# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**204957Orig1s000**

# CLINICAL PHARMACOLOGY REVIEW(S)

# Office of Clinical Pharmacology Review

| | |
|---|---|
| **NDA or BLA Number** | 204957 |
| **Link to EDR** | \\CDSESUB1\EVSPROD\NDA204957\0001 |
| **Submission Date** | 12/13/16; 1/17/17; PDUFA date: 10/13/17 |
| **Submission Type** | Standard Review |
| **Brand Name** | Acetaminophen Injection |
| **Generic Name** | Acetaminophen Injection in the PAB Container |
| **Dosage Form and Strength** | Solution; 500 mg/50 mL and 1000 mg/100 mL |
| **Route of Administration** | Intravenous infusion |
| **Proposed Indication** | • The management of mild to moderate pain<br>• The management of moderate to severe pain with adjunctive opioid analgesics<br>• The reduction of fever |
| **Dosage Regimen** | • Acetaminophen Injection may be given as a single or repeated dose<br>• Acetaminophen Injection should be administered only as a 15-minute intravenous infusion<br>Adults and Adolescents Weighing 50 kg and Over:<br>• 1000 mg every 6 hours to a maximum of 4000 mg per day<br>Adults and Adolescents Weighing Under 50 kg:<br>• 15 mg/kg every 6 hours to a maximum of 75 mg/kg per day<br>Children:<br>Children 2 to 12 years of age: 15 mg/kg every 6 hours to a maximum of 75 mg/kg per day |
| **Applicant** | B. Braun Medical, Inc. |
| **Associated IND** | 111161 |
| **OCP Reviewer** | David Lee, Ph.D. |
| **OCP Team leader** | Yun Xu, Ph.D. |

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# 1. EXECUTIVE SUMMARY

## 1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application, NDA 204957, for Acetaminophen Injection in the Partial Additive Bag (PAB®*) Container (with administration port and blocked medication port), submitted on 12/13/16. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable. No further communication is necessary with the Applicant at this point.

| Review Issue | Recommendations and Comments |
|---|---|
| **Pivotal or supportive evidence of effectiveness** | The current submission is solely based on a bioequivalence study (HC-G-H-1506) using 1000 mg/100 mL (10 mg/mL) formulation. No other studies were conducted. Study HC-G-H-1506 was a Phase 1, open-label, randomized, single-dose, 2-way crossover study to determine the bioequivalence of single IV administration of 1000 mg of Acetaminophen Injection versus the listed drug 1000 mg of Ofirmev® (acetaminophen) Injection in healthy adult subjects. The study results indicated that the bioequivalence was established between the Applicant's product and Ofirmev. |
| **General dosing instructions** | The proposed dosage regimens are the same as Ofirmev.<br>Adults and Adolescents Weighing 50 kg and Over:<br>1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day; minimum dosing interval of 4 hours<br>Adults and Adolescents Weighing Under 50 kg:<br>15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day; minimum dosing interval of 4 hours<br>Children:<br>Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day; minimum dosing interval of 4 hours |
| **Dosing in patient subgroups (intrinsic and extrinsic factors)** | No formal assessment was conducted with the Applicant's product. The Applicant is referring to the information in listed drug products labels. |
| **Labeling** | The proposed Labeling are the same as Ofirmev. |
| **Bridge between the to-be-marketed and clinical trial formulations** | The final to-be-marketed formulation was used in the bioequivalence study. |
| **Other (specify)** | Not applicable. |

## 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

The Applicant has submitted Acetaminophen Injection in the Partial Additive Bag (PAB®*) Container (with administration port and blocked medication port) as a 505(b)(2) submission. The basis for submission is reliance on the previous findings of safety and efficacy of Ofirmev® (Mallinckrodt NDA 22450) by providing bioequivalence information only (acetaminophen, acetaminophen sulfate and acetaminophen glucuronide exposures) between Acetaminophen Injection and Ofirmev. No other studies were conducted. The Applicant relies on previous findings of Ofirmev for metabolism and DDI information.

The proposed indication and dosage regimen are the same as Ofirmev. The indications are: the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and, the reduction of fever. The proposed dosing regimen are: acetaminophen injection may be given as a single or repeated dose; acetaminophen injection should be administered only as a 15-minute intravenous infusion; for adults and adolescents Weighing 50 kg and Over - 1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day; minimum dosing interval of 4 hours. ; for adults and adolescents Weighing Under 50 kg - 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day; minimum dosing interval of 4 hours.; for children 2 to 12 years of age - Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day; minimum dosing interval of 4 hours.

The proposed dosage form is a solution for intravenous (IV) infusion with two different configurations: 1000 mg/100 mL (10 mg/mL) and 500 mg acetaminophen in 50 mL (10 mg/mL). Acetaminophen Injection was developed under IND 111161. [*Note: There are other FDA approved NDA (e.g., 16730, 17464, 18900, 19212, etc.) and ANDA (e.g., 62814, 76414, etc.) products packaged in the PAB Containers.]

505(b)(2) submission based on pharmacokinetic study (Study HC-G-H-1506)

The Applicant indicated that the proposed Acetaminophen Injection contains the same active ingredient in the same concentration as Ofirmev; however, it contains different excipients. Therefore, in support of the current submission, one bioequivalence study (Study HC-G-H-1506) was performed using 1000 mg/100 mL (10 mg/mL) formulation. No other studies were conducted. The final to-be-marketed formulation was used in the bioequivalence study.

Office of Study Integrity and Surveillance (OSIS) inspection request

Since the current submission is solely based on Study HC-G-H-1506, a request was submitted to Office of Study Integrity and Surveillance (OSIS) inspect the clinical study site(s) [Office of Study Integrity and Surveillance (OSIS) Consult: Request for Biopharmaceutical Inspections; DARRTS date 2/8/17 by Ogochukwu U Ogoegbunam].

OSIS recommendation

Division of New Drug Bioequivalence Evaluation (DNDBE), OSIS, recommended that the Division accept the Applicant's data without an on-site inspection (DARRTS date 04/17/2017; Shila S Nkah). The rationale for this decision is based on the fact that "OSIS recently inspected the sites" listed in the Consult form and that the "inspection outcome from the inspections was classified as No Action Indicted (NAI)":

**Rationale**

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

| Facility Type | Facility Name | Facility Address |
|---|---|---|
| Clinical | PPD Phase I Clinic | 7551 Metro Center Drive, Suite 200, Austin, TX |
| Analytical | (b) (4) | |

(Decline to Inspect Memo_NDA 204957; DARRTS date 04/17/2017; Shila S Nkah)

Reviewer's comment: No issues are identified at this juncture and there are no comments to be conveyed to the Applicant regarding the inspection.

## 2.1 Pharmacology and Clinical Pharmacokinetics

### *2.1.1. What is the proposed indication?*

The proposed indications for Acetaminophen Injection in the Partial Additive Bag (PAB®*) Container are the same as Ofirmev. The indications are: the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and, the reduction of fever.

## 2.2 Dosing and Therapeutic Individualization

### *2.2.1 General dosing*

The proposed dosage regimens for Acetaminophen Injection are the same as Ofirmev. The following general dosing is proposed according to the Label:

2.1 General Dosing Information
Adults and adolescents weighing 50 kg and over: the recommended dosage of Acetaminophen Injection is 1000 mg every 6 hours or 650 mg every 4 hours, with

a maximum single dose of Acetaminophen Injection of 1000 mg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 4000 mg per day (includes all routes of administration and all acetaminophen-containing products including combination products).
Adults and adolescents weighing under 50 kg: the recommended dosage of Acetaminophen Injection is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of Acetaminophen Injection of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day (includes all routes of administration and all acetaminophen-containing products including combination products).

2.2 Recommended Dosage: Adults and Adolescents

Adults and adolescents weighing 50 kg and over: the recommended dosage of Acetaminophen Injection is 1000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of Acetaminophen Injection of 1000 mg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 4000 mg per day (includes all routes of administration and all acetaminophen-containing products including combination products).
Adults and adolescents weighing under 50 kg: the recommended dosage of Acetaminophen Injection is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of Acetaminophen Injection of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day (includes all routes of administration and all acetaminophen-containing products including combination products).

| **Age group** | **Dose given every 4 hours** | **Dose given every 6 hours** | **Maximum single dose** | **Maximum total daily dose of acetaminophen (by all routes)** |
|---|---|---|---|---|
| **Adults and adolescents (13 years and older) weighing greater than or equal to 50 kg** | 650 mg | 1000 mg | 1000 mg | 4000 mg in 24 hours |
| **Adults and adolescents (13 years and older) weighing less than 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) |

2.3 Recommended Dosage: Children

Children 2 to 12 years of age: the recommended dosage of Acetaminophen Injection is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of Acetaminophen Injection of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day.

| Age group | Dose given every 4 hours | Dose given every 6 hours | Maximum single dose | Maximum total daily dose of acetaminophen (by all routes) |
|---|---|---|---|---|
| **Children 2 to 12 years of age** | 12.5 mg/kg | 15 mg/kg | 15 mg/kg (up to 750 mg) | 75 mg/kg in 24 hours (up to 3750 mg) |

### *2.2.2 Therapeutic individualization*

#### *2.2.2.1 Pediatric development iPSP*

With respect to pediatric development plan, the Applicant states that the Pediatric Research Equity Act (PREA) is not triggered since the Applicant's submission is not for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. During the pre-IND stage, the Agency stated that the Applicant's product will not trigger PREA.

#### *2.2.2.2 Clinical pharmacokinetic findings*

*Summary: In Study HC-G-H-1506, following a single IV infusion of Acetaminophen Injection 1000 mg and Ofirmev 1000 mg, mean plasma concentrations versus time profiles of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide looked similar between the two treatments. The results indicated that Acetaminophen Injection is bioequivalent to Ofirmev based on the 90% CIs (within the predefined bioequivalence acceptance limits of 80% to 125%) for the geometric least squares means ratios for AUC0-t, AUC0-inf, and Cmax for acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide.*

*Reviewer's comment: Acceptable and there are no comments to be conveyed to the Applicant.*

Study HC-G-H-1506 was a Phase 1, open-label, randomized, single-dose, 2-way crossover study to determine the bioequivalence of single IV administration of 1000 mg of Acetaminophen Injection versus 1000 mg of Ofirmev Injection in healthy adult subjects.

Plasma pharmacokinetic parameters (mean and SD) of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide are presented in Tables 1, 2, and 3, respectively.

Table 1 Mean (SD) Plasma Pharmacokinetic Parameters of Acetaminophen (Pharmacokinetic Population)

| Parameter (unit) | Acetaminophen Injection 1000 mg (N = 28) | Ofirmev® 1000 mg (N = 28) |
|---|---|---|
| $AUC_{0-t}$ (µg•h/mL) | 57.23 (17.33) | 58.77 (17.0) |
| $AUC_{0-inf}$ (µg•h/mL) | 59.91 (18.60) | 61.68 (18.34) |
| $C_{max}$ (µg/mL) | 24.92 (8.40) | 24.98 (7.57) |
| $T_{max}$ (h)[a] | 0.25 (0.08, 0.50) | 0.250 (0.25, 0.50) |
| $t_{1/2}$ (h) | 2.67 (0.36) | 2.72 (0.39) |
| CL (L/h) | 17.72 (5.37) | 17.38 (4.40) |
| $V_z$ (L) | 67.69 (20.59) | 67.49 (17.04) |

Abbreviations: SD: standard deviation; h: hours; N: number of subjects in the population; PK: pharmacokinetic.
a For Tmax, the median (minimum, maximum) values are presented.
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population.
Source: End-of-Text Table 14.2.2.1.

Table 2 Mean (SD) Plasma Pharmacokinetic Parameters of Acetaminophen Sulfate (Pharmacokinetic Population)

| Parameter (unit) | Acetaminophen Injection 1000 mg (N = 28) | Ofirmev® 1000 mg (N = 28) |
|---|---|---|
| $AUC_{0-t}$ (µg•h/mL) | 34.01 (11.91) | 34.91 (12.16) |
| $AUC_{0-inf}$ (µg•h/mL) | 37.49 (13.36) | 38.47 (13.60) |
| $C_{max}$ (µg/mL) | 5.85 (1.87) | 5.88 (1.93) |
| $T_{max}$ (h)[a] | 1.50 (0.50, 2.50) | 1.50 (0.50, 3.00) |
| $t_{1/2}$ (h) | 3.22 (0.43) | 3.23 (0.44) |

Abbreviations: SD: standard deviation; h: hours; N: number of subjects in the population; PK: pharmacokinetic.
a For Tmax, the median (minimum, maximum) values are presented.
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population.
Source: End-of-Text Table 14.2.2.2.

Table 3 Mean (SD) Plasma Pharmacokinetic Parameters of Acetaminophen Glucuronide (Pharmacokinetic Population)

| Parameter (unit) | Acetaminophen Injection 1000 mg (N = 28) | Ofirmev® 1000 mg (N = 28) |
|---|---|---|
| $AUC_{0-t}$ (µg•h/mL) | 133.50 (32.35) | 137.38 (34.75) |
| $AUC_{0-inf}$ (µg•h/mL) | 148.31 (36.15) | 152.03 (39.28) |
| $C_{max}$ (µg/mL) | 22.01 (5.49) | 22.50 (5.6) |
| $T_{max}$ (h)[a] | 2.25 (1.50, 3.50) | 2.50 (1.50, 4.50) |
| $t_{1/2}$ (h) | 3.22 (0.50) | 3.16 (0.45) |

Abbreviations: SD: standard deviation; h: hours; N: number of subjects in the population; PK: pharmacokinetic.
a For Tmax, the median (minimum, maximum) values are presented.
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population.
Source: End-of-Text Table 14.2.2.3.

Statistical analysis of the log-transformed plasma PK parameters of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide is presented in Table 6.

Table 4 Statistical analysis of pharmacokinetic parameters of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide: geometric LS means and 90% Confidence interval

| Parameter (unit) | Treatment a | N | Geometric LS Means | Ratio (%) of Geometric LS Means (A/Ba) | 90% Confidence Interval of the Ratio (%) |
|---|---|---|---|---|---|
| Acetaminophen | | | | | |
| $AUC_{0-t}$ (µg•h/mL) | A | 28 | 54.92 | 96.81 | (95.14, 98.50) |
| | B | 28 | 56.74 | | |
| $AUC_{0-inf}$ (µg•h/mL) | A | 28 | 57.37 | 96.52 | (94.75, 98.33) |
| | B | 28 | 59.43 | | |
| $C_{max}$ (µg/mL) | A | 28 | 23.47 | 97.91 | (91.33, 104.96) |
| | B | 28 | 23.98 | | |
| Acetaminophen Sulfate | | | | | |
| AUC0-t (µg•h/mL) | A | 28 | 31.82 | 97.21 | (95.02, 99.46) |
| | B | 28 | 32.73 | | |
| AUC0-inf (µg•h/mL) | A | 28 | 34.99 | 97.22 | (94.70, 99.81) |
| | B | 28 | 36.00 | | |
| Cmax (µg/mL) | A | 28 | 5.52 | 99.86 | (96.89, 102.91) |
| | B | 28 | 5.53 | | |
| Acetaminophen Glucuronide | | | | | |
| AUC0-t (µg•h/mL) | A | 28 | 129.35 | 97.56 | (95.24, 99.94) |
| | B | 28 | 132.58 | | |
| AUC0-inf (µg•h/mL) | A | 28 | 143.71 | 97.98 | (95.33, 100.70) |
| | B | 28 | 146.68 | | |
| Cmax (µg/mL) | A | 28 | 21.22 | 97.94 | (94.63, 101.37) |
| | B | 28 | 21.66 | | |

Abbreviations: IV: intravenous; LS: least squares; N: number of subjects in the population; PK: pharmacokinetic.
Note: The estimates were from a linear mixed effect model with the natural log-transformed PK parameters as the dependent variable, treatment, sequence, and period as fixed effects, and subject nested within sequence as a random effect.
a Treatment A: Acetaminophen Injection (1000 mg IV infusion; B. Braun Medical Inc.) and Treatment B: Ofirmev® (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).
Source: End-of-Text Tables 14.2.3.1, 14.2.3.2, and 14.2.3.3.

The bioequivalence analysis results indicated that Acetaminophen Injection 1000 mg and Ofirmev® 1000 mg were bioequivalent; the 90% CIs for the geometric least squares mean ratios of AUC0-t, AUC0-inf, and Cmax for all analytes were within the 80% to 125% range.

#### *2.2.2.3 Request for in vivo bioequivalence waiver for the 500 mg/50 mL strength*

The Applicant requested a biowaiver for the 500 mg/50 mL strength in accordance with 21 CFR 320.22(d)(2), which has the same concentration as the 1000 mg/100 mL configuration except for

a different volume. The Biopharmaceutics Team's input is required in order to assess the adequacy of the biowaiver.

## 2.3 Outstanding Issues

There are no outstanding issues.

## 2.4 Summary of Labeling Recommendations

The proposed Label for APAP Injection is based on Ofirmev Label. The majority of information is retained from Ofirmev. *There were no changes proposed to Section 12, Clinical Pharmacology; no pharmacokinetic information has been updated in the proposed Label from the Study HC-G-H-1506.* This is acceptable from clinical pharmacology perspective.

The noticeable differences in APAP Injection Label are 1) removal of (b) (4) (b) (4) (b) (4) (b) (4) 2) instruction for administration due to PAB container in product presentation (Section 2.3); 3) addition of 500 mg/50 mL dosage strength presentation; 4) product description to included 500 mg/50 mL and PAB container information (Section 11).

Acetaminophen Injection proposed label compared to Ofirmev

2.2 Recommended Dosage: Adults and Adolescents

| **Age group** | **Dose given every 4 hours** | **Dose given every 6 hours** | **Maximum single dose** | **Maximum total daily dose of acetaminophen (by all routes)** |
|---|---|---|---|---|
| **Adults and adolescents (13 years and older) weighing greater than or equal to 50 kg** | 650 mg | 1000 mg | 1000 mg | 4000 mg in 24 hours |
| **Adults and adolescents (13 years and older) weighing less than 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) |

2.3 Recommended Dosage: Children

| **Age group** | **Dose given every 4 hours** | **Dose given every 6 hours** | **Maximum single dose** | **Maximum total daily dose of acetaminophen (by all routes)** |
|---|---|---|---|---|
| **Children 2 to 12 years of age** | 12.5 mg/kg | 15 mg/kg | 15 mg/kg (up to 750 mg) | 75 mg/kg in 24 hours (up to 3750 mg) |

# 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

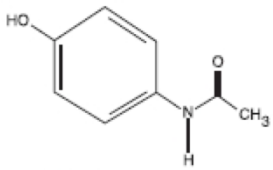
## 3.1 Overview of the Product and Regulatory Background

### *3.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substances in Acetaminophen Injection?*

Acetaminophen Injection in the Partial Additive Bag (PAB®*) Container (with administration port and blocked medication port) contains APAP as an active ingredient.

Acetaminophen, USP: The chemical name for APAP is N-acetyl-p-aminophenol. Its chemical formula is: C8H9NO2. APAP is an odorless, white crystalline powder with a slightly bitter taste. The molecular weight of is 151.16. It is soluble in boiling water and freely soluble in alcohol and has a melting point of 168 to 172°C. Acetaminophen structural formula is shown in Figure 1.

Figure 1 Acetaminophen structural formula




Acetaminophen

$C_8H_9NO_2$ MW = 151.16

(Source: m3/32-body-data/32s-drug-sub/all-manufacturer/32s1-gen-info/structure.pdf)

See Table 5 below for the physico-chemical properties of acetaminophen. See Table 6 below for a solubility profile of acetaminophen in common solvents.

Table 5: Physico-Chemical Properties of Acetaminophen

| | |
|---|---|
| pH of the solution (b) (4) | (b) (4) |
| pH of the solution (b) (4) | (b) (4) |
| Melting Point | 168 to 172°C |
| pKa (b) (4) | 9.5 |
| pKa (b) (4) | 9.7 |
| Specific Gravity (b) (4) | 1.29 |
| Partition coefficient (b) (4) | Octanol / water partition coefficient as log Pow: |
| Hygroscopicity (b) (4) | Hygroscopic |
| Polymorphism, Isomerism and Chirality (b) (4) | No Polymorphism, Isomers or Chirality |

(Source: m3/32-body-data/32s-drug-sub/all-manufacturer/32s1-gen-info/general-properties.pdf)

Table 6: Solubility of Acetaminophen in Common Solvents (Reference [redacted])

| Solvent | Concentration (w/v) | Temperature (°C) |
|---|---|---|
| Water | 12mg/mL | 22°C |
| Water | 80mg/mL | 70°C |
| Methanol | 216mg/mL | 22°C |
| Isopropanol | 100mg/mL | 22°C |
| Ethanol | 150mg/mL | 20°C |

(Source: m3/32-body-data/32s-drug-sub/all-manufacturer/32s1-gen-info/general-properties.pdf)

### *3.1.2 APAP Injection formulation*

The proposed dosage form is a solution for intravenous infusion with two different configurations: 1000 mg/100 mL (10 mg/mL) and 500 mg acetaminophen in 50 mL (10 mg/mL). Acetaminophen Injection was developed under IND 111161. [*Note: There are other FDA approved NDA (e.g., 16730, 17464, 18900, 19212, etc.) and ANDA (e.g., 62814, 76414, etc.) products packaged in the PAB Containers.]

The composition of the to-be marketed formulation is presented in Table 7 below.

Table 7 Composition of APAP Injection per 50 and 100 mL

| Component | Grade | Function | 500 mg/50 mL Concentration (g/50 mL) | 1000 mg/100 mL Concentration (g/100 mL) |
|---|---|---|---|---|
| Acetaminophen | USP | Active Ingredient | 0.50 | 1.00 |
| Mannitol | USP | [redacted] | 1.90 | 3.80 |
| Sodium citrate dihydrate | USP | [redacted] | 0.015 | 0.03 |
| Glacial acetic acid | USP | pH Adjuster | [redacted] | [redacted] |
| Water for Injection (WFI) | USP | [redacted] | QS[2] | QS[2] |

[redacted]

(Source: m3/32-body-data/32p-drug-prod/all-injection/32p1-desc-comp/description-and-composition-1.pdf)

A comparison of Acetaminophen Injection with Ofirmev's formulation can be found in Table 8.

