline	121	11.50 (2.910)	455	11.87 (2.924)	576	11.79 (2.923)	342	11.42 (2.653)
Δ to last value	121	-0.66 (2.036)	455	-0.26 (1.855)	576	-0.35 (1.900)	342	-0.07 (1.495)
Hematocrit (%)								
Baseline	121	35.7 (5.44)	454	36.5 (5.73)	575	36.3 (5.67)	342	35.9 (4.35)
Δ to last value	121	-1.5 (5.13)	454	-0.7 (5.02)	575	-0.9 (5.05)	342	-0.2 (4.69)
Leukocytes (10^9/L)								
Baseline	120	9.58 (4.442)	453	9.93 (4.370)	573	9.86 (4.383)	341	10.76 (4.841)
Δ to last value	120	-1.12 (4.442)	453	-1.89 (4.316)	573	-1.73 (4.350)	341	-2.97 (4.700)
Platelets (10^9/L)								
Baseline	120	254.4 (87.18)	448	256.6 (86.89)	568	256.2 (86.88)	334	260.2 (70.55)
Δ to last value	120	119.8 (124.65)	448	78.8 (95.09)	568	87.5 (103.30)	334	85.4 (96.33)

Definitions: IV APAP= intravenous acetaminophen; SD=standard deviation; g=grams; dL=deciliter; L=liter; Δ=change
Source: Applicant's submission (ISS – Adults, pg. 140)

Overall, mean hematological parameters (hemoglobin, hematocrit, leukocytes and platelets) at baseline were comparable between IV acetaminophen and placebo groups in that all of these values in both groups were within normal ranges. The hematology parameters remained comparable for both groups with respect to the last value on trial remained in normal range. There were slightly lower baseline hemoglobin and

hematocrit values in the placebo group as compared to the IV acetaminophen groups; and slightly lower baseline leukocyte and platelet values in the IV acetaminophen group as compared to the placebo group however these differences do not appear to be meaningful. Finally, with exception of the IVAP 650 mg subgroup and change (from baseline to last trial value) in platelet value as compared to IV APAP 1000 mg subgroup and placebo group, there were no meaningful differences between the IV acetaminophen groups and placebo group for changes in hematology parameters from baseline to the last trial value. In giving repeated doses of IV acetaminophen, there appears to be no meaningful changes in hematologic parameters of hemoglobin, hematocrit, leukocytes and platelets as compared to placebo.

Analysis focused on outliers or shifts from normal to abnormal

Hematology shifts from baseline to the worst value on trial for the IV acetaminophen and placebo groups in the all adult patient pool are displayed in Table 9 that follows.

Table 10: Hematology shifts from Baseline to Worse Value on Study: All Adult Patient Studies (Safety Population)

Parameter	Shift	IV APAP (N = 1020) n/N (%)[1]	Placebo (N = 525) n/N (%)[1]
Hemoglobin – Worst high	Shift to High[4]	4/890 (0.4)	1/459 (0.2)
	Shift to Low[5]	96/890 (10.8)	45/459 (9.8)
Hemoglobin – Worst low	Shift to High[2]	4/890 (0.4)	1/459 (0.2)
	Shift to Low[3]	133/890 (14.9)	87/459 (18.9)
Leukocytes – Worst high	Shift to High[4]	84/886 (9.5)	38/458 (8.3)
	Shift to Low[5]	6/886 (0.7)	5/458 (1.1
Leukocytes – Worst low	Shift to High[2]	51/886 (5.8)	13/458 (2.8)
	Shift to Low[3]	19/886 (2.1)	16/458 (3.5)
Platelets – Worst high	Shift to High[4]	133/881 (15.1)	102/450 (22.7)
	Shift to Low[5]	10/881 (1.1)	10/450 (2.2)
Platelets – Worst low	Shift to High[2]	50/881 (5.7)	19/450 (4.2)
	Shift to Low[3]	26/881 (2.9)	20/450 (4.4)

Definitions

1 n=number of patients with shift N=total number of patients in analysis
2 Shift from normal or low value at baseline to a lowest value on trial that was above the upper limit of normal range (high)
3 Shift from normal or high value at baseline to a lowest value on trial that was below the lower limit of normal range (low)
4 Shift from normal or low value at baseline to a highest value on trial that was above the upper limit of the normal range (high)
5 Shift from normal or high value at baseline to a highest value on trial that was below the lower limit of the normal range (low)

Source: Applicant's submission (ISS – Adults, pg. 141)

Hemoglobin values that were normal to high at baseline and shifted to the worst low were seen in 14.9% of the IV acetaminophen group as compared to 18.9 % in the placebo group. No major differences in hemoglobin values that were normal to high at baseline and shifted to the worst high were noted between the IV acetaminophen group and placebo group (0.4% and 0.2 % respectively).

Leukocyte values that were normal to high at baseline and shifted to the worst low were seen in 2.1% of the IV acetaminophen group as compared to 3.5% of the placebo group. The incidence of leukocytes shifts from normal to high at baseline to worst high was 9.5% in the IV acetaminophen group as compared to the placebo group (8.3%). Finally, the incidence of platelet shifts from baseline to worst high was higher in the placebo group (22.7%) versus the IV acetaminophen group (15.1%) The incidence of platelet shift from baseline to worst low were comparable between IV acetaminophen and placebo groups (2.9% and 4.4 % respectively)

Overall, no clinically meaningful differences were noted in the incidence of hematology shift trends between the IV acetaminophen and placebo groups.

Marked outliers and dropouts for hematology abnormalities

There were no adult cases of marked outliers and dropouts for hematology abnormalities.

7.4.2.2 Chemistry (other than LFT) analysis

The chemistry parameters analyzed in the submission included: sodium, potassium, chloride, glucose, albumin, blood urea nitrogen (BUN) and creatinine.

Analysis Focused on Measures of Central Tendency

A summary of mean chemistry values at baseline and changes form baseline to the last value is provided in Table 10 for the IV acetaminophen and placebo groups in the seven repeat dose trials (RC 210 2 002, 136-02-03, 136-03-03, CPI-APA-101, CPI-APA-201, CPI-APA-304 and CPI-APA-351). I analyzed the repeated- dose trials rather than the single dose trials to evaluate for any changes in chemistry values over repeated doses.

Table 11: Mean (SD) Chemistry Values at Baseline and Change from Baseline to Last Value on Trial: All Repeat-dose Studies (Safety Population

Parameter	IV APAP							
	650 mg (N = 134)		1000 mg (N = 485)		Total (N = 619)		Placebo (N = 379)	
Timepoint	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Sodium (mmol/L)								
Baseline	121	138.4 (3.43)	463	139.1 (2.97)	584	138.9 (3.08)	350	139.5 (2.83)
Δ to last value	121	-0.0 (3.55)	463	-0.1 (3.21)	584	-0.1 (3.28)	350	-0.2 (3.05)
Potassium (mmol/L)								
Baseline	121	4.01 (0.442)	461	4.04 (0.451)	582	4.04 (0.449)	350	3.99 (0.418)
Δ to last value	121	0.18 (0.574)	461	0.17 (0.554)	582	0.18 (0.558)	350	0.28 (0.565)
Chloride (mmol/L)								
Baseline	121	104.3 (4.11)	421	104.2 (3.17)	542	104.2 (3.40)	309	104.7 (2.83)
Δ to last value	121	-1.7 (4.62)	421	-1.4 (3.75)	542	-1.5 (3.96)	309	-1.8 (3.35)
Glucose (mg/dL)								
Baseline	120	122.0 (47.64)	461	117.3 (40.37)	581	118.3 (41.98)	349	116.9 (37.40)
Δ to last value	120	-14.0 (52.73)	461	-14.6 (44.60)	581	-14.5 (46.35)	349	-14.5 (40.30)
Albumin (g/dL)								
Baseline	111	3.55 (0.685)	414	3.83 (0.633)	525	3.77 (0.654)	308	3.83 (0.526)
Δ to last value	111	0.08 (0.682)	414	0.17 (0.675)	525	0.15 (0.677)	308	0.32 (0.537)
BUN (mg/dL)								
Baseline	120	13.1 (6.53)	464	13.4 (6.84)	584	13.4 (6.77)	350	11.8 (4.64)
Δ to last value	120	1.0 (6.12)	464	-0.7 (5.64)	584	-0.3 (5.78)	350	0.3 (4.40)
Creatinine (mg/dL)								
Baseline	121	0.90 (0.301)	466	0.83 (0.282)	587	0.84 (0.287)	354	0.77 (0.189)
Δ to last value	121	-0.03 (0.190)	466	-0.02 (0.195)	587	-0.02 (0.194)	354	-0.02 (0.139)

Definitions: IV APAP= intravenous acetaminophen; SD= standard deviation; Mmol=millimoles; mg=milligrams; g=grams; dL=deciliter; L=liter; Δ=change
Source: Applicant's submission (ISS – Adults, pg. 146)

In general, mean chemistry values for the above parameters at baseline were within normal ranges for both IV acetaminophen and placebo groups and baseline values were comparable between both groups. Furthermore, the change to the last value on trial between IV acetaminophen and placebo groups was comparable

Overall, there were no clinically meaningful differences noted in the mean chemistry values at baseline and change from baseline to last value on trial between the IV acetaminophen and placebo groups.

Analyses focused on outliers or shifts from normal to abnormal

I reviewed the shift table prepared by the applicant. Table 11 reflects clinical chemistry shifts from baseline to worst value on trial in all adult patient pool. Because this pool included uncontrolled data, it is not possible to attribute these events to IV acetaminophen.

Table 12: Clinical Chemistry Shifts from Baseline to Worst Value on Study: All Adult Patient Pool (Safety population)

Parameter	Shift	IV APAP (N = 1020) n/N (%)[1]	Placebo (N = 525) n/N (%)[1]
Albumin – Worst low	Shift to High[2]	20/803 (2.5)	1/379 (0.3)
	Shift to Low[3]	117/803 (14.6)	70/379 (18.5)
Sodium – Worst high	Shift to High[4]	0/931 (0)	1/474 (0.2)
	Shift to Low[5]	26/931 (2.8)	1/474 (0.2)
Sodium – Worst low	Shift to High[2]	0/931 (0)	0/474 (0)
	Shift to Low[3]	47/931 (5.0)	43/474 (9.1)
Potassium – Worst high	Shift to High[4]	10/929 (1.1)	8/474 (1.7)
	Shift to Low[5]	16/929 (1.7)	2/474 (0.4)
Potassium – Worst low	Shift to High[2]	6/929 (0.6)	3/474 (0.6)
	Shift to Low[3]	51/929 (5.5)	46/474 (9.7)
Glucose – Worst high	Shift to High[4]	98/614 (16.0)	76/390 (19.5)
	Shift to Low[5]	5/614 (0.8)	0/390 (0)
Glucose – Worst low	Shift to High[2]	58/614 (9.4)	27/390 (6.9)
	Shift to Low[3]	9/614 (1.5)	6/390 (1.5)
Creatinine – Worst high	Shift to High[4]	16/934 (1.7)	2/479 (0.4)
	Shift to Low[5]	14/934 (1.5)	5/479 (1.0)

Definitions: IV APAP= intravenous acetaminophen
1 n= number of patients with shift, N= total number of patients included in analysis
2 shift from normal or low value at baseline to a lowest value on study that was above the upper limit of normal range (high)
3 shift from normal or high value at baseline to a lowest value on study value that was below the lower limit of the normal range (low)
4 Shift from normal or low value at baseline to a highest value on study that was above the upper limit of the normal range (high)
5 Shift from normal or high value at baseline to a highest value on study that was below the lower limit of the normal range

Source: Applicant's submission (ISS – Adults, pg. 147)

The incidence of shifts from normal or high at baseline to worst low was higher in the placebo group than in the IV acetaminophen groups for albumin (14.6% for IV acetaminophen vs. 18.5% placebo), sodium (5.0% IV acetaminophen vs. 9.1% placebo), and potassium (5.5% IV acetaminophen vs. 9.7% placebo). The overall incidence of shifts from normal or high at baseline to worst high was low and comparable between IV acetaminophen and placebo groups for sodium (0% IV acetaminophen vs. 0.2 % placebo), and potassium (1.1% IV acetaminophen vs. 1.7 % placebo). With respect to glucose, the incidence of shifts from normal to worst high was higher in the placebo group vs. IV acetaminophen (19.5% vs. 16.0% respectively). The incidence of shifts from normal to worst low for creatinine was 1.5 % for both IV

acetaminophen and placebo groups. Last, the incidence of shifts form normal to worst high for creatinine was noted to be higher in the IV acetaminophen group (1.7%) vs. the placebo group (0.4%). Overall, there were no meaningful clinical differences in the chemistry shifts from baseline to worse value between the IV acetaminophen and placebo groups.

Marked outliers and dropouts for Chemistry abnormalities

One IV acetaminophen patient enrolled in the open-label five day study experienced a chemistry event that resulted in discontinuation. A brief narrative for this patient follows:

> **Patient 011-10**, a 64-year-old male, enrolled in trial CPI-APA-351.underwent a radical cystectomy (b) (6) and received a total of 16 out of 20 planned doses of IV acetaminophen 1000 mg Q6h for pain between (b) (6) . His reported medical history included adenocarcinoma of the bladder, right hydronephrosis, renal insufficiency, anemia, leukocytosis, low back strain, and asthma. Prior surgical history included resection of bladder tumor. Concomitant medications included famotidine, fentanyl, cefazolin, metclopramide, oxycodone. The patient's creatinine at screening was 1.55 mg/dL (ULN 1.1 mg/dL). As previously mentioned, chemistry labs in the open label trial were obtained at screening, trial completion or early termination as was this case for this patient. On Day 2 (b) (6) moderate acute renal failure was reported as a serious TEAE; per the SAE report the creatinine was 2.97 mg/dL at that time. The patient was reported as withdrawn from the study for this event although dosing continued through (b) (6) at which time the creatinine was 2.75 mg/dL. On Day 8, one day after discontinuation from the study the CRF reports a Cr of 1.72 mg/dL. The acute renal failure was reported as resolved on (b) (6) at which time the patient's Cr was 1.09 mg/dL.

The marked Cr level (reported max of 2.97) reported in this patient with a history of renal insufficiency could have been due to etiologies other than IV acetaminophen including: use of concomitant medication (i.e. cefazolin) associated with increased BUN and Cr levels as well as renal failure, and adverse event associated with the surgical procedure. However, careful review of this the CRF shows the Cr normalizing after IV acetaminophen discontinuation despite continuation of cefazolin until last Cr of 1.0 mg/dL.

7.4.2.3 Special Assessment (Hepatic enzyme analysis)

The issue of acetaminophen-induced liver damage remains an area of major concern. In addition to acute suicide or accidental overdose, the literature suggests that long term administration of therapeutic doses of acetaminophen in patients compromised by illness, chronic ethanol use, genetic predisposition, and co-ingestion with substances

metabolized by liver and other factors (age, gender, obesity), may also cause hepatic injury especially in the adult population. [1]

The applicant has grouped liver function tests (LFTs) for the safety analysis which include: alanine aminotransferase ALT; U/L), aspartate aminotransferase (AST; U/L), gamma-glutamyl transferase (GGT; U/L), total bilirubin (TBL; mg/dL), and alkaline phosphatase (ALP; U/L). The applicant has evaluated the hepatic safety of acetaminophen in the following ways:

- Descriptive statistics for LFTs for the all adult patient pool at baseline and last value on trial
- Summary statistics (mean) for change from baseline to last value on trial
- Shifts form baseline to the worst treatment deviation from the normal range and from baseline to last value on trial
- Number and percentage of patients with AST or ALT that increased from normal to abnormal, or if abnormal at baseline, increased by at least 20% from baseline to the worst value on trial for all adult patient pool, single-dose and repeated-dose study pools
- Summary that includes number and percentage of patients who had values of AST, ALT, AST or ALT, GGT, ALP, or TBL ≤ 3, > 3 to ≤ 5, > 5 to ≤10 or > 10 times upper limit of normal (ULN) after initiation of acetaminophen.
- Scatter plots of maximum ALT versus maximum TLB for all adult patient pool, repeated-dose pool, and repeated-dose placebo –control pool.

Analysis Focused on Measures of Central Tendency

A summary of mean liver function test values at baseline and changes form baseline to the last value on trial is provided in Table 12 that follows for the IV acetaminophen and placebo groups in the all adult patient pool.

Table 13: Mean (SD) Liver Function Test Values at Baseline and Change from Baseline to Last Value on Trial: All Adult Patient Studies (Safety Population)

Parameter Timepoint	IV APAP[1] (N = 1020)		Placebo (N = 525)	
	n	Mean (SD)	n	Mean (SD)
AST (U/L)				
Baseline	1004	25.5 (20.26)	502	22.5 (15.19)
Δ to last value	1004	3.5 (113.75)	502	-0.1 (18.16)
ALT (mmol/L)				
Baseline	1003	24.0 (17.19)	504	21.2 (13.12)
Δ to last value	1003	5.3 (67.29)	504	3.2 (18.08)
GGT (U/L)				
Baseline	987	28.5 (37.47)	496	25.0 (24.14)
Δ to last value	987	14.4 (50.24)	496	10.9 (28.14)
TBL (mg/dL)				
Baseline	1002	0.66 (0.484)	500	0.54 (0.371)
Δ to last value	1002	0.00 (0.421)	500	0.00 (0.277)
ALP (g/dL)				
Baseline	1003	85.0 (44.00)	500	78.1 (34.14)
Δ to last value	1003	13.4 (36.65)	500	10.7 (28.30)

Definitions: Δ = change; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transaminase; IV APAP = intravenous acetaminophen; Phos = phosphatase; TBL = total bilirubin; U = units; L = liter

Source: Applicant's submission (ISS- Adults, pg. 160)

In general, mean baseline LFTs were in normal ranges for both for the IV acetaminophen group and placebo groups, however mean baseline LFT values were slightly higher in the IV acetaminophen group as compared to the placebo. The change to the last value on trial for ALT, AST, GGT and ALP levels were higher in IV acetaminophen group as compared to the placebo group changes are small and are not clinically meaningful. There were no differences in TBL between the two groups. Overall, there were no clinically meaningful changes in mean LFT values from baseline to end of trial for the all adult patient pool.

Analyses focused on outlier or shifts from normal to abnormal

The shift frequency Table13 shows the number of patients who shifted from normal LFTs at baseline to above normal for last value the all adult patient pool.