Table 8 Formulation Comparison of IVA (BBM) vs Ofirmev®

| Name of ingredient | Name | APAP Injection | Ofirmev® |
|---|---|---|---|
| | Description | Acetaminophen (10 mg/mL) Solution in PAB® Container | Acetaminophen (10 mg/mL) Solution in Glass Vials |
| | NDC No: | 0264-4500-80 & 0264-4500-90 | 43825-102-01 |
| | Container type | Plastic (PAB®) | Glass vials |
| | Container size | 100 mL & 150 mL | 100 mL |
| | Fill volume | 50 mL & 100 mL | 100 mL |
| | Function | 100 mL contains: (w/v, %) | 100 mL contains: (w/v, %) |
| Acetaminophen USP, g | Active | 1.00 | 1.00 |
| Sodium Citrate $2H_2O$ USP, g | (b) (4) | 0.03 | N/A |
| Mannitol USP, g | | 3.80 | 3.85 |
| Glacial Acetic Acid USP, g* | pH Adjuster | (b) (4) | N/A |
| Water for Injection, g** | (b) (4) | QS | QS |
| HCl, g* | | N/A | pH Adjuster |
| NaOH, g* | | N/A | pH Adjuster |
| Cysteine HCl, $H_2O$, USP, mg | | N/A | 25.0 |
| $Na_2HPO_4$, USP, mg | | N/A | 10.4 |
| pH | | (b) (4) | ~5.5 |
| (b) (4) | | | |
| Osmolality, mOs/kg | | ~ 290 | ~290 |

(b) (6)

(Source: m3/32-body-data/32p-drug-prod/all-injection/32p1-desc-comp/description-and-composition-2.pdf)

Acetaminophen Injection TBM formulation used in PK study HC-G-H-1506, 1000 mg in 100 mL, (B. Braun Medical Inc.; batch number STBJ5J677) information is listed below (Tables 9 and 10).

Table 9 Batch Formula - Stability Batches Acetaminophen Injection

| Component | Grade | BBM Batch# STBJ5H721 | BBM Batch# STBJ5H722 | BBM Batch# STBJ5H723 | BBM Batch# STBJ5H724 | BBM Batch# STBJ5H725 | BBM Batch# STBJ5H726 | BBM Batch# STBJ5H728 | BBM Batch# STBJ5J677 | BBM Batch# S6C651 | BBM Batch# S6C652 | BBM Batch# S6C653 | BBM Batch# S6C683 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acetaminophen | USP | (b) (4) | | | | | | | | | | | |
| Mannitol | USP | | | | | | | | | | | | |
| Sodium Citrate Dihydrate | USP | | | | | | | | | | | | |
| Glacial Acetic Acid[1] | NF | | | | | | | | | | | | |
| Water for Injection (WFI)[2] | USP | | | | | | | | | | | | |

(Source: m3/32-body-data/32p-drug-prod/all-injection/32p3-manuf/batch-formula.pdf)

Table 10 Acetaminophen Stability Batch Information

| Batch | Batch # | Cat # | API Supplier | Strength | Tank Size (L) | PAB® Container Fill/Size | Manufacture Date |
|---|---|---|---|---|---|---|---|
| 1 | STBJ5H721 | (b) (4) | | 500 mg/50 mL | (b) (4) | | 06/24/2015 |
| 2 | STBJ5H722 | | | 500 mg/50 mL | | 50/100mL | 06/24/2015 |
| 3 | STBJ5H723 | | (b) (4) | 500 mg/50 mL | | | 06/25/2015 |
| 4 | STBJ5H725 | | | 1000 mg/100 mL | | | 06/26/2015 |
| 5 | STBJ5H726 | | | 1000 mg/100 mL | | 100/150mL | 06/26/2015 |
| 6 | STBJ5J677 | | | 1000 mg/100 mL | | | 07/14/2015 |
| 7 | STBJ5H724 | | | 500 mg/50 mL | | 50/100mL | 06/25/2015 |
| 8 | STBJ5H728 | | (b) (4) | 1000 mg/100 mL | | 100/150mL | 06/29/2015 |
| 9 | S6C651 | | | 1000 mg/100 mL | | 100/150mL | 03/02/2016 |
| 10 | S6C652 | | | 500 mg/50 mL | | 50/100mL | 03/02/2016 |
| 11 | S6C653 | | | 500 mg/50 mL | | 50/100mL | 03/03/2016 |
| 12 | S6C683 | | | 1000 mg/100 mL | | 100/150mL | 03/01/2016 |

(Source: m3/32-body-data/32p-drug-prod/all-injection/32p5-cont-drug-prod/32p54-batch-analys/batch-analyses-1.pdf)

### *3.1.4 What is proposed route of administration for Acetaminophen Injection?*

Acetaminophen Injection is proposed to be administered via an intravenous route.

## 3.2 General Pharmacology and Pharmacokinetic Characteristics

### *3.2.1 What are the proposed mechanism(s) of actions and known clinical pharmacology information for acetaminophen?*

The following information has been obtained from Ofirmev Label with respect acetaminophen. Ofirmev's active ingredient is acetaminophen. [Source: Ofirmev®; 12.2 Pharmacodynamics; N 22450].

12.2 Pharmacodynamics

Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human studies. Single doses of Ofirmev up to 3000 mg and repeated doses of 1000 mg every 6 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation. Acetaminophen does not have any immediate or delayed effects on small-vessel hemostasis. Clinical studies of both healthy subjects and patients with hemophilia showed no significant changes in bleeding time after receiving multiple doses of oral acetaminophen.

## 3.3 Clinical Pharmacology Review Questions

### *3.3.1 To what extent does the available clinical pharmacology information from bioequivalence study HC-G-H-1506 provide pivotal or supportive evidence?*

*Summary: Following a single IV infusion of Acetaminophen Injection 1000 mg or Ofirmev® 1000 mg, mean plasma concentrations of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide were similar between treatments. Acetaminophen Injection 1000 mg is bioequivalent to Ofirmev® 1000 mg, as assessed by AUC0-t, AUC0-inf, and Cmax for plasma acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide (the 90% CIs for the geometric least squares means ratios for AUC0-t, AUC0-inf, and Cmax for all analytes were within the predefined bioequivalence acceptance limits of 80% to 125%).*

*Reviewer comment: The results from Study HC-G-H-1506 are acceptable.*

As indicated previously the basis for submission is reliance on the previous findings of safety and efficacy of Ofirmev® (Mallinckrodt NDA 22450) by providing bioequivalence information only (acetaminophen, acetaminophen sulfate and acetaminophen glucuronide exposures). No other studies were conducted.

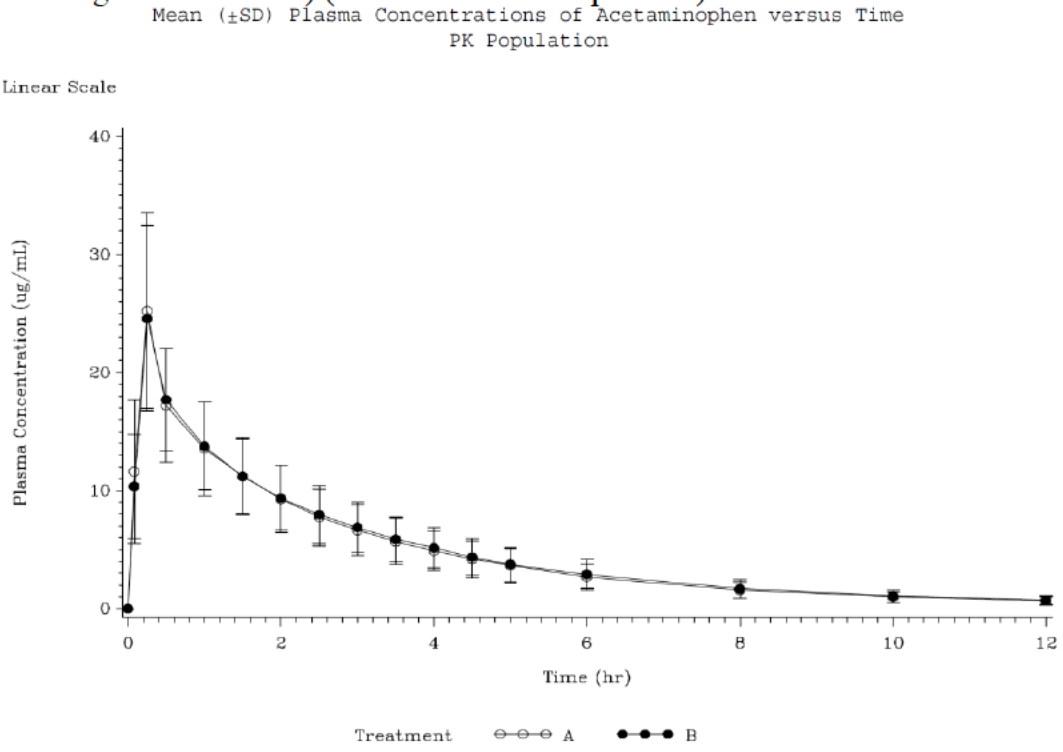
Study HC-G-H-1506 was a Phase 1, open-label, randomized, single-dose, 2-way crossover study to determine the bioequivalence of single IV administration of 1000 mg of Acetaminophen Injection (B. Braun Medical Inc.; batch number STBJ5J677) versus 1000 mg of Ofirmev® (acetaminophen) Injection (Mallinckrodt; lot number AAC3617) in healthy adult subjects.

Each drug was administered as intravenous infusions over 15 minutes, following an overnight fast of at least 10 hours. Subjects fasted for an additional 4 hours after the start of dosing. Each treatment period was separated by a washout interval of at least 6 days. Thirty subjects participated, which all were included in the safety population and 28 subjects included in the PK population. Blood samples (4.0 mL) for plasma PK analysis of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide were collected at pre-dose, 5, 15, and 30 minutes, and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 hours after dosing. The 15-minute collection occurred immediately after the end of the IV infusion. Blood was obtained by direct venipuncture in the arm or via an optional indwelling cannula in the non-infusion arm.

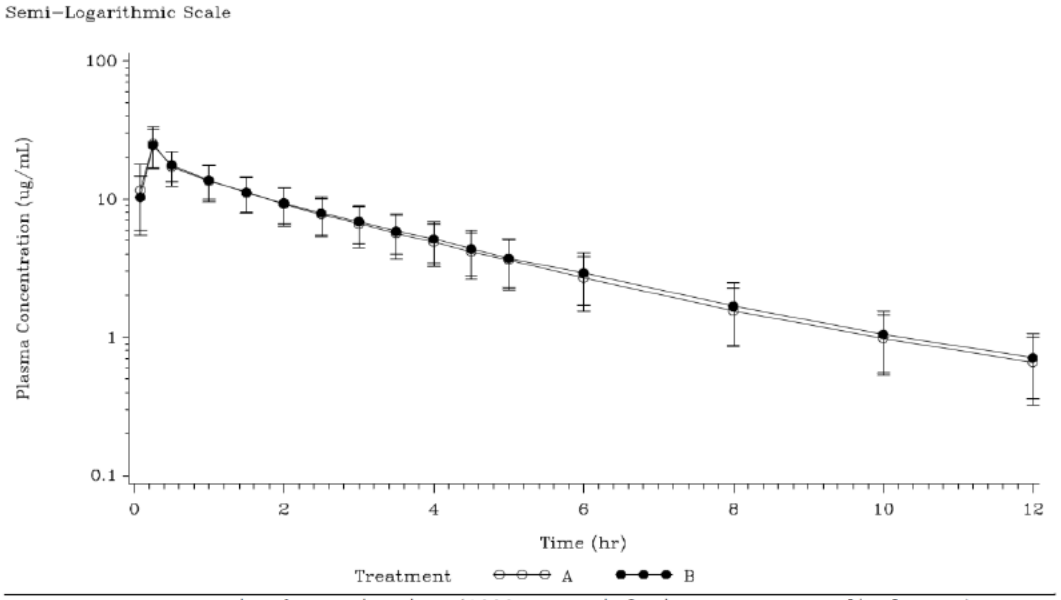
Overall, subjects' age ranged from 19 to 51 years (overall mean age: 33.0 years). The overall mean body mass index was 25.58 kg/m$^2$. The majority of subjects were white (76.7%), female (63.3%), and not Hispanic or Latino (60.0%). Two subjects discontinued from the study and were not included in the PK population; Subject (b) (6) discontinued the study due to withdrawal of consent and Subject (b) (6) discontinued the study due to an unrelated serious adverse event (SAE) of rhabdomyolysis that required hospitalization.

The mean (±SD) plasma concentrations profiles of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide are presented in Figures 2, 3, and 4, respectively.

Figure 2 Mean (±SD) Plasma Concentrations of Acetaminophen Versus Time (Linear and Semilogarithmic Scales) (Pharmacokinetic Population)



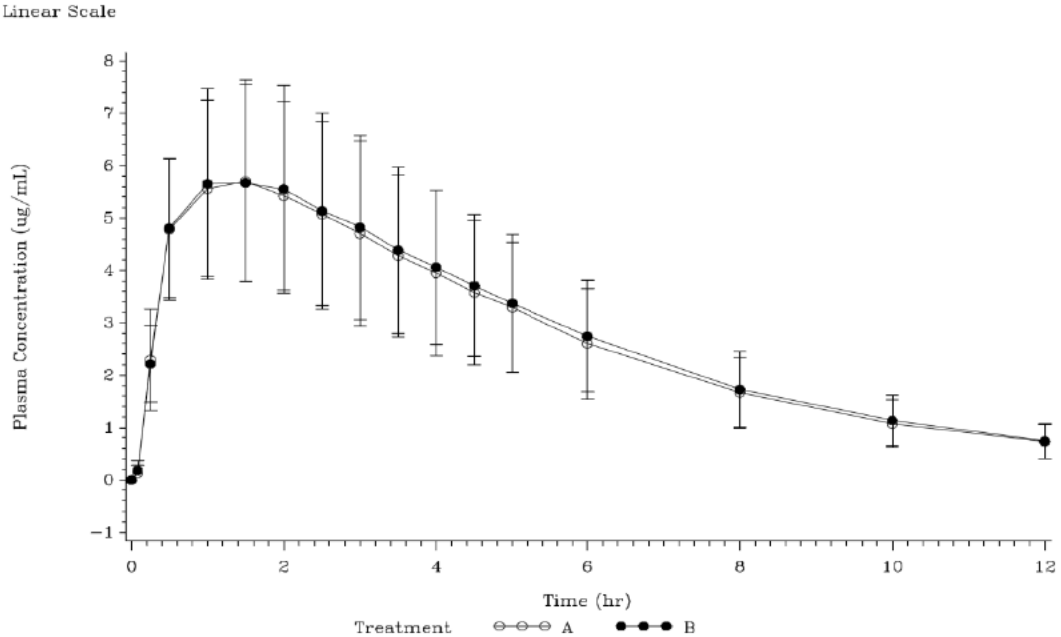

Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population




Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population
Source Data: Table 14.2.1.1

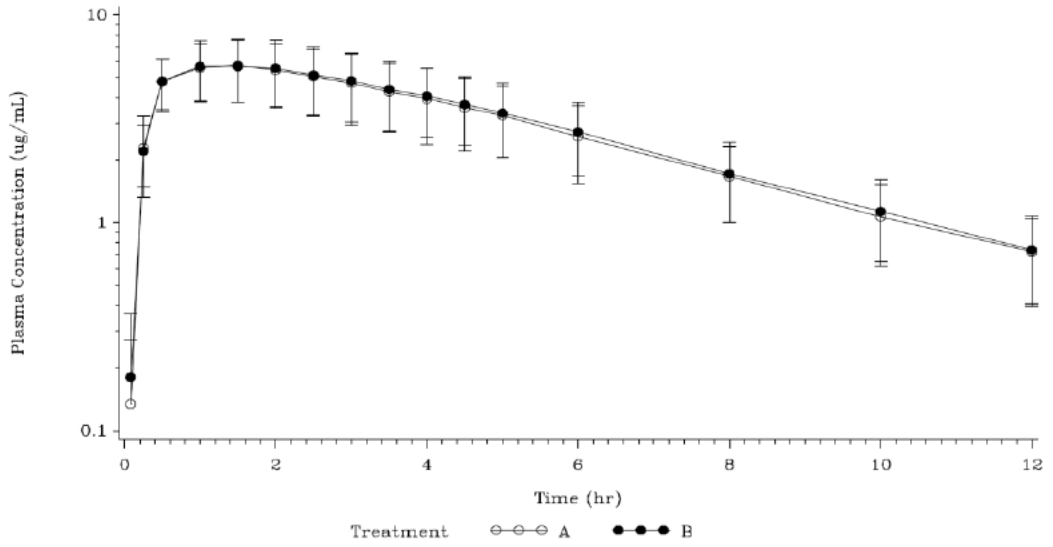
Figure 3 Mean (±SD) Plasma Concentrations of Acetaminophen Sulfate Versus Time (Linear and Semilogarithmic Scales) (Pharmacokinetic Population)

Mean (±SD) Plasma Concentrations of Acetaminophen Sulfate versus Time
PK Population




Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population

Semi-Logarithmic Scale

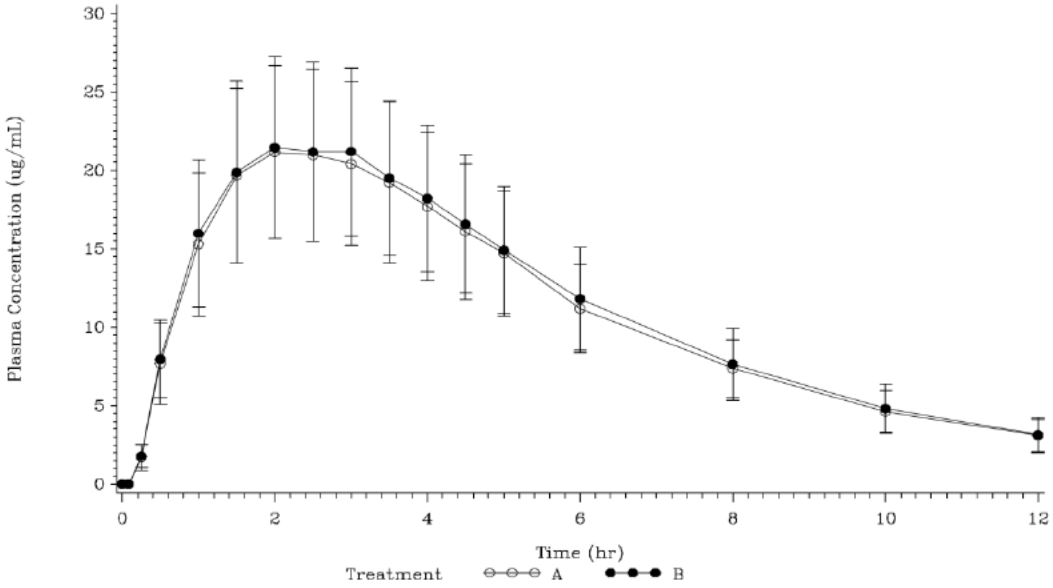



Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population
Source Data: Table 14.2.1.2

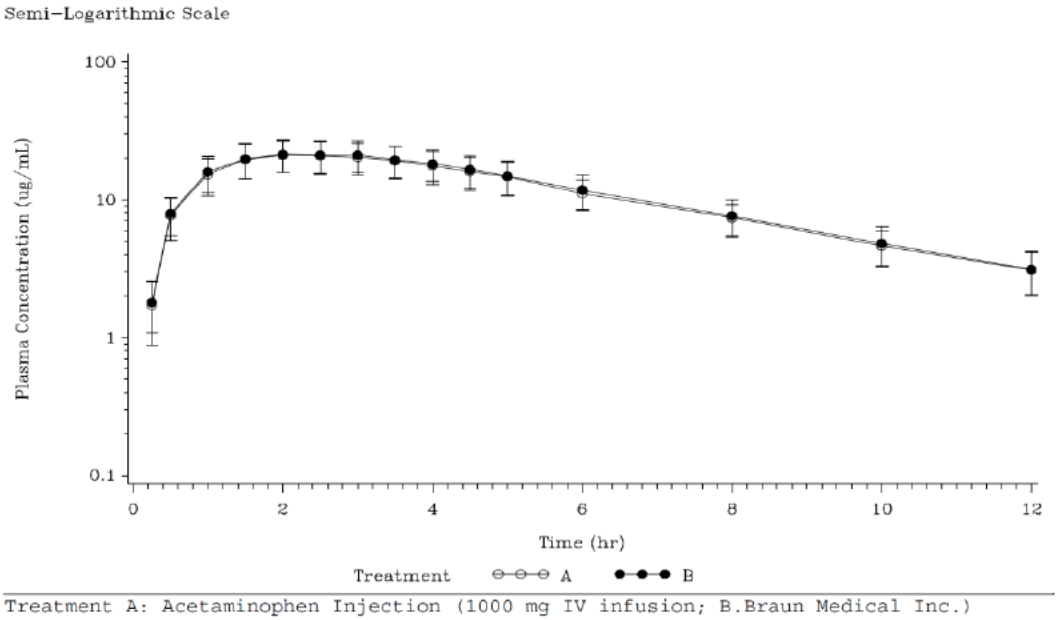
Figure 4 Mean (±SD) Plasma Concentrations of Acetaminophen Glucuronide Versus Time (Linear and Semilogarithmic Scales) (Pharmacokinetic Population)

Mean (±SD) Plasma Concentrations of Acetaminophen Glucuronide versus Time
PK Population

Linear Scale




Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population




Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmaceuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population
Source Data: Table 14.2.1.3

Plasma pharmacokinetic parameters (mean and SD) of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide are presented in Tables 11, 12, and 13, respectively.

Table 11 Mean (SD) Plasma Pharmacokinetic Parameters of Acetaminophen (Pharmacokinetic Population)

| Parameter (unit) | Acetaminophen Injection 1000 mg (N = 28) | Ofirmev® 1000 mg (N = 28) |
|---|---|---|
| $AUC_{0-t}$ (µg•h/mL) | 57.23 (17.33) | 58.77 (17.0) |
| $AUC_{0-inf}$ (µg•h/mL) | 59.91 (18.60) | 61.68 (18.34) |
| $C_{max}$ (µg/mL) | 24.92 (8.40) | 24.98 (7.57) |
| $T_{max}$ (h)[a] | 0.25 (0.08, 0.50) | 0.250 (0.25, 0.50) |
| $t_{1/2}$ (h) | 2.67 (0.36) | 2.72 (0.39) |
| CL (L/h) | 17.72 (5.37) | 17.38 (4.40) |
| $V_z$ (L) | 67.69 (20.59) | 67.49 (17.04) |

Abbreviations: SD: standard deviation; h: hours; N: number of subjects in the population; PK: pharmacokinetic.
a For Tmax, the median (minimum, maximum) values are presented.
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population.
Source: End-of-Text Table 14.2.2.1.

The mean acetaminophen total exposure (AUC0-t and AUC0-inf) was similar for both treatments. Acetaminophen mean AUC0-t and AUC0-inf values for Acetaminophen Injection were approximately 57 µg•h/mL and 60 µg•h/mL, respectively. Acetaminophen mean Cmax was approximately 25.0 µg/mL for both Acetaminophen Injection and Ofirmev®, with a median Tmax of 0.25 hours for both treatments. Acetaminophen mean elimination t1/2 was

approximately 2.7 hours for both treatments. Acetaminophen mean CL was similar for Acetaminophen Injection and Ofirmev®, with a value of approximately 17 L/h.

Table 12 Mean (SD) Plasma Pharmacokinetic Parameters of Acetaminophen Sulfate (Pharmacokinetic Population)

| Parameter (unit) | Acetaminophen Injection 1000 mg (N = 28) | Ofirmev® 1000 mg (N = 28) |
|---|---|---|
| $AUC_{0-t}$ (µg•h/mL) | 34.01 (11.91) | 34.91 (12.16) |
| $AUC_{0-inf}$ (µg•h/mL) | 37.49 (13.36) | 38.47 (13.60) |
| $C_{max}$ (µg/mL) | 5.85 (1.87) | 5.88 (1.93) |
| $T_{max}$ (h)[a] | 1.50 (0.50, 2.50) | 1.50 (0.50, 3.00) |
| $t_{1/2}$ (h) | 3.22 (0.43) | 3.23 (0.44) |

Abbreviations: SD: standard deviation; h: hours; N: number of subjects in the population; PK: pharmacokinetic.
a For Tmax, the median (minimum, maximum) values are presented.
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population.
Source: End-of-Text Table 14.2.2.2.

The mean acetaminophen sulfate total exposure (AUC0-t and AUC0-inf) was similar for both treatments. Acetaminophen sulfate mean AUC0-t and AUC0-inf for Acetaminophen Injection were approximately 34 µg•h/mL and 38 µg•h/mL, respectively. Acetaminophen sulfate mean Cmax was approximately 5.9 µg/mL for both Acetaminophen Injection and Ofirmev®, with a median Tmax of 1.5 hours for both treatments. Acetaminophen sulfate mean elimination t1/2 was approximately 3.2 hours for both treatments.

Table 13 Mean (SD) Plasma Pharmacokinetic Parameters of Acetaminophen Glucuronide (Pharmacokinetic Population)

| Parameter (unit) | Acetaminophen Injection 1000 mg (N = 28) | Ofirmev® 1000 mg (N = 28) |
|---|---|---|
| $AUC_{0-t}$ (µg•h/mL) | 133.50 (32.35) | 137.38 (34.75) |
| $AUC_{0-inf}$ (µg•h/mL) | 148.31 (36.15) | 152.03 (39.28) |
| $C_{max}$ (µg/mL) | 22.01 (5.49) | 22.50 (5.6) |
| $T_{max}$ (h)[a] | 2.25 (1.50, 3.50) | 2.50 (1.50, 4.50) |
| $t_{1/2}$ (h) | 3.22 (0.50) | 3.16 (0.45) |

Abbreviations: SD: standard deviation; h: hours; N: number of subjects in the population; PK: pharmacokinetic.
a For Tmax, the median (minimum, maximum) values are presented.
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population.
Source: End-of-Text Table 14.2.2.3.

The mean acetaminophen glucuronide total exposure (AUC0-t and AUC0-inf) was similar for both treatments. Acetaminophen glucuronide mean AUC0-t and AUC0-inf for Acetaminophen Injection were approximately 134 µg•h/mL and 148 µg•h/mL, respectively. Acetaminophen glucuronide mean Cmax was approximately 22 µg/mL for both treatments, with a median Tmax of 2.25 and 2.50 h for Acetaminophen Injection and Ofirmev®, respectively. Acetaminophen glucuronide mean elimination t1/2 was approximately 3.2 hours for both treatments.

Statistical analysis of the log-transformed plasma PK parameters of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide is presented in Table 14.

Table 14 Statistical analysis of pharmacokinetic parameters of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide: geometric LS means and 90% Confidence interval

| Parameter (unit) | Treatment a | N | Geometric LS Means | Ratio (%) of Geometric LS Means (A/Ba) | 90% Confidence Interval of the Ratio (%) |
|---|---|---|---|---|---|
| Acetaminophen | | | | | |
| $AUC_{0-t}$ (µg•h/mL) | A | 28 | 54.92 | 96.81 | (95.14, 98.50) |
| | B | 28 | 56.74 | | |
| $AUC_{0-inf}$ (µg•h/mL) | A | 28 | 57.37 | 96.52 | (94.75, 98.33) |
| | B | 28 | 59.43 | | |
| $C_{max}$ (µg/mL) | A | 28 | 23.47 | 97.91 | (91.33, 104.96) |
| | B | 28 | 23.98 | | |
| Acetaminophen Sulfate | | | | | |
| AUC0-t (µg•h/mL) | A | 28 | 31.82 | 97.21 | (95.02, 99.46) |
| | B | 28 | 32.73 | | |
| AUC0-inf (µg•h/mL) | A | 28 | 34.99 | 97.22 | (94.70, 99.81) |
| | B | 28 | 36.00 | | |
| Cmax (µg/mL) | A | 28 | 5.52 | 99.86 | (96.89, 102.91) |
| | B | 28 | 5.53 | | |
| Acetaminophen Glucuronide | | | | | |
| AUC0-t (µg•h/mL) | A | 28 | 129.35 | 97.56 | (95.24, 99.94) |
| | B | 28 | 132.58 | | |
| AUC0-inf (µg•h/mL) | A | 28 | 143.71 | 97.98 | (95.33, 100.70) |
| | B | 28 | 146.68 | | |
| Cmax (µg/mL) | A | 28 | 21.22 | 97.94 | (94.63, 101.37) |
| | B | 28 | 21.66 | | |

Abbreviations: IV: intravenous; LS: least squares; N: number of subjects in the population; PK: pharmacokinetic.
Note: The estimates were from a linear mixed effect model with the natural log-transformed PK parameters as the dependent variable, treatment, sequence, and period as fixed effects, and subject nested within sequence as a random effect.
a Treatment A: Acetaminophen Injection (1000 mg IV infusion; B. Braun Medical Inc.) and Treatment B: Ofirmev® (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).
Source: End-of-Text Tables 14.2.3.1, 14.2.3.2, and 14.2.3.3.

The bioequivalence analysis results indicated that Acetaminophen Injection 1000 mg and Ofirmev® 1000 mg were bioequivalent; the 90% CIs for the geometric least squares mean ratios of AUC0-t, AUC0-inf, and Cmax for all analytes were within the 80% to 125% range.

### *3.3.4 What are the characteristics of the dose-systemic exposure relationships for safety?*

No formal PK/PD studies were conducted in this NDA to establish the relationship between exposure and safety.

# 4. APPENDICES

## 4.1 Summary of Bioanalytical Method Validation and Performance

Human plasma samples were analyzed at (b) (4) using validated HPLC with MS/MS method for APAP, APAP sulfate and APAP glucuronide in human plasma. The Applicant stated that 982 plasma samples containing dipotassium EDTA were received frozen from (b) (4) on 2/2/16. The samples were stored frozen at -20°C. Pharmacokinetic (PK) samples were analyzed according to (b) (4) Method P852.03, entitled "Determination of Acetaminophen and Metabolites in Human Plasma by LC/MS/MS" (validated under Project Code "AEBW"). All samples were analyzed within the 141 days demonstrated long-term storage stability in human plasma containing dipotassium EDTA at -20°C.

Analytical information according to the application:

Title: Quantitation of Acetaminophen, Acetaminophen Sulfate, and Acetaminophen Glucuronide in Human Plasma via HPLC with MS/MS Detection

Calibration standard concentrations for acetaminophen and acetaminophen sulfate were 0.100, 0.200, 0.320, 1.20, 4.00, 15.0, 40.0, and 50.0 µg/mL. Calibration standard concentrations for acetaminophen glucuronide were 0.500, 0.800, 1.50, 4.00, 12.0, 38.0, 80.0, and 100 µg/mL. Quality Control (QC) concentrations for acetaminophen and acetaminophen sulfate were 0.250, 0.600, 2.40, 8.00, and 37.5 µg/mL. QC concentrations for acetaminophen glucuronide were 1.00, 2.50, 7.50, 20.0, and 75.0 µg/mL. Calibration standards are acceptable if the back-calculated concentrations are within twenty percent (20.0%) of the theoretical concentration at the intended lower limit of quantitation (LLOQ) and within fifteen percent (15.0%) of the theoretical concentration for all other levels. For acetaminophen and acetaminophen sulfate each calibration curve was calculated using a linear (1/concentration$^2$ weighted) least-squares regression algorithm. For acetaminophen glucuronide each calibration curve was calculated using a linear (1/concentration weighted) least-squares regression algorithm. QCs are acceptable if the calculated concentrations are within fifteen percent (15.0%) of the theoretical value. An analytical run is considered acceptable when two-thirds of the quality controls analyzed in the run meet the acceptance criteria. In addition, at least 50% of the quality control results analyzed for each level must be within the acceptance limits for a run to be acceptable.

Back-calculated calibration data are found in Tables 1A through 1C for APAP, APAP sulfate and APAP glucuronide, respectively. Precision and accuracy were evaluated by replicate analyses of human plasma quality control pools prepared at five concentrations spanning the calibration range. Precision was measured as the percent coefficient of variation (%C.V.) of the set of values for each pool. Accuracy was expressed as the percent difference of the mean value

for each pool from the theoretical concentration. Inter-assay data are presented in Tables 2A through 2C for APAP, APAP sulfate and APAP glucuronide, respectively.

Table 1A Average Back-calculated Calibration Standards for Acetaminophen

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| Run ID | CAL 1 (µg/mL) | CAL 2 (µg/mL) | CAL 3 (µg/mL) | CAL 4 (µg/mL) | CAL 5 (µg/mL) | CAL 6 (µg/mL) | CAL 7 (µg/mL) | CAL 8 (µg/mL) |
|---|---|---|---|---|---|---|---|---|
| 1AIZT1 | 0.0952 | 0.201 | 0.344 | 1.25 | 4.03 | 15.1 | 38.4 | 46.7 |
| | 0.0995 | 0.206 | 0.324 | 1.25 | 4.16 | 15.1 | 37.9 | 47.1 |
| 2AIZT1 | 0.0957 | 0.217 | 0.330 | 1.29 | 3.89 | 15.0 | 36.7 | 48.7 |
| | 0.0968 | 0.205 | 0.326 | 1.19 | 4.09 | 14.9 | 40.1 | 48.7 |
| 3AIZT1 | 0.0912 | 0.201 | 0.328 | 1.25 | 4.18 | 14.3 | 39.2 | 46.1 |
| | 0.103 | 0.210 | 0.336 | 1.24 | 4.11 | 15.1 | 38.3 | 48.0 |
| 4AIZT1 | 0.109 | 0.189 | 0.324 | 1.23 | 4.23 | 15.4 | 38.5 | 50.5 |
| | 0.0949 | 0.192 | 0.320 | 1.20 | 4.06 | 15.0 | 39.1 | 48.5 |
| 5AIZT1 | 0.102 | 0.206 | 0.328 | 1.19 | 4.12 | 15.2 | 37.6 | 49.7 |
| | 0.0950 | 0.203 | 0.320 | 1.21 | 4.00 | 15.0 | 40.4 | 48.5 |
| 6AIZT1 | 0.100 | 0.197 | 0.330 | 1.22 | 4.09 | 15.0 | 39.3 | 47.6 |
| | 0.0980 | 0.203 | 0.323 | 1.27 | 4.16 | 14.9 | 38.0 | 48.6 |
| 7AIZT1 | 0.104 | 0.191 | 0.327 | 1.18 | 4.13 | 14.9 | 40.7 | 49.8 |
| | 0.0955 | 0.204 | 0.327 | 1.20 | 4.06 | 14.5 | 39.7 | 49.1 |
| 8AIZT1 | 0.102 | 0.203 | 0.324 | 1.25 | 4.09 | 15.2 | 37.5 | 48.1 |
| | 0.0924 | 0.212 | 0.331 | 1.25 | 4.14 | 15.0 | 36.4 | 48.7 |
| 9AIZT1 | 0.101 | 0.180 | 0.320 | 1.17 | 4.06 | 15.0 | 39.6 | 48.8 |
| | 0.101 | 0.203 | 0.336 | 1.25 | 4.03 | 15.1 | 40.1 | 49.7 |
| N | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| Theoretical Concentration | 0.100 | 0.200 | 0.320 | 1.20 | 4.00 | 15.0 | 40.0 | 50.0 |
| Mean | 0.0987 | 0.201 | 0.328 | 1.23 | 4.09 | 15.0 | 38.7 | 48.5 |
| S.D. | 0.00458 | 0.00889 | 0.00620 | 0.0334 | 0.0776 | 0.255 | 1.26 | 1.13 |
| %C.V. | 4.64 | 4.42 | 1.89 | 2.72 | 1.90 | 1.70 | 3.26 | 2.33 |
| % Difference from Theoretical | -1.27 | 0.582 | 2.42 | 2.20 | 2.29 | -0.0624 | -3.14 | -3.01 |

Table 1B Average Back-calculated Calibration Standards for Acetaminophen Sulfate

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| Run ID | CAL 1 (µg/mL) | CAL 2 (µg/mL) | CAL 3 (µg/mL) | CAL 4 (µg/mL) | CAL 5 (µg/mL) | CAL 6 (µg/mL) | CAL 7 (µg/mL) | CAL 8 (µg/mL) |
|---|---|---|---|---|---|---|---|---|
| 1AIZT3 | 0.102 | 0.194 | 0.320 | 1.22 | 3.87 | 15.6 | 39.5 | 48.8 |
| | 0.0970 | 0.208 | 0.319 | 1.25 | 4.13 | 15.3 | 38.1 | 48.2 |
| 2AIZT3 | 0.104 | 0.208 | 0.349 | a | 4.22 | 15.7 | 37.1 | 47.0 |
| | 0.0870 | 0.214 | 0.324 | 1.19 | 3.94 | 15.5 | 39.0 | 46.0 |
| 3AIZT3 | 0.0937 | 0.202 | 0.332 | 1.24 | 4.12 | 14.3 | 40.1 | 46.0 |
| | 0.101 | 0.209 | 0.327 | 1.20 | 4.21 | 15.1 | 39.0 | 48.3 |
| 4AIZT3 | 0.105 | 0.215 | 0.316 | 1.19 | 4.30 | 15.7 | 35.6 | 50.0 |
| | 0.0932 | 0.191 | 0.318 | 1.31 | 4.34 | 14.2 | 38.1 | 46.7 |
| 5AIZT3 | 0.101 | 0.190 | 0.347 | 1.27 | 4.17 | 15.4 | 36.7 | 47.7 |
| | 0.0979 | 0.205 | 0.308 | 1.30 | 4.09 | 15.3 | 38.2 | 45.6 |
| 6AIZT3 | 0.0998 | 0.189 | 0.330 | 1.21 | 4.07 | 15.1 | 38.9 | 47.9 |
| | 0.0989 | 0.207 | 0.328 | 1.26 | 4.14 | 14.9 | 38.0 | 48.9 |
| 7AIZT3 | 0.0948 | 0.179 | 0.354 | 1.26 | 4.23 | 15.3 | 38.2 | 46.3 |
| | 0.105 | 0.203 | 0.327 | 1.28 | 4.39 | 14.0 | 37.6 | 46.3 |
| 8AIZT3 | 0.102 | 0.198 | 0.338 | 1.28 | 4.10 | 15.6 | 37.8 | 48.1 |
| | 0.0957 | 0.197 | 0.326 | 1.25 | 4.13 | 14.4 | 37.5 | 47.6 |
| 9AIZT3 | 0.0961 | 0.211 | 0.348 | 1.31 | 4.25 | 14.6 | 38.3 | 47.7 |
| | 0.0952 | 0.193 | 0.355 | 1.27 | 4.03 | 13.9 | 37.2 | 45.4 |
| N | 18 | 18 | 18 | 17 | 18 | 18 | 18 | 18 |
| Theoretical Concentration | 0.100 | 0.200 | 0.320 | 1.20 | 4.00 | 15.0 | 40.0 | 50.0 |
| Mean | 0.0983 | 0.201 | 0.331 | 1.25 | 4.15 | 15.0 | 38.1 | 47.4 |
| S.D. | 0.00470 | 0.00999 | 0.0140 | 0.0404 | 0.130 | 0.610 | 1.06 | 1.27 |
| %C.V. | 4.79 | 4.98 | 4.21 | 3.23 | 3.13 | 4.07 | 2.78 | 2.69 |
| % Difference from Theoretical | -1.70 | 0.324 | 3.58 | 4.44 | 3.82 | -0.0771 | -4.86 | -5.27 |

Legend:
a Excluded from calculations due to unacceptable quantitation per SOPs.

## Table 1C Average Back-calculated Calibration Standards for Acetaminophen Glucuronide

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| Run ID | CAL 1 (µg/mL) | CAL 2 (µg/mL) | CAL 3 (µg/mL) | CAL 4 (µg/mL) | CAL 5 (µg/mL) | CAL 6 (µg/mL) | CAL 7 (µg/mL) | CAL 8 (µg/mL) |
|---|---|---|---|---|---|---|---|---|
| 1AIZT2 | 0.453 | 0.775 | 1.50 | 4.28 | 12.3 | 40.2 | 81.8 | 98.8 |
| | 0.463 | 0.784 | 1.49 | 4.19 | 12.5 | 39.2 | 78.0 | 96.8 |
| 2AIZT2 | 0.439 | 0.818 | 1.71 | a | 12.6 | 40.3 | 79.5 | 99.1 |
| | 0.464 | 0.780 | 1.45 | 3.99 | 12.0 | 38.8 | 82.2 | 95.5 |
| 3AIZT2 | a | 0.730 | 1.53 | 4.04 | 12.9 | 38.4 | 84.4 | 93.5 |
| | 0.460 | 0.761 | 1.52 | 4.03 | 12.6 | 40.1 | 79.8 | 98.3 |
| 4AIZT2 | 0.481 | 0.790 | 1.53 | 4.14 | 12.6 | 41.6 | 78.1 | 104 |
| | 0.447 | 0.766 | 1.56 | 3.89 | 12.5 | 38.1 | 79.8 | 93.7 |
| 5AIZT2 | 0.450 | 0.753 | 1.54 | 4.36 | 12.9 | 40.9 | 77.5 | 98.6 |
| | 0.457 | a | 1.40 | 4.10 | 12.6 | 39.1 | 81.4 | 96.7 |
| 6AIZT2 | 0.431 | 0.730 | 1.53 | 4.14 | 12.8 | 39.6 | 82.5 | 97.0 |
| | 0.436 | 0.822 | 1.52 | 4.27 | 13.1 | 39.9 | 77.7 | 97.2 |
| 7AIZT2 | 0.472 | 0.709 | 1.61 | 4.24 | 12.9 | 38.4 | 82.0 | 100 |
| | 0.465 | 0.789 | 1.50 | 4.11 | 12.6 | 37.0 | 78.8 | 98.0 |
| 8AIZT2 | 0.466 | 0.745 | 1.59 | 4.51 | 13.2 | 41.4 | 80.8 | 99.7 |
| | 0.404 | 0.735 | 1.46 | 4.21 | 12.7 | 38.9 | 74.5 | 98.3 |
| 9AIZT2 | 0.437 | 0.784 | 1.56 | 4.07 | 12.9 | 39.0 | 86.6 | 97.6 |
| | 0.464 | 0.777 | 1.61 | 4.12 | 12.2 | 36.5 | 80.3 | 94.6 |
| N | 17 | 17 | 18 | 17 | 18 | 18 | 18 | 18 |
| Theoretical Concentration | 0.500 | 0.800 | 1.50 | 4.00 | 12.0 | 38.0 | 80.0 | 100 |
| Mean | 0.452 | 0.768 | 1.53 | 4.16 | 12.7 | 39.3 | 80.3 | 97.6 |
| S.D. | 0.0186 | 0.0309 | 0.0703 | 0.148 | 0.315 | 1.37 | 2.81 | 2.42 |
| %C.V. | 4.12 | 4.03 | 4.58 | 3.56 | 2.49 | 3.49 | 3.50 | 2.48 |
| % Difference from Theoretical | -9.55 | -4.06 | 2.27 | 3.93 | 5.46 | 3.39 | 0.410 | -2.38 |

Legend:
a Excluded from calculations due to unacceptable quantitation per SOPs.