Table 14: Liver Function Test: Frequency of Shifts from Normal at Baseline to Above Normal for Last Value on Study: All Adult Patient Pool (Safety Population)

Laboratory Parameter	IV APAP[1] (N = 1020) n/N (%)[2]	Placebo (N = 525) n/N (%)[2]
AST	103/1004 (10.3)	46/502 (9.2)
ALT	81/1003 (8.1)	41/504 (8.1)
GGT	142/987 (14.4)	69/496 (13.9)
ALP	43/1003 (4.3)	27/500 (5.4)
TBL	50/1002 (5.0)	15/500 (3.0)

Definitions: ALP=alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transaminase;
IV APAP = intravenous acetaminophen; TBL = total bilitrubin
1 Includes 650 mg (n=134), 1000mg (n-754) and 2000 mg (n=132) IV acetaminophen doses
2 n = number of patients with shift, N = total number of patients in analysis
Source: Applicant's submission (ISS – Adults, pg. 161)

Table 13 shows that a slighter higher percentage of patients in the IV acetaminophen group in comparison to the placebo group had a shift from normal/low baseline to above normal post-baseline value > ULN for AST (10.3% IV APAP vs. 9.2 % placebo), GGT (14.4% IV APAP vs. 13.9% placebo), ALP (4.3 % IV APAP vs. 5.4% placebo) and TBL (5.0% IV APAP vs. 3.0% placebo). There was no difference in the percentage of patients between the two groups experiencing a ALT shift from normal/low baseline to above normal last value (8.1% IV APAP vs. 8.1 % placebo). Overall, there were no meaningful differences in the proportion of patients in the IV acetaminophen and placebo groups that had a shift normal/low baseline value to a worst post-baseline for liver function tests.

In addition to reviewing the shift tables of normal to abnormal LFT, patient data were reviewed for LFT maximum elevations of > 3x ULN in AST, ALT, TBL, ALP and GGT. These results are summarized in Table 14 that follows:

Table 15: Post-Baseline Liver Function Test Results Relative to the Normal range: All Adult Patient Pool (Safety Population)

Laboratory Test Abnormality	IV APAP[1] (N = 1020) n (%)	Placebo (N = 525) n (%)
AST or ALT (maximum AT), n	1009	505
≤ 3×ULN	983 (97.4)	496 (98.2)
> 3 - ≤ 5×ULN	15 (1.5)	4 (0.8)
> 5 - ≤ 10×ULN	8 (0.8)	4 (0.8)
> 10×ULN	3 (0.3)	1 (0.2)
AST, n	1008	503
≤ 3×ULN	986 (97.8)	497 (98.8)
> 3 - ≤ 5×ULN	12 (1.2)	1 (0.2)
> 5 - ≤ 10×ULN	7 (0.7)	4 (0.8)
> 10×ULN	3 (0.3)	1 (0.2)
ALT, n	1007	505
≤ 3×ULN	992 (98.5)	496 (98.2)
> 3 - ≤ 5×ULN	13 (1.3)	6 (1.2)
> 5 - ≤ 10×ULN	1 (0.1)	2 (0.4)
> 10×ULN	1 (0.1)	1 (0.2)
TBL, n	1007	505
≤ 3×ULN	1004 (99.7)	505 (100.0)
> 3 - ≤ 5×ULN	3 (0.3)	0
> 5 - ≤ 10×ULN	0	0
> 10×ULN	0	0
GGT, n	1006	504
≤ 3×ULN	941 (93.5)	479 (95.0)
> 3 - ≤ 5×ULN	38 (3.8)	13 (2.6)
> 5 - ≤ 10×ULN	22 (2.2)	12 (2.4)
> 10×ULN	5 (0.5)	0
ALP, n	1008	506
≤ 3×ULN	1005 (99.7)	506 (100.0)
> 3 - ≤ 5×ULN	3 (0.3)	0
> 5 - ≤ 10×ULN	0	0
> 10×ULN	0	0

Definitions: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transaminase; IV APAP = intravenous acetaminophen; TBL = total bilirubin; ULN = upper limit of normal

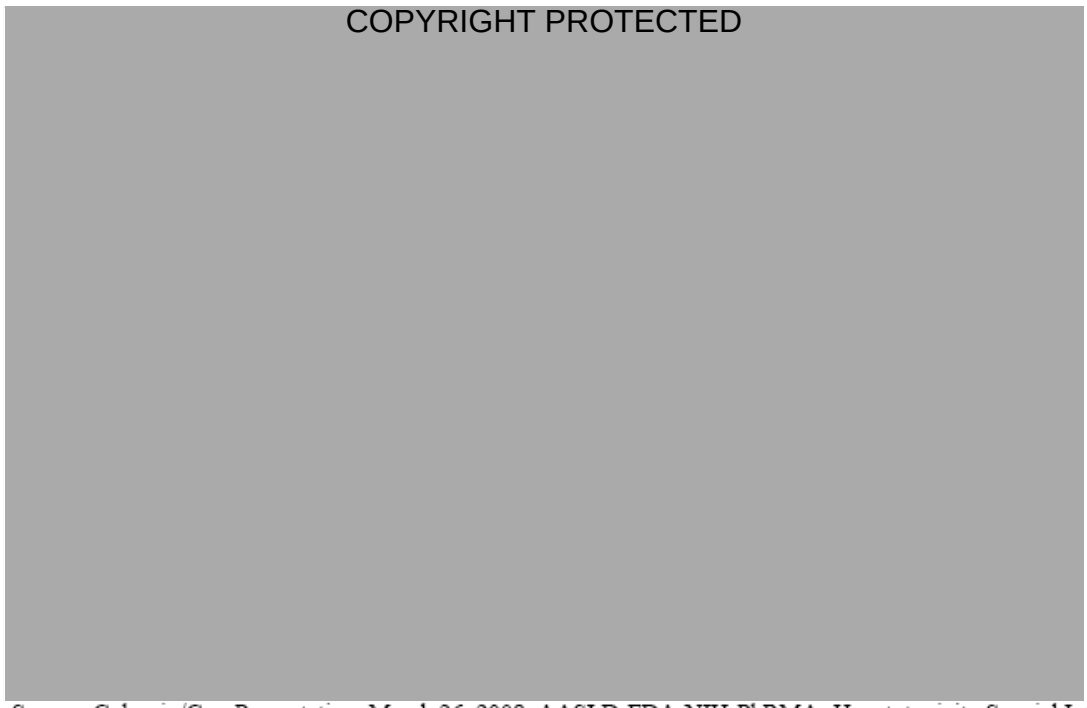
1 Includes 650 mg (n=134), 1000 mg (n=754), and 2000 mg (n=132) IV acetaminophen group

Source: Applicant submission (ISS – Adults, pg. 163)

The percentage of patients with elevations in either ALT or AST > 3x ULN is slighter higher in the IV acetaminophen group as compared to the placebo group (1.5 % vs. 0.8 % respectively. More specifically, AST, ALT, TBL GGT and ALP values > 3x - ≤5x ULN are proportionally higher in the IV acetaminophen group versus the placebo group

A scatterplot diagram of patients with maximum ALT and maximum TBL levels was produced by the applicant to evaluate electronically for drug-induced serious hepatotoxicity using the eDISH methodology. These concepts are illustrated graphically in Figure 1 below.

Figure 1: eDISH, A Graphic Presentation of Hy's Law



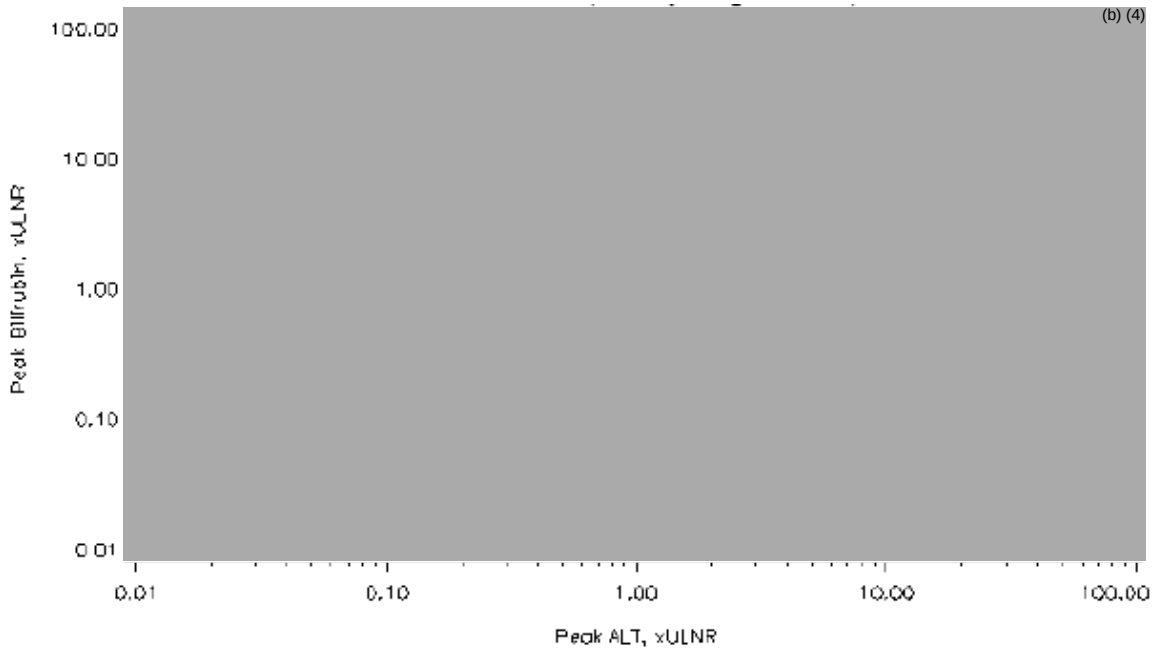
Source: Gelperin/Guo Presentation, March 26, 2008, AASLD-FDA-NIH-PhRMA- Hepatotoxicity Special Interest Group Meeting: http://www.fda.gov/cder/livertox/presentations2008/D-GelperinGuo2.pdf
Source: Applicant's submission (ISS – Adults, pg.154)

The eDISH tool helps visualize graphically peak ALT vs. peak TBL on a logarithmic scale for each patient in a clinical trial so as to aid in detecting potential serious liver injury.[2] Values within the normal reference range (< ULN) for ALT and TBL are found in the left lower quadrant. Potential Hy's Law cases are located in the upper right quadrant. Cases involving cholestasis or Gilbert's disease are typically found in the upper left quadrant, and cases involving ALT elevations without significant hepatic impairment (i.e. without increased TBL) are found in the lower right quadrant.

A scatterplot diagram of patients with maximum ALT and maximum TBL levels was produced by the applicant to evaluate electronically for drug-induced serious hepatotoxicity (eDISH). Specifically, the applicant has produced "eDISH" scatterplots of peak ALT and TBL values for the entire adult safety pool as well as the adult placebo-

controlled safety population. The scatterplot for the placebo-controlled patient pool is displayed in Figure 2.

Figure 2: Scatterplot of Post-baseline Peak ALT versus Peak Bilirubin: All Placebo-controlled Patient Studies (Safety Population)

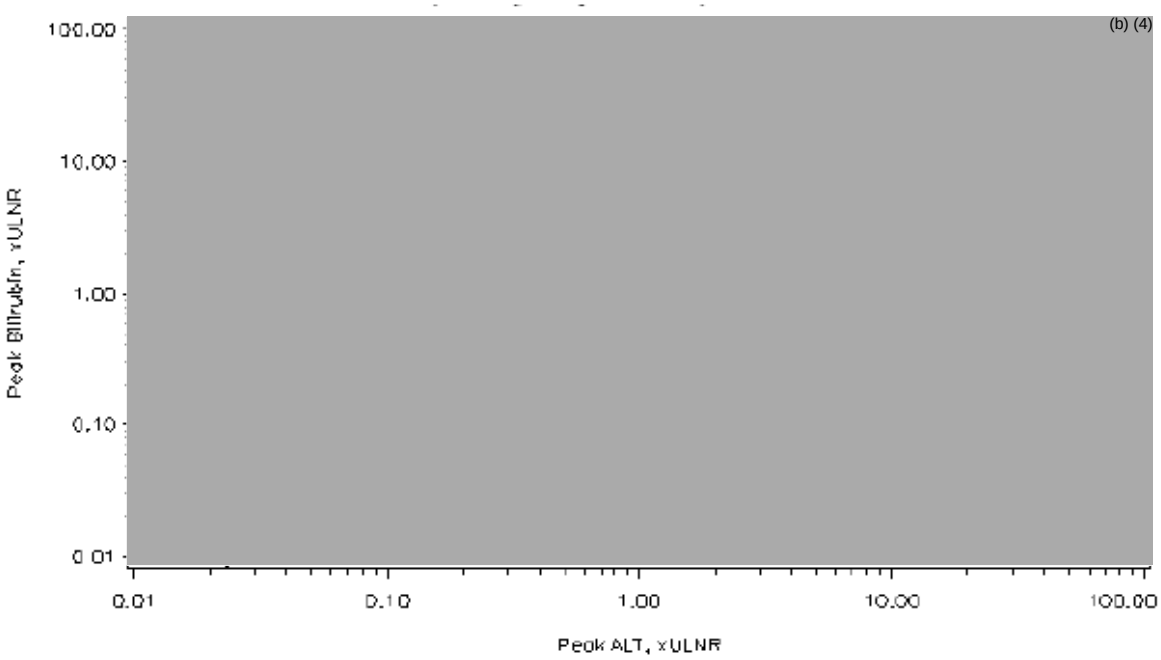


Definitions: IV APAP = intravenous acetaminophen; ALT = alanine transaminase; ULNR = upper limit of normal range
Source: Applicant's submission (ISS – Adults, pg. 156)

This diagram demonstrates that the proportion of patients within the normal range (left lower quadrant) for peak ALT and peak TBL values are similar between the IV acetaminophen and placebo groups. In addition, the proportion of patients having peak ALT elevations (>3x ULN) without significant liver injury (right lower quadrant) appears to be similar between IV acetaminophen and placebo groups. There are several IV acetaminophen cases represented in the peak bilirubin range (> 2x ULN) without concurrent ALT elevation (left upper quadrant). There are no graphical cases of Hy's law illustrated in the placebo-control trials.

The scatterplot of post-baseline peak ALT versus peak bilirubin for the all adult patient pool is displayed in Figure 3 that follows. .

Figure 3: Scatterplot of Post-baseline Peak ALT versus Peak Bilirubin: All Adult Patients Studies (Safety Population)



Source: Applicant's submission (ISS – Adults, pg. 165)

From this figure, the proportion of patients having peak ALT elevations (>3x ULN) without significant liver injury (right lower quadrant) appears to be similar between IV acetaminophen and placebo groups. More importantly, the "eDISH" scatterplot shows two IV acetaminophen cases (both from open label trial CPI-APA-351) that appear in the left upper quadrant which may potentially represent Hy's law cases. The discussion of these marked outliers will be provided in the following section.

Marked outliers and dropouts for liver function test abnormalities

There were 2 patients who had concurrent elevations in both ALT/AST > 3x ULN with TBL > 2x ULN. Review of these cases reveal that both patients were enrolled in the five day open - label study (CPI-APA-351) that had no comparative group The case narratives for these patients are following:

> **Patient 008-14** in Study CPI-APA-351, a 70-year-old female was admitted to the hospital (b) (6) because of chest pain resulting from a myocardial infarction. The patient's medical history was also significant for coronary artery disease, hypertension, diabetes mellitus, hypercholesterolemia, and hypothyroidism. Concomitant medications included diazepam, furosemide, metoprolol, hydroxyzine, famotidine, enoxaparin, cefuroxime, ketorolac, calcium

chloride, magnesium sulfate, insulin, morphine, heparin and albumin. Screening LFTs were normal except normal except for an AST of 168 U/L (3.5x ULN). Baseline LFTs were AST of 65 U/L (ULN 45 U/L), ALT of 28 U/L (ULN of 55 U/L), ALP of 24 U/L (ULN of 147 U/L) and TBL of 1.3 mg/dl (ULN 1.5 mg/dL). The patient underwent an emergent coronary artery bypass graft (b) (6) and received her first dose of IV acetaminophen 1000 mg Q6h for pain following surgery (b) (6). She received a total of 7 out of 30 planned doses of 1000 mg Q6h between (b) (6) (day 2 of trial). Her immediate postoperative course was unremarkable (b) (6); the patient developed severe prolonged hypotension with a reported blood pressure of 60/40 mmHg. Her hypotension was corrected after several hours; however, she subsequently developed acute renal failure followed by acute liver failure with jaundice (multi-organ failure). That evening, she had decreased urine output associated with acute elevations of her BUN at 29 mg/dL and creatinine at 2.6 mg/dL. AST at that time was 3575 /L (> 10x ULN), ALT was 2042 U/L (> 10x ULN), TBL was 5.8 U/L (> 4x ULN) and ALP was 30 U/L (normal). The following 00 ALday (AST was 5204 U/L (> 10x ULN), ALT was 2862 U/L (> 10x ULN), and TBL was 6.4 mg/dL (4x ULN). (b) (6) two days after discontinuation of trial drug she became acidotic, suffered a cardiac arrest, and died.

Table 16: Patient 008-14 (Study CPI-APA-351) LFT Assessments

Value (X ULN)	Screening	T0/Day 1	Day 1	Day 2	Day 2 /ET	Post ET Day	Days 3, 4, & 5
ALT	60	28	28	2004 (>10x)	2042 (>10x)	2862 (>10x)	N/A
AST	168 (3.5x)	65	55	3575 (>10x)	>2600 (>10x)	5204 (>10x)	N/A
GGT	18	10	11	28	34	52	N/A
TBL	1.1	1.3	1.2	5.4 (3.5x)	5.8	6.4 (4x)	N/A
ALP	37	24	22	34	30	48	N/A

Definitions: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ALP = alkaline phosphatase
GGT = gamma-glutamyl transferase
Source: Applicant's submission (ISS – Adults, pg. 169 & CRF)

Table 15 above shows the daily LFT values for this patient. Significant elevations of ALT, AST and TBL values occurred on Day 2 of IV acetaminophen treatment, as well as the day in which she suffered a prolonged hypotensive episode followed by multi-organ failure. After thorough review of the case it appears that the patient did not meet criteria for Hy's Law. Her multi-organ failure secondary to hypotension/hypoxia is the likely process that contributed to her hepatotoxicity and ultimate liver failure.