## Table 2A Inter-assay Precision and Accuracy for Acetaminophen

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| Run ID | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|
| 1AIZT1 | 0.230 | 0.565 | 1.72 | 7.67 | 33.4 |
| | 0.263 | 0.607 | 2.42 | 7.79 | 36.9 |
| 2AIZT1 | 0.243 | 0.593 | 2.38 | 7.27 | 36.5 |
| | 0.248 | 0.825 | 2.48 | 8.13 | 36.8 |
| 3AIZT1 | 0.266 | 0.625 | 2.49 | 8.30 | 37.0 |
| | 0.272 | 0.640 | 2.52 | 8.11 | 37.3 |
| 4AIZT1 | 0.254 | 0.624 | 2.47 | 8.09 | 39.1 |
| | 0.271 | 0.660 | 2.48 | 8.10 | 38.7 |
| 5AIZT1 | 0.249 | 0.619 | 2.41 | 8.12 | 36.5 |
| | 0.262 | 0.632 | 2.46 | 8.38 | 36.9 |
| 6AIZT1 | 0.267 | 0.650 | 2.54 | 8.29 | 41.8 |
| | 0.265 | 0.668 | 2.45 | 7.88 | 37.0 |
| 7AIZT1 | 0.253 | 0.629 | 2.44 | 8.13 | 36.7 |
| | 0.260 | 0.611 | 2.42 | 8.08 | 36.3 |
| 8AIZT1 | 0.258 | 0.632 | 2.55 | 8.33 | 38.1 |
| | 0.275 | 0.645 | 2.55 | 8.16 | 37.6 |
| 9AIZT1 | 0.259 | 0.590 | 2.34 | 7.72 | 36.6 |
| | 0.215 | 0.590 | 2.13 | 7.82 | 32.4 |
| N | 18 | 18 | 18 | 18 | 18 |
| Theoretical Concentration | 0.250 | 0.600 | 2.40 | 8.00 | 37.5 |
| Mean | 0.256 | 0.634 | 2.40 | 8.02 | 37.0 |
| S.D. | 0.0151 | 0.0546 | 0.196 | 0.282 | 1.99 |
| %C.V. | 5.91 | 8.61 | 8.15 | 3.51 | 5.37 |
| % Difference from Theoretical | 2.44 | 5.61 | 0.0746 | 0.251 | -1.38 |
| Low Limit | 0.213 | 0.510 | 2.04 | 6.80 | 31.9 |
| High Limit | 0.288 | 0.690 | 2.76 | 9.20 | 43.1 |

## Table 2B Inter-assay Precision and Accuracy for Acetaminophen Sulfate

Report 3065273

| Run ID | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|
| 1AIZT3 | 0.216 | 0.507 | 1.53 | 7.12 | 31.5 |
| | 0.237 | 0.542 | 2.18 | 7.13 | 35.9 |
| 2AIZT3 | 0.238 | 0.582 | 2.38 | 7.69 | 34.8 |
| | 0.237 | 0.788 | 2.35 | 7.60 | 32.7 |
| 3AIZT3 | 0.251 | 0.583 | 2.26 | 7.60 | 35.2 |
| | 0.242 | 0.587 | 2.31 | 7.39 | 36.0 |
| 4AIZT3 | 0.262 | 0.619 | 2.30 | 7.58 | 34.9 |
| | 0.250 | 0.600 | 2.28 | 7.70 | 34.3 |
| 5AIZT3 | 0.228 | 0.607 | 2.24 | 7.51 | 32.4 |
| | 0.248 | 0.590 | 2.28 | 7.31 | 33.7 |
| 6AIZT3 | 0.236 | 0.595 | 2.25 | 7.74 | 39.8 |
| | 0.244 | 0.633 | 2.24 | 7.39 | 34.9 |
| 7AIZT3 | 0.240 | 0.601 | 2.28 | 7.65 | 35.0 |
| | 0.246 | 0.638 | 2.42 | 7.69 | 33.9 |
| 8AIZT3 | 0.244 | 0.597 | 2.36 | 7.83 | 37.5 |
| | 0.258 | 0.598 | 2.44 | 7.58 | 35.9 |
| 9AIZT3 | 0.238 | 0.612 | 2.37 | 7.28 | 32.5 |
| | 0.201 | 0.562 | 1.90 | 7.09 | 28.7 |
| N | 18 | 18 | 18 | 18 | 18 |
| Theoretical Concentration | 0.250 | 0.600 | 2.40 | 8.00 | 37.5 |
| Mean | 0.240 | 0.602 | 2.24 | 7.49 | 34.4 |
| S.D. | 0.0143 | 0.0558 | 0.213 | 0.228 | 2.41 |
| %C.V. | 5.97 | 9.26 | 9.49 | 3.04 | 7.01 |
| % Difference from Theoretical | -4.09 | 0.378 | -6.56 | -6.33 | -8.19 |
| Low Limit | 0.213 | 0.510 | 2.04 | 6.80 | 31.9 |
| High Limit | 0.288 | 0.690 | 2.76 | 9.20 | 43.1 |

Table 2C Inter-assay Precision and Accuracy for Acetaminophen Glucuronide

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| Run ID | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|
| 1AIZT2 | 0.817 | 2.19 | 4.72 | 18.5 | 64.7 |
| | 0.926 | 2.33 | 6.94 | 18.0 | 71.2 |
| 2AIZT2 | 0.964 | 2.30 | 7.34 | 18.5 | 72.0 |
| | 0.960 | 3.10 | 7.50 | 18.9 | 68.4 |
| 3AIZT2 | 0.932 | 2.48 | 7.55 | 19.8 | 71.3 |
| | 0.912 | 2.48 | 7.48 | 19.0 | 72.1 |
| 4AIZT2 | 1.03 | 2.50 | 7.40 | 19.8 | 75.1 |
| | 1.01 | 2.45 | 7.47 | 19.4 | 69.5 |
| 5AIZT2 | 0.885 | 2.51 | 6.99 | 20.1 | 69.2 |
| | 0.925 | 2.46 | 7.18 | 18.3 | 70.5 |
| 6AIZT2 | 0.907 | 2.54 | 7.52 | 20.0 | 81.4 |
| | 0.928 | 2.72 | 7.38 | 19.3 | 70.7 |
| 7AIZT2 | 0.938 | 2.53 | 7.22 | 19.8 | 75.4 |
| | 0.940 | 2.65 | 7.38 | 18.5 | 74.1 |
| 8AIZT2 | 0.924 | 2.59 | 7.88 | 20.9 | 76.8 |
| | 0.968 | 2.53 | 7.83 | 19.8 | 73.8 |
| 9AIZT2 | 0.859 | 2.43 | 7.21 | 19.4 | 72.8 |
| | 0.749 | 2.21 | 6.19 | 18.1 | 58.7 |
| N | 18 | 18 | 18 | 18 | 18 |
| Theoretical Concentration | 1.00 | 2.50 | 7.50 | 20.0 | 75.0 |
| Mean | 0.921 | 2.50 | 7.18 | 19.2 | 71.5 |
| S.D. | 0.0648 | 0.203 | 0.717 | 0.809 | 4.84 |
| %C.V. | 7.03 | 8.13 | 9.99 | 4.21 | 6.77 |
| % Difference from Theoretical | -7.94 | 0.00308 | -4.32 | -3.84 | -4.62 |
| Low Limit | 0.850 | 2.13 | 6.38 | 17.0 | 63.8 |
| High Limit | 1.15 | 2.88 | 8.63 | 23.0 | 86.3 |

Validation of analytical report: AEBW Validation Report History P852 - Quantitation of Acetaminophen, Acetaminophen-Sulphate, and p-Acetamidophenyl-β-D-glucuronide in Human Plasma via HPLC with MS/MS Detection

The Applicant stated that validation experiments were conducted on three separate validation runs beginning on 10/5/06 and ending on 10/12/06. The method is applicable to the quantitation of acetaminophen within a nominal range of 0.100 to 50.0 µg/mL, acetaminophen-sulphate within a nominal range of 0.100 to 50.0 µg/mL; and p-acetamidophenyl-β-D-glucuronide within a nominal range of 0.500 to 100.0 µg/mL. The assay requires a 50-µL human plasma aliquot containing K3EDTA. Samples are kept frozen at approximately -20°C prior to analysis.

Linearity:
Eight calibration standards were used over the nominal concentration range of 0.100 to 50.0 µg/mL for acetaminophen and acetaminophen-sulphate, and, 0.500 to 100.0 µg/mL for p-acetamidophenyl-β-D-glucuronide. A linear-weighted, 1/concentration$^2$, and linear-weighted, 1/concentration (a least-squares regression algorithm was used to plot the peak area) were used for acetaminophen and acetaminophen-sulphate and p-acetamidophenyl-β-D-glucuronide, respectively, of the appropriate analyte to its internal standard versus concentration. Average back-calculated values and reproducibility from each level of the calibration curve are presented in Tables 3A through 3C.

Table 3A Average Back-Calculated Calibration Standards for Acetaminophen

| Run ID | CAL 1 (µg/mL) | CAL 2 (µg/mL) | CAL 3 (µg/mL) | CAL 4 (µg/mL) | CAL 5 (µg/mL) | CAL 6 (µg/mL) | CAL 7 (µg/mL) | CAL 8 (µg/mL) |
|---|---|---|---|---|---|---|---|---|
| 1AEBW1 | 0.100 | 0.201 | 0.327 | 1.24 | 4.14 | 15.0 | 38.3 | 47.6 |
| | 0.0969 | 0.201 | 0.328 | 1.25 | 4.12 | 15.1 | 38.3 | 47.7 |
| 3AEBW1 | 0.0987 | 0.209 | 0.331 | 1.25 | 4.07 | 15.2 | 38.6 | 47.9 |
| | 0.0980 | 0.199 | 0.318 | 1.22 | 4.12 | 14.9 | 38.6 | 48.3 |
| 4AEBW1 | 0.103 | 0.203 | 0.320 | 1.25 | 4.14 | 15.4 | 39.6 | 48.1 |
| | 0.0963 | 0.199 | 0.313 | 1.20 | 4.12 | 15.1 | 38.8 | 48.0 |
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.100 | 0.200 | 0.320 | 1.20 | 4.00 | 15.0 | 40.0 | 50.0 |
| Mean | 0.0989 | 0.202 | 0.323 | 1.23 | 4.12 | 15.1 | 38.7 | 47.9 |
| S.D. | 0.00263 | 0.00369 | 0.00690 | 0.0217 | 0.0264 | 0.168 | 0.469 | 0.248 |
| %C.V. | 2.65 | 1.83 | 2.14 | 1.75 | 0.641 | 1.11 | 1.21 | 0.517 |
| % Difference from Theoretical | -1.07 | 1.00 | 0.863 | 2.89 | 3.00 | 0.716 | -3.26 | -4.13 |

Table 3B Average Back-Calculated Calibration Standards for Acetaminophen-Sulphate

| Run ID | CAL 1 (µg/mL) | CAL 2 (µg/mL) | CAL 3 (µg/mL) | CAL 4 (µg/mL) | CAL 5 (µg/mL) | CAL 6 (µg/mL) | CAL 7 (µg/mL) | CAL 8 (µg/mL) |
|---|---|---|---|---|---|---|---|---|
| 1AEBW2 | 0.0985 | 0.198 | 0.321 | 1.23 | 4.03 | 15.5 | 38.6 | 47.7 |
| | 0.0986 | 0.207 | 0.328 | 1.26 | 4.15 | 15.3 | 37.7 | 47.1 |
| 3AEBW2 | 0.0994 | 0.204 | 0.319 | 1.24 | 4.08 | 15.4 | 38.0 | 46.6 |
| | 0.0998 | 0.200 | 0.315 | 1.23 | 4.17 | 15.5 | 38.9 | 48.7 |
| 4AEBW2 | 0.100 | 0.200 | 0.314 | 1.24 | 4.14 | 15.3 | 38.7 | 47.4 |
| | 0.0992 | 0.199 | 0.330 | 1.23 | 4.13 | 15.5 | 38.8 | 46.8 |
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.100 | 0.200 | 0.320 | 1.20 | 4.00 | 15.0 | 40.0 | 50.0 |
| Mean | 0.0992 | 0.201 | 0.321 | 1.24 | 4.12 | 15.4 | 38.4 | 47.4 |
| S.D. | 0.000601 | 0.00343 | 0.00664 | 0.0111 | 0.0497 | 0.104 | 0.486 | 0.738 |
| %C.V. | 0.605 | 1.71 | 2.07 | 0.892 | 1.21 | 0.674 | 1.27 | 1.56 |
| % Difference from Theoretical | -0.753 | 0.620 | 0.338 | 3.20 | 2.89 | 2.85 | -3.91 | -5.23 |

Table 3C Average Back-Calculated Calibration Standards for p-Acetamidophenyl-β-D-glucuronide

| Run ID | CAL 1 (µg/mL) | CAL 2 (µg/mL) | CAL 3 (µg/mL) | CAL 4 (µg/mL) | CAL 5 (µg/mL) | CAL 6 (µg/mL) | CAL 7 (µg/mL) | CAL 8 (µg/mL) |
|---|---|---|---|---|---|---|---|---|
| 1AEBW3 | 0.512 | 0.765 | 1.44 | 3.79 | 11.3 | 38.1 | 79.1 | 100 |
| | 0.528 | 0.833 | 1.56 | 4.04 | 12.1 | 38.3 | 80.1 | 101 |
| 3AEBW3 | 0.507 | 0.820 | 1.45 | 3.94 | 11.9 | 38.6 | 79.2 | 93.6 |
| | 0.497 | 0.803 | 1.47 | 3.94 | 12.3 | 39.1 | 82.5 | 103 |
| 4AEBW3 | 0.503 | 0.770 | 1.28 | 3.77 | 11.3 | 37.4 | 76.9 | 95.4 |
| | 0.530 | 0.846 | 1.57 | 4.16 | 12.6 | 40.9 | 83.0 | 103 |
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.500 | 0.800 | 1.50 | 4.00 | 12.0 | 38.0 | 80.0 | 100 |
| Mean | 0.513 | 0.806 | 1.46 | 3.94 | 11.9 | 38.7 | 80.1 | 99.3 |
| S.D. | 0.0133 | 0.0334 | 0.108 | 0.149 | 0.503 | 1.20 | 2.29 | 3.88 |
| %C.V. | 2.59 | 4.14 | 7.39 | 3.80 | 4.22 | 3.10 | 2.85 | 3.91 |
| % Difference from Theoretical | 2.58 | 0.774 | -2.61 | -1.52 | -0.627 | 1.95 | 0.170 | -0.720 |

Limit of Quantitation:
The lower limit of quantitation was 0.100 µg/mL for acetaminophen and acetaminophensulphate, and 0.500 µg/mL for p-acetamidophenyl-β-D-glucuronide.

Precision and accuracy:
Intra- and inter-assay were evaluated by analyzing using QC samples. The intra-assay quality control data for all three analytes are shown in Tables 4A through 4C.

Table 4A Intra-Assay Precision and Accuracy for Acetaminophen

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 1AEBW1 | 0.0985 | 0.248 | 0.645 | 2.34 | 6.73 | 37.8 |
| | 0.101 | 0.256 | 0.617 | 2.35 | 8.09 | 35.5 |
| | 0.0934 | 0.253 | 0.612 | 2.36 | 8.21 | 37.7 |
| | 0.0972 | 0.249 | 0.613 | 2.37 | 7.99 | 36.7 |
| | 0.0918 | 0.258 | 0.631 | 2.38 | 8.45 | 35.9 |
| | 0.103 | 0.260 | 0.641 | 2.39 | 8.39 | 35.2 |
| N | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.100 | 0.250 | 0.600 | 2.40 | 8.00 | 37.5 |
| Mean | 0.0975 | 0.254 | 0.627 | 2.37 | 7.98 | 36.5 |
| S.D. | 0.00439 | 0.00470 | 0.0145 | 0.0197 | 0.636 | 1.12 |
| %C.V. | 4.50 | 1.85 | 2.31 | 0.834 | 7.98 | 3.07 |
| % Difference from Theoretical | -2.46 | 1.60 | 4.45 | -1.40 | -0.306 | -2.75 |
| Low Limit | 0.0800 | 0.213 | 0.510 | 2.04 | 6.80 | 31.9 |
| High Limit | 0.120 | 0.288 | 0.690 | 2.76 | 9.20 | 43.1 |

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 3AEBW1 | 0.0984 | 0.259 | 0.611 | 2.35 | 8.28 | 36.0 |
| | 0.0950 | 0.257 | 0.616 | 2.37 | 8.21 | 35.2 |
| | 0.0975 | 0.253 | 0.619 | 2.38 | 8.48 | 36.6 |
| | 0.0982 | 0.265 | 0.594 | 2.41 | 8.15 | 37.7 |
| | 0.0985 | 0.254 | 0.621 | 2.38 | 7.90 | 37.3 |
| | 0.0988 | 0.256 | 0.628 | 2.35 | 8.15 | 37.3 |
| N | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.100 | 0.250 | 0.600 | 2.40 | 8.00 | 37.5 |
| Mean | 0.0977 | 0.257 | 0.615 | 2.37 | 8.19 | 36.7 |
| S.D. | 0.00140 | 0.00438 | 0.0115 | 0.0211 | 0.190 | 0.963 |
| %C.V. | 1.44 | 1.70 | 1.88 | 0.890 | 2.32 | 2.63 |
| % Difference from Theoretical | -2.26 | 2.95 | 2.45 | -1.11 | 2.43 | -2.16 |
| Low Limit | 0.0800 | 0.213 | 0.510 | 2.04 | 6.80 | 31.9 |
| High Limit | 0.120 | 0.288 | 0.690 | 2.76 | 9.20 | 43.1 |

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 4AEBW1 | 0.0973 | 0.259 | 0.615 | 2.35 | 7.97 | 37.2 |
| | 0.0957 | 0.257 | 0.611 | 2.26 | 8.19 | 37.6 |
| | 0.105 | 0.267 | 0.628 | 2.29 | 8.22 | 39.2 |
| | 0.0944 | 0.251 | 0.607 | 2.17 | 8.11 | 36.8 |
| | 0.0949 | 0.264 | 0.604 | 2.28 | 8.10 | 36.9 |
| | 0.0957 | 0.249 | 0.603 | 2.37 | 8.16 | 37.5 |
| N | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.100 | 0.250 | 0.600 | 2.40 | 8.00 | 37.5 |
| Mean | 0.0971 | 0.258 | 0.611 | 2.29 | 8.13 | 37.5 |
| S.D. | 0.00377 | 0.00713 | 0.00919 | 0.0720 | 0.0886 | 0.890 |
| %C.V. | 3.88 | 2.77 | 1.50 | 3.14 | 1.09 | 2.37 |
| % Difference from Theoretical | -2.92 | 3.06 | 1.89 | -4.65 | 1.58 | 0.0906 |
| Low Limit | 0.0800 | 0.213 | 0.510 | 2.04 | 6.80 | 31.9 |
| High Limit | 0.120 | 0.288 | 0.690 | 2.76 | 9.20 | 43.1 |

Table 4B Intra-Assay Precision and Accuracy for Acetaminophen-Sulphate

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 1AEBW2 | 0.100 | 0.241 | 0.620 | 2.38 | 6.69 | 37.5 |
| | 0.0999 | 0.264 | 0.629 | 2.35 | 8.17 | 34.2 |
| | 0.0868 | 0.263 | 0.614 | 2.39 | 8.23 | 36.5 |
| | 0.0992 | 0.253 | 0.601 | 2.43 | 8.00 | 36.0 |
| | 0.100 | 0.260 | 0.635 | 2.40 | 8.57 | 37.0 |
| | 0.103 | 0.256 | 0.635 | 2.40 | 8.52 | 34.8 |
| N | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.100 | 0.250 | 0.600 | 2.40 | 8.00 | 37.5 |
| Mean | 0.0982 | 0.256 | 0.622 | 2.39 | 8.03 | 36.0 |
| S.D. | 0.00573 | 0.00866 | 0.0134 | 0.0268 | 0.691 | 1.29 |
| %C.V. | 5.84 | 3.38 | 2.16 | 1.12 | 8.61 | 3.57 |
| % Difference from Theoretical | -1.79 | 2.58 | 3.72 | -0.349 | 0.397 | -3.94 |
| Low Limit | 0.0800 | 0.213 | 0.510 | 2.04 | 6.80 | 31.9 |
| High Limit | 0.120 | 0.288 | 0.690 | 2.76 | 9.20 | 43.1 |

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 3AEBW2 | 0.0936 | 0.248 | 0.602 | 2.36 | 8.07 | 35.4 |
| | 0.0954 | 0.247 | 0.602 | 2.41 | 8.15 | 34.6 |
| | 0.0979 | 0.257 | 0.616 | 2.29 | 8.56 | 37.0 |
| | 0.0904 | 0.261 | 0.606 | 2.33 | 8.41 | 37.3 |
| | 0.0970 | 0.249 | 0.607 | 2.37 | 7.91 | 37.1 |
| | 0.0937 | 0.258 | 0.633 | 2.32 | 8.37 | 37.0 |
| N | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.100 | 0.250 | 0.600 | 2.40 | 8.00 | 37.5 |
| Mean | 0.0947 | 0.253 | 0.611 | 2.35 | 8.24 | 36.4 |
| S.D. | 0.00270 | 0.00615 | 0.0119 | 0.0413 | 0.243 | 1.12 |
| %C.V. | 2.86 | 2.43 | 1.95 | 1.76 | 2.95 | 3.07 |
| % Difference from Theoretical | -5.33 | 1.29 | 1.84 | -2.25 | 3.05 | -2.90 |
| Low Limit | 0.0800 | 0.213 | 0.510 | 2.04 | 6.80 | 31.9 |
| High Limit | 0.120 | 0.288 | 0.690 | 2.76 | 9.20 | 43.1 |

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 4AEBW2 | 0.0981 | 0.260 | 0.595 | 2.35 | 8.05 | 36.4 |
| | 0.0925 | 0.256 | 0.604 | 2.39 | 8.28 | 37.4 |
| | 0.0954 | 0.270 | 0.617 | 2.28 | 8.33 | 38.6 |
| | 0.101 | 0.261 | 0.618 | 2.27 | 8.04 | 36.0 |
| | 0.0925 | 0.273 | 0.614 | 2.37 | 8.28 | 36.1 |
| | 0.0966 | 0.259 | 0.641 | 2.44 | 8.15 | 37.1 |
| N | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.100 | 0.250 | 0.600 | 2.40 | 8.00 | 37.5 |
| Mean | 0.0960 | 0.263 | 0.615 | 2.35 | 8.19 | 36.9 |
| S.D. | 0.00322 | 0.00663 | 0.0157 | 0.0649 | 0.128 | 0.956 |
| %C.V. | 3.35 | 2.52 | 2.56 | 2.76 | 1.56 | 2.59 |
| % Difference from Theoretical | -4.04 | 5.33 | 2.49 | -2.05 | 2.35 | -1.50 |
| Low Limit | 0.0800 | 0.213 | 0.510 | 2.04 | 6.80 | 31.9 |
| High Limit | 0.120 | 0.288 | 0.690 | 2.76 | 9.20 | 43.1 |

Table 4 Intra-Assay Precision and Accuracy for p-Acetamidophenyl-β-D-glucuronide

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 1AEBW3 | 0.520 | 0.995 | 2.56 | 7.32 | 15.8 | 77.9 |
| | 0.518 | 1.01 | 2.52 | 7.14 | 20.1 | 71.8 |
| | 0.503 | 1.03 | 2.41 | 7.45 | 19.9 | 76.1 |
| | 0.517 | 0.994 | 2.44 | 7.43 | 19.6 | 75.7 |
| | 0.520 | 1.03 | 2.52 | 7.34 | 20.9 | 77.9 |
| | 0.546 | 1.04 | 2.55 | 7.56 | 20.6 | 73.3 |
| N | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.500 | 1.00 | 2.50 | 7.50 | 20.0 | 75.0 |
| Mean | 0.521 | 1.01 | 2.50 | 7.37 | 19.5 | 75.5 |
| S.D. | 0.0139 | 0.0185 | 0.0621 | 0.144 | 1.88 | 2.48 |
| %C.V. | 2.67 | 1.83 | 2.48 | 1.95 | 9.63 | 3.29 |
| % Difference from Theoretical | 4.18 | 1.49 | -0.0296 | -1.71 | -2.59 | 0.609 |
| Low Limit | 0.400 | 0.850 | 2.13 | 6.38 | 17.0 | 63.8 |
| High Limit | 0.600 | 1.15 | 2.88 | 8.63 | 23.0 | 86.3 |

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 3AEBW3 | 0.488 | 1.03 | 2.43 | 7.38 | 20.0 | 74.3 |
| | 0.521 | 1.02 | 2.45 | 7.28 | 20.2 | 72.5 |
| | 0.503 | 1.04 | 2.59 | 7.48 | 21.3 | 76.9 |
| | 0.473 | 1.02 | 2.41 | 7.34 | 21.2 | 78.5 |
| | 0.487 | 1.04 | 2.47 | 7.45 | 19.6 | 79.4 |
| | 0.499 | 1.03 | 2.60 | 6.89 | 20.5 | 78.5 |
| N | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.500 | 1.00 | 2.50 | 7.50 | 20.0 | 75.0 |
| Mean | 0.495 | 1.03 | 2.49 | 7.30 | 20.5 | 76.7 |
| S.D. | 0.0163 | 0.00791 | 0.0838 | 0.213 | 0.667 | 2.70 |
| %C.V. | 3.28 | 0.768 | 3.37 | 2.92 | 3.25 | 3.52 |
| % Difference from Theoretical | -0.990 | 2.98 | -0.388 | -2.63 | 2.42 | 2.25 |
| Low Limit | 0.400 | 0.850 | 2.13 | 6.38 | 17.0 | 63.8 |
| High Limit | 0.600 | 1.15 | 2.88 | 8.63 | 23.0 | 86.3 |

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 4AEBW3 | 0.527 | 1.03 | 2.38 | 7.04 | 19.9 | 72.8 |
| | 0.506 | 1.01 | 2.44 | 7.17 | 20.4 | 73.9 |
| | 0.512 | 1.08 | 2.50 | 7.06 | 20.8 | 79.7 |
| | 0.517 | 1.12 | 2.61 | 7.32 | 20.2 | 77.2 |
| | 0.502 | 1.12 | 2.58 | 7.57 | 20.2 | 78.1 |
| | 0.530 | 1.08 | 2.65 | 7.56 | 20.4 | 81.2 |
| N | 6 | 6 | 6 | 6 | 6 | 6 |
| Theoretical Concentration | 0.500 | 1.00 | 2.50 | 7.50 | 20.0 | 75.0 |
| Mean | 0.516 | 1.07 | 2.53 | 7.29 | 20.3 | 77.1 |
| S.D. | 0.0111 | 0.0456 | 0.105 | 0.238 | 0.324 | 3.26 |
| %C.V. | 2.16 | 4.25 | 4.16 | 3.26 | 1.60 | 4.23 |
| % Difference from Theoretical | 3.11 | 7.20 | 1.10 | -2.84 | 1.58 | 2.85 |
| Low Limit | 0.400 | 0.850 | 2.13 | 6.38 | 17.0 | 63.8 |
| High Limit | 0.600 | 1.15 | 2.88 | 8.63 | 23.0 | 86.3 |

The inter-assay data obtained during the validation met the performance criteria specified in the validation project definition and applicable (b) (4) SOPs and are shown in Tables 5A through 5C.