Patient 001-02 a 39-year-old male in Study CPI-APA-351, with a history of severe kyphotic spinal deformity from ankylosing spondylitis was admitted for T11-12 fracture dislocation with subluxation and underwent a two stage surgical stabilization. The first procedure involving a posterior approach was performed 8 days prior to IV acetaminophen use. The second procedure involved a left anterior thoracolumbar approach and was performed the same day of but prior to the start of IV acetaminophen and he received a total of 27 out of 30 planned doses of IV acetaminophen 650 mg Q4h for pain between (b) (6) The patient did not receive dose #2 of drug on Day 2, dose #2 of drug on day 4 and dose #3 of drug on day 5 due to nursing error in locating drug as reported in the case report form. In addition to the above history, the patient's medical history included hypertension, depression, asthma, morbid obesity (BMI = 40.6), anemia, chronic back pain, lower extremity paresthesias and weakness, and multiple T8-T12 spinal procedures for discogenic disease. Concomitant medications included trazodone, naproxen, nicotine patch, ascorbic acid, methadone, lisinopril, cyclobenzaprine, famotidine, senna, docusate and multivitamins. Table 15 below shows the daily LFT values for this patient.

Table 17: Patient 001-02 Study CPI-APA-351 LFT Assessments

Value (X ULN)	Screening	T0/Day 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 9 (F/U)
ALT	ND	81 (1.5)	48	39	83 (1.5)	134 (2.4)	208 (3.8)	102 (1.9)	56
AST	ND	310 (6.9)	262 (5.8)	253 (5.6)	361 (8.0)	456 (10.1)	670 (14.0)	238 (5.2)	122
GGT	ND	88 (1.7)	54	50	258 (5.0)	269 (5.0)	342 (7.0)	230 (4.5)	141 (2.5)
TBL	ND	0.9	0.8	0.8	2.3 (1.5)	2.6 (1.7)	3.9 (2.6)	1.4	1.4
ALP	ND	87	71	74	267 (1.8)	264 (1.8)	320 (2.2)	252 (1.7)	189

Definitions: ALT = alanine aminotransferase; AST = aspartate aminotransferase
GGT= gamma-glutamyl transferase; TBL = total bilirubin
ALP = alakaline phosphatase; ND = not done
Source: Applicant's submission (ISS – Adults, pg.170 & CRF)

Screening labs were not performed on this patient.. Baseline LFTs (T0/Day 1, post surgery but prior to IV acetaminophen) showed AST of 310 U/L (6x ULN)), ALT of 81 U/L (1.5x ULN), GGT of 88 U/L (1.7x ULN); ALP of 87 U/L and TBL of 0.9 mg/dL as seen in (Table 16). On Day 3 (b) (6) an elevation in GGT to 258 U/L was reported as an adverse event. ALT was similar to baseline (83 U/L) and AST, ALP and TBL had increased (361 U/L, 267 U/L and 2.3 mg/dL, respectively. All LFT values

continued to rise till last day (Day 5) of IV acetaminophen treatment in which values reported were: AST 670 U/L, ALT 208 U/L, GGT 342 U/L, ALP 320 U/L and TBL 3.9 mg/dL. Concurrent adverse event included muscle spasms. By 2 days post treatment,(day 7on table CC) LFTs were returning toward baseline values: AST 238 U/L, ALT 102 U/L, GGT 230 U/L, ALP 252 U/L and TBL 1.4 mg/dL Four days after completion of IV acetaminophen, LFT values continued to improve (ALT 56 U/L, AST 122 U/L, TBL 1.4 , GGT 141 U/L, ALP 189) but were not back to initial values on Day 1 (T0) of trial.

This patients' hepatic enzyme data initially raised concern of a possible Hy's Law case. The applicant was queried and we received further information including: the emergency room record, hospital progress notes, operative reports and lab reports.. The applicant has reported that there are no other LFT values available other than those supplied. My review of this information revealed this patient had a social history of 18 drinks per week. This is a possible explanation for the AST level > than the ALT value at baseline in that cirrhosis and/or alcohol abuse are associated with higher AST levels than ALT values.

In summary, this 39 year old male with a medical history significant for ankylosing spondylitis received a total of 27 doses of IV acetaminophen after an extensive anterior/posterior reconstructive surgery for a thoracic (T11 – T12) fracture dislocation. He also had a social history significant for consuming 18 alcohol drinks per week. His baseline AST level > ALT level is consistent with excessive alcohol use. There was a daily increase in LFTs starting from Day 3 of IV acetaminophen to their respective maximum levels on Day 5. After completion of IV acetaminophen treatment, follow-up LFT values were shown to be normalizing to his baseline values. While this case does not technically fit Hy's law criteria, it further reinforces concepts regarding high risk populations. This patient as evidenced by his history and LFT values was at higher risk for AT & GGT elevations because of a possible underlying alcoholic hepatitis as well as potential nonalcoholic fatty liver disease due to his morbid obesity. This case emphasizes the importance of addressing high risk groups in the IV acetaminophen label.

7.4.3 Vital Signs

All 14 clinical studies with data reported utilized standard vital sign assessments prior to and following study treatment. Additionally, in trials CPI-APA-101, CPI-APA-301, CPI-APA-304, CPI-APF-302, and CPI-APF-303 vital signs were taken immediately prior to and after each infusion of IV acetaminophen or placebo medication. Normal range limits used for the evaluation of vital signs are as follows:

• Systolic Blood Pressure (SBP):
Lower Limit = 90 mmHg; Upper Limit = 140 mmHg;

• Diastolic Blood Pressure (DBP):
Lower Limit = 60 mmHg; Upper Limit = 90 mmHg;
• Heart Rate (HR):
Lower Limit = 60 beats per minute; Upper Limit = 100 beats per minute;
• Respiratory Rate:
Lower Limit = 12 breaths per minute; Upper Limit = 18 breaths per minute.

For each patient, the baseline value was defined as the value collected at the time closest but prior to the start of study medication administration.

Analyses Focused on Outliers or Shifts from Normal to Abnormal

The applicant analyzed vital sign shifts from baseline to last value on study for the IV acetaminophen and placebo groups in the all adult patient pool as seen in Table 17

Table 18: Vital Sign shifts from Baseline to Last value on Study (All Adult Patient Safety Pool)

Parameter	Shift	IV APAP[1] (N = 1020) n/N (%)[2]	Placebo (N = 525) n/N (%)[2]
Systolic blood pressure	Shift to High[3]	71/1020 (7.0)	53/523 (10.1)
	Shift to Low[4]	2/1020 (0.2)	0/523 (0)
Diastolic blood pressure	Shift to High[3]	45/1020 (4.4)	7/523 (13.4)
	Shift to Low[4]	51/1020 (5.0)	31/523 (5.9)
Heart rate	Shift to High[3]	51/1020 (5.0)	27/523 (5.2)
	Shift to Low[4]	51/1020 (5.0)	17/523 (3.3)
Respiratory rate	Shift to High[3]	33/303 (10.9)	40/302 (13.2)
	Shift to Low[4]	0/303 (0)	2/302 (0.6)

Definitions: IV APAP = intravenous acetaminophen.
Note: For the 11 studies included in this study pool see Table 4.
Note: Information on the active control (n = 81 PO APAP or standard of care) and IV propacetamol 2000 mg (n = 50) are included in Appendix Table 1.4.1
1 Includes 650 mg (n = 134), 1000 mg (n = 754) and 2000 mg (n = 132) IV acetaminophen doses.
2 n = number of patients with shift, N = total number of patients included in analysis.
3 Shift from normal or low value at baseline to high value (relative to normal range) at last evaluation.
4 Shift from normal or high value at baseline to low value (relative to normal range) at last evaluation.

Source: Applicant's submission (Adult – ISS, pg. 174)

There are no clinically meaningful differences noted in the incidence of shifts in vital signs from baseline to last value on study between the IV acetaminophen group and the placebo group.

In addition to analyzing abnormal shifts from baseline to last value on study, the applicant also included a summary of vital signs abnormalities reported as TEAEs in the all adult patient safety pool as seen in Table 18 that follows.

Table 19: TEAEs associated with Vital signs Abnormalities: All Adult Patient Studies (Safety Population)

MedDRA Preferred Term	IV APAP[1] (N = 1020) n (%)	Placebo (N = 525) n (%)
Blood Pressure Events		
Hypotension	29 (2.8)	2 (0.4)
Hypertension	12 (1.2)	2 (0.4)
Orthostatic hypotension	3 (0.3)	0
Diastolic hypotension	1 (0.1)	0
Blood pressure increased	1 (0.1)	1 (0.2)
Blood pressure decreased	0	1 (0.2)
Body Temperature Events		
Pyrexia	43 (4.2)	57 (10.9)
Hypothermia	2 (0.2)	0
Body temperature increased	1 (0.1)	7 (1.3)
Heart Rate Events		
Tachycardia	23 (2.3)	18 (3.4)
Bradycardia	2 (0.2)	0
Heart rate decreased	0	1 (0.2)
Respiratory Rate Events		
Tachypnoea	1 (0.1)	0
Respiratory rate decreased	1 (0.1)	0
Respiratory rate increased	1 (0.1)	0

Definitions: IV APAP = intravenous acetaminophen.
Note: For the 11 studies included in this study pool see Table 4.
Note: Information on the active control (n = 81; PO APAP or standard of care) and IV propacetamol 2000 mg (n = 50) are included in Appendix Table 1.2.3A
[1] Includes 650 mg (n = 134), 1000 mg (n = 754) and 2000 mg (n = 132) IV acetaminophen doses.
Source: Applicant's submission (Adult – ISS, pg. 175)

Per the applicant, the majority of TEAES were reported as mild to moderate in severity. Vital sign abnormalities reported as SAEs included 1 patient each in the IV acetaminophen group and placebo groups with pyrexia. A higher incidence of hypotension was seen in the IV acetaminophen group as compared to the placebo group (2.8% vs. 0.4 %) respectively. Otherwise, there were no clinically meaningful differences between IV acetaminophen and placebo groups in TEAEs associated with vital sign abnormalities.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed for any of the adult trials.

7.4.5 Special Safety Studies/Clinical Trials

No additional special safety studies or clinical trials were performed during the adult clinical development program

7.4.6 Immunogenicity

No new data regarding the immunogenic potential of intravenous acetaminophen was included in this submission

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

I reviewed the common incidence of treatment emergent adverse events by frequency in IV APAP group in the repeat dose, randomized, placebo-controlled adult patient study safety population. I verified the counts by using the Jump software and found on random selection of common adverse events my counts matched exactly to the applicant's table (Table 19) as seen below.

Table 20: Common (≥ 1%) Incidence of Treatment Emergent Adverse Events by Frequency in IV APAP Group: Repeat Dose Randomized, Double-blind, Placebo-controlled Adult Patient Studies Safety Population

	IV APAP			
Preferred Term	650 mg (N=43)	1g (N=359)	Total (N=402)	Placebo (N=379)
Nausea	4 (9.3%)	134 (37.3%)	138 (34.3%)	119 (31.4%)
Constipation	5 (11.6%)	79 (22.0%)	84 (20.9%)	85 (22.4%)
Vomiting	4 (9.3%)	58 (16.2%)	62 (15.4%)	42 (11.1%)
Flatulence	4 (9.3%)	35 (9.7%)	39 (9.7%)	38 (10.0%)
Headache	3 (7.0%)	36 (10.0%)	39 (9.7%)	33 (8.7%)
Pruritus	0	32 (8.9%)	32 (8.0%)	37 (9.8%)
Insomnia	3 (7.0%)	27 (7.5%)	30 (7.5%)	21 (5.5%)
Pyrexia	0	22 (6.1%)	22 (5.5%)	52 (13.7%)
Anaemia	0	21 (5.8%)	21 (5.2%)	20 (5.3%)
Abdominal distension	1 (2.3%)	17 (4.7%)	18 (4.5%)	14 (3.7%)
Dizziness	0	13 (3.6%)	13 (3.2%)	19 (5.0%)
Injection site extravasation	0	11 (3.1%)	11 (2.7%)	9 (2.4%)
Tachycardia	1 (2.3%)	9 (2.5%)	10 (2.5%)	14 (3.7%)
Abdominal pain	2 (4.7%)	8 (2.2%)	10 (2.5%)	7 (1.8%)
Infusion site pain	1 (2.3%)	8 (2.2%)	9 (2.2%)	4 (1.1%)
Dysuria	0	8 (2.2%)	8 (2.0%)	7 (1.8%)
Dyspepsia	1 (2.3%)	7 (1.9%)	8 (2.0%)	6 (1.6%)
Hypotension	0	7 (1.9%)	7 (1.7%)	1 (0.3%)
Incision site pain	0	7 (1.9%)	7 (1.7%)	1 (0.3%)
Back pain	2 (4.7%)	4 (1.1%)	6 (1.5%)	16 (4.2%)
Diarrhoea	0	6 (1.7%)	6 (1.5%)	14 (3.7%)
Muscle spasms	0	6 (1.7%)	6 (1.5%)	5 (1.3%)
Aspartate aminotransferase increased	1 (2.3%)	5 (1.4%)	6 (1.5%)	3 (0.8%)

Table 19: Common (≥ 1%) Incidence of Treatment Emergent Adverse Events by Frequency in IV APAP Group: Repeat Dose Randomized, Double-blind, Placebo-controlled Adult Patient Studies Safety Population

Prothrombin time prolonged	0	5 (1.4%)	5 (1.2%)	6 (1.6%)
Fatigue	2 (4.7%)	3 (0.8%)	5 (1.2%)	5 (1.3%)
Oedema peripheral	0	5 (1.4%)	5 (1.2%)	3 (0.8%)
Pain in extremity	0	5 (1.4%)	5 (1.2%)	3 (0.8%)
Chills	0	5 (1.4%)	5 (1.2%)	1 (0.3%)
Gamma-glutamyltransferase increased	0	5 (1.4%)	5 (1.2%)	1 (0.3%)
Hypokalaemia	0	4 (1.1%)	4 (1.0%)	6 (1.6%)
Rash	0	4 (1.1%)	4 (1.0%)	6 (1.6%)
Urinary retention	0	4 (1.1%)	4 (1.0%)	6 (1.6%)
Blood glucose increased	1 (2.3%)	3 (0.8%)	4 (1.0%)	5 (1.3%)
Dyspnoea	3 (7.0%)	1 (0.3%)	4 (1.0%)	3 (0.8%)
Alanine aminotransferase increased	1 (2.3%)	3 (0.8%)	4 (1.0%)	1 (0.3%)
Palpitations	1 (2.3%)	3 (0.8%)	4 (1.0%)	0
Accidental overdose	0	3 (0.8%)	3 (0.7%)	8 (2.1%)
Hyperhidrosis	0	3 (0.8%)	3 (0.7%)	5 (1.3%)
Musculoskeletal pain	0	3 (0.8%)	3 (0.7%)	4 (1.1%)
Pharyngolaryngeal pain	0	3 (0.8%)	3 (0.7%)	4 (1.1%)
Anxiety	1 (2.3%)	2 (0.6%)	3 (0.7%)	3 (0.8%)
Cough	1 (2.3%)	2 (0.6%)	3 (0.7%)	2 (0.5%)
Hypertension	1 (2.3%)	2 (0.6%)	3 (0.7%)	2 (0.5%)
Ileus	0	2 (0.6%)	2 (0.5%)	5 (1.3%)
Urinary tract infection	0	2 (0.6%)	2 (0.5%)	5 (1.3%)
Chest pain	0	2 (0.6%)	2 (0.5%)	4 (1.1%)

[1] Defined as all 5 repeated dose studies: RC 210 3 002, 136-02-03, 136-03-03, CPI-APA-301, CPI-APA-304

Source: Applicant's submission (Amendment 8, Response to Clinical Information Request, Table 4C, pp. 97-98)

The 1 gram (g) IV acetaminophen dose group has higher incidences of several meaningful clinical adverse events as compared to the placebo group including: nausea (37.3% vs. 31.4%), vomiting (16.2 % vs. 11.1%), hypotension (1.9% vs. 0.3%) and increased aspartate aminotransferase values (1.4 % vs. 0.8%) respectively.

7.5.2 Time Dependency for Adverse Events

This section is not applicable to this sNDA.

7.5.3 Drug-Demographic Interactions

The applicant included in the submission separate tabulations of TEAEs reported in ≥ 2% of IV acetaminophen patients in the all adult patient pool by age category, gender, race, ethnicity and body mass index (BMI). Within the age category tabulation, patients ≥ 65 years of age in the IV acetaminophen group had notable higher incidences of nausea, hypotension, and hypokalaemia as compared to patients ≥ 65 years of age in the placebo group In comparing the < 65 year age group with the > 65 year age group treated IV acetaminophen, as expected the incidence of TEAES in the age group > 65 treated with IV acetaminophen were generally higher.

In tabulating TEAEs by gender, overall the types and incidence of these events were not different across gender. Gastrointestinal events including nausea, constipation and vomiting occurred more frequently in females as compared to males however these

differences were noted with similar frequency in both IV acetaminophen and placebo groups.

In tabulating TEAEs by race, in general non-Caucasians appeared to have experienced higher rates of TEAEs as compared to Caucasians. For ethnicity, a higher proportion of Hispanic Latinos in the IV acetaminophen group experienced nausea as compared to Non-Hispanic Latinos (41.3% vs. 28.2 respectively). The difference in nausea rates between Hispanic and Non-Hispanic Latinos was not observed in the placebo group (26.2% vs. 34.2%). There were no other meaningful differences noted across treatment groups by race and ethnicity.

In tabulating TEAEs by BMI, differences were across BMI categories and treatment categories in procedural pain where those patients in the IV acetaminophen group with a BMI < 25 experienced the higher proportion of this event as compared to the placebo group. Otherwise, there were no other meaningful differences among across treatment groups by BMI.

7.5.4 Drug-Disease Interactions

This section is not applicable to this sNDA.

7.5.5 Drug-Drug Interactions

There were no drug-drug interaction (DDI) studies conducted with IV acetaminophen in support of this NDA. The applicant has submitted a literature review of relevant DDI interactions with oral acetaminophen. Relevant portions of this literature review are summarized in the IV acetaminophen label below:

> Substances that regulate hepatic cyctochromes (mainly CYP2E) can alter the metabolism of acetaminophen and subsequently alter the drug's hepatotoxic potential. Substances that have been reported to possibly regulate relevant human cytochromes such as CYP2E1 include but are not limited to barbiturates, clofibrate, isonazid, omeprazole, paclitaxel, rifampin, troglidazone, oral anticoagulants, zidovudine, and clauvulinic acid. Substances that have been reported to possibly alter the PK or increase the hepatotoxic potential of acetaminophen in experiments include phenytoin, salicylamide, probenecid, retinol, diflusnisal and doxapram.