Table 5A Inter-Assay Precision and Accuracy for Acetaminophen

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 1AEBW1 | 0.0985 | 0.248 | 0.645 | 2.34 | 6.73 | 37.8 |
| | 0.101 | 0.256 | 0.617 | 2.35 | 8.09 | 35.5 |
| | 0.0934 | 0.253 | 0.612 | 2.36 | 8.21 | 37.7 |
| | 0.0972 | 0.249 | 0.613 | 2.37 | 7.99 | 36.7 |
| | 0.0918 | 0.258 | 0.631 | 2.38 | 8.45 | 35.9 |
| | 0.103 | 0.260 | 0.641 | 2.39 | 8.39 | 35.2 |
| 3AEBW1 | 0.0984 | 0.259 | 0.611 | 2.35 | 8.28 | 36.0 |
| | 0.0950 | 0.257 | 0.616 | 2.37 | 8.21 | 35.2 |
| | 0.0975 | 0.253 | 0.619 | 2.38 | 8.48 | 36.6 |
| | 0.0982 | 0.265 | 0.594 | 2.41 | 8.15 | 37.7 |
| | 0.0985 | 0.254 | 0.621 | 2.38 | 7.90 | 37.3 |
| | 0.0988 | 0.256 | 0.628 | 2.35 | 8.15 | 37.3 |
| 4AEBW1 | 0.0973 | 0.259 | 0.615 | 2.35 | 7.97 | 37.2 |
| | 0.0957 | 0.257 | 0.611 | 2.26 | 8.19 | 37.6 |
| | 0.105 | 0.267 | 0.628 | 2.29 | 8.22 | 39.2 |
| | 0.0944 | 0.251 | 0.607 | 2.17 | 8.11 | 36.8 |
| | 0.0949 | 0.264 | 0.604 | 2.28 | 8.10 | 36.9 |
| | 0.0957 | 0.249 | 0.603 | 2.37 | 8.16 | 37.5 |
| N | 18 | 18 | 18 | 18 | 18 | 18 |
| Theoretical Concentration | 0.100 | 0.250 | 0.600 | 2.40 | 8.00 | 37.5 |
| Mean | 0.0975 | 0.256 | 0.618 | 2.34 | 8.10 | 36.9 |
| S.D. | 0.00324 | 0.00548 | 0.0131 | 0.0577 | 0.375 | 1.05 |
| %C.V. | 3.33 | 2.14 | 2.12 | 2.46 | 4.63 | 2.84 |
| % Difference from Theoretical | -2.55 | 2.54 | 2.93 | -2.39 | 1.23 | -1.61 |
| Low Limit | 0.0800 | 0.213 | 0.510 | 2.04 | 6.80 | 31.9 |
| High Limit | 0.120 | 0.288 | 0.690 | 2.76 | 9.20 | 43.1 |

Table 5B Inter-Assay Precision and Accuracy for Acetaminophen-Sulphate

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 1AEBW2 | 0.100 | 0.241 | 0.620 | 2.38 | 6.69 | 37.5 |
| | 0.0999 | 0.264 | 0.629 | 2.35 | 8.17 | 34.2 |
| | 0.0868 | 0.263 | 0.614 | 2.39 | 8.23 | 36.5 |
| | 0.0992 | 0.253 | 0.601 | 2.43 | 8.00 | 36.0 |
| | 0.100 | 0.260 | 0.635 | 2.40 | 8.57 | 37.0 |
| | 0.103 | 0.256 | 0.635 | 2.40 | 8.52 | 34.8 |
| 3AEBW2 | 0.0936 | 0.248 | 0.602 | 2.36 | 8.07 | 35.4 |
| | 0.0954 | 0.247 | 0.602 | 2.41 | 8.15 | 34.6 |
| | 0.0979 | 0.257 | 0.616 | 2.29 | 8.56 | 37.0 |
| | 0.0904 | 0.261 | 0.606 | 2.33 | 8.41 | 37.3 |
| | 0.0970 | 0.249 | 0.607 | 2.37 | 7.91 | 37.1 |
| | 0.0937 | 0.258 | 0.633 | 2.32 | 8.37 | 37.0 |
| 4AEBW2 | 0.0981 | 0.260 | 0.595 | 2.35 | 8.05 | 36.4 |
| | 0.0925 | 0.256 | 0.604 | 2.39 | 8.28 | 37.4 |
| | 0.0954 | 0.270 | 0.617 | 2.28 | 8.33 | 38.6 |
| | 0.101 | 0.261 | 0.618 | 2.27 | 8.04 | 36.0 |
| | 0.0925 | 0.273 | 0.614 | 2.37 | 8.28 | 36.1 |
| | 0.0966 | 0.259 | 0.641 | 2.44 | 8.15 | 37.1 |
| N | 18 | 18 | 18 | 18 | 18 | 18 |
| Theoretical Concentration | 0.100 | 0.250 | 0.600 | 2.40 | 8.00 | 37.5 |
| Mean | 0.0963 | 0.258 | 0.616 | 2.36 | 8.15 | 36.5 |
| S.D. | 0.00414 | 0.00806 | 0.0138 | 0.0489 | 0.414 | 1.13 |
| %C.V. | 4.30 | 3.13 | 2.24 | 2.07 | 5.08 | 3.09 |
| % Difference from Theoretical | -3.72 | 3.06 | 2.68 | -1.55 | 1.93 | -2.78 |
| Low Limit | 0.0800 | 0.213 | 0.510 | 2.04 | 6.80 | 31.9 |
| High Limit | 0.120 | 0.288 | 0.690 | 2.76 | 9.20 | 43.1 |

Table 5C Inter-Assay Precision and Accuracy for p-Acetamidophenyl-β-D-glucuronide

| Run ID | QC 0 (µg/mL) | QC 1 (µg/mL) | QC 2 (µg/mL) | QC 3 (µg/mL) | QC 4 (µg/mL) | QC 5 (µg/mL) |
|---|---|---|---|---|---|---|
| 1AEBW3 | 0.520 | 0.995 | 2.56 | 7.32 | 15.8 | 77.9 |
| | 0.518 | 1.01 | 2.52 | 7.14 | 20.1 | 71.8 |
| | 0.503 | 1.03 | 2.41 | 7.45 | 19.9 | 76.1 |
| | 0.517 | 0.994 | 2.44 | 7.43 | 19.6 | 75.7 |
| | 0.520 | 1.03 | 2.52 | 7.34 | 20.9 | 77.9 |
| | 0.546 | 1.04 | 2.55 | 7.56 | 20.6 | 73.3 |
| 3AEBW3 | 0.488 | 1.03 | 2.43 | 7.38 | 20.0 | 74.3 |
| | 0.521 | 1.02 | 2.45 | 7.28 | 20.2 | 72.5 |
| | 0.503 | 1.04 | 2.59 | 7.48 | 21.3 | 76.9 |
| | 0.473 | 1.02 | 2.41 | 7.34 | 21.2 | 78.5 |
| | 0.487 | 1.04 | 2.47 | 7.45 | 19.6 | 79.4 |
| | 0.499 | 1.03 | 2.60 | 6.89 | 20.5 | 78.5 |
| 4AEBW3 | 0.527 | 1.03 | 2.38 | 7.04 | 19.9 | 72.8 |
| | 0.506 | 1.01 | 2.44 | 7.17 | 20.4 | 73.9 |
| | 0.512 | 1.08 | 2.50 | 7.06 | 20.8 | 79.7 |
| | 0.517 | 1.12 | 2.61 | 7.32 | 20.2 | 77.2 |
| | 0.502 | 1.12 | 2.58 | 7.57 | 20.2 | 78.1 |
| | 0.530 | 1.08 | 2.65 | 7.56 | 20.4 | 81.2 |
| N | 18 | 18 | 18 | 18 | 18 | 18 |
| Theoretical Concentration | 0.500 | 1.00 | 2.50 | 7.50 | 20.0 | 75.0 |
| Mean | 0.511 | 1.04 | 2.51 | 7.32 | 20.1 | 76.4 |
| S.D. | 0.0174 | 0.0367 | 0.0820 | 0.194 | 1.18 | 2.76 |
| %C.V. | 3.41 | 3.54 | 3.27 | 2.65 | 5.89 | 3.61 |
| % Difference from Theoretical | 2.10 | 3.89 | 0.226 | -2.39 | 0.472 | 1.90 |
| Low Limit | 0.400 | 0.850 | 2.13 | 6.38 | 17.0 | 63.8 |
| High Limit | 0.600 | 1.15 | 2.88 | 8.63 | 23.0 | 86.3 |

Stability:

Freeze/thaw stability was evaluated by analyzing low- and high-level quality controls subjected to five freeze/thaw cycles. Samples were thawed at room temperature and frozen at -20°C. No apparent abnormalities associated with up to five freeze/thaw cycles were observed. Results are shown in Tables 6A through 6C.

Table 6A Freeze/Thaw Stability for Acetaminophen

**Five Freeze/Thaw Cycles**

| Run ID | 5FT 1 (µg/mL) | 5FT 5 (µg/mL) |
|---|---|---|
| 4AEBW1 | 0.260 | 36.2 |
| | 0.254 | 37.3 |
| | 0.247 | 37.2 |
| | 0.251 | 35.3 |
| | 0.241 | 35.9 |
| | 0.257 | 35.1 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.252 | 36.2 |
| S.D. | 0.00692 | 0.909 |
| %C.V. | 2.75 | 2.52 |
| % Difference from Theoretical | 0.658 | -3.60 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Table 6B Freeze/Thaw Stability for Acetaminophen-Sulphate

**Five Freeze/Thaw Cycles**

| Run ID | 5FT 1 (µg/mL) | 5FT 5 (µg/mL) |
|---|---|---|
| 4AEBW2 | 0.251 | 36.0 |
| | 0.250 | 36.6 |
| | 0.250 | 36.5 |
| | 0.258 | 34.7 |
| | 0.246 | 34.3 |
| | 0.264 | 34.6 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.253 | 35.4 |
| S.D. | 0.00661 | 1.01 |
| %C.V. | 2.61 | 2.86 |
| % Difference from Theoretical | 1.28 | -5.47 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Table 6C Freeze/Thaw Stability for p-Acetamidophenyl-β-D-glucuronide

**Five Freeze/Thaw Cycles**

| Run ID | 5FT 1 (µg/mL) | 5FT 5 (µg/mL) |
|---|---|---|
| 4AEBW3 | 1.03 | 74.9 |
| | 1.02 | 76.0 |
| | 0.985 | 77.5 |
| | 1.08 | 74.6 |
| | 0.991 | 75.2 |
| | 1.07 | 75.3 |
| N | 6 | 6 |
| Theoretical Concentration | 1.00 | 75.0 |
| Mean | 1.03 | 75.6 |
| S.D. | 0.0414 | 1.03 |
| %C.V. | 4.02 | 1.37 |
| % Difference from Theoretical | 3.02 | 0.787 |
| Low Limit | 0.850 | 63.8 |
| High Limit | 1.15 | 86.3 |

Analyte stability in thawed matrix for APAP, APAP sulfate and APAP glucuronides are presented in Tables 7A to 7C.

Table 7A Analyte Stability in Thawed Matrix for Acetaminophen

**Quality Controls at Room Temperature for 31.5 Hours**

| Run ID | TM 1 (µg/mL) | TM 5 (µg/mL) |
|---|---|---|
| 4AEBW1 | 0.246 | 37.5 |
| | 0.248 | 36.3 |
| | 0.245 | 36.6 |
| | 0.247 | 37.4 |
| | 0.251 | 35.9 |
| | 0.251 | 35.5 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.248 | 36.5 |
| S.D. | 0.00263 | 0.831 |
| %C.V. | 1.06 | 2.27 |
| % Difference from Theoretical | -0.780 | -2.55 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Table 7B Analyte Stability in Thawed Matrix for Acetaminophen-Sulphate
**Quality Controls at Room Temperature for 31.5 Hours**

| Run ID | TM 1 (µg/mL) | TM 5 (µg/mL) |
|---|---|---|
| 4AEBW2 | 0.239 | 36.9 |
| | 0.259 | 36.1 |
| | 0.242 | 36.1 |
| | 0.256 | 36.8 |
| | 0.261 | 35.6 |
| | 0.255 | 35.4 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.252 | 36.2 |
| S.D. | 0.00931 | 0.606 |
| %C.V. | 3.69 | 1.68 |
| % Difference from Theoretical | 0.770 | -3.57 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Table 7C Analyte Stability in Thawed Matrix for p-Acetamidophenyl-β-D-glucuronide
**Quality Controls at Room Temperature for 31.5 Hours**

| Run ID | TM 1 (µg/mL) | TM 5 (µg/mL) |
|---|---|---|
| 4AEBW3 | 0.963 | 75.9 |
| | 0.999 | 75.0 |
| | 0.981 | 76.2 |
| | 1.08 | 79.3 |
| | 1.12 | 78.4 |
| | 1.07 | 76.4 |
| N | 6 | 6 |
| Theoretical Concentration | 1.00 | 75.0 |
| Mean | 1.04 | 76.9 |
| S.D. | 0.0636 | 1.64 |
| %C.V. | 6.14 | 2.13 |
| % Difference from Theoretical | 3.63 | 2.48 |
| Low Limit | 0.850 | 63.8 |
| High Limit | 1.15 | 86.3 |

Short-term analyte stability in frozen (-20°C) matrix was evaluated for a period covering the age of the oldest calibrators and quality controls used during the validation. Low- and high-level quality controls were analyzed versus freshly prepared calibration standards at the end of the validation. No apparent abnormalities associated with storage for up to six days at -20°C were observed. Data from the short-term stability run (Run 4AEBW) are shown in Tables 8A through 8C and are supported by acceptable data from the freshly prepared calibrators and quality controls.

Table 8A Short-Term Stability in Frozen Matrix - Six Days at -20°C for Acetaminophen

| Run ID | STAB 1 (µg/mL) | STAB 5 (µg/mL) |
|---|---|---|
| 4AEBW1 | 0.263 | 37.0 |
| | 0.245 | 38.2 |
| | 0.259 | 36.1 |
| | 0.253 | 35.8 |
| | 0.249 | 36.8 |
| | 0.241 | 35.7 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.252 | 36.6 |
| S.D. | 0.00860 | 0.963 |
| %C.V. | 3.41 | 2.63 |
| % Difference from Theoretical | 0.738 | -2.39 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Table 8B Short-Term Stability in Frozen Matrix - Six Days at -20°C for Acetaminophen-Sulphate

| Run ID | STAB 1 (µg/mL) | STAB 5 (µg/mL) |
|---|---|---|
| 4AEBW2 | 0.269 | 36.7 |
| | 0.252 | 36.3 |
| | 0.263 | 34.6 |
| | 0.247 | 35.9 |
| | 0.248 | 36.0 |
| | 0.246 | 35.7 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.254 | 35.9 |
| S.D. | 0.00943 | 0.745 |
| %C.V. | 3.71 | 2.08 |
| % Difference from Theoretical | 1.65 | -4.32 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Table 8C Short-Term Stability in Frozen Matrix - Six Days at -20°C for p-Acetamidophenyl-β-D-glucuronide

| Run ID | STAB 1 (µg/mL) | STAB 5 (µg/mL) |
|---|---|---|
| 4AEBW3 | 1.11 | 75.3 |
| | 1.05 | 75.3 |
| | 1.06 | 72.3 |
| | 1.11 | 76.0 |
| | 0.981 | 77.7 |
| | 1.02 | 76.4 |
| N | 6 | 6 |
| Theoretical Concentration | 1.00 | 75.0 |
| Mean | 1.06 | 75.5 |
| S.D. | 0.0521 | 1.79 |
| %C.V. | 4.94 | 2.38 |
| % Difference from Theoretical | 5.65 | 0.664 |
| Low Limit | 0.850 | 63.8 |
| High Limit | 1.15 | 86.3 |

Addendum 1: Long-Term Matrix Stability - 643 Days at -20°C and Method Revision (audit 8/12/08; signed off 8/25/08;

The long-term stability samples were analyzed utilizing the method P852.00. A batch of low and high quality controls was prepared on 10/4/06. Six replicates each were stored at -20 ºC and then extracted along with a freshly prepared calibration curve and quality controls that are within the established stability timeframe in Run 102RAEXF of Project AEXF on 7/8/08. Data are considered acceptable if the accuracy of the mean value for each quality control level is within 15.0% of the theoretical concentration and the coefficient of variation for the replicate determinations does not exceed 15.0%.

Long-term matrix stability data are presented in Table 9. The calculation output including all calibration standard and quality control data are found on Pages 136 through 139. Based on the results shown, acetaminophen is stable in human plasma at approximately -20 °C for a period of at least 643 days.

Table 9 Long-Term Matrix Stability Data for Acetaminophen

**643 Days Stability at -20 °C**

| Run ID | STAB 1 (µg/mL) | STAB 5 (µg/mL) |
|---|---|---|
| 102RAEXF | 0.254 | 34.9 |
| | 0.252 | 41.2 |
| | 0.295 | 37.5 |
| | 0.254 | 38.0 |
| | 0.261 | 40.0 |
| | 0.228 | 38.2 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.257 | 38.3 |
| S.D. | 0.0214 | 2.18 |
| %C.V. | 8.29 | 5.71 |
| % Difference from Theoretical | 2.99 | 2.09 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Addendum 4: Quantitation of Acetaminophen, Acetaminophen-Sulphate, and p-Acetamidophenyl-β-D-glucuronide in Human Plasma via HPLC with MS/MS Detection (issue date 4/12/10)

Long-term analyte stability in frozen matrix was demonstrated by analyzing quality controls which were prepared on 12 February 2008 and stored at -20 °C for 772 days prior to analysis with a freshly prepared calibration curve in Run 1AEBW4 on 25 March 2010. No apparent abnormalities associated with long-term storage for up to 772 days at -20 °C were observed. Results are shown in Tables 10A through 10C.

Table 10A Long-term Stability in Frozen Matrix for Acetaminophen

| Run ID | STAB 1 (µg/mL) | STAB 5 (µg/mL) |
|---|---|---|
| 1AEBW4_1 | 0.245 | 38.6 |
| | 0.254 | 38.8 |
| | 0.264 | 39.7 |
| | 0.263 | 38.9 |
| | 0.253 | 38.5 |
| | 0.254 | 39.1 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.255 | 38.9 |
| S.D. | 0.00703 | 0.443 |
| %C.V. | 2.75 | 1.14 |
| % Difference from Theoretical | 2.17 | 3.81 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Table 10B Long-term Stability in Frozen Matrix for Acetaminophen-Sulphate

| Run ID | STAB 1 (µg/mL) | STAB 5 (µg/mL) |
|---|---|---|
| 1AEBW4_2 | 0.252 | 38.9 |
| | 0.255 | 38.2 |
| | 0.252 | 39.7 |
| | 0.262 | 39.7 |
| | 0.267 | 38.2 |
| | 0.258 | 38.8 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.258 | 38.9 |
| S.D. | 0.00606 | 0.672 |
| %C.V. | 2.35 | 1.73 |
| % Difference from Theoretical | 3.10 | 3.78 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Table 10C Long-term Stability in Frozen Matrix for p-Acetamidophenyl-β-D-glucuronide

| Run ID | STAB 1 (µg/mL) | STAB 5 (µg/mL) |
|---|---|---|
| 1AEBW4_3 | 1.05 | 81.6 |
| | 1.08 | 78.2 |
| | 1.06 | 80.3 |
| | 1.09 | 80.8 |
| | 1.09 | 77.0 |
| | 1.11 | 79.9 |
| N | 6 | 6 |
| Theoretical Concentration | 1.00 | 75.0 |
| Mean | 1.08 | 79.7 |
| S.D. | 0.0207 | 1.73 |
| %C.V. | 1.91 | 2.17 |
| % Difference from Theoretical | 8.15 | 6.21 |
| Low Limit | 0.850 | 63.8 |
| High Limit | 1.15 | 86.3 |

Addendum 5: Quantitation of Acetaminophen, Acetaminophen-Sulphate, and p-Acetamidophenyl-ß-D-glucuronide in Human Plasma via HPLC with MS/MS Detection (issue date 2/18/15)

Analyte stability in frozen matrix was evaluated in Run 9AEBW5 by analyzing samples which had been stored for 141 days at -20 °C (STABF) versus freshly prepared calibration standards. The analyte in frozen matrix stability data met the acceptance criteria specified in the applicable (b) (4) SOPs. Analyte stability in frozen matrix data are shown in Tables 11A through 11C.