Please see Dr. Ping Ji's clinical pharmacology review for full discussion of DDI related to IV acetaminophen.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Due to the short duration of IV acetaminophen exposure (≤ 5 days), an assessment for carcinogenic effects was not performed in support for this NDA.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy Category B has been assigned to IV acetaminophen. Clinical experience with intravenous administration of acetaminophen is limited. However, epidemiological data from the use of oral therapeutic doses of acetaminophen indicate no undesirable effects on pregnant women or on the health of the fetus.

There have been no adequate and well-controlled studies with IV acetaminophen in labor and delivery.

7.6.3 Pediatrics and Assessment of Effects on Growth

This section of the review will be dedicated to the review of safety data from the pediatric safety database. The format of the safety review will be identical to that of the adults

7.6.3.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from a total of 5 studies conducted in pediatric patients are included in the submission. An overview of these trials is presented in Table 20.

There are no placebo-controlled data in the pediatric population. Two of the five pediatric studies were Phase 3, randomized, double-blind, active-control, single-dose efficacy and safety studies (CN145-001 and RC 210 3 006). One study was an open-label, repeated-dose efficacy and safety study for up to 7 days for the treatment of either pain or fever (CPI-APA-352). The remaining two studies were phase 1, open-label, repeated dose, PK evaluations.

Table 21: Overview of Pediatric Clinical Studies of IV Acetaminophen

Protocol	Phase	Population	Indication	Study design	Single (S) Repeated (R) dose Duration	Dose and No.		
						IV APAP	Control	Total
CPI-APA-102	1	Inpatient	Pain Fever	O/L, PK, safety	R/48h	N=75	N/A	75
EHRC #26095	1	Inpatient	Pain or Fever	O/L, PK, safety	R/72h	N=50	N/A	50
CN145-001	3	Inpatient	Fever	Randomized, DB,AC, efficacy, safety	S/6h	N=35	PPA n=32	67
RC 210 3 006	3	Inpatient	Pain	Randomized, DB, AC, inguinal herniorrhaphy efficacy, safety	S/6h	N=74	N/A	75
CPI-APA-352	3	Inpatient	Pain or Fever	O/L, efficacy, safety	R/168 h	N=100	N/A	100

Source: Applicant's submission (ISS-Pediatric, pg. 16)

A brief description of each trial follows:

1. Study CPI-APA-102: was a Phase 1, prospective, multicenter, open-label, repeat-dose PK study that examined the PK and safety of IV acetaminophen in pediatric populations of various age groups (full-term neonates, infants, children and adolescents) using a weight-based dosing regimen of IV acetaminophen over a 48 hour period
2. Study EHRC # 26095: was a Phase 1, prospective, investigator-initiated, single center (Royal Children's Hospital in Melbourne, Australia), open-label, repeat-dose PK study that examined the PK of IV acetaminophen in premature and full-term neonates weighing at least 1 kilogram (kg), and infants up to 6 months of age using a gestational age-and weight-based dose regimen of IV acetaminophen given Q6h over a 72-hour period.
3. Study CN 145-001: was a phase 3, prospective, multi-center, parallel groups, active-controlled, single-dose study comparing 15 mg IV acetaminophen to 30

mg IV propacetamol in infants and children (ages 1 month to 12 years) with fever (38.5 degrees Celsius to 41 degrees Celsius) of infectious origin.

4. Study RC 210 3 006: was a phase 3, prospective, multi-center, parallel group, active-controlled, single-dose study comparing 15 mg IV acetaminophen to 30 mg IV propacetamol in infants and children (ages 1 to 12 years) status post hernia repair
5. Study CPI-APA-352: was a phase 3, prospective, multi-center, open-label, repeat-dose, 5 day study examining safety and efficacy of IV acetaminophen in pediatric inpatients (full-term neonates to adolescents) with pain and fever.

7.6.3.2 Categorization of Adverse Events

All adverse events from these studies were coded using version 10.0 of the Medical Dictionary for Regulatory Activities (MEDRA) (Q1, 2008: English language version) The appropriateness of the applicant's coding was assessed by comparing the preferred term to the verbatim terms recorded by investigators within a sampling of case report forms . The coding was found to be accurate.

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

The data for pediatric patients who received IV acetaminophen from all 5 studies conducted were pooled according to age category as seen in Table 21 below.

Table 22: Distribution by Study and Age Category for Analysis of Pediatric Safety Data

Protocol Identifier	Number Exposed to IV acetaminophen			
	Neonates[1]	Infants[2]	Children[3]	Adolescents[4]
CN145-001	0	15	20	0
RC210 3 006	0	9	86	0
CPI-APA-102	3	25	25	22
CPI-APA-352	1	8	40	51
EHRC #26095 (Palmer)	**43**	**7**	**0**	**0**
Total Dosed with IV acetaminophen	47	64	171	73

[1] Neonates: ≤ 28 days old
[2] Infants: 29 days to < 2 years old
[3] Children: 2 years to < 12 years old
[4] Adolescents: 12 years to < 18 years old

Source: Applicant's Submission (ISS- Pediatrics, pg. 21)

The summary tabulations as seen in Table 2 for the pediatric clinical trials include the following categories based on age of patient at time of IV acetaminophen exposure;

1. Neonates (≤ 28 days old)

- Premature neonates (< 37 weeks post- menstrual age at birth)
- Full –term neonates (≥ 37 weeks post –menstrual age at birth)

2. Infants (29 days to < 2 years old)
3. Children (2 years to < 12 years old)
4. Adolescents (12 years to < 18 years old)

The safety dataset for Pediatrics was reviewed in toto.

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

Table 22 that follows shows the exposure of IV acetaminophen in the pediatric population by age stratum

Table 23: Exposure to IV Acetaminophen (Pediatric Safety Population)

Parameter	Neonates (N = 47)	Infants (N = 64)	Children (N = 171)	Adolescents (N = 73)
No. doses, N (%)				
1	0	24 (37.5)	106 (62.0)	0
2-4	2 (4.3)	3 (4.7)	5 (2.9)	3 (4.1)
5-6	4 (8.5)	1 (1.6)	2 (1.2)	2 (2.7)
7-10	9 (19.1)	12 (18.8)	20 (11.7)	9 (12.3)
> 10	32 (68.1)	24 (37.5)	38 (22.2)	59 (80.8)
No. of doses				
Mean (SD)	12.5 (4.80)	7.8 (6.69)	6.0 (7.91)	16.0 (6.76)
Median	13.0	8.0	1.0	15.0
Min, Max	3, 24	1, 24	1, 30	4, 34
Duration (days)				
Mean (SD)	3.64 (1.534)	1.77 (1.594)	1.38 (1.754)	3.67 (1.595)
Median	3.43	2.01	0.26	4.02
Min, Max	0.7, 7.7	0.3, 6.4	0.3, 6.8	0.8, 7.1
Total dose (mg)				
Mean (SD)	532.0 (247.61)	886.7 (528.29)	2018.7 (3086.65)	10895.4 (4915.73)
Median	510.00	1000.00	600.00	10500.0
Min, Max	90.0, 1260.0	114.0, 2760.0	140.0, 20000.0	2100.0, 21000.0
Ave. Daily Dose (mg)[1]				
Mean (SD)	150.9 (49.30)	401.1 (185.91)	1453.8 (802.24)	3069.2 (750.72)
Median	148.26	399.60	1190.48	3233.53
Min, Max	36.0, 262.3	100.0, 835.8	477.8, 3976.1	1365.8, 4306.7

Definitions: Ave. = average; min = minimum; max = maximum; No. = number; SD = standard deviation
[1] For patients who received repeated doses.

Source: Applicant's submission (ISS-Pediatrics, pg. 30)

Overall, 60% (212/355) of pediatric patients received ≥ 5 doses of IV acetaminophen including: 96% (45/47) of neonates, 58% (37/64) of infants, 35% (60/171) of children and 96 % (70/73) of adolescents. Adolescents and neonates both have the highest percentages of patients (96%) who received 5 or more doses of IV acetaminophen.

Table 23 summarizes the demographic and descriptive characteristics including sex, age, race, ethnicity, and weight across age category for all 355 pediatric patients who received IV acetaminophen.

Table 24: Demographics (Pediatric Safety Population)

Parameter	**Neonates (N=47)**	**Infants (N=64)**	**Children (N=171)**	**Adolescents (N=73)**
Gender				
Male	30 (63.8 %)	37 (57.8%)	103 (60.2%)	30 (41.1%)
Female	17 (36.2%)	27 (42.2%)	68 (39.8%)	43 (58.9%)
Age				
N	47	64	171	73
Mean (SD)	8.2 (7.87)	9.6 (7.02)	5.7 (2.82)	14.3 (1.35)
Median	5.0	7.0	5.0	15.0
Min-Max	1-27	1-23	2-11	12-16
Race				
American Indian	0	0	0	0
Asian	0	3 (4.7%)	3 (1.8%)	2 (2.75)
Black	0	6 (9.4%)	11 (6.4%)	4 (5.5%)
Hispanic	0	0	0	0
Native Hawaiian	0	1 (1.6%)	2 (1.2%)	0
Caucasian	3 (6.4%)	36 (56.3%)	65 (38%)	65 (89%)
Unknown	43 (91.5%)	16 (25%)	86 (50.3%)	0
Other	1 (2.1%)	2 (3.1%)	4 (2.3%)	2 (2.7%)
Ethnicity				
Hispanic/Latino	0	8 (12.5%)	11 (6.4%)	8 (11%)
Non-Hispanic/Latino	4 (8.5%)	25 (39.1%)	53 (31%)	65 (89%)
Unknown	43 (91.5%)	31(48.4%)	107 (62.6%)	0

Parameter	Neonates (N=47)	Infants (N=64)	Children (N=171)	Adolescents (N=73)
Body weight (kg)				
<50	47 (100%)	64 (100%)	165 (96.5%)	25 (34.2%)
>=50	0	0	6 (3.5%)	48 (65.8%)
Mean (SD)	2.98 (0.69)	7.51 (2.8)	22.58 (10.8)	56.07 (14.4)
Median	3.00	7.65	19.80	54.70
Min-Max	1.2-4.5	1.8-12.4	10.0-76.6	31.5-105.5

Definitions: SD = standard deviation; KG = kilograms
Neonates (<28 days), infants (>28 days - < 24 months), children (2 years - < 12 years) , adolescents (12 years - < 18 years)
Age of neonates presented as days, infants as months, and children/adolescents as years
Source: Applicant Submission (ISS-Pediatrics Appendix table 2.1.2, pp. 196-197)

Overall, there were more males than females (56% and 44 % respectively) in the pediatric safety base and there were more males than females across age categories except for the adolescent population. Across racial lines, Caucasians represented 48% of the pediatric safety database. Mean ages were 8.2 for neonates, 9.6 months for infants, 5.7 years for children and 14.3 years for adolescents. All infants and neonates were less than 50 kg in body weight as were the majority (97%) of children. A higher percentage (65.8%) of adolescents weighed more than 50 kg in body weight.

7.6.3.5 Routine Clinical Testing

Four out of the five pediatric trials (CN145-001, RC 210 3 006, CPI-APA-102, and CPI-APA-352) used standard clinical testing to evaluate the safety of IV acetaminophen including monitoring for adverse events, physical examinations, clinical laboratory tests (hematology, chemistry and liver function tests), and vital signs prior to and following drug treatment. In addition, in trials CPI-APA-102 and trial CPI-APA-352 a urinalysis was also performed at screening and end of study/early termination.

In trial RC 210 3 006 no clinical lab tests were performed. In the investigator-initiated trial (EHRC #26095) safety testing included monitoring for adverse events, clinical labs (liver function tests only at baseline and once daily during dosing). Also, in the investigator trial, physical exams were not performed and vital signs were not collected. The applicant's rationale for exclusion of these safety monitors was that due to the nature of the neonatal patient population, blood sampling and vital sign assessments were limited.

The primary safety concern for intravenous acetaminophen is drug induced liver injury. Per the requirements set forth by the Division at the EOP2 meeting, the applicant was required to have 300 pediatric exposures to IV acetaminophen of which 50 having been exposed for at least 5 days. In Study RC 210 3 006, a single-dose, active-controlled study involving post-operative hernia repair patients, all 95 patients enrolled did not

have lab data collected. The clinical lab (specifically LFTs) information utilized from a single-dose trial would have been limited. Despite the lack of clinical lab data from the single-dose study (RC 210 3 006), and, in light of the negative findings in adults and the pediatric population for which laboratory data are available, I do not believe that the fact that laboratory data was not available for all 300 pediatric patients affected our ability to assess risks in the pediatric population.

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

Please see section 7.3.5 for discussion of this topic.

7.6.3.7 Deaths

There were no deaths that occurred in the pediatric population during the study periods.

7.6.3.8 Nonfatal Serious Adverse Events

In the pediatric population 8.5% (30/355) of patients experienced a serious TEAE, including 2.1% of neonates, 6.3 % of infants, 10.5 % of children and 9.6% of adolescents. There were no placebo groups in the five clinical studies.

Case narratives for 15/30 pediatric patients with serious TEAEs were reviewed and are discussed in detail following. My selection of cases involved safety issues that I believe are relevant to pediatric patients receiving IV acetaminophen including: hepatic events, renal events, and the most common serious adverse events by organ system.

Patient 00303, a 3-year-old male in Study CPI-APA-352, received a total of 20 doses of IV acetaminophen at 15 mg/kg (wt = 15 kg) = 225 mg q6h for pain between 21 July 2008 and 26 July 2008 following a laparoscopic appendectomy (b) (6). His medical history was significant only for a several day history of bilious emesis, abdominal pain and fever. His admission diagnosis was appendicitis and peritonitis that was confirmed by CT scan.

Table 25: Patient 00303: Liver Function Test Values

LFT:	Screening	Day: 1	2	3	4	5	7	10	28
IV APAP dosed:		*X*	*X*	*X*	*X*	*X*			
ALT (U/L)	21	19	17	21	24	210*	144	105	14
AST (U/L)	35	29	35	34	48	257*	108	47	33
ALP (U/L)	76	80	101	106	123	189	194	196	NR
GGT (U/L)	18	20	27	29	51	174	150	131	NR
TBL (mg/dL)	ND	0.2	0.2	0.2	0.2	0.2	0.2	0.2	NR

* ALT or AST value >3 x ULN (> 165 or > 132, respectively)
Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); GGT = Gamma Glutamyltransferase (ULN =56 U/L); IV APAP=IV acetaminophen; LFT = Liver function test; ND = Not done; NR=Not reported; TBL = Total bilirubin (ULN = 1.5 mg/dL)

Source: Applicant's submission (ISS- Pediatrics, pg. 48)

As seen in Table 24, this patient's LFT values were normal at screening and until day 5 of IV acetaminophen treatment. Approximately 6 hours after receiving his last dose of IV acetaminophen the patient was reported to have bilious emesis and abdominal distension. At that time, ALT and AST values were 210 U/L (3x ULN) and 257 U/L (5.6x ULN) respectively with a normal TBL of 0.2 mg/dL. He was made NPO, reportedly for symptoms consistent with a small bowel obstruction and begun on treatment for this diagnosis. On days 7 and 10, post IV acetaminophen treatment LFT values have improved and returning to normal. At a follow-up visit on Day 28 (23 days post IV acetaminophen treatment) ALT (14 U/L) and AST (33 U/L) values had returned to normal. This patient 's isolated ALT/AST elevations occurred 6 hours after the last dose of IV acetaminophen .

This SAE of hepatic enzyme elevations is not likely to be related to IV acetaminophen.

Patient 00310, a 15-year-old female enrolled in Study CPI-APA-352 received a total of 13 doses of IV acetaminophen at 15mg/kg (wt = 63.6 kg) = 954 mg q6h for lower extremity pain from Guillain-Barre syndrome (GBS) between 21 October 2008 and 24 October 2008. Her medical history was insignificant until over 2.5 weeks prior to IV acetaminophen treatment when she developed symptoms of fever, cough, headache and malaise which subsequently progressed into pain in bilateral lower extremities followed by weakness, areflexia and tingling in her extremities. After presentation to an emergency department she was subsequently diagnosed with GBS and received a 5 day course of IV immunoglobulin (IVIG). Her IVIG treatment ended 3 days prior to begninning IV acetaminophen treatment. Concomitant medications included enoxaparin, famotidine, gabapentin, labetalol, odansetron, methadone, macrogol, biscodyl, hydralazine, and ketamine.

Table 26: Patient 00310 Liver Function Test Values

LFT	Screening	Day: 1	2	3	3, #2	4	7	10	27
IV APAP dosed:		*X*	*X*	*X*	*X*				
ALT (U/L)	42	47	43	134	162	218*	504*	157	56
AST (U/L)	57	55	52	137	171*	193*	295*	59	60
ALP (U/L)	104	95	82	105	104	90	102	81	NR
GGT (U/L)	31	28	30	52	58	60	70	40	NR
TBL (mg/dL)	0.9	0.8	0.4	0.5	0.6	0.4	0.4	0.2	NR

*ALT or AST value > 3 × ULN (> 165 or > 135, respectively)
Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); GGT = Gamma Glutamyltransferase (ULN =50 U/L); IV APAP=IV acetaminophen; LFT=Liver function test; NR=Not reported; TBL = Total bilirubin (ULN = 1.5 mg/dL) (Patient 00310)

Source: Applicant's submission (ISS – Pediatrics, pg. 49))

As displayed in Table 25, the patient's LFTs up to Day 3 of IV acetaminophen treatment were normal except for slightly elevated AST levels of 57 U/L, 55 U/L, and 52 U/L respectively, however on day 3 of IV acetaminophen ALT and AST were 134 U/L (2.4x ULN) and 137 3x ULN) respectively and the decision was made to discontinue IV acetaminophen. Later on the same day, her labs showed an ALT of 162 U/L and AST of 171 U/L with normal ALP, GGT and TBL values. Her ALT and AST values continued to rise 1 day after and 3 days after early termination of IV acetaminophen as displayed in Table 8 on days 4 and 7 respectively. On her follow up visit on Day 10, her ALT and AST values were returning to normal. During a subsequent hospitalization and treatment for GBS symptoms, her liver enzymes were normal as seen on Day 27 with an ALT of 56 U/L and AST of 60 U/L. I cannot completely rule out possible involvement of IV acetaminophen in this patient's LFT elevation.

This SAE of hepatic enzymes elevation is possibly related to IV acetaminophen.

Patient 00704, a 15-year-old male enrolled in Study CPI-APA-352 received a total of 10 doses of IV acetaminophen at 10 mg/kg (wt= 65.6 kg) = 650 mg q4h for pain between 18 August 2008 and 20 August 2008 following T4 - L1 posterior spinal fusion surgery (b) (6). The patient's medical history was significant for scoliosis. Concomitant medications included vancomycin, cefazolin, diazepam, morphine, and midazolam.

Table 27: Patient 00704 Liver Function Test Values

LFT	Screening 18 Aug Day -1 08:20	Day: -1 18 Aug 14:00 Prior T0	1 19 Aug 07:11 Post T0	2 20 Aug 07:18 ET	2 20 Aug 16:28 Post	3 21 Aug	4 22 Aug
IV APAP dosed:			*X*	*X*			
ALT (U/L)	11	16	25	84	77	65	55
AST (U/L)	40	31	143	240*	222*	169	137
ALP (U/L)	144	94	84	93	93	NR	NR
GGT (U/L)	24	20	24	62	58	NR	NR
TBL (mg/dL)	0.4	0.2	1.0	0.7	0.3	NR	NR

* ALT or AST value > 3 × ULN (> 165 or > 135, respectively)
Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); ET = Early termination; GGT = Gamma Glutamyltransferase (ULN =50 U/L); IV APAP=IV acetaminophen; NR = Not reported; TBL = Total bilirubin (ULN = 1.5 mg/dL)
Source: Applicant's submission (ISS – Pediatrics, pg. 52))

Table 26 shows screening and daily LFTs for this patient were normal until day 2 of IV acetaminophen treatment when ALT and AST were both elevated at 84 U/L and 240 U/L (5x ULN) respectively. The patient was discontinued from the trial the same day (20 Aug 08) but started on oral acetaminophen at 10 mg/kg Q4h the following day (21 Aug 08) with LFT values decreasing and returning to normal by follow-up on 22 August 2008. Although muscle injury has been associated with transaminase elevations (particularly AST) and given the nature of this patient's surgery this is the most likely, however I cannot completely rule out IV acetaminophen. In addition, his LFT values remained elevated while being given oral acetaminophen.

This patient's SAE of hepatic enzyme (AST) elevation is possibly related to IV acetaminophen.

Patient 00608, an 8-year-old male in Study CPI-APA-352 received a total of 4 doses of IV acetaminophen at 10 mg/kg (wt= 27.1 kg) = 270 mg q6h for pain between 23 May 2008 to 24 May 2008 following video-assisted thoracic surgery for spinal release and posterior spinal fusion (b) (6). Post-operative complications included tachycardia, hypotension and fever to 39.1˚ C which were treated with fluid resuscitation and prophylactic cefazolin respectively. He also experienced an episode of airway obstruction which was treated with neck support and racemic epinephrine. His medical history included neuromuscular scoliosis, hydrocephalus, seizure disorder, static encephalopathy, macrocephaly, asthma, gastroesophageal reflux disease and developmental delay. His prior surgical history included ventriculoperitoneal shunt and

gastrostomy tube placement. His concomitant medications included cefazolin, docusate, levetiracetam, phenobarbital, diazepam, clonazepam, salbutamol, ibuprofen, epinephrine for inhalation and budesonide.

Table 28: Patient 00608 Liver Function Test Values

LFT	Screening	Day: 1	2	3	4	7
IV APAP dosed:		*X*	*X*			
ALT (U/L)	32	198	229*	115	80	23
AST (U/L)	67	291*	207	72	58	28
ALP (U/L)	95	100	100	103	118	103
GGT (U/L)	20	66	63	57	73	48
TBL (mg/dL)	0.4	0.5	0.3	0.2	0.1	0.2

* ALT or AST value > 3 × ULN (> 165 or > 135, respectively)
Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); GGT = Gamma Glutamyltransferase (ULN =50 U/L); IV APAP=IV acetaminophen; TBL = Total bilirubin (ULN = 1.5 mg/dL)
Source: Applicant's submission (ISS – Pediatrics, pg. 51)

Table 27 shows LFT screening labs were normal. Between day 1 and day 2 of IV acetaminophen treatment the patient experienced peak elevations in ALT and AST values of 229 U/L (4x ULN) and 207 U/L (4.5x ULN) respectively with a normal TBL. The patient was discontinued from trial medication on Day 2 and ALT and AST showed a marked decrease the following day (ALT of 115 U/L and AST of 72 U/L) with subsequent normalizing of LFT over the next several days. Possible etiologies of this patient's hepatic enzyme elevation include: hypovolemia, hypoxia, concomitant potential hepatotoxic medications (phenobarbital, levetiracetam) and IV acetaminophen. This patient's SAE of hepatic enzyme elevation is possibly related to IV acetaminophen.

Patient 01402, a 13-year-old male enrolled in Study CPI-APA-352 received a total of 16 doses of IV acetaminophen at 15 mg/kg (wt = 61.8 kg) = 927 mg q6h for pain between 30 October 2008 and 04 November 2008 following surgical debridement and irrigation of spinal surgical incision due to infection (b) (6). His medical history was significant for idiopathic scoliosis, and postoperative spine infection. His prior surgical history included scoliosis surgery. Concomitant medications included morphine, vancomycin, nafcillin, rifampin, and ondansetron. Following surgical debridement of spinal abscess, the patient's surgical cultures were positive for methicillin-resistant Staphylococcus aureus for which he was started on vancomycin, nafcillin and rifampin. Per the patient narrative in the applicant submission, by day 3 of IV acetaminophen treatment the patient's serum creatinine had increased from 0.5 mg/dL at screening to

2.5 mg/dL at which time the vancomycin antibiotic was discontinued. The following day this creatinine was reported to have decreased to 1.8 mg/dL and cefazolin antibiotic was added to the treatment plan. On follow-up visit, the creatinine was down to 1.0 mg/dL. Vancomycin well known for its nephrotoxicity, as well as rifampin and nafcillin being associated with cases of interstial nephritis are the most likely etiologies of this patient's acute renal failure.

This SAE of acute renal failure is not likely related to IV acetaminophen

Patient 00515, a 14-year-old female enrolled in Study CPI-APA-352 received a total of 25 doses of IV acetaminophen at 10 mg/kg (wt = 82.0 kg) = 820 mg q4h for pain initially between 22 October 2008 and 25 October 2008 following craniotomy for resection of a pineal tumor (b) (6). On the 3rd day of IV acetaminophen a protocol deviation for having exceeding the 4000 mg daily maximum was noted and thereafter, from 26 Oct 2008 to 27 Oct 2008 the patient received 4 doses of IV acetaminophen. Other than the protocol deviation, her hospital course was remained unremarkable and she completed the trial without event and discharged home. Approximately, 10 days after her last dose of IV acetaminophen the patient was readmitted to the hospital due to worsening headaches and which time CT scan reportedly showed a pseudomenigocele.

This patient's SAE of headache is not related to IV acetaminophen treatment.

Patient 00201, a 16-year-old male enrolled in Study CPI-APA-352 received a total of 8 doses of IV acetaminophen at 15 mg/kg (wt = 51 kg) = 750 mg q6h for pain between 18 June 2008 and 20 June 2008 following total colectomy and ileal pouch ileostomy (b) (6). Her medical history was significant for familial adenopolyposis and early colon adenocarcinoma. There was no prior surgical history reported. Concomitant medications included ketorolac, ondansetron, and hydromorphone. She was reported to have an uneventful postoperative course, completed the course of trial medications and discharged to home without event. Approximately 3 days after her last dose of IV acetaminophen the patient was re-admitted to the hospital for complaints of abdominal pain, vomiting and inability to pass stools at which time history, physical and x-rays revealed a localized ileus. She was subsequently discharged the next day after treatment with hydration.

This patient's SAE of abdominal pain is not related to IV acetaminophen treatment.

Patient 00510, a 4-year-old male enrolled in Study CPI-APA-352 received a total of 20 doses of IV acetaminophen at 10 mg/kg (wt = 16.3 kg) = 160 mg q6h for pain between 03 June 2008 and 08 June 2008 following a reanastomosis surgery, colsostomy

takedown and appendectomy (b) (6). His medical history included Crohn's disease, Meckel's diverticulum, colonic perforation, asthma, allergic rhinitis, eczema, and multiple food allergies. His prior surgical history included a previous diverting colostomy. Concomitant medications included clonidine, ropivacaine, morphine, , hydrocortisone, inhaled albuterol, salbutamol, diphenhydramine, lorazepam, multivitamins, calcium, prednisone, hydromorphone and topical ointments for eczema. The patient was reported to have a uneventful post-operative course, completed the course of IV acetaminophen and was subsequently discharged home (b) (6). The (b) (6) after his last dose of IV acetaminophen), the patient presented to the emergency department with complaints of abdominal pain with distention and was subsequently re-admitted to the hospital with a tentative diagnosis of small bowel obstruction. He was treated with IV hydration and bowel rest, advanced to a regular diet over the next 3 days and discharged home.

This patient's SAE of bowel obstruction is not related to IV acetaminophen treatment.

Patient 01001, an 8-year-old male enrolled in Study CPI-APA-352 received a total of 20 doses of IV acetaminophen at 15 mg/kg (wt = 35.1 kg) = 530 mg q6h for pain between 11 June 2008 and 16 June 2008 following bladder augmentation (b) (6). His medical history included hydrocephalus, neurogenic bowel and bladder, bilateral club feet, myelomeningocele, reactive airway disease, history of urinary tract infections, cauda equine syndrome and hypermetropia. His prior surgical history included VP shunt placement, repair of myelomeningocele, tonsillectomy and eye surgery Concomitant mediations included ciprofloxacin, fluticasone, melatonin, metronidazole, montelukast, vancomycin, ondanestron, , potassium chloride, Fleets enema, bisacodyl, inhaled albuterol, inhaled fluticasone-salmeterol, furesomide, morphine and chlorpheniramine/phenylephrine. Two days after completion IV acetaminophen treatment, the patient was reported to complain of severe abdominal pain and found to have an abdominal abscess for which he underwent surgical drainage and nasogastric tube placement and started on antibiotic treatment consisting of clindamycin, fluconazole, and meropenem. The remainder of his hospital course was benign and was discharged home without event.

This patient's SAE of an abdominal abscess is not related to IV acetaminophen treatment.

Patient 00618, a 3-year-old male in Study CPI-APA-352 received a total of 16 doses of IV acetaminophen at 10 mg/kg (wt = 13.4 kg) = 134 mg q6h for pain between 12 December 2008 and 16 December 2008 following open heart surgery on (b) (6). His medical history was significant for double-outlet right ventricle, dextro-rotation of the great arteries, ventricular septal defect, coarctation of the aorta, tricuspid valve regurgitation, left diaphragm paresis and cyanosis at birth. His surgical history included

Damus-Kaye-Stansel procedure, aortic arch reconstruction, balloon angioplasty of the aorta, bidirectional Glenn procedure, Blalock-Taussig shunt and Rastelli procedure. His concomitant medications included ranitidine, metoclopramide, vancomycin, furosemide, silver sulfadiazine, pancuronium, naloxone,acetaminophen, sodium bicarbonate, sulfamethoxazole, cefazolin, spironolactone, midazolam, glycerin, diphenhydramine, epinephrine, morphine, lorazepam, dopamine, milrinone, vasopressin and heparin. Post-operative complications included chylous fluid drainage from chest tube that begain 3 days after the last dose of IV acetaminophen and multiple failed extubations over the course of several days. Subsequent echocardiogram and chest ultrasound procedures demonstrated a possible left diaphragmatic paresis which required placation. The following day the patient was able to be extubated, he required biphasic positive intermittent pressure support (BiPap) for one day, however the remainder of his hospital course was uneventful and he was discharged home in stable condition on room air.

This patient's SAEs including chylothorax and left diaphragm paresis are not related to IV acetaminophen.

Patient 00314, a 15-year-old female enrolled in Study CPI-APA-352 received a total of 4 doses of IV acetaminophen at 10 mg/kg (wt = 70 kg) = 700 mg q6h for pain between 17 December 2008 and 18 December 2008 following a laparascopic appendectomy (b) (6) for a ruptured appendicitis. Her medical and surgical history was significant for her admitting ruptured appendicitis and subsequent appendectomy. Concomitant medications included morphine, famotidine, ondanestron and ertapenem Her post-operative and hospital course was reported as uneventful, and she was discharged home without event. Approximately, (b) (6) days after her last dose of IV acetaminophen the patient was re-admitted to the hospital secondary to fever of 102 °F and abdominal pain and subsequent abdominal CT scan showed multiple abdominal abscesses. She received broad spectrum antibiotics, oral acetaminophen and IV hydration and was discharged home on antibiotic therapy.

This patient's SAE of fever secondary to multiple abdominal abscesses is not related to IV acetaminophen.

Patient 00305, a 11-year-old female enrolled in Study CPI-APA-352 received a total of 20 doses of IV acetaminophen at 15 mg/kg (wt = 50 kg) = 750mg q6h for pain between 23 July 2008 and 25 July 2008 and then 500 mg (10 mg/kg) Q6h from 25 July 2008 to 28 July 2008 following colectomy with ilneoanal pouch anastomosis (b) (6). I note that, on review of the CRF, this patient received 700 mg of IV acetaminophen. Her medical history included familial adenomatous polyposis and seasonal allergic rhinitis. There is was no reported prior surgical history. Concomitant medications included morphine, ropivacaine, metronidazole and ampicillin/sulbactam. Her post-operative and hospital course was reported as uneventful and she was discharge home. Approximately 10 days after her last dose of IV acetaminophen, the patient was re-

admitted to the hospital secondary to presenting with erythema, induration and purulent drainage from the surgical site. She was treated with antibiotic therapy for a presumed wound infection without complications and subsequently discharged home.

This patient's SAE of wound infection is not related to IV acetaminophen.

Patient 00609, a 4-year-old female enrolled in Study CPI-APA-352 received a total of 27 doses of IV acetaminophen at 10 mg/kg (wt = 16.2 mg) = 162 mg q6h for pain between 04 June 2008 and 09 June 2008 following repeat laryngotracheal reconstruction to treat stridor and airway obstruction. Her medical history was significant for prematurity,subglottic stenosis from a prolonged intubation, inspiratory stridor, grade IV intraventricular hemorrhage, aspiration pneumonia, RSV infection, tracheal infections, developmental delay, bronchopulmonary dysplasia, cerebral palsy,and seizure disorder. She was also s/p PDA ligation, supraglottoplasty, laryngotrachealreconstruction, and tracheostomy. Her concomitant medications included azithromycin, cefepime, levofloxacin, docusate, Lacriube/Refresh eye ointment, fentanyl, ibuprofen, bacitracin ointment, chloral hydrate, diphenhydramine, glycerin suppository, hydralazine, racemic epinephrine, salbutamol, budesonide, ipratropium, lorazepam, ketamine, dexmedetomidine, vecuronium, propofol, midazolam, rocuronium, pentobarbital, pantoprazol, and montelukast. The patient failed multiple attempts at extubation after her surgery and 5 days after her last dose of IV acetaminophen she was taken back to the operating room for tracheostomy and permanent tracheostomy tube placement. The remainder of hospital course was uneventful.

This patient's SAE of respiratory failure is not related to IV acetaminophen.

Patient 00617, a 5-week-old infant enrolled in Study CPI-APA-352 received a total of 15 doses of IV acetaminophen at 10 mg/kg (wt= 3.1 kg) = 310 mg q8h for pain between !4 November 2008 and 19 November 2008 following a primary transanal endorectal pull-through procedure (b) (6). His medical history was significant for Hirschsprung's disease. No prior surgical history was reported. Concomitant medictions included: morphine and ranitidine. His postoperative course was uneventful and he was subsequently discharged home. Approximately (b) (6) days after the last dose of IV acetaminophen, the patient was re-admitted to the hospital after presenting to surgery clinic with a one day history of abdominal distension, irritability, loss of appetite and occasional emesis with a greenish tint. He was afebrile with a negative physical exam. His treatment included IV hydration and parental nutrition, daily Hagar dilations per rectum, ciprofloxacin, metronidazole, multivitamins, and rantidine. Two days after admission he resumed passing stools and was subsequently discharged home.

This patient's SAE of exacerbation of Hirshsprung's disease is not related to IV acetaminophen.

Patient 00615, a 4-month-old male enrolled in Study CPI-APA-352 received a total of 20 doses of IV acetaminophen at 10 mg/kg (wt = 6.0 kg) = 60 mg q6h for pain between [redacted] following a hemi-Fontan procedure (HFP) and triscuspid valve repair [redacted]. His medical history included left hypoplastic heart syndrome, congestive heart failure, chylous effusion, systemic to pulmonary artery shunt, pneumothorax and positive C. difficiletoxin in stools. Prior surgical history included a Norwood repair procedure. Concomitant medications included pancuronium, dexamethasone, furosemide, spironolactone, sodium bicarbonate, chlorothiazide, levalbuterol, cefazolin, metronidazole,acetaminophen, lorazepam, ipratropium, vecuronium, milrinone, morphine, dopamine, vasopressin, ranitidine, dexmedetomidine, midazolam, and heparin. On day four of IV acetaminophen, the patient was reported to be unable to tolerate extubation and had to be reintubated. An ultrasound showed an immobile diaphragm at which time the patient returned to the operating room for bilateral diaphragm placation. The patient remained intubated over the next 3 weeks with a labile respiratory course but was extubated with high flow oxygen. Approximately 5.5 weeks after his last dose of IV acetaminophen, due to persistent respiratory insufficiency the patient underwent a tracheostomy to promote continued ventilatatory support.

This patient's SAE of respiratory failure secondary to left hypoplastic heart syndrome is not related to IV acetaminophen.

7.6.3.9 Dropouts and/or Discontinuations

A review of the safety database shows 5 out of the 355 pediatric patients were reported to have been discontinued from IV acetaminophen treatment due to an adverse event, including 2 children and 3 adolescents. All 5 patients were discontinued due to elevations in hepatic enzymes, including 3 patients were serious TEAES that have been previously discussed in Section 7.6.3.7 (Non-fatal Serous Adverse Events) and 2 patients with non serious TEAES of which their narratives are included below.

Patient 1001-005, a 15-year-old male enrolled in Study CPI-APA-102 received a total of 4 doses of IV acetaminophen at 15 mg/kg (wt = 55. 9 kg) = 835 mg q6h between 17 July 2007 and 18 July 2008 for pain following C4 to T12 posterior-spinal fusion surgery [redacted]. Intra-operative complications reported were hypotension that was treated by IV fluids and phenylephrine. His medical history included severe congenital scoliosis, Ehler-Danlos syndrome, astigmatism, and acne. No other surgical history was reported in the CRF. Concomitant medications included cefazolin, fentanyl, furosemide, magnesium sulfate, rantidine, lorazepam, midazolam, morphine, potassium, calcium gluconate and phenylephrine.