Table 11A Analyte Stability in Frozen Dipotassium EDTA Plasma for Acetaminophen (-20 °C) 141 Days

Report 2711621

| Run ID | STABF 1 (µg/mL) | STABF 5 (µg/mL) |
|---|---|---|
| 9AEBW5_1 | 0.247 | 38.8 |
| | 0.273 | 39.0 |
| | 0.241 | 37.1 |
| | 0.257 | 38.2 |
| | 0.261 | 37.4 |
| | 0.271 | 37.1 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.258 | 37.9 |
| S.D. | 0.0127 | 0.854 |
| %C.V. | 4.93 | 2.25 |
| % Difference from Theoretical | 3.31 | 1.19 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Table 11B Analyte Stability in Frozen Dipotassium EDTA Plasma for Acetaminophen-Sulphate (-20 °C) 141 Days

Report 2711796

| Run ID | STABF 1 (µg/mL) | STABF 5 (µg/mL) |
|---|---|---|
| 9AEBW5_3 | 0.233 | 35.9 |
| | 0.250 | 36.0 |
| | 0.234 | 35.0 |
| | 0.258 | 35.5 |
| | 0.237 | 35.0 |
| | 0.263 | 35.2 |
| N | 6 | 6 |
| Theoretical Concentration | 0.250 | 37.5 |
| Mean | 0.246 | 35.4 |
| S.D. | 0.0128 | 0.443 |
| %C.V. | 5.22 | 1.25 |
| % Difference from Theoretical | -1.77 | -5.52 |
| Low Limit | 0.213 | 31.9 |
| High Limit | 0.288 | 43.1 |

Table 11C Analyte Stability in Frozen Dipotassium EDTA Plasma for p-Acetamidophenyl-ß-D-glucuronide (-20 °C) 141 Days

Report 2711805

| Run ID | STABF 1 (µg/mL) | STABF 5 (µg/mL) |
|---|---|---|
| 9AEBW5_2 | 1.02 | 78.7 |
| | 1.03 | 80.3 |
| | 1.01 | 77.4 |
| | 1.04 | 78.2 |
| | 0.971 | 76.3 |
| | 1.10 | 75.7 |
| N | 6 | 6 |
| Theoretical Concentration | 1.00 | 75.0 |
| Mean | 1.03 | 77.8 |
| S.D. | 0.0435 | 1.68 |
| %C.V. | 4.23 | 2.16 |
| % Difference from Theoretical | 3.05 | 3.69 |
| Low Limit | 0.850 | 63.8 |
| High Limit | 1.15 | 86.3 |

## 4.2 Clinical PK and/or PD Assessments

### *4.2.1 Bioequivalence study HC-G-H-1506*

Title: A Phase I, Open-label, Randomized, Single-dose, 2-way Crossover Study to Determine the Bioequivalence of Acetaminophen Injection Versus Ofirmev® Injection in Healthy Volunteers

Report Date: 01 June 2016

*The following synopsis report was provided by the Applicant.*

Investigator: Rebecca N. Wood-Horrall, MD
Study site: PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin TX 78744
Publication (reference): None
Studied period (years): 06 January 2016 (b) (6) 08 February 2016 (b) (6) (b) (6)
Phase of development: Phase 1

Objectives:
The primary objective of the study was to determine the bioequivalence of 1000 mg of Acetaminophen Injection (B. Braun Medical Inc.) versus 1000 mg of Ofirmev® following a single intravenous (IV) administration in healthy adult subjects.
The secondary objective of the study was to evaluate the safety and tolerability of a single IV administration of 1000 mg of Acetaminophen Injection (B. Braun Medical Inc.) in healthy adult subjects.

Methodology: This was a Phase 1, open-label, randomized, single-dose, 2-way crossover study to determine the bioequivalence of a single IV administration of 1000 mg of Acetaminophen Injection (B. Braun Medical Inc.) versus 1000 mg of Ofirmev® in healthy adult subjects.
After giving written informed consent, screening was performed within 21 days prior to the first dose. Following confirmation of eligibility, subjects participated in 2 treatment periods.
For each treatment period, subjects were confined to the clinic for approximately 3 days and 2 nights, commencing the evening before dosing (Days –1 and 7) until at least 24 hours after dosing (morning of Days 2 and 9). Each subject participated in the study for approximately 10 days (excluding screening).

Each subject received the following study drugs in a randomized, crossover manner (1 study drug at each treatment period):

• Test: Acetaminophen Injection (1000 mg IV infusion)
• Reference: Ofirmev® (1000 mg IV infusion)

Each drug administration was separated by a washout interval of at least 6 days. Subjects were discharged from the clinic after the 24-hour postdose procedures were completed. Study exit procedures occurred approximately 24 hours after the last study drug administration (i.e., Day 9 of Treatment Period 2).
Blood samples for plasma pharmacokinetic (PK) analysis of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide were collected up to 12 hours after IV infusion. Safety assessments included type and incidence of adverse events (AEs), vital sign measurements, clinical laboratory test results, concomitant medications, and physical examination findings.

Number of subjects (planned and analyzed): A total of 30 subjects were randomly assigned, to ensure evaluable data were collected from approximately 25 subjects. Twenty-eight (93.3%) subjects completed the study. Thirty subjects were included in the safety population and 28 subjects were included in the PK population. Two subjects (6.7%) discontinued the study. One

subject discontinued due to withdrawal of consent and 1 subject discontinued due to an unrelated serious AE (SAE).

Diagnosis and main criteria for inclusion: Healthy, nonsmoking male and female subjects 18 to 55 years of age with a body weight of greater than or equal to 50 kg and a body mass index from 18.0 to 30.0 kg/m2 (inclusive) were eligible for enrollment.

Duration of treatment: A single dose of study drug was administered on Days 1 and 8 with a washout interval of at least 6 days. Each subject participated in the study for approximately 10 days, excluding screening.

Test product, dose and mode of administration, batch number:
Acetaminophen Injection, 1000 mg in 100 mL, single dose, IV administration (B. Braun Medical Inc.; batch number STBJ5J677)

Reference therapy, dose and mode of administration, batch number:
Ofirmev® (acetaminophen) Injection, 1000 mg in 100 mL, single dose, IV administration (lot number AAC3617)

Criteria for evaluation:
Pharmacokinetics:
The following noncompartmental PK parameters were calculated for each study drug:
• AUC0-t area under the plasma concentration versus time curve from time = 0 (dosing) to the last quantifiable concentration; • AUC0-inf area under the plasma concentration versus time curve from time = 0 (dosing) to infinity; • Cmax maximum observed plasma concentration; • Tmax time from dosing to the maximum observed plasma concentration; • kel elimination rate constant; • t1/2 terminal half-life; • CL total body clearance; • Vz volume of distribution during the terminal phase

Safety:
The following safety parameters were recorded at regular intervals during the study:
• Type and incidence of AEs; • Vital sign measurements (systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature); • Clinical laboratory findings (hematology, coagulation, serum chemistry, and urinalysis parameters); • Concomitant medications; • Physical examination findings

Statistical methods:
All safety analyses were based on the safety population, whereas all PK analyses were based on the PK population.

Pharmacokinetics:
Pharmacokinetic plasma concentration data of acetaminophen, acetaminophen sulfate, acetaminophen glucuronide, and the associated parameters were listed by subject and summarized by treatment and nominal time point, as applicable, using descriptive statistics (number of subjects, mean, SD, coefficient of variation, median, minimum, and maximum). In addition, geometric means were calculated for AUC0-t, AUC0-∞, and Cmax. Mean and

individual plasma concentrations versus time were presented graphically on linear and semilogarithmic scales.

A linear mixed-effect model (SAS PROC MIXED) with treatment, sequence, and period as fixed effects, and subject nested within sequence as a random effect were fitted to the natural log-transformed PK parameters AUC0-t, AUC0-inf, and Cmax for use in estimation of effects and construction of 90% confidence intervals (CIs) for Acetaminophen Injection versus Ofirmev®. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for the ratios of geometric means and respective 90% CIs on the original scale. Acetaminophen Injection was considered to be bioequivalent to Ofirmev® if the 90% CI of the geometric mean ratio of AUC0-t, AUC0-inf, and Cmax between Acetaminophen Injection and Ofirmev® fell within 80.00% and 125.00%.

Safety:
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1. All treatment-emergent AEs were summarized by treatment and overall, with the number and percentage of subjects who experienced at least 1 AE, and presented in a data listing. Serious AEs were also summarized. Treatment-emergent AEs (TEAEs) were summarized by system organ class and preferred term, relationship to study drug, and severity. All AEs that led to early discontinuation were presented in a data listing. Clinical laboratory test results and vital sign measurements were summarized by actual value and change from baseline. Shifts from baseline in hematology, coagulation, and serum chemistry test results relative to the reference range (low, normal, or high) were summarized by visit and overall. Clinical laboratory tests, vital sign measurements, electrocardiogram (ECG) data, and physical examination findings were presented in data listings.

RESULTS:
Pharmacokinetic results:
Statistical analysis of the plasma PK parameters of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide is presented in Table 1.

Table 1 Statistical Analysis of Plasma Pharmacokinetic Parameters of Acetaminophen, Acetaminophen Sulfate, and Acetaminophen Glucuronide (Pharmacokinetic Population)

| Parameter (unit) | Ratio (%) of Geometric LS Means (Acetaminophen Injection/ Ofirmev®) | 90% Confidence Interval |
|---|---|---|
| **Acetaminophen** | | |
| $AUC_{0-t}$ (µg•h/mL) | 96.81 | (95.14, 98.50) |
| $AUC_{0-inf}$ (µg•h/mL) | 96.52 | (94.75, 98.33) |
| $C_{max}$ (µg/mL) | 97.91 | (91.33, 104.96) |
| **Acetaminophen Sulfate** | | |
| $AUC_{0-t}$ (µg•h/mL) | 97.21 | (95.02, 99.46) |
| $AUC_{0-inf}$ (µg•h/mL) | 97.22 | (94.70, 99.81) |
| $C_{max}$ (µg/mL) | 99.86 | (96.89, 102.91) |
| **Acetaminophen Glucuronide** | | |
| $AUC_{0-t}$ (µg•h/mL) | 97.56 | (95.24, 99.94) |
| $AUC_{0-inf}$ (µg•h/mL) | 97.98 | (95.33, 100.70) |
| $C_{max}$ (µg/mL) | 97.94 | (94.63, 101.37) |

Abbreviation: LS: least squares; PK: pharmacokinetic.
Note: The estimates were from a linear mixed effect model with the natural log-transformed PK parameters as the dependent variable, treatment, sequence, and period as fixed effects, and subject nested within sequence as a random effect.
Source: hcgh1506-body.pdf

A formal statistical analysis of bioequivalence between Acetaminophen Injection 1000 mg and Ofirmev® 1000 mg was performed for plasma acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide. The 90% CIs for the geometric least squares mean ratios of AUC0-t, AUC0-inf, and Cmax for each analyte were within the predefined range of 80% to 125%, indicating bioequivalence between Acetaminophen Injection 1000 mg and Ofirmev® 1000 mg.

Safety results:
Overall, 6 of 30 subjects (20.0%) reported at least 1 TEAE. Treatment-emergent AEs were reported by 3 subjects (10.3%) after administration of Acetaminophen Injection (1000 mg IV infusion) and 3 subjects (10.3%) after administration of Ofirmev® (1000 mg IV infusion). Two of 30 subjects (6.7%) experienced TEAEs that were considered unlikely to be related to study drug. All other subjects who reported TEAEs only had TEAEs that were considered unrelated to study drug. No TEAEs were considered possibly or probably related to study drug. Except for 1 SAE of moderate severity, all TEAEs were mild in severity. There were no severe TEAEs or deaths.
One subject (Subject (b) (6) was discontinued from the study due to an unrelated SAE of rhabdomyolysis that resulted in hospitalization. The SAE and all TEAEs resolved by the end of the study. With the exception of the abnormalities in 1 subject (Subject (b) (6) there were no clinically significant findings noted or TEAEs reported that resulted from clinical laboratory assessments, vital sign measurements, physical examination findings, or ECG results.

CONCLUSIONS:
Pharmacokinetics:
• Following a single IV infusion of Acetaminophen Injection 1000 mg or Ofirmev® 1000 mg, mean plasma concentrations of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide were similar between treatments across the entire concentration versus time profile.
• Acetaminophen Injection 1000 mg is bioequivalent to Ofirmev® 1000 mg, as assessed by AUC0-t, AUC0-inf, and Cmax for plasma acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide; the 90% CIs for the geometric least squares means ratios for AUC0-t, AUC0-inf, and Cmax for each analyte were within the predefined bioequivalence acceptance limits of 80% to 125%.

*Reviewer comments: There are no issues identified with the Applicant's synopsis report.*

Additional information pertinent from the main study report:

Clinical Laboratories
PPD Central Laboratory, 7551 Metro Center Drive, Suite 200, Austin, TX 78744
LabCorp, 7207 North Gessner, Houston, TX 77040

Bioanalytical Laboratory
(b) (4)

(b) (4) served as the contract research organization for this study and was responsible for program and project management, clinical and medical monitoring, clinical data management, pharmacokinetic (PK) and biostatistical analysis, and final reporting.

9.3.1 Inclusion Criteria
For inclusion in the study, each subject was required to meet all of the following criteria:
1. Subject voluntarily agreed to participate in this study and signed an IRB-approved ICF and Health Insurance Portability and Accountability Act Authorization before any of the study procedures were performed.
2. Subject was a male or nonpregnant, nonlactating female subject 18 to 55 years of age, inclusive.
3. Subject had a body weight of ≥50 kg and a body mass index within the range of 18.0 to 30.0 kg/m2, inclusive.
4. If the subject was a female of childbearing potential, she agreed to practice abstinence or use a medically acceptable form of birth control (hormonal contraceptives [oral, patch, or vaginal ring], intrauterine device, or barrier method [ie, male condom or diaphragm]) for at least 14 days before screening (at least 3 months for hormonal contraceptives and intrauterine devices), throughout the study, and for at least 3 days after the last study drug administration.
5. If the subject was a female of nonchildbearing potential, she had undergone successful surgical sterilization (bilateral tubal ligation with surgery at least 6 weeks before screening, hysterectomy, or bilateral oophorectomy, as determined by the subject's medical history) or must

have been postmenopausal (amenorrheic for at least 12 consecutive months without another cause).
6. If the subject was a female of childbearing potential, she had a negative serum human chorionic gonadotropin pregnancy test at screening and at admission on Day –1.
7. Subject was healthy, in the opinion of the investigator, as determined by prestudy medical history, physical examination, vital signs, and 12-lead electrocardiogram (ECG).
8. Subject had clinical laboratory tests within the reference ranges or clinically acceptable to the investigator.
9. Subject was a nonsmoker (self-reported) for at least 3 months before screening.
10. Subject was willing and able to abide by all study requirements and restrictions.

9.3.2 Exclusion Criteria
A subject who met 1 or more of the following criteria was not considered eligible for participation in the clinical study:
1. Subject had clinically significant abnormalities, physical or psychological illnesses, or conditions contraindicating acetaminophen treatment.
2. Subject used any drugs known to induce or inhibit hepatic drug metabolism of acetaminophen within 30 days before the first study drug administration (anticonvulsants, cimetidine, diflunisal, isoniazid, or anticoagulants).
3. Subject had a history or presence of any clinically significant illness (eg, respiratory, gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological, or connective tissue diseases or disorders) or any other condition which, in the opinion of the investigator, would have interfered with the ability to provide written informed consent or comply with study instructions, or that might have confounded the interpretation of the study results or put the subject at undue risk.
4. Subject had evidence of impaired liver function, eg, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 times the upper limit of normal, bilirubin ≥2 times upper limit of normal, 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, 4th Edition, cirrhosis, or chronic hepatitis).
5. Subject had a self-reported history of drug abuse or dependence.
6. Subject was a male who consumed more than 21 units of alcohol a week or a female who consumed more than 14 units of alcohol a week (where 1 unit of alcohol is equivalent to 1.5 ounces of hard liquor, 5 ounces of wine, or 12 ounces of beer).
7. Subject had a significant infection or known inflammatory process at screening.
8. Subject had an acute infection such as influenza at the time of screening or admission on Day -1.
9. Subject used a prohibited medication (ie, prescription drugs within 14 days of first dosing or nonprescription drugs, vitamins, or herbal supplements within 7 days of first dosing), as specified in Section 9.4.7.
10. Subject had a positive urine drug screen at screening or at admission on Day –1.
11. Subject had a positive serum alcohol test at screening or at admission on Day –1.
12. Subject had a history of allergy or hypersensitivity to acetaminophen or related drugs.

13. Subject had a history of allergy or hypersensitivity to excipients of Acetaminophen Injection or Ofirmev®.
14. Subject had positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVAb), or human immunodeficiency virus (HIV) type 1 and 2 tests at screening.
15. Subject had a serum osmolality of ≤250 mOsm/kg or ≥320 mOsm/kg.
16. Subject had hyponatremia (sodium level <125 mEq/L [125 mmol/L]) or hypernatremia (sodium level >155 mEq/L [155 mmol/L]) at screening.
17. Subject had hypokalemia (potassium level <3 mEq/L [3 mmol/L]) or hyperkalemia (potassium level >6 mEq/L [6 mmol/L]) at screening.
18. Subject was anuric or had a serum creatinine level ≥2.5 mg/dL (221 μmol/L) at screening.
19. Subject had uncontrolled hypertension (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg) at screening.
20. Subject had a prothrombin time or partial thromboplastin time ≥1.5 × upper limit of normal at screening.
21. Subject had QT prolongation (QT interval corrected using the Fridericia method [QTcF] >430 ms for male subjects and >450 ms for female subjects) or clinically significant abnormalities in 12-lead ECG at screening.
22. Subject donated or lost more than 500 mL of blood or blood products within 4 weeks preceding the first study drug administration.
23. Subject received an investigational product in a clinical study within 30 days before randomization or was concurrently enrolled in any other type of medical research, judged not to be scientifically or medically compatible with this study.
24. Subject previously received dosing in this study.
25. Subject was an employee of the sponsor or clinic staff directly affiliated with this study or their immediate family members defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
26. Subject who, in the opinion of the investigator or designee, was not considered to be suitable and was unlikely to comply with the clinical study protocol for any reason.

Removal of subjects from therapy or assessment:
Withdrawn subjects were not replaced who voluntarily withdrew consent or was discontinued (e.g., as a result of an AE) from the study before completion.

Randomization:
Subjects were randomly assigned in a 1:1 ratio (AB or BA) (Table 2).

Table 2 Randomization table

| | Treatment Period | |
|---|---|---|
| **Sequence** | **1** | **2** |
| 1 | A | B |
| 2 | B | A |

Abbreviation: IV: intravenous.
Treatment A: Acetaminophen Injection (1000 mg IV infusion; B. Braun Medical Inc.).
Treatment B: Ofirmev® (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).

Test product, dose and mode of administration, batch number:
Acetaminophen Injection, 1000 mg in 100 mL, single dose, IV administration (B. Braun Medical Inc.; batch number STBJ5J677) (Each 100 mL of Acetaminophen Injection contained 1000 mg acetaminophen, USP; 3800 mg mannitol, USP; and 30 mg sodium citrate dihydrate. The pH was adjusted (b) (4) with glacial acetic acid.)

Reference therapy, dose and mode of administration, batch number:
Ofirmev® (acetaminophen) Injection, 1000 mg in 100 mL, single dose, IV administration (lot number AAC3617) (Each 100 mL of Ofirmev® contained 1000 mg acetaminophen, USP; 3850 mg mannitol, USP; 25 mg cysteine hydrochloride, monohydrate, USP; and 10.4 mg dibasic sodium phosphate, USP. The pH was adjusted with hydrochloric acid and/or sodium hydroxide.)

Acetaminophen Injection was supplied in 150-mL plastic bags. Ofirmev® was supplied in 100-mL glass vials. Both study drugs were stored between 20ºC and 25ºC, and were used within 6 hours after opening.

Selection of Doses in the Study:
Acetaminophen Injection is being developed as 500 mg/50 mL and 1000 mg/100 mL formulations. The approved adult dosage of Ofirmev® is 1000 mg every 6 hours. The current study assessed a single 1000 mg given as IV infusions over 15 minutes, following an overnight fast of at least 10 hours. Subjects fasted for an additional 4 hours post dosing.

Prior and Concomitant Therapy:
Subjects were required to avoid using over-the-counter (OTC) medications, vitamins or herbal supplements within 7 days before the first drug administration and throughout the study. Subjects who had taken an OTC medication may still have been entered or remained in the study if the medication did not interfere with the study procedures, data integrity or compromise the safety of the subjects. Subjects were required to avoid using prescription medications (except hormonal contraceptives) within 14 days prior to the first drug administration and throughout the study unless the product did not interfere with the study procedures, data integrity or compromise the safety of the subjects. The drugs known to induce/inhibit hepatic drug metabolism of acetaminophen (e.g., anticonvulsants, cimetidine, diflunisal, isoniazid, or anticoagulants) were restricted within 30 days prior to the first drug administration. Concomitant medications were prohibited in this study unless prescribed by the investigator to treat clinical events or were exempted by the investigator and the sponsor on a case-by-case basis. All medications taken by subjects were documented as concomitant medications. The reported medications were reviewed and evaluated by the investigator to determine whether they affected a subject's eligibility to participate or continue to participate in the study.