Table 29: Patient 1001-005 Liver Function Test Values

Date	Visit	Liver Function Test				
		ALT (U/L)	ALP (U/L)	AST (U/L)	TBL (mg/dL)	GGT (U/L)
17Jul07	Screen[1]	12	84	27	0.8	22
18Jul07	24-hour	45	64	112	1.4	23
19Jul07	ET	54	75	113	1.3	37

Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); GGT = Gamma Glutamyltransferase (ULN =50 U/L); LFT=Liver function test; TBL = Total bilirubin (ULN = 1.5 mg/dL)

[1] Postoperative baseline LFT values were not obtained

Source: Applicant's submission (ISS-Pediatrics, pg.46)

Liver function values for this patient are displayed in Table 28. Baseline LFT values were normal. At 24 hours, the AST value is elevated at 112 U/L (2.5 x ULN) and on the beginning of Day 2 of trial drug the patient was discontinued from the trial and switched to oral acetaminophen (650 mg Q6h as needed for fever) . The AST value remained elevated at 113 U/L (2.5x ULN) on that same day. No other LFT values were reported on this patient. Other possible etiologies [surgical muscle trauma, concomitant medication (ranitidine), and intra-operative complication (hypotension)] of this patient's AST elevation have to be considered, I cannot completely rule out IV acetaminophen as a possible etiology as well.

The adverse event of LFT elevation leading to this patient's discontinuation is possibly related to IV acetaminophen.

Patient 00412, a 10-year-old female enrolled in Study CPI-APA-412 received a total of 12 doses of IV acetaminophen at 12.5 mg/kg (wt = 35.5 kg) = 420 mg q6h for pain between 18 November 2008 and 21 November 2009 following posterior spinal fusion surgery (b) (6). Her medical history was significant for neuromuscular scoliosis, spastic cerebral palsy, seizure disorder, mental retardation and allergic rhinitis. There was no reported prior surgical history. Concomitant medications included diazepam, ketamine, morphine, cefazolin, bisacodyl, rantidine, risperidone, and albuterol inhalation.

Table 30: Patient 00412 Liver Function Tests

LFT:	Screening	Day: 1	2	3 ~8 a.m.	3 ~4 p.m.	4	6	7
IV APAP dosed:		*X*	*X*	*X*				
ALT (U/L)	21	46	55	76	84	75	56	64
AST (U/L)	21	108	144	165*	169*	115	42	35
ALP (U/L)	80	91	98	115	116	104	86	118
GGT (U/L)	12	20	18	27	33	36	31	40
TBL (mg/dL)	1.2	0.3	0.4	0.4	ND	0.5	0.2	0.2

* ALT or AST value > 3 × ULN (> 165 or > 135, respectively)
Definitions: ALT = Alanine Aminotransferase (ULN = 55 U/L); ALP = Alkaline Phosphatase (ULN = 147 U/L); AST = Aspartate Aminotransferase (ULN = 45 U/L); GGT = Gamma Glutamyltransferase (ULN =50 U/L); IV APAP=IV acetaminophen; ND = not done; TBL = Total bilirubin (ULN = 1.5 mg/dL)
Source: Applicant's submission (ISS- Pediatrics, pg. 50)

As seen in Table 29, all LFTs were normal at screening. Her AST level was elevated on Days 1 and 2, however when her AST peaked at 169 U/L (3.8x ULN) with a ALT of 84 (1.5x ULN) of day 3 of IV acetaminophen, the patient was discontinued from treatment. Her follow up labs show AST and ALT levels returning to normal range. Although, the pattern of AST > ALT elevation is more likely indicative of surgical muscle trauma I cannot completely rule out IV acetaminophen as a etiology as well.

The adverse event of hepatic enzyme elevation leading to this patient's discontinuation is possibly related to IV acetaminophen.

Patient 00608, Patient 00310 and Patient 00740 were all participants in IV acetaminophen treatment that were discontinued secondary to reported serious adverse events. Please refer to the section on non-fatal serious events for their case narratives.

7.6.3.10 Significant Adverse Events

Please see section 7.6.3.11

7.6.3.11 Submission Specific Primary Safety Concerns

Hepatic Events

Similar to the adult population, the MedDRA SMQ of hepatic disorders was used to assess the incidence, severity, and baseline characteristics of pediatric patients who

experienced a hepatic event. The overall incidence of hepatic events was 3.9 % (14/355) with a higher incidence in adolescents (8.2%) compared to children (4.1%), infants (1.6%) and neonates (0%). There was no meaningful difference in the incidence of hepatic events between males (n=200, 4.0%) and females (n=155, 3.9%). There were no deaths related to a hepatic TEAE. The incidence of serious hepatic TEAE was 1.1 % (4/355). The incidence of hepatic TEAE resulting in discontinuations was 1.4 % (5/355).

Four patients had hepatic events that were assessed as serious. Three patients had their study drug discontinued. Three of the four patients were enrolled post-surgical procedures (appendectomy, posterior spinal fusion) and the remaining patient was enrolled post IVIG treatment for Guillain-Barre syndrome (GBS). Three of the four patients had elevations in both ALT and AST> 3x ULN with normal TBL. The remaining patient had an isolated elevation in AST > 3x ULN. All four cases of serious hepatic TEAEs were deemed possibly related to IV acetaminophen treatment.

Five patients experienced hepatic TEAEs that resulted in discontinuations from their trials. Four of the five patients enrolled had posterior spinal fusion surgeries and the remaining patient was enrolled post IVIG treatment for GBS. The AST>ALT pattern of elevation in the patients involving posterior spinal fusion suggests that muscle trauma was a plausible etiology in addition to concomitant hepatotoxic medications. In the GBS patient, both ALT and AST were elevated > 3x ULN however these values remained elevated up to 7 days post drug early termination. In all 5 cases, the hepatic events leading to discontinuation were deemed possibly related to IV acetaminophen treatment.

Although there were no cases that met Hy's Law criteria, there were pediatric patients who had marked LFT levels (AST/ALT > 3x ULN) with normal TBL. These cases primarily involved patients with congenital heart disease who had elevated LFTs at baseline.

7.6.3.12 Common Adverse Events

Treatment emergent adverse events reported in ≥ 1% of the 355 pediatric patients who received IV acetaminophen are displayed in Table 30 by MedDRA preferred term in descending order of frequency. I verified the counts submitted by the applicant using jmp software and found identical total adverse events except for nausea (n=57), vomiting (n=42) and headache (n=10) common TEAEs where the applicant chose to count patients experiencing the same adverse event > 1 as one event. These differences do not substantially affect my perception of the adverse event profile and I accept the Applicant's table.

Table 31: Most Common ≥1 % of All Patients TEAEs Pediatric Safety Population

MedDRA Preferred Term	Neonates (N=47) n (%)	Infants (N=64) n (%)	Children (N=171) n (%)	Adolescents (N=73) n (%)	Total (N=355) n (%)
Nausea	0	2 (3.1)	19 (11.1)	33 (45.2)	54 (15.2)
Vomiting	0	1 (1.6)	18 (10.5)	18 (24.7)	37 (10.4)
Constipation	0	3 (4.7)	12 (7.0)	14 (19.2)	29 (8.2)
Pruritus	0	3 (4.7)	13 (7.6)	12 (16.4)	28 (7.9)
Agitation	0	9 (14.1)	8 (4.7)	3 (4.1)	20 (5.6)
Atelectasis	2 (4.3)	6 (9.4)	7 (4.1)	4 (5.5)	19 (5.4)
Pyrexia	0	0	9 (5.3)	6 (8.2)	15 (4.2)
Hypokalaemia	0	8 (12.5)	5 (2.9)	1 (1.4)	14 (3.9)
Hypomagnesaemia	1 (2.1)	4 (6.3)	4 (2.3)	5 (6.8)	14 (3.9)
Pleural effusion	1 (2.1)	5 (7.8)	3 (1.8)	4 (5.5)	13 (3.7)
Anaemia	0	4 (6.3)	3 (1.8)	4 (5.5)	11 (3.1)
Injection site pain	0	1 (1.6)	11 (6.4)	0	12 (3.4)
Headache	0	0	1 (0.6)	8 (11.0)	9 (2.5)
Hypotension	0	1 (1.6)	5 (2.9)	3 (4.1)	9 (2.5)
Pulmonary oedema	1 (2.1)	4 (6.3)	3 (1.8)	1 (1.4)	9 (2.5)
Wheezing	0	7 (10.9)	1 (0.6)	0	8 (2.3)
Diarrhoea	0	0	5 (2.9)	3 (4.1)	8 (2.3)
Muscle spasms	0	0	1 (0.6)	6 (8.2)	7 (2.0)
Stridor	0	4 (6.3)	3 (1.8)	0	7 (2.0)
Hypoalbuminaemia	0	1 (1.6)	4 (2.3)	1 (1.4)	6 (1.7)
Hypophosphataemia	0	1 (1.6)	2 (1.2)	2 (2.7)	5 (1.4)
Oliguria	0	3 (4.7)	1 (0.6)	1 (1.4)	5 (1.4)
Abdominal pain	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Hepatic enzyme increased	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Hypertension	0	2 (3.1)	2 (1.2)	0	4 (1.1)
Hypervolaemia	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Hypoxia	0	0	1 (0.6)	3 (4.1)	4 (1.1)
Insomnia	0	1 (1.6)	2 (1.2)	1 (1.4)	4 (1.1)
Oedema peripheral	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Pain in extremity	0	0	2 (1.2)	2 (2.7)	4 (1.1)
Periorbital oedema	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Rash	0	1 (1.6)	3 (1.8)	0	4 (1.1)
Tachycardia	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Wound infection	0	0	4 (2.3)	0	4 (1.1)

Definitions: TEAE = Treatment-Emergent Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities

Source: Applicant's submission (ISS – Pediatrics, pg. 33)

The most commonly reported TEAEs involved the gastrointestinal system: nausea (15.2%), vomiting (10.4 %) and constipation (8.2%). Other common TEAEs reported included pruritus (7.9%), agitation (5.6%) and atelectasis (5.4%) with the remainder of TEAEs being reported in < 5% of all pediatric patients.

In the adolescent category the most common TEAEs reported were nausea (45.2%), vomiting (24.7%), constipation (19.2%), pruritus (16.4%) and injection site pain (11.0%). In the children category the most common TEAEs reported were nausea (11.1%), vomiting (10.5%), pruritus (7.6%), constipation (7.0%) and injection site pain (6.4%). In the infant's category the most common TEAEs reported were agitation (14.1%), hypokalemia (12.5%), wheezing (10.9%), atelectasis (9.4%) and pleural effusion (7.8%). In the neonate category, very small percentages of this population were reported to have experienced common TEAEs including atelectasis (4.3%), hypomagnesaemia (2.1%), pleural effusion (2.1%) and pulmonary edema (2.1%).

7.6.3.13 Laboratory Findings

In the pediatric clinical development program, the laboratory evaluation of safety was conducted using standard hematology and chemistry (including liver function tests) investigations. At times the analysis of laboratory safety data was confounded by

- Lack of comparator group
- Physiological differences among the age categories
- In trial RC 210 3 006 that enrolled 95 patients (86-children, 9-infants) no clinical laboratory data was collected
- In trial EHRC #26095 that enrolled 50 patients (43 –neonates, 7-infants) only liver function tests were reported

Hematology Analysis
Analysis focused on measures of central tendency

A summary of mean hematology values at baseline and mean changes from baseline to last value on study is displayed in Table 31 by age statum.

Table 32: **Mean (SD) Hematology Values at Baseline and Change from Baseline to Last Value on Study (Pediatric Safety Population)**

Parameter	Neonates (N = 47)		Infants (N = 64)		Children (N = 171)		Adolescents (N = 73)	
Timepoint	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Hemoglobin (g/dL)								
Baseline	4	14.75 (0.580)	44	12.05 (2.474)	70	11.78 (1.987)	67	11.74 (2.249)
Δ to last value	4	0.55 (1.418)	44	0.13 (1.802)	70	-0.23 (1.844)	67	-0.61 (2.422)
Hematocrit (%)								
Baseline	4	41.8 (2.01)	44	35.4 (7.13)	70	34.5 (5.89)	67	33.9 (6.28)
Δ to last value	4	2.1 (4.34)	44	0.4 (5.47)	70	-0.5 (5.41)	67	-1.3 (6.89)
Leukocytes (10^9/L)								
Baseline	4	10.70 (3.868)	44	11.56 (7.173)	70	11.27 (6.150)	67	8.46 (4.368)
Δ to last value	4	-1.38 (4.094)	44	-0.36 (7.124)	70	-0.83 (6.864)	67	0.71 (4.046)
Platelets (10^9/L)								
Baseline	4	234.3 (105.48)	43	326.6 (148.93)	69	274.7 (117.99)	66	257.7 (83.96)
Δ to last value	4	31.0 (199.81)	43	-13.9 (178.69)	69	107.3 (225.23)	66	195.4 (255.19)

Source: Applicant's submission (ISS – Pediatrics, pg. 92))

Mean hemoglobin, hematocrit and leukocytes counts at baseline varied across age categories. The changes in values from baseline to last visit for all hematology parameters across age categories were not clinically meaningful.

Analysis focused on outliers or shifts from normal to abnormal

Hematology shifts from baseline to worst value on study are presented in Table 32.

Table 33: Hematology Shifts from Baseline to Last Value on Study (Pediatric Safety Population)

Parameter	Shift	Neonates (N = 47) n/N (%)[1]	Infants (N = 64) n/N (%)[1]	Children (N = 171) n/N (%)[1]	Adolescents (N = 73) n/N (%)[1]
Hemoglobin	Shift to High[2]	0/4	5/43 (11.6)	3/70 (4.3)	0/67
	Shift to Low[3]	0/4	3/43 (7.0)	12/70 (17.1)	17/67 (25.4)
Leukocytes	Shift to High[2]	1/4 (25.0)	8/43 (18.6)	14/70 (20.0)	9/67 (13.4)
	Shift to Low[3]	0/4	1/43 (2.3)	2/70 (2.9)	1/67 (1.5)
Platelets	Shift to High[2]	1/4 (25.0)	4/42 (9.5)	21/69 (30.4)	27/66 (40.9)
	Shift to Low[3]	1/4 (25.0)	2/42 (4.8)	7/69 (10.1)	1/66 (1.5)

[1] n=number of patients with shift, N = total number of patients included in analysis.
[2] Shift from normal or low value at baseline to a last value on study that was above the upper limit of the normal range (high).
[3] Shift from normal or high value at baseline to a last value on study value that was below the lower limit of the

Source: Applicant's submission (ISS- Pediatrics, pg. 92))

As previously stated, in the context of no placebo comparator group assessing clinical meaningful hematology the assessment of shifts is difficult. Shifts to low hemoglobin were highest in the adolescent category as well shift to high platelets were highest in this sub-population as well.

Marked outliers and dropouts for hematology abnormalities

There were no marked outliers and dropouts for hematology abnormalities within the pediatric population.

Chemistry analysis

Analysis focused on measures of central tendency

A summary of mean clinical chemistry values at baseline and mean changes from baseline to last visit is provided in Table 33.

Table 34: Mean (SD) Chemistry Values at Baseline and Change from Baseline to Last Value on Study (Pediatric Safety Population)

Parameter	Neonates (N = 47)		Infants (N = 64)		Children (N = 171)		Adolescents (N = 73)	
Timepoint	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Sodium (mmol/L)								
Baseline	4	142.8 (3.30)	44	138.9 (5.12)	70	138.4 (3.86)	70	138.7 (2.44)
Δ to last value	4	-5.3 (4.99)	44	-1.1 (5.16)	70	-0.6 (4.70)	70	0.1 (3.82)
Potassium (mmol/L)								
Baseline	4	3.55 (0.640)	43	4.32 (0.812)	69	3.94 (0.503)	70	4.09 (0.437)
Δ to last value	4	0.25 (0.332)	43	-0.27 (1.021)	69	0.18 (0.634)	70	0.08 (0.624)
Chloride (mmol/L)								
Baseline	4	105.8 (7.41)	31	103.1 (4.60)	54	105.3 (4.67)	70	105.5 (3.45)
Δ to last value	4	-8.3 (5.91)	31	-3.4 (6.81)	54	-3.6 (5.68)	70	-4.0 (4.22)
Glucose (mg/dL)								
Baseline	4	96.3 (22.31)	32	109.4 (32.94)	66	119.0 (41.49)	67	102.2 (28.89)
Δ to last value	4	0.5 (30.43)	32	-8.3 (44.85)	66	-10.3 (91.84)	67	-12.2 (29.46)
Albumin (g/dL)								
Baseline	44	2.53 (0.650)	27	3.85 (0.973)	18	3.74 (0.618)	19	3.44 (0.627)
Δ to last value	44	0.06 (0.661)	27	-0.53 (0.556)	18	-0.34 (0.579)	19	-0.32 (0.567)
BUN (mg/dL)								
Baseline	4	19.0 (7.79)	28	11.8 (6.16)	53	11.1 (4.82)	69	11.5 (4.75)
Δ to last value	4	-4.0 (9.69)	28	0.8 (7.94)	53	1.8 (7.48)	69	-0.2 (5.03)
Creatinine (mg/dL)								
Baseline	3	0.50 (0.000)	42	0.52 (1.029)	70	0.46 (0.170)	70	0.60 (0.175)
Δ to last value	3	-0.13 (0.058)	42	-0.21 (1.030)	70	0.07 (0.779)	70	0.01 (0.112)

Definitions: SD = standard deviation; mmol = millimoles, mg = milligrams, g = grams; dL = deciliter; L = liter, Δ = change

Source: Applicant's submission (ISS- Pediatric, pg. 94))

Mean chemistry parameters and the mean change from baseline to last value were comparable across each age stratum except for the neonate age stratum. The differences noted in neonates can be attributed to physiologic factors in newborns.

Analysis focused on outliers or shifts from normal to abnormal

Chemistry shifts from baseline to the last value on study across each age stratum are presented in Table 34 that follows.

Table 35: Clinical Chemistry shifts from Baseline to Last Value on Study (Pediatric Safety Population)

Parameter	Shift	Neonates (N = 47) n/N (%)[1]	Infants (N = 64) n/N (%)[1]	Children (N = 171) n/N (%)[1]	Adolescents (N = 73) n/N (%)[1]
Albumin	Shift to High[2]	0/44	1/27 (3.7)	1/18 (5.6)	0/19
	Shift to Low[3]	6/44 (13.6)	5/27 (18.5)	5/18 (27.8)	5/19 (26.3)
Sodium	Shift to High[2]	0/4	0/44	0/70	0/70
	Shift to Low[3]	0/4	6/44 (13.6)	7/70 (10.0)	6/70 (8.6)
Potassium	Shift to High[2]	0/4	2/43 (4.7)	2/69 (2.9)	2/70 (2.9)
	Shift to Low[3]	0/4	8/43 (18.6)	5/69 (7.2)	4/70 (5.7)
Glucose	Shift to High[2]	0/4	5/32 (15.6)	5/66 (7.6)	3/67 (4.5)
	Shift to Low[3]	0/4	2/32 (6.3)	4/66 (6.1)	0/67
Creatinine	Shift to High[2]	0/3	0/42	2/70 (2.9)	0/70
	Shift to Low[3]	0/3	1/42 (2.4)	4/70 (5.7)	4/70 (5.7)

[1] n=number of patients with shift, N = total number of patients included in analysis.
[2] Shift from normal or low value at baseline to a last value on study that was above the upper limit of the normal range (high).
[3] Shift from normal or high value at baseline to a last value on study value that was below the lower limit of the normal range (low).

Source: Applicant's submission (ISS – Pediatrics, pg. 95)

The most frequent shift seen was in the albumin parameter (shift to low) with 26.3% of adolescents, 27.8 % of children, 18.5 % of infants and 13.6% of neonates included in the analysis experiencing this shift. Neonates did not experience any shifts in chemistry parameters except for what was previously noted. Two children experienced creatinine shifts to high levels. One of these cases will be briefly discussed in the next section on marked outlier.

Marked outliers and dropouts for chemistry abnormalities

There were no cases of marked outliers that were discontinued for chemistry abnormalities however there was one case of acute renal failure with a maximum creatinine of 2.5 mg/dL that has been previously discussed in the section on non-fatal serious adverse events. Per the applicant, this patient's creatinine elevation was thought to be secondary to nephrotoxic aminoglylycoside therapy (vancomycin) so, the patient was continued on IV acetaminophen treatment. Aminoglycosides can be nephrotoxic especially in combination with another aminoglyoside or other nephrotoxic

drugs such as rifampin and naficillin which were this patient's other concomitant medications.

Hepatic enzyme analysis

Analysis focused on measures of central tendency

A summary of mean liver function test values at baseline to last value on trial are displayed in Table 35

Table 36: Mean (SD) Liver Function Test Values at Baseline and Change from Baseline to Last Value on Study (Pediatric Safety Population)

Parameter Timepoint	Neonates (N=47)		Infants (N=64)		Children (N=171)		Adolescents (N=73)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
AST (U/L)								
Baseline	4	253.5 (373.99)	43	67.7 (53.01)	80	51.4 (68.45)	73	31.2 (20.48)
Δ to last value	4	-215.3 (360.14)	43	-21.3 (58.05)	80	70.3 (673.82)	73	5.4 (34.76)
ALT (mmol/L)								
Baseline	44	46.0 (84.76)	50	33.0 (20.29)	80	31.0 (28.63)	73	23.8 (10.14)
Δ to last value	44	-10.4 (76.45)	50	6.9 (44.40)	80	16.7 (147.86)	73	7.3 (23.57)
GGT (U/L)								
Baseline	43	96.2 (102.64)	22	35.0 (37.49)	44	22.0 (36.31)	49	18.1 (15.26)
Δ to last value	43	23.4 (94.05)	22	21.0 (69.52)	44	8.3 (33.00)	49	35.2 (48.73)
TBL (mg/dL)								
Baseline	47	5.19 (3.227)	37	1.19 (1.387)	63	0.76 (0.728)	62	0.63 (0.450)
Δ to last value	47	-1.47 (4.177)	37	-0.20 (0.884)	63	-0.22 (0.504)	62	-0.17 (0.482)
ALP (g/dL)								
Baseline	44	120.2 (57.73)	43	250.4 (192.28)	74	183.1 (82.19)	73	110.5 (55.72)
Δ to last value	44	19.4 (47.87)	43	-38.2 (113.09)	74	-15.9 (79.19)	73	9.4 (51.32)

Definitions: Δ=change; ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase;

Source: Applicant's submission (ISS – Pediatric, pg. 97)

LFT parameters (AST, ALT, GGT, TBL and ALP) in the neonate category were overall higher and are likely reflective of issues related to premature and gestational neonates such as hyperbilirubinemia. A larger increase in ALT and AST from baseline to last value was seen in the children's category and per the applicant is due to a marked outlier that will be discussed later. Overall, it is difficult to assess a trend in mean LFT parameters due to no comparative placebo-population for each age category and physiologic differences across pediatric age categories.

Analysis focused on outliers or shifts from normal to abnormal

A summary of Pediatric patient data for maximum elevations of > 3x ULN in ALT, AST, TBL, ALP and GGT are summarized in Table 36 below.

Table 37: Post-baseline Liver Function Test Results Relative to the Normal Range (Safety Population)

Laboratory Test Abnormality	Neonates (N = 47) n (%)	Infants (N = 64) n (%)	Children (N = 171) n (%)	Adolescents (N = 73) n (%)
AST or ALT (maximum AT), n	47	52	81	73
≤ 3xULN	45 (95.7)	47 (90.4)	72 (88.9)	67 (91.8)
> 3 - ≤ 5xULN	1 (2.1)	4 (7.7)	5 (6.2)	4 (5.5)
> 5 - ≤ 10xULN	1 (2.1)	1 (1.9)	3 (3.7)	2 (2.7)
> 10xULN	0	0	1 (1.2)[1]	0
AST, n	4	45	81	73
≤ 3xULN	3 (75.0)	41 (91.1)	72 (88.9)	67 (91.8)
> 3 - ≤ 5xULN	0	3 (6.7)	5 (6.2)	4 (5.5)
> 5 - ≤ 10xULN	1 (25.0)	1 (2.2)	3 (3.7)	2 (2.7)
> 10xULN	0	0	1 (1.2)[1]	0
ALT, n	47	52	80	73
≤ 3xULN	45 (95.7)	50 (96.2)	77 (96.3)	72 (98.6)
> 3 - ≤ 5xULN	2 (4.3)	1 (1.9)	2 (2.5)	0
> 5 - ≤ 10xULN	0	1 (1.9)	0	1 (1.4)
> 10xULN	0	0	1 (1.3)[1]	0
TBL, n	47	46	73	69
≤ 3xULN	18 (38.3)	43 (93.5)	73 (100.0)	69 (100.0)
> 3 - ≤ 5xULN	10 (21.3)	1 (2.2)	0	0
> 5 - ≤ 10xULN	14 (29.8)	1 (2.2)	0	0
> 10xULN	5 (10.6)	1 (2.2)	0	0
ALP, n	47	48	76	73
≤ 3xULN	47 (100.0)	46 (95.8)	75 (98.7)	73 (100.0)
> 3 - ≤ 5xULN	0	1 (2.1)	1 (1.3)	0
> 5 - ≤ 10xULN	0	1 (2.1)	0	0
> 10xULN	0	0	0	0

Definitions: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; AT = alanine or aspartate transaminase; TBL = total bilirubin; ULN = upper limit of normal

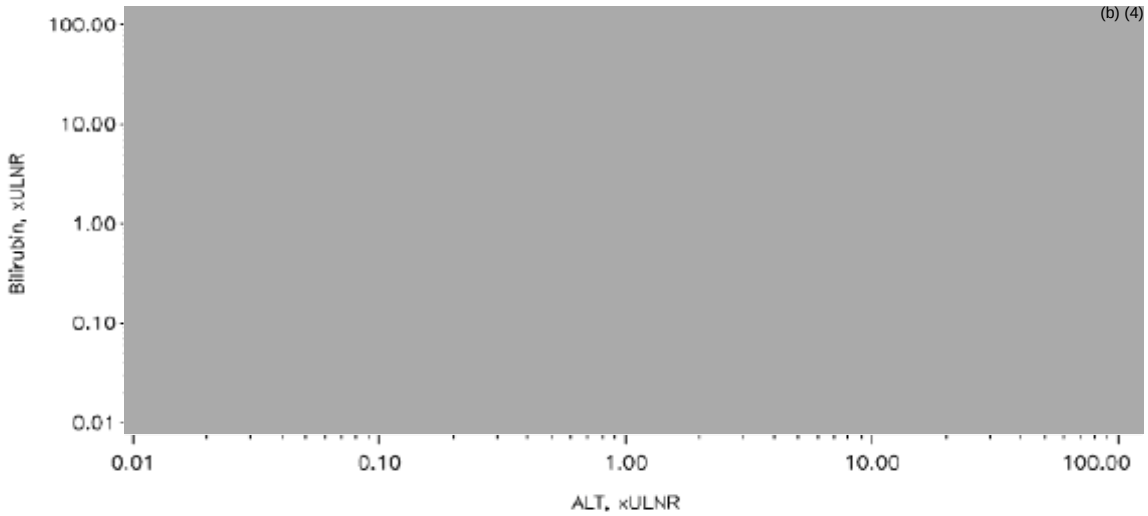
[1] Patient 00322 in Study CPI-APA-102; with L-transposition of the great arteries, dextrocardia, double outlet right ventricle, ventricular septal defect, subpulmonic and pulmonic stenosis, cyanosis, and elevated liver enzymes who was granted a waiver for study entry. The increased AST and ALT were associated with multi-organ failure and the patient's underlying condition.

Source: Applicant's submission (ISS – Pediatric, pg. 99)

There was one patient in the children age category that experienced >10x ULN in ALT and ALT, this outlier will be discussed in the next sub-section. Elevations > 3 - ≤ 5x ULN and >5 - ≤ 10x ULN were comparable between infants, children and adolescents. Elevations in TBL > 3X ULN were seen more frequently in neonates as compared to other age groups.

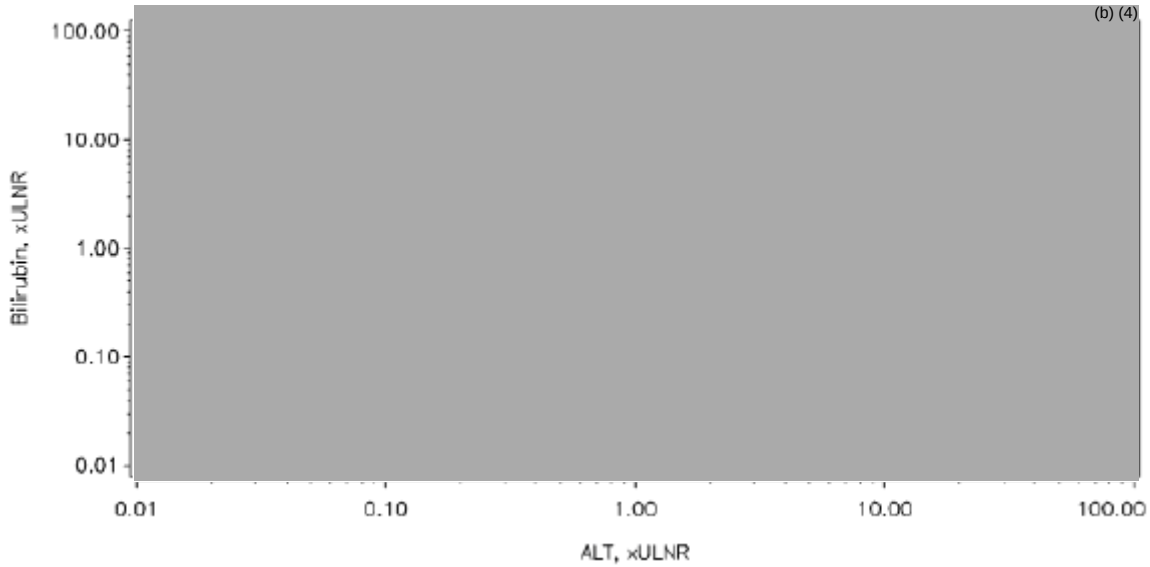
Figures 3 and 4 are scatterplots of baseline and worst baseline ALT versus TBL value in the pediatric safety population.

Figure 4: Scatterplot of Baseline ALT versus TBL: Pediatric Safety Population



Source: Applicant's submission (ISS- Pediatric, pg. 103))

Figure 5: Scatterplot of Worst Baseline ALT versus TBL: Pediatric Safety Population



Source: Applicant's submission (ISS – Pediatric, pg. 103))

The case located in the Hy's Law quadrant is present in both baseline and worst baseline ALT and TBL plots. The cases represented in the left upper quadrant

(elevated TBL and normal/near ULN ALT quadrant) were, according to the applicant, submission patients from the trial that enrolled mainly premature neonates and the remainder of cases were neonates or infants that undergone surgical repairs of congenital heart disease and had received blood transfusions. The cases in this quadrant were proportionately similar baseline and worst baseline. Finally, there were approximately 7 patients with ALT values > 3x ULN for worse value post baseline (right lower quadrant) **.** Three of these seven cases involved patients with complicated congenital heart disease (i.e. Tetralogy of Fallot, Coarctation of Aorta, Transposition of Great Arteries), with one of the three having elevated ALT levels at baseline and the remaining two patients suffering post-operatively complications of either hypotension or blood loss requiring transfusion. One of the seven patients was admitted with a diagnosis of gastroenteritis with dehydration and had elevated ALT levels at baseline. One patient received IV acetaminophen post-operatively from posterior spinal fusion surgery and suffered post-operative complications including hypoxia, hypovolemia and was on concomitant hepatotoxic medications (phenobarbital and levetiracetam). One patient experienced ALT elevations after his last dose of IV acetaminophen, and coinciding with his symptoms of bilious emesis and abdominal pain for which he was later diagnosed with a small bowel obstruction. The seventh patient in the quadrant displaying ALT values >3x ULN received IV acetaminophen while hospitalized for treatment for Guillain-Barre Syndrome and experienced LFT elevations from day 3 of study drug treatment until 4 days post early termination from study. In all of seven patients having ALT values >3x ULN for worst post baseline, there were confounding factors that may have contributed to this finding.

Marked outliers and dropouts for liver function test abnormalities

There was one Pediatric patient (1 child) who had marked LFT elevations and was subsequently discontinued from IV acetaminophen treatment. This outlier case is seen on Figures 1 and 2 DISH displays in the Hy's Law quadrant. Her case narrative is discussed below.

Patient 00322, a 10 year-old female enrolled in Study CPI-APA-102 received a total of 3 doses of IV acetaminophen at 10 mg/kg (wt=67 kg) = 660 mg Q4h for pain on 28 June 2008 following a Fontan procedure. Her medical history was significant for L-transposition of the great arteries, dextrocardia, double outlet right ventricle, ventricular septal defect, subpulmonic and pulmonic stenosis, cyanosis, and elevated liver enzymes. Her surgical history was significant for a Blalock-Taussig shunt, bidirectional Glenn shunt with Blalock-Taussig shunt takedown, and repair of the right coronary artery secondary to pacing wire injury. Concomitant medications included aspirin, morphine, cefazolin, heparin, milrinone, protamine, dopamine, epinephrine, and amiodarone

Table 38: Patient 00322 LFT Values

Patient 00322 (12.5 mg/kg q4h)	ALT (U/L)	AST (U/L)	AP (U/L)	TBL (mg/dL)
Screening	225	549	100	3.3
24 hour	ND	ND	ND	ND
48 hour/ET	1533	6565	116	2.3

Definition: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; EOS = end of study; TBL = total bilirubin; ND = not done

Source: Applicant's submission (ISS – Pediatric, pg. 108)

The patient was granted an exemption to enter the study with elevated liver enzymes (see Table 37), but with plans for treatment discontinuation if the enzymes failed to decrease as expected on reassessment later that day. No decreases in liver enzymes were observed and the patient was discontinued from the trial after the third dose. Postoperatively she experienced low cardiac output syndrome with marked diastolic dysfunction, respiratory failure, acute renal failure, acute liver failure (maximum ALT and AST of 1533 and 6565 U/L respectively with TBL of 3.3 mg/dL), disseminated intravascular coagulation, heparin-induced thrombocytopenia, extremity ischemic necrosis, delirium and withdrawal syndrome. Resuscitative efforts included numerous vasoactive infusions, continuous renal replacement therapy, and multiple transfusions. She suffered massive multiorgan failure with presumed sepsis that did not respond to treatments including several broad spectrum antibiotics. She died in the post-stduy period greater than 30 days after her last dose of IV acetaminophen

This outlier case does not represent an Hy's Law case because this patient's AST and ALT > 3x ULN with TBL > 2x ULN existed before the start of IV acetaminophen treatment and were likely due to her underlying complex heart disease.

7.6.3.14 Vital signs

Vital signs were collected in all the pediatric clinical trials. Standard vital sign assessments included systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR) and temperature (T).

Interpreting vital sign changes was confounded by the following:

- No placebo control group
- Large differences in the number of patients included in each age category analysis population
- Vital sign data was not included for patients who did not have completed trial information (i.e. early termination, discontinuation due to early hospital discharge)

Analysis focused on outliers or shifts from normal to abnormal

Vital signs shifts from baseline to the last value on study are displayed in Table 38.

Table 39: Vital Sign Shifts from Baseline to Last Study on Trial (Pediatric Safety Population)

VS	Shift	Neonates (N = 47) n/N[1] (%)	Infants (N = 64) n/N[1] (%)	Children (N = 171) n/N[1] (%)	Adolescents (N = 73) n/N[1] (%)
SBP	Shift to High[2]	0/4	7/56 (12.5)	10/170 (5.9)	1/73 (1.4)
	Shift to Low[3]	0/4	0/56	2/170 (1.2)	4/73 (5.5)
DBP	Shift to High[2]	0/4	2/56 (3.6)	3/170 (1.8)	0/73
	Shift to Low[3]	0/4	4/56 (7.1)	7/170 (4.1)	1/73 (1.4)
HR	Shift to High[2]	1/4 (25.0)	6/56 (10.7)	4/168 (2.4)	9/73 (12.3)
	Shift to Low[3]	0/4	0/56	6/168 (3.6)	1/73 (1.4)
RR	Shift to High[2]	0/3	5/19 (26.3)	5/55 (9.1)	5/57 (8.8)
	Shift to Low[3]	0/3	3/19 (15.8)	6/55 (10.9)	0/57

Definitions: VS = vital sign; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; RR = respiratory rate.

1 n=number of patients with shift, N = total number of patients included in analysis.