Pharmacokinetic Assessments:
Blood samples (4.0 mL) for plasma PK analysis of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide were collected at pre-dose, 5, 15, and 30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 hours post dosing. The 15-minute collection occurred immediately after the end of the IV infusion. Blood was obtained by direct venipuncture in the arm or via an optional indwelling cannula in the non-infusion arm.

Blood Sample analysis:
The plasma samples were analyzed by (b) (4) bioanalytical laboratory, using validated methods. Plasma samples were shipped frozen on dry ice from the clinic to the bioanalytical laboratory.

Statistical and Analytical Plans:
All analyses were conducted using SAS Version 9.2 (SAS Institute Inc., Cary, NC) or Phoenix® WinNonlin® Version 6.2.1 (Certara, Princeton, NJ). Bioequivalence was concluded if the 90% CIs for the ratios of geometric means were contained within 80.00% and 125.00% for AUC0-t, AUC0-inf, and Cmax of acetaminophen from Acetaminophen Injection versus Ofirmev®. Twenty-five completed subjects with evaluable PK information provided at least 90% power to conclude bioequivalence if the true difference between the treatments was no greater than 5% (presumes that parameters are log-normally distributed and that the intrasubject CV% was no greater than 20%; there is currently no reference for the intrasubject CV% and was assumed to be similar to the reported intersubject CV% (Singla et al., 2012)).

RESULTS

1. Summary of subject demographics (Table 3)

Table 3 Summary of subject demographics and baseline characteristics

| | Treatment Sequence[a] | | |
|---|---|---|---|
| | AB (N = 15) | BA (N = 15) | Overall (N = 30) |
| Age (years) | | | |
| Mean (SD) | 31.7 (8.92) | 34.3 (9.81) | 33.0 (9.30) |
| Minimum, maximum | 21, 49 | 19, 51 | 19, 51 |
| Gender, n (%) | | | |
| Female | 7 (46.7) | 12 (80.0) | 19 (63.3) |
| Male | 8 (53.3) | 3 (20.0) | 11 (36.7) |
| Race, n (%) | | | |
| White | 11 (73.3) | 12 (80.0) | 23 (76.7) |
| Black or African American | 4 (26.7) | 3 (20.0) | 7 (23.3) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 8 (53.3) | 4 (26.7) | 12 (40.0) |
| Not Hispanic or Latino | 7 (46.7) | 11 (73.3) | 18 (60.0) |
| Height (cm) | | | |
| Mean (SD) | 169.34 (11.501) | 165.40 (8.208) | 167.37 (10.020) |
| Minimum, maximum | 151.8, 190.2 | 150.5, 182.8 | 150.5, 190.2 |
| Weight (kg) | | | |
| Mean (SD) | 74.93 (14.141) | 69.35 (11.828) | 72.14 (13.120) |
| Minimum, maximum | 54.7, 100.9 | 53.1, 94.8 | 53.1, 100.9 |
| Body mass index (kg/m$^2$) | | | |
| Mean (SD) | 25.91 (2.362) | 25.25 (2.909) | 25.58 (2.625) |
| Minimum, maximum | 21.5, 29.2 | 19.0, 28.9 | 19.0, 29.2 |

Abbreviations: IV: intravenous; N: number of subjects in the population; n: number of subjects with data.
Note: Percentages were calculated based on the number of subjects who were randomly assigned to each treatment sequence and overall.
[a] Treatment A: Acetaminophen Injection (1000 mg IV infusion; B. Braun Medical Inc.) and Treatment B: Ofirmev® (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).

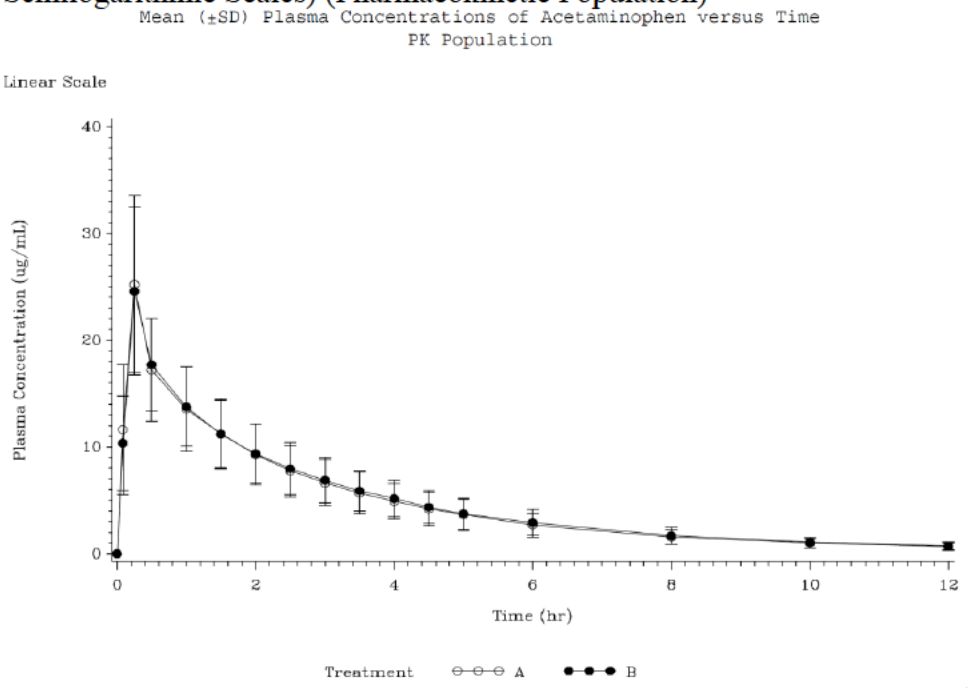
Overall, subjects ranged in age from 19 to 51 years with an overall mean age of 33.0 years. The overall mean body mass index was 25.58 kg/m$^2$. The majority of subjects were white (76.7%), female (63.3%), and not Hispanic or Latino (60.0%).

Subjects excluded:
Subject (b) (6) discontinued the study due to withdrawal of consent. Subject (b) (6) discontinued the study due to an unrelated SAE of rhabdomyolysis that required hospitalization.

2. Pharmacokinetic Analysis

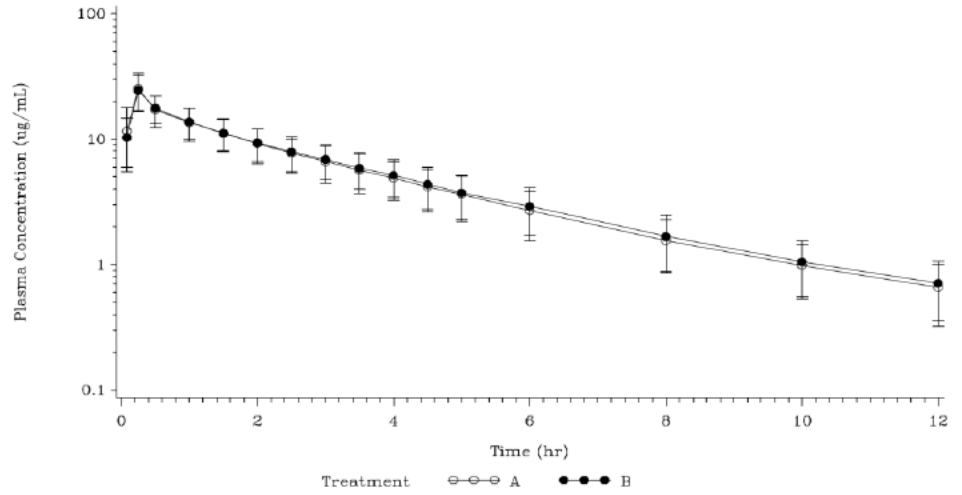
The mean (±SD) plasma concentrations profiles of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide are presented in Figures 1, 2, and 3, respectively.

Figure 1 Mean (±SD) Plasma Concentrations of Acetaminophen Versus Time (Linear and Semilogarithmic Scales) (Pharmacokinetic Population)




Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population

Semi-Logarithmic Scale

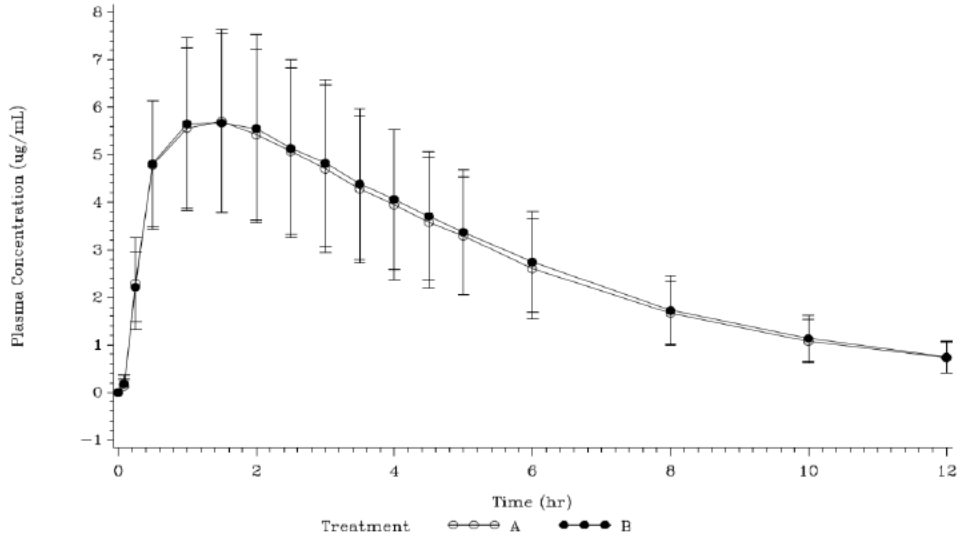



Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population
Source Data: Table 14.2.1.1

Figure 2 Mean (±SD) Plasma Concentrations of Acetaminophen Sulfate Versus Time (Linear and Semilogarithmic Scales) (Pharmacokinetic Population)

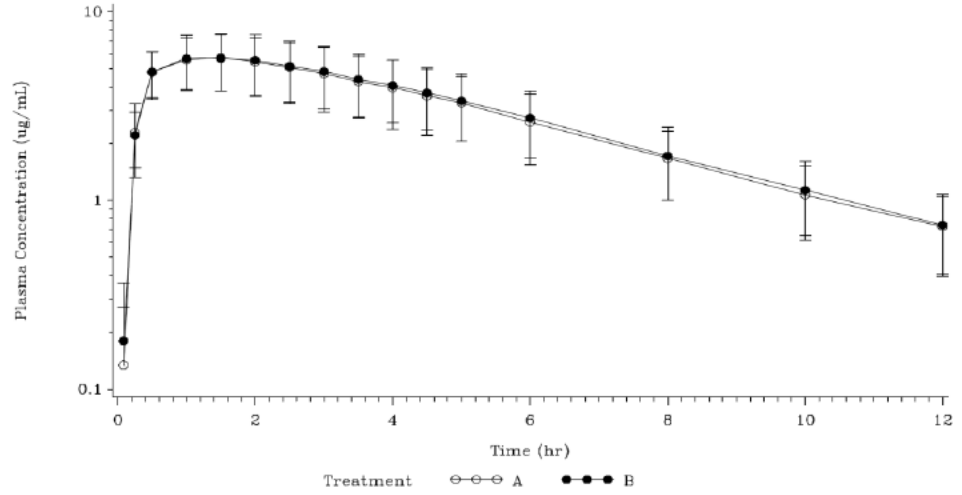
Mean (±SD) Plasma Concentrations of Acetaminophen Sulfate versus Time
PK Population

Linear Scale




Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population

Semi-Logarithmic Scale

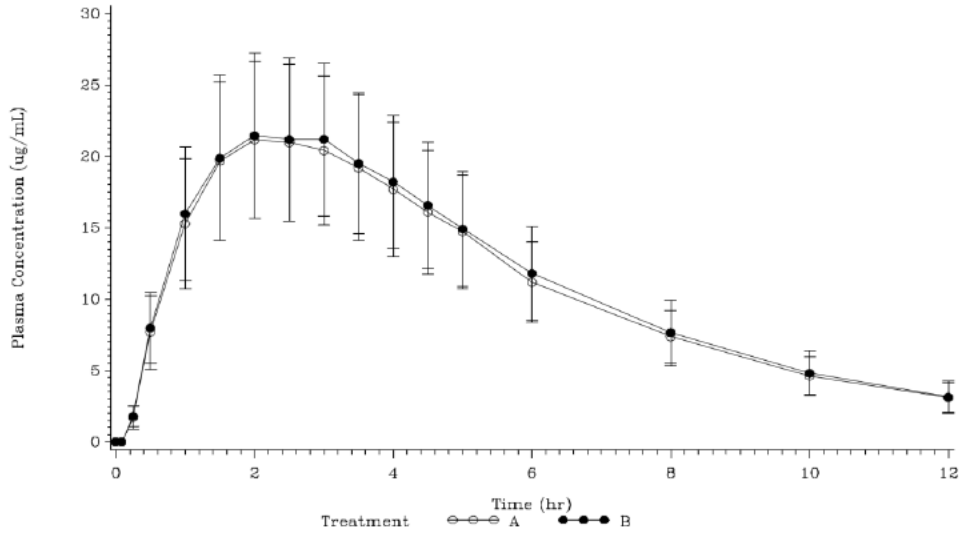



Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population
Source Data: Table 14.2.1.2

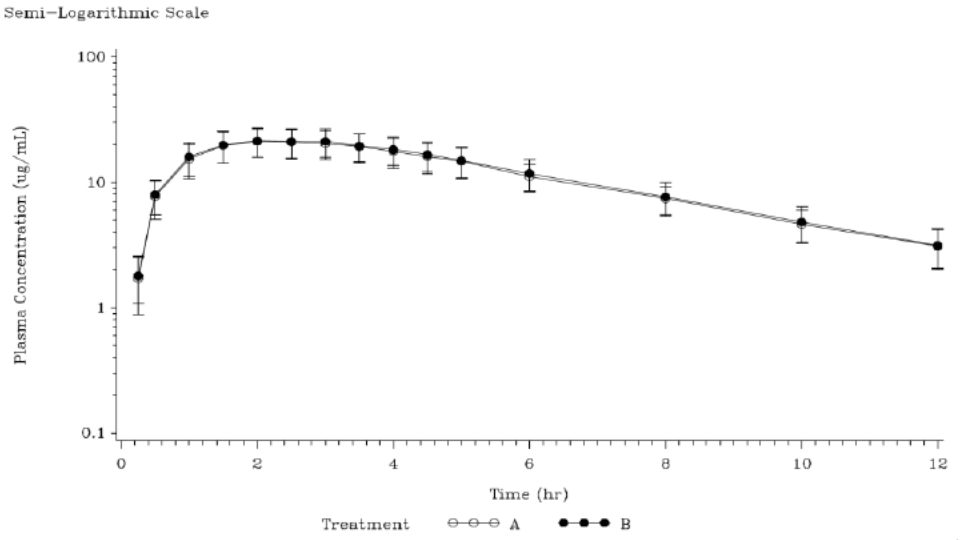
Figure 3 Mean (±SD) Plasma Concentrations of Acetaminophen Glucuronide Versus Time (Linear and Semilogarithmic Scales) (Pharmacokinetic Population)

Mean (±SD) Plasma Concentrations of Acetaminophen Glucuronide versus Time
PK Population

Linear Scale




Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population




Treatment A: Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.)
Treatment B: Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmacecuticals)
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population
Source Data: Table 14.2.1.3

Plasma pharmacokinetic parameters (mean and SD) of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide are presented in Tables 4, 5, and 6, respectively.

Table 4 Mean (SD) Plasma Pharmacokinetic Parameters of Acetaminophen (Pharmacokinetic Population)

| Parameter (unit) | Acetaminophen Injection 1000 mg (N = 28) | Ofirmev® 1000 mg (N = 28) |
|---|---|---|
| $AUC_{0-t}$ (µg•h/mL) | 57.23 (17.33) | 58.77 (17.0) |
| $AUC_{0-inf}$ (µg•h/mL) | 59.91 (18.60) | 61.68 (18.34) |
| $C_{max}$ (µg/mL) | 24.92 (8.40) | 24.98 (7.57) |
| $T_{max}$ (h)[a] | 0.25 (0.08, 0.50) | 0.250 (0.25, 0.50) |
| $t_{1/2}$ (h) | 2.67 (0.36) | 2.72 (0.39) |
| CL (L/h) | 17.72 (5.37) | 17.38 (4.40) |
| $V_z$ (L) | 67.69 (20.59) | 67.49 (17.04) |

Abbreviations: SD: standard deviation; h: hours; N: number of subjects in the population; PK: pharmacokinetic.
a For Tmax, the median (minimum, maximum) values are presented.
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population.
Source: End-of-Text Table 14.2.2.1.

The mean acetaminophen total exposure (AUC0-t and AUC0-inf) was similar for both treatments. Acetaminophen mean AUC0-t and AUC0-inf values for Acetaminophen Injection were approximately 57 µg•h/mL and 60 µg•h/mL, respectively. Acetaminophen mean Cmax was approximately 25.0 µg/mL for both Acetaminophen Injection and Ofirmev®, with a median Tmax of 0.25 hours for both treatments. Acetaminophen mean elimination t1/2 was approximately 2.7 hours for both treatments. Acetaminophen mean CL was similar for Acetaminophen Injection and Ofirmev®, with a value of approximately 17 L/h.

Table 5 Mean (SD) Plasma Pharmacokinetic Parameters of Acetaminophen Sulfate (Pharmacokinetic Population)

| Parameter (unit) | Acetaminophen Injection 1000 mg (N = 28) | Ofirmev® 1000 mg (N = 28) |
|---|---|---|
| $AUC_{0-t}$ (µg•h/mL) | 34.01 (11.91) | 34.91 (12.16) |
| $AUC_{0-inf}$ (µg•h/mL) | 37.49 (13.36) | 38.47 (13.60) |
| $C_{max}$ (µg/mL) | 5.85 (1.87) | 5.88 (1.93) |
| $T_{max}$ (h)[a] | 1.50 (0.50, 2.50) | 1.50 (0.50, 3.00) |
| $t_{1/2}$ (h) | 3.22 (0.43) | 3.23 (0.44) |

Abbreviations: SD: standard deviation; h: hours; N: number of subjects in the population; PK: pharmacokinetic.
a For Tmax, the median (minimum, maximum) values are presented.
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population.
Source: End-of-Text Table 14.2.2.2.

The mean acetaminophen sulfate total exposure (AUC0-t and AUC0-inf) was similar for both treatments. Acetaminophen sulfate mean AUC0-t and AUC0-inf for Acetaminophen Injection were approximately 34 µg•h/mL and 38 µg•h/mL, respectively. Acetaminophen sulfate mean Cmax was approximately 5.9 µg/mL for both Acetaminophen Injection and Ofirmev®, with a median Tmax of 1.5 hours for both treatments. Acetaminophen sulfate mean elimination t1/2 was approximately 3.2 hours for both treatments.

Table 6 Mean (SD) Plasma Pharmacokinetic Parameters of Acetaminophen Glucuronide (Pharmacokinetic Population)

| Parameter (unit) | Acetaminophen Injection 1000 mg (N = 28) | Ofirmev® 1000 mg (N = 28) |
|---|---|---|
| $AUC_{0-t}$ (µg•h/mL) | 133.50 (32.35) | 137.38 (34.75) |
| $AUC_{0-inf}$ (µg•h/mL) | 148.31 (36.15) | 152.03 (39.28) |
| $C_{max}$ (µg/mL) | 22.01 (5.49) | 22.50 (5.6) |
| $T_{max}$ (h)[a] | 2.25 (1.50, 3.50) | 2.50 (1.50, 4.50) |
| $t_{1/2}$ (h) | 3.22 (0.50) | 3.16 (0.45) |

Abbreviations: SD: standard deviation; h: hours; N: number of subjects in the population; PK: pharmacokinetic.
a For Tmax, the median (minimum, maximum) values are presented.
Subjects (b) (6) and (b) (6) did not complete both treatments and were excluded from the PK population.
Source: End-of-Text Table 14.2.2.3.

The mean acetaminophen glucuronide total exposure (AUC0-t and AUC0-inf) was similar for both treatments. Acetaminophen glucuronide mean AUC0-t and AUC0-inf for Acetaminophen Injection were approximately 134 µg•h/mL and 148 µg•h/mL, respectively. Acetaminophen glucuronide mean Cmax was approximately 22 µg/mL for both treatments, with a median Tmax of 2.25 and 2.50 h for Acetaminophen Injection and Ofirmev®, respectively. Acetaminophen glucuronide mean elimination t1/2 was approximately 3.2 hours for both treatments.

Statistical analysis of the log-transformed plasma PK parameters of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide is presented in Table 6.

Table 6 Statistical analysis of pharmacokinetic parameters of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide: geometric LS means and 90% Confidence interval

| Parameter (unit) | Treatment a | N | Geometric LS Means | Ratio (%) of Geometric LS Means (A/Ba) | 90% Confidence Interval of the Ratio (%) |
|---|---|---|---|---|---|
| Acetaminophen | | | | | |
| $AUC_{0-t}$ (µg•h/mL) | A | 28 | 54.92 | 96.81 | (95.14, 98.50) |
| | B | 28 | 56.74 | | |
| $AUC_{0-inf}$ (µg•h/mL) | A | 28 | 57.37 | 96.52 | (94.75, 98.33) |
| | B | 28 | 59.43 | | |
| $C_{max}$ (µg/mL) | A | 28 | 23.47 | 97.91 | (91.33, 104.96) |
| | B | 28 | 23.98 | | |
| Acetaminophen Sulfate | | | | | |
| AUC0-t (µg•h/mL) | A | 28 | 31.82 | 97.21 | (95.02, 99.46) |
| | B | 28 | 32.73 | | |
| AUC0-inf (µg•h/mL) | A | 28 | 34.99 | 97.22 | (94.70, 99.81) |
| | B | 28 | 36.00 | | |
| Cmax (µg/mL) | A | 28 | 5.52 | 99.86 | (96.89, 102.91) |
| | B | 28 | 5.53 | | |
| Acetaminophen Glucuronide | | | | | |
| AUC0-t (µg•h/mL) | A | 28 | 129.35 | 97.56 | (95.24, 99.94) |
| | B | 28 | 132.58 | | |
| AUC0-inf (µg•h/mL) | A | 28 | 143.71 | 97.98 | (95.33, 100.70) |
| | B | 28 | 146.68 | | |
| Cmax (µg/mL) | A | 28 | 21.22 | 97.94 | (94.63, 101.37) |
| | B | 28 | 21.66 | | |

Abbreviations: IV: intravenous; LS: least squares; N: number of subjects in the population; PK: pharmacokinetic.
Note: The estimates were from a linear mixed effect model with the natural log-transformed PK parameters as the dependent variable, treatment, sequence, and period as fixed effects, and subject nested within sequence as a random effect.
a Treatment A: Acetaminophen Injection (1000 mg IV infusion; B. Braun Medical Inc.) and Treatment B: Ofirmev® (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).
Source: End-of-Text Tables 14.2.3.1, 14.2.3.2, and 14.2.3.3.

The bioequivalence analysis results indicated that Acetaminophen Injection 1000 mg and Ofirmev® 1000 mg were bioequivalent; the 90% CIs for the geometric least squares mean ratios of AUC0-t, AUC0-inf, and Cmax for all analytes were within the 80% to 125% range.

Display of Adverse Events:
A summary of TEAEs is presented in Table 7.

Table 7 Treatment-Emergent Adverse Events (Safety Population)

| System Organ Class<br>Preferred Term, n (%) | Acetaminophen Injection 1000 mg (N = 29) | Ofirmev® 1000 mg (N = 29) | Overall (N = 30) |
|---|---|---|---|
| Number of subjects with at least 1 TEAE | 3 (10.3) | 3 (10.3) | 6 (20.0) |
| Probably related | 0 | 0 | 0 |
| Possibly related | 0 | 0 | 0 |
| Unlikely to be related | 2 (6.9) | 0 | 2 (6.7)[a] |
| Unrelated | 1 (3.4) | 3 (10.3) | 4 (13.3) |
| General disorders and administration site conditions | 0 | 2 (6.9) | 2 (6.7) |
| Influenza-like illness | 0 | 1 (3.4) | 1 (3.3) |
| Vessel puncture site bruise | 0 | 1 (3.4) | 1 (3.3) |
| Nervous system disorders | 1 (3.4) | 1 (3.4) | 2 (6.7) |
| Dizziness | 0 | 1 (3.4) | 1 (3.3) |
| Presyncope | 1 (3.4) | 0 | 1 (3.3) |
| Ear and labyrinth disorders | 1 (3.4) | 0 | 1 (3.3) |
| Tinnitus | 1 (3.4) | 0 | 1 (3.3) |
| Musculoskeletal and connective tissue disorders | 1 (3.4) | 0 | 1 (3.3) |
| Back pain | 1 (3.4) | 0 | 1 (3.3) |
| Rhabdomyolysis | 1 (3.4) | 0 | 1 (3.3) |

Abbreviations: N: number of subjects in the population; n: number of subjects at each level of summarization; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Note: A TEAE was defined as an adverse event that began or that worsened in intensity after at least 1 dose of the study drug had been administered. At each level of subject summarization, a subject was counted once if the subject reported 1 or more events. Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.1. Percentages were based on the number of subjects in the safety population within each treatment and overall.

[a] One of these subjects is Subject (b) (6) who experienced a TEAE of back pain that was considered unlikely to be related to study drug. Therefore this subject was not counted among the subjects with an event judged to be unrelated to study drug (Subject (b) (6) experienced an SAE of rhabdomyolysis that was unrelated to study drug).

Source: End-of-Text Tables 14.3.1.2 and 14.3.1.4.

Analysis of Adverse Events:
Treatment-emergent AEs (TEAS) were reported by 3 subjects each after administration of Acetaminophen Injection and Ofirmev. According to the Applicant 2 of 30 subjects (6.7%) experienced TEAEs that were considered unlikely to be related to study drug; all other subjects who reported TEAEs had TEAEs that were considered unrelated to study drug; no TEAEs were considered possibly or probably related to study drug. The Applicant stated that, except for 1 SAE (moderate severity), all TEAEs were mild in severity. The SAE and all TEAEs resolved by the end of the study. There were no deaths reported in the study. Subject (b) (6) was discontinued from the study due to an unrelated SAE of rhabdomyolysis that resulted in hospitalization.

Pharmacokinetic Conclusions:
• Following a single IV infusion of Acetaminophen Injection 1000 mg or Ofirmev® 1000 mg, mean plasma concentrations of acetaminophen, acetaminophen sulfate, and acetaminophen glucuronide were similar between treatments across the entire concentration versus time profile.

• Acetaminophen Injection 1000 mg is bioequivalent to Ofirmev® 1000 mg, as assessed by AUC0-t, AUC0-inf, and Cmax for plasma acetaminophen, acetaminophen sulfate, and

acetaminophen glucuronide; the 90% CIs for the geometric least squares means ratios for AUC0-t, AUC0-inf, and Cmax for all analytes were within the predefined bioequivalence acceptance limits of 80% to 125%.

Safety conclusions:
• The Acetaminophen Injection (1000 mg IV infusion) and Ofirmev® (1000 mg IV infusion) were generally safe in this study.
• The Acetaminophen Injection (1000 mg IV infusion) and Ofirmev® (1000 mg IV infusion) were well tolerated by the healthy subjects in this study.
• A total of 6 subjects (20.0%) reported at least 1 TEAE, 3 subjects (10.3%) after administration of Acetaminophen Injection (1000 mg IV infusion) and 3 subjects (10.3%) after administration of Ofirmev® (1000 mg IV infusion).
• No deaths occurred during this study, and except for 1 moderate SAE, all TEAEs were mild in severity.
• One subject (Subject (b) (6) was discontinued from study treatment due to a moderate, unrelated SAE of rhabdomyolysis that led to hospitalization. The SAE and all TEAEs resolved by the end of the study.
• With the exception of the abnormalities in 1 subject (Subject (b) (6) of high ALT, AST, and creatinine kinase values that were considered clinically significant by the investigator and were associated with the TEAE of rhabdomyolysis, there were no clinically significant findings noted or TEAEs reported that resulted from clinical laboratory assessments, vital sign measurements, physical examination findings, or ECG results.

Appendix

1. Plasma Pharmacokinetic Parameters and Descriptive Statistics of Acetaminophen by Treatment

Treatment: A

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) | CL (L/h) | Vz (L) |
|---|---|---|---|---|---|---|---|---|
| (b) (6) | 75.18 | 79.31 | 24.2 | 0.25 | 0.2694 | 2.57 | 12.48 | 46.34 |
| | 30.95 | 32.11 | 10.1 | 0.25 | 0.2616 | 2.65 | 31.14 | 119.03 |
| | 39.74 | 41.62 | 17.8 | 0.25 | 0.2499 | 2.77 | 24.02 | 96.14 |
| | 60.99 | 63.52 | 18.8 | 0.25 | 0.2655 | 2.61 | 14.96 | 56.33 |
| | 35.09 | 36.02 | 13.0 | 0.50 | 0.3038 | 2.28 | 27.76 | 91.38 |
| | 45.77 | 49.83 | 29.5 | 0.25 | 0.1953 | 3.55 | 20.07 | 102.76 |
| | 72.12 | 78.96 | 23.9 | 0.28 | 0.1943 | 3.57 | 12.66 | 65.17 |
| | 46.37 | 47.47 | 26.1 | 0.25 | 0.3077 | 2.25 | 21.06 | 68.45 |
| | 93.60 | 97.58 | 29.0 | 0.25 | 0.2664 | 2.60 | 10.25 | 38.47 |
| | 73.00 | 76.06 | 41.4 | 0.25 | 0.2567 | 2.70 | 12.49 | 48.65 |
| | 48.91 | 51.06 | 15.3 | 0.25 | 0.2623 | 2.64 | 19.39 | 73.92 |
| | 67.16 | 69.88 | 39.9 | 0.25 | 0.2648 | 2.62 | 13.31 | 50.26 |
| | 61.69 | 63.05 | 25.8 | 0.25 | 0.3075 | 2.25 | 14.75 | 47.97 |
| | 57.34 | 61.30 | 22.9 | 0.27 | 0.2258 | 3.07 | 15.82 | 70.08 |
| | 40.49 | 41.48 | 14.9 | 0.25 | 0.3016 | 2.30 | 23.86 | 79.14 |
| | 46.33 | 47.69 | 33.3 | 0.25 | 0.2778 | 2.50 | 20.34 | 73.22 |
| | 39.53 | 40.80 | 14.7 | 0.50 | 0.2825 | 2.45 | 24.02 | 85.02 |
| | 60.28 | 62.02 | 26.1 | 0.32 | 0.3009 | 2.30 | 15.64 | 51.97 |
| | 53.64 | 55.46 | 31.3 | 0.25 | 0.2738 | 2.53 | 17.31 | 63.22 |
| | 99.18 | 107.01 | 31.7 | 0.25 | 0.2158 | 3.21 | 8.78 | 40.71 |
| | 47.19 | 50.27 | 14.1 | 0.25 | 0.2340 | 2.96 | 19.70 | 84.16 |
| | 44.34 | 47.46 | 24.4 | 0.25 | 0.2150 | 3.22 | 20.86 | 97.03 |
| | 52.11 | 53.90 | 39.7 | 0.25 | 0.2729 | 2.54 | 17.81 | 65.26 |
| | 90.12 | 94.11 | 34.6 | 0.23 | 0.2557 | 2.71 | 10.20 | 39.89 |
| | 61.26 | 63.91 | 27.0 | 0.23 | 0.2523 | 2.75 | 14.08 | 55.82 |
| | 62.65 | 65.03 | 22.8 | 0.08 | 0.2693 | 2.57 | 15.07 | 55.96 |
| | 48.95 | 50.08 | 24.8 | 0.25 | 0.3035 | 2.28 | 19.17 | 63.17 |
| | 66.15 | 67.85 | 24.6 | 0.25 | 0.3018 | 2.30 | 14.74 | 48.84 |
| | 48.94 | 50.34 | 20.6 | 0.25 | 0.2900 | 2.39 | 19.07 | 65.75 |

Treatment A : Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.);
Treatment B : Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).
Subjects (b) (6) and (b) (6) did not complete both treatments; Subject (b) (6) completed only Treatment B and Subject (b) (6) completed only Treatment A.

Treatment: A

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) | CL (L/h) | Vz (L) |
|---|---|---|---|---|---|---|---|---|
| Descriptive Statistics (Safety Population) | | | | | | | | |
| N | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 29 |
| Mean | 57.554 | 60.179 | 24.91 | 0.264 | 0.26475 | 2.661 | 17.615 | 67.039 |
| SD | 17.0942 | 18.3196 | 8.2463 | 0.0740 | 0.032574 | 0.3646 | 5.3034 | 20.5243 |
| Min | 30.95 | 32.11 | 10.1 | 0.08 | 0.1943 | 2.25 | 8.78 | 38.47 |
| Median | 53.636 | 55.455 | 24.60 | 0.250 | 0.26636 | 2.602 | 17.311 | 65.173 |
| Max | 99.18 | 107.01 | 41.4 | 0.50 | 0.3077 | 3.57 | 31.14 | 119.03 |
| CV% | 29.7 | 30.4 | 33.1 | 28.0 | 12.3 | 13.7 | 30.1 | 30.6 |
| Descriptive Statistics (Completers) | | | | | | | | |
| N | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| Mean | 57.247 | 59.905 | 24.92 | 0.265 | 0.26343 | 2.674 | 17.718 | 67.689 |
| SD | 17.3262 | 18.5951 | 8.3974 | 0.0753 | 0.032370 | 0.3644 | 5.3713 | 20.5947 |
| Min | 30.95 | 32.11 | 10.1 | 0.08 | 0.1943 | 2.25 | 8.78 | 38.47 |
| Median | 52.874 | 54.679 | 24.60 | 0.250 | 0.26594 | 2.606 | 17.560 | 65.217 |
| Max | 99.18 | 107.01 | 41.4 | 0.50 | 0.3077 | 3.57 | 31.14 | 119.03 |
| CV% | 30.3 | 31.0 | 33.7 | 28.4 | 12.3 | 13.6 | 30.3 | 30.4 |

Treatment: B

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) | CL (L/h) | Vz (L) |
|---|---|---|---|---|---|---|---|---|
| (b) (6) | 68.84 | 72.65 | 24.0 | 0.50 | 0.2548 | 2.72 | 13.76 | 54.01 |
| | 36.38 | 37.56 | 13.6 | 0.50 | 0.2710 | 2.56 | 26.62 | 98.23 |
| | 47.08 | 49.62 | 27.7 | 0.25 | 0.2372 | 2.92 | 20.15 | 84.95 |
| | 60.54 | 62.81 | 17.0 | 0.50 | 0.2795 | 2.48 | 15.92 | 56.96 |
| | 37.53 | 38.54 | 17.7 | 0.27 | 0.2963 | 2.34 | 25.95 | 87.57 |
| | 48.52 | 53.79 | 20.2 | 0.27 | 0.1825 | 3.80 | 18.59 | 101.87 |
| | 68.07 | 73.02 | 27.9 | 0.25 | 0.2142 | 3.24 | 13.70 | 63.93 |
| | 50.45 | 52.01 | 28.2 | 0.27 | 0.2872 | 2.41 | 19.23 | 66.96 |
| | 110.89 | 118.18 | 31.0 | 0.25 | 0.2317 | 2.99 | 8.46 | 36.52 |
| | 68.23 | 70.74 | 31.4 | 0.25 | 0.2689 | 2.58 | 14.14 | 52.57 |
| | 50.07 | 52.04 | 17.2 | 0.25 | 0.2656 | 2.61 | 19.22 | 72.34 |
| | 63.80 | 66.82 | 20.2 | 0.50 | 0.2626 | 2.64 | 14.97 | 56.99 |
| | 61.85 | 62.97 | 25.0 | 0.25 | 0.3279 | 2.11 | 15.88 | 48.43 |
| | 62.44 | 67.22 | 30.0 | 0.25 | 0.2155 | 3.22 | 14.88 | 69.04 |
| | 47.20 | 48.70 | 24.5 | 0.25 | 0.2755 | 2.52 | 20.53 | 74.53 |
| | 62.05 | 64.08 | 24.0 | 0.27 | 0.2785 | 2.49 | 15.61 | 56.04 |
| | 40.18 | 41.82 | 16.8 | 0.25 | 0.2644 | 2.62 | 23.91 | 90.44 |
| | 44.71 | 45.99 | 20.0 | 0.25 | 0.3137 | 2.21 | 21.74 | 69.31 |
| | 65.98 | 68.41 | 29.2 | 0.25 | 0.2766 | 2.51 | 14.62 | 52.85 |
| | 49.88 | 51.93 | 18.3 | 0.25 | 0.2648 | 2.62 | 19.26 | 72.72 |
| | 92.94 | 100.38 | 21.8 | 0.27 | 0.2162 | 3.21 | 9.96 | 46.08 |
| | 53.49 | 57.28 | 21.1 | 0.25 | 0.2218 | 3.12 | 17.46 | 78.69 |
| | 50.39 | 54.37 | 34.0 | 0.25 | 0.2003 | 3.46 | 18.39 | 91.81 |
| | 53.40 | 55.72 | 33.1 | 0.25 | 0.2618 | 2.65 | 17.59 | 67.19 |
| | 89.21 | 92.68 | 48.4 | 0.27 | 0.2690 | 2.58 | 10.79 | 40.11 |
| | 55.76 | 57.98 | 22.5 | 0.25 | 0.2647 | 2.62 | 17.25 | 65.16 |
| | 71.18 | 74.46 | 36.7 | 0.25 | 0.2592 | 2.67 | 13.43 | 51.82 |
| | 47.17 | 48.26 | 18.4 | 0.25 | 0.3108 | 2.23 | 20.72 | 66.67 |
| | 49.38 | 51.05 | 23.4 | 0.25 | 0.2725 | 2.54 | 19.59 | 71.88 |

Treatment A : Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.);
Treatment B : Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).
Subjects (b) (6) and (b) (6) did not complete both treatments; Subject (b) (6) completed only Treatment B and Subject (b) (6) completed only Treatment A.

Treatment: B

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) | CL (L/h) | Vz (L) |
|---|---|---|---|---|---|---|---|---|
| Descriptive Statistics (Safety Population) | | | | | | | | |
| N | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 29 |
| Mean | 58.882 | 61.762 | 24.94 | 0.288 | 0.26016 | 2.712 | 17.321 | 67.092 |
| SD | 16.6999 | 18.0148 | 7.4351 | 0.0866 | 0.033955 | 0.3871 | 4.3300 | 16.8662 |
| Min | 36.38 | 37.56 | 13.6 | 0.25 | 0.1825 | 2.11 | 8.46 | 36.52 |
| Median | 53.486 | 57.282 | 24.00 | 0.250 | 0.26479 | 2.618 | 17.458 | 66.962 |
| Max | 110.89 | 118.18 | 48.4 | 0.50 | 0.3279 | 3.80 | 26.62 | 101.87 |
| CV% | 28.4 | 29.2 | 29.8 | 30.1 | 13.1 | 14.3 | 25.0 | 25.1 |
| Descriptive Statistics (Completers) | | | | | | | | |
| N | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| Mean | 58.769 | 61.679 | 24.98 | 0.289 | 0.25951 | 2.720 | 17.382 | 67.487 |
| SD | 16.9951 | 18.3397 | 7.5693 | 0.0881 | 0.034392 | 0.3918 | 4.3966 | 17.0388 |
| Min | 36.38 | 37.56 | 13.6 | 0.25 | 0.1825 | 2.11 | 8.46 | 36.52 |
| Median | 53.441 | 56.499 | 23.70 | 0.250 | 0.26473 | 2.618 | 17.523 | 67.076 |
| Max | 110.89 | 118.18 | 48.4 | 0.50 | 0.3279 | 3.80 | 26.62 | 101.87 |
| CV% | 28.9 | 29.7 | 30.3 | 30.5 | 13.3 | 14.4 | 25.3 | 25.2 |

2. Plasma Pharmacokinetic Parameters and Descriptive Statistics of Acetaminophen sulfate by Treatment

Treatment: A

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) |
|---|---|---|---|---|---|---|
| (b) (6) | 22.20 | 24.82 | 4.27 | 1.00 | 0.2190 | 3.17 |
| | 20.93 | 22.47 | 4.08 | 0.50 | 0.2219 | 3.12 |
| | 26.83 | 29.57 | 4.79 | 2.00 | 0.2080 | 3.33 |
| | 35.68 | 39.19 | 7.35 | 1.50 | 0.2121 | 3.27 |
| | 22.53 | 24.34 | 3.80 | 1.50 | 0.2350 | 2.95 |
| | 32.90 | 37.97 | 5.25 | 0.50 | 0.1725 | 4.02 |
| | 30.63 | 36.08 | 4.79 | 1.00 | 0.1677 | 4.13 |
| | 44.16 | 47.20 | 8.11 | 1.02 | 0.2475 | 2.80 |
| | 38.00 | 41.51 | 5.92 | 2.00 | 0.2173 | 3.19 |
| | 44.06 | 48.53 | 7.08 | 1.50 | 0.2160 | 3.21 |
| | 37.78 | 42.64 | 5.97 | 1.50 | 0.1921 | 3.61 |
| | 36.03 | 39.29 | 6.19 | 1.50 | 0.2259 | 3.07 |
| | 45.56 | 48.06 | 8.52 | 1.50 | 0.2627 | 2.64 |
| | 53.94 | 61.71 | 7.66 | 2.50 | 0.1880 | 3.69 |
| | 21.74 | 22.90 | 4.78 | 0.50 | 0.2597 | 2.67 |
| | 37.35 | 40.48 | 7.48 | 1.50 | 0.2210 | 3.14 |
| | 21.49 | 22.77 | 4.35 | 0.50 | 0.2517 | 2.75 |
| | 62.98 | 68.50 | 10.5 | 1.50 | 0.2409 | 2.88 |
| | 25.90 | 27.87 | 4.94 | 1.00 | 0.2289 | 3.03 |
| | 54.39 | 63.40 | 7.75 | 2.00 | 0.1731 | 4.00 |
| | 31.25 | 35.46 | 4.95 | 1.00 | 0.1904 | 3.64 |
| | 20.98 | 24.04 | 3.41 | 1.50 | 0.1815 | 3.82 |
| | 30.39 | 33.78 | 4.80 | 1.50 | 0.2053 | 3.38 |
| | 38.12 | 41.72 | 6.48 | 1.50 | 0.2190 | 3.17 |
| | 35.79 | 39.30 | 5.64 | 1.50 | 0.2185 | 3.17 |
| | 9.07 | 9.89 | 1.49 | 2.00 | 0.2295 | 3.02 |
| | 41.88 | 44.71 | 7.64 | 1.00 | 0.2494 | 2.78 |
| | 32.07 | 34.05 | 5.70 | 1.50 | 0.2516 | 2.76 |
| | 29.83 | 31.39 | 5.87 | 1.00 | 0.2729 | 2.54 |

Treatment A : Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.);
Treatment B : Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).
Subjects (b) (6) and (b) (6) did not complete both treatments; Subject (b) (6) completed only Treatment B and Subject (b) (6) completed only Treatment A.

Treatment: A

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) |
|---|---|---|---|---|---|---|
| Descriptive Statistics (Safety Population) | | | | | | |
| N | 29 | 29 | 29 | 29 | 29 | 29 |
| Mean | 33.946 | 37.367 | 5.847 | 1.345 | 0.21996 | 3.205 |
| SD | 11.7004 | 13.1390 | 1.8372 | 0.5014 | 0.028340 | 0.4328 |
| Min | 9.07 | 9.89 | 1.49 | 0.50 | 0.1677 | 2.54 |
| Median | 32.901 | 37.973 | 5.700 | 1.500 | 0.21898 | 3.165 |
| Max | 62.98 | 68.50 | 10.5 | 2.50 | 0.2729 | 4.13 |
| CV% | 34.5 | 35.2 | 31.4 | 37.3 | 12.9 | 13.5 |
| Descriptive Statistics (Completers) | | | | | | |
| N | 28 | 28 | 28 | 28 | 28 | 28 |
| Mean | 34.013 | 37.486 | 5.852 | 1.340 | 0.21883 | 3.221 |
| SD | 11.9094 | 13.3643 | 1.8707 | 0.5097 | 0.028188 | 0.4319 |
| Min | 9.07 | 9.89 | 1.49 | 0.50 | 0.1677 | 2.54 |
| Median | 34.288 | 38.583 | 5.755 | 1.500 | 0.21897 | 3.165 |
| Max | 62.98 | 68.50 | 10.5 | 2.50 | 0.2729 | 4.13 |
| CV% | 35.0 | 35.7 | 32.0 | 38.0 | 12.9 | 13.4 |

Treatment