2 Shift from normal or low value at baseline to high value (relative to normal range) at last evaluation.

3 Shift from normal or high value at baseline to low value (relative to normal range) at last evaluation.

Source: Applicant's submission (ISS – Pediatric, pg. 111)

Overall, infants included in the analysis had a higher frequency of vital sign shifts to high and low values in comparison to neonates, children, and adolescents. Neonates included in the analysis had only 1 case of an abnormal vital sign shift (HR from normal to high). Shifts to low SBP were seen in 6 out of the 303 pediatric patients analyzed. Shifts to low DBP were seen in 12 out of the 303 pediatric patients analyzed

Table 39 below shows vital sign abnormalities reported as TEAES overall and across pediatric age stratum

Table 40: TEAEs associated with Vital Sign Abnormalities (Pediatric Safety Population)

MedDRA Preferred Term	Neonates (N = 47) n (%)	Infants (N = 64) n (%)	Children (N = 171) n (%)	Adolescents (N = 73) n (%)	Total (N = 355) n (%)
Blood Pressure Events					
Hypotension	0	1 (1.6)	5 (2.9)	3 (4.1)	9 (2.5)
Hypertension	0	2 (3.1)	2 (1.2)	0	4 (1.1)
Blood pressure increased	0	0	1 (0.6)	0	1 (0.3)
Heart Rate Events					
Tachycardia	0	0	3 (1.8)	1 (1.4)	4 (1.1)
Body Temperature Events					
Pyrexia	0	0	9 (5.3)	6 (8.2)	15 (4.2)

Definitions: MedDRA = Medical Dictionary for Regulatory Activities.

Source: Applicant submission (ISS – Pediatric, pg. 112)

The most common vital sign abnormality reported as a TEAE was pyrexia at 4.2 % in all pediatric patients. In the neonate age category no TEAEs associated with vital sign abnormalities were reported. Adolescents had a higher number of TEAEs (13.6 %)

associated with vital sign abnormalities as compared to children (11.6%), infants (4.7%) and neonates (0%) respectively.

7.6.3.15 Electrocardiograms

Electrocardiograms were not performed for any of the pediatric clinical trials.

7.6.3.16 Special Safety Studies/Clinical Trials

No additional special safety studies or clinical trials were performed during the pediatric clinical development program.

7.6.3.17 Drug-Demographic Interactions

The applicant tabulated TEAEs reported in ≥ 3 infants, children, or adolescents who received IV acetaminophen and presented this data by gender and race category. Overall, there were no clinically meaningful differences in the incidence rates of common TEAEs between genders across age categories(neonates vs. infants vs. children vs. adolescents).. Similarly, as with gender there were no clinically meaningful differences in the occurrences of common TEAEs between races (caucasian vs. non-caucasian). I will note that how the applicant chose to analyze drug-demographics with the pediatric data base by stratifying by age, then by gender or race made it difficult to discuss these interactions.

7.6.3.18 Drug-Disease Interactions

This section is not applicable to this sNDA.

7.6.3.19 Drug-Drug Interactions

Please see section 7.5.5

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Please see Section 7.3.5

7.7 Additional Submissions / Safety Issues

The applicant submitted the 120 day safety update on 11 September 2009. The safety review incorporates all submitted data. A total of three additional submissions regarding safety were made in response to queries from the Division and these submissions are displayed in Table 40.

Table 41: Additional Requested Clinical Submissions to NDA 22-450

Submission Date	Information Submitted
29 June 2009	Datasets containing all adverse event data for all patients, repeated-dose trials
28 July 2009	Additional clinical information for one patient 001-32
11 August 2009	Additional clinical information for patients

8 Post market Experience

Since 2001, an IV formulation of acetaminophen identical to the proposed commercial formulation for marketing in the US has been approved for use, initially in France and subsequently in approximately 80 countries. This product has been marketed by Bristol-Myers Squibb as Perfalgan in most countries; however, other trade names have also been used. Perfalgan is marketed for the same indications of acute pain and fever, both alone and in conjunction with parental opioids and non-steroidal anti-inflammatory drugs, and in both the adult and pediatric populations.

To date, the applicant has provided periodic safety update reports (PSURs) on an annual basis since June 2001. Per the applicant, approximately (b) (4) patients have been treated with IV acetaminophen to date.

The summary of safety in foreign post-marketing experience has been prepared by the applicant using nine clinical categories identified in the periodic safety update reports from June 2001 to January 2009. These 9 categories are organized as follows:

- Adverse events with death as an outcome
- Hepatic adverse events
- Allergic/Hypersensitivity/Dermatologic adverse events
- Overdose
- Medication errors
- Cardiovascular adverse events

- Renal adverse events
- Respiratory adverse events
- Hematologic adverse events

In the review of the categories: adverse events with death as outcome, hepatic adverse events, anaphylaxis, angioedema, and serious cutaneous reactions), the applicant has indentified certain individuals as independent experts.

Adverse events with death as an outcome in IV acetaminophen post-marketing experience

Per the applicant's submission, a total of 55 reports with one or more AEs resulted in death from the estimated (b) (4) patients exposed during the review period (June 2001 – January 2009) including 48 adults and 5 pediatric patients (3- neonates, 1-infant, 1-child) . The applicant has chosen to summarize deaths with a reasonable causal association with IV acetaminophen as deemed by an independent expert analysis performed (b) (4)
I performed a review of the line listings of all adverse events with death as an outcome as well as an evaluation of the causal relationship table as assessed by this independent "expert" (b) (4) and found that a higher proportion of death events occurred in the hepatic category (i.e. fulminant hepatitis, hepatic failure, acute hepatic failure, and hepatotoxicity) as compared to cardiovascular, allergic, hematologic, respiratory, overdose and other event categories (See Table 41 below). Several of these patients had medical histories significant for alcoholism, and /or prior liver disease.

Table 42: Summary of Events with Death as Outcomes, by Causal Relationship as Assessed by an Independent Expert (b) (4)

Event category	Reasonable causal association with IV acetaminophen	Causal relationship with IV acetaminophen not definitely excluded	Total
Hepatic	7	5	12
Cardiovascular	1	4	5
Allergic	1	1	2
Hematologic	0	4	4
Respiratory	0	1	1
Overdose	0	1	1
Other	0	3	3

Source: Applicant's submission (Post-Marketing safety data analysis)

Hepatic adverse events in IV acetaminophen post-marketing experience

Per the applicant's submission, there were 171 reports of medically significant hepatic adverse events from the estimated (b) (4) patients exposed during the review period (June, 2001 to January 2009) including 123 adults and 23 pediatric patients (4- neonates, 3–infants, 8–children, 7- adolescents), and 26 reports where the age of the patient was not given.

Similarly as in the analysis of deaths, the applicant consulted, (b) (4)
to review the reports of liver injury associated with IV acetaminophen and to assess the relative safety of the drug. (b) (4) review shows 12 out of the 171 reports where the available data met the quantitative criteria of "Hy's Law." Of these 12 reports there were 2 liver transplants, 3 deaths, and the remaining 7 cases recovered. Also (b) (4) reports in his review that 10 cases raised a strong index for drug-induced liver injury (DILI); three of which were assessed as probably due to IV acetaminophen, seven assessed as possibly due to IV acetaminophen and one fatality. I reviewed the PSUR for the suspected DILI case that was fatal. The patient involved was a 58 year old female with a reported history of alcohol abuse who received IV acetaminophen 1 gram three times daily and oral acetaminophen 1 gram 4 times daily concomitantly for two consecutive days for analgesia following hospitalization for humeral fracture and subsequent surgery. On Day #3 of treatment with of IV and oral acetaminophen the patient experienced fulminant hepatitis, cardio-circulatory collapse, and cardio-respiratory arrest with corresponding lab data showing an acetaminophen level of 51 mmol/l (normal 10-30 mmol/l, SGOT – 5400 UI, SGPT – 800 UI, and bilirubin of 96 umol/l. . She received N-acetylcysteine however death occurred over the next 36 hours. The post-mortem hepatic biopsy was reported to show acute alcoholic hepatitis with necrosis evoking acetaminophen toxicity on alcoholic hepatitis. In addition to this case the applicant reports that a total of four of the suspected cases of DILI were reported as having received excess doses of IV acetaminophen

I reviewed a substantial number of the 171 case narratives for this category as well. The narratives and PSURs within this category showed that a large proportion of hepatic adverse events involved patients with conditions including: hepatocellular dysfunction, alcoholism, malnutrition, dehydration or severe renal insufficiency. These patients may have been at increased risk for developing acetaminophen induced hepatotoxicity. The postmarketing summary provided by the Applicant is consistent with the known safety profile of oral acetaminophen.

Allergic, Hypersensitivity and Dermatologic adverse events In IV acetaminophen post-marketing experience

Per the applicant's submission, there were 240 reports of medically significant allergic/dermatologic adverse events from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including 190 adults, 26 pediatric patients (2-infants, 14-children, 10-adolescents) and 24 reports that did not include the age of the patient.

These events were grouped and reported by the applicant in the following categories:

- Anaphylactic shock (n=39)
- Anaphylactoid reactions (n=24)
- Angioedema (n=12)
- Urticaria (n=32)
- Stevens-Johnson syndrome (n=5)
- Toxic epidermal necrolysis (n=6)
- Erythema multiforme (n=2)
- Acute generalized exanthematous pustulosis (n=14)
- Minor immediate hypersensitivity cutaneous and other allergic reactions such as erythema, rashes, localized edema or swelling, and pruritus

The applicant idenitfied (b) (4) as an independent expert to review the cases of allergic/hypersensitivity and dermatologic adverse events and provide his own assessment of diagnosis and causality in each of these 240 cases. Overall, (b) (4) diagnosis and causality assessment was similar to that of the applicant across categories. For example, in (b) (4) review 73 cases were considered to be anaphylaxis or anaphylactoid reactions as compared to the applicant's review showing 63 cases of anaphylaxis or anaphylactoid reactions out of approximately (b) (4) patients exposed.

The post-marketing reports associated with this category of adverse events were limited due to several factors including limited medical history reported; diagnoses without supportive documentation, and presence of concomitant medications.

Overdose events in IV acetaminophen post-marketing experience

Per the applicant's submission, there were 50 reports of overdose events from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including 13 adults, 23 pediatric patients (8-neonates, 9-infants, 7-children) and 14 reports where the age of the patient was not given. The following categories were used to summarize the data from post-marketing experience:

1. Adults who received > 4 grams total daily dose: the applicant reports seven adult cases where multiple doses of IV acetaminophen exceeded the cumulative maximum recommended. Of these 7 cases, six cases had adverse reactions (five reports of LFT elevations and one report of creatinine elevation)

2. Adults) who received > 10 grams total daily dose: the applicant reports one adult case that exceeded this threshold, a patient who received 12 g of IV acetaminophen in a 24 hour period , with no adverse sequelae reported

3. Pediatric patients receiving more than applicant recommended maximum dose: the applicant reports 17 cases including infants and children and 7 cases of neonates who met this criteria. Of these 17 reports, five cases were reported to have adverse sequelae (two reports of vomiting, and three reports of LFT elevations)

4. Pediatric patients receiving > 140 mg/kg total daily dose: the applicant reports five pediatric cases including 1 neonate and 4 infants) who received doses > 140 mg/k total daily dose. Of these five reports, three were reported to have increased LFTs with no sequalae and one patient received N-acetylcysteine empirically. Two of these five patients died however the applicant purports that relationship of IV acetaminophen in these cases in uncertain.

Overall, there were more reports of overdoses in the pediatric population as compared to the adult population. Most cases that had adverse sequelae involved LFT elevations.

Medication errors in IV acetaminophen post-marketing experience

Per the applicant submission, there have been 101 medication error reports from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including 31 adults, 7 pediatric cases (1-neonate, 1-infant, 3-children, 2-adolescents) and 63 reports where the ages of the patients were not given. Of these 101 reports, four included fatal events. I reviewed PSUR for these deaths and found that one event involving an air embolism after administration of IV acetaminophen was possibly related and possibly related to this patient's death. The following categories were used to summarize medications errors with and without adverse sequelae:

1. Drug maladministration (n=32) : the administration errors involved subcutaneous infusion, intramuscular infusion, epidural infusion, enteral infusion, and intra-arterial infusions
2. Medication error (n=58): the medication errors involved infusion times either < or > recommended times, expired drug given, air in infusion set, accidental exposure, medication bottle breakage and patients with medical conditions representing possible contraindication to IV acetaminophen.

Cardiovascular adverse events in IV acetaminophen post-marketing experience

Per the applicant submission, there have been 107 cardiovascular adverse events reported from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including 73 adults, nine pediatric patients (4-neonates, 1-infant, 1-child, 3-adolescents) and 25 reports where the age of the patient was not given. Of these 107 reports, the events were classified as follows:

- Hypotension (n = 53)
- Cardiac arrest (n = 6)
- Cardiovascular or circulatory collapse (n = 5)
- Shock (n = 4)
- Ventricular tachycardia (n = 2)
- Ventricular fibrillation (n = 1)
- Torsade de Pointes (n = 1)

Hypotension was the most frequently reported event in this category with a total of 55 case reports. In my review of some of the cardiovascular case narratives involving hypotension, cardiovascular or circulatory collapse, and shock there were other etiologies (i.e. trauma, post operative hypovolemia/hemorrhage, and anesthesia) possibly related to these adverse events. In the cases of arrhythmia, medication errors involving incorrect infusion times were noted. The case report of Torsade de Pointes involved a patient with a pre-existing cardiac condition undergoing cardiac procedures.

Renal adverse events in IV acetaminophen post-marketing experience

Per the applicant submission, there have been 27 renal adverse events reported as primary or in conjunction with hepatic adverse events from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including 23 adults, two pediatric patients (1-neonate, 1-child) and 2 reports where the age of the patient was not given. Three of these 27 reports included fatal events of which 2/3 included renal failure as a part of multi-organ failure (including hepatic failure). The renal adverse events were classified in the following categories:

- Renal failure (n =7)
- Acute renal failure (n = 13)
- Renal tubular necrosis (n = 3)
- Urinary retention (n = 1)
- Interstitial nephritis (n = 1)
- Decreased creatinine clearance (n=1)

The applicant purports that in the majority of cases of renal failure, there was documentation that supported other possible etiologies that were more likely to cause nephrotoxicity including the use of IV contrast and antibiotics such as aminoglycosides and vancomycin.

Respiratory adverse events in IV acetaminophen post-marketing experience

Per the applicant submission, there have been 50 respiratory adverse events reported from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including 30 adults, 9 pediatric patients (3-neonates, 1- infant, 3-children, 2-adolescents) and 11 reports where the age of the patient was not given. Of these 50 reports, these medical significant events were classified as:

- Respiratory depression (n = 8)
- Respiratory distress (n = 8)
- Respiratory failure (n = 2)
- Bronchospasm (n = 2)
- Respiratory arrest (n = 3)
- Respiratory disorder (n = 3)
- Respiratory acidosis (n = 1)

I will note that of these 50 reports, eight included fatal events, one of which the applicant states that the event (anaphylaxis with dyspnea) was possibly related to IV acetaminophen. Otherwise, the majority of respiratory adverse events occurred in the respiratory distress and respiratory depression category

Hematologic adverse events in IV acetaminophen post-marketing experience

Per the applicant submission there have been 65 hematologic adverse events reported from the estimated (b) (4) patients exposed during the review period (June 2001 to January 2009) including 57 in adults, 8 in pediatric patients (1-neonate, 1-infant, 4-children, 2-adolescents). Of these 65 reports, the events were classified as follows:

- Thrombocytopenia (n = 22)
- Agranulocytosis or neutropenia (n = 20)
- Hemolytic anemia (n = 5)
- Coagulopathy (n = 3)
- Pancytopenia (n = 3)

Thrombocytopenia appears to be the most commonly reported hematologic adverse event in the post-marketing analysis.

In summary, review of safety data from foreign post-marketing use of IV acetaminophen appears to show a similar pattern of adverse events compared to oral acetaminophen. Like oral acetaminophen, the applicant's post-marketing analysis of IV acetaminophen shows the drug has the potential to increase hepatic adverse outcomes when used in "high risk" conditions (alcoholic disease, and prior and current liver dysfunction) at therapeutic doses and when given in excess of the recommended dose (accidental overdose). Overall, IV acetaminophen accidental overdoses were more prevalent in the pediatric population as compared to adults. In the majority of the pediatric accidental overdose cases the most common adverse sequelae involved LFT elevations. In the severe overdose cases an IV acetaminophen induced hepatotoxic picture was observed requiring anecdotal (n-acetyl-cysteine) treatment in some cases. The applicant has addressed the potential for these specific adverse events in the warning and precautions section of the proposed IV acetaminophen label.

9 Appendices

9.1 Literature Review/References

To support its claims regarding the safety of IV acetaminophen, the applicant relied upon the safety experience of oral acetaminophen.

9.2 Labeling Recommendations

The proposed label for IV acetaminophen has been reviewed and recommendations include the following:

- The Highlights' section should be limited in length to one-half page
- Do not include the pregnancy category in the Hightights'section

9.3 Advisory Committee Meeting

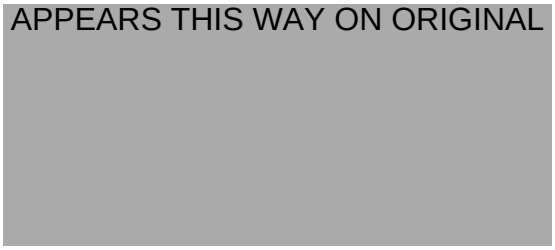
In June 2009, an expert panel was convened at the Center for Drug Evaluation and Research Joint Meeting of the Drug Safety and Risk Management Advisory Committee, the Agency's Nonprescription Drugs Advisory Committee and the Anesthetic and Life Support Drugs Advisory Committee to discuss safety issues of acetaminophen and greater regulation of this commonly used drug. This particular drug was not discussed.

Key recommendations from the panel included:

- Decrease the maximum total daily dose of acetaminophen in non-prescription single ingredient and combination products to less than 4 grams/day

- Decrease the maximum non-prescription single adult dose of acetaminophen to 650 mg
- Require a boxed warning for prescription acetaminophen combination products
- Unbundle prescription acetaminophen narcotic combination products
- Provide label dosing directions for pediatric patients < 2 years of age
- Limit the non-prescription acetaminophen liquid suspension to a single concentration.

The overall theme that came out of the acetaminophen advisory committee meeting is that preventing and decreasing the misuse and overdose of acetaminophen is critical.



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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	ACETAMINOPHEN FOR INJECTION FOR IV USE

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/s/

JACQUELINE A SPAULDING
10/13/2009

ROBERT B SHIBUYA
10/13/2009
I concur with Dr. Spaulding's review and conclusions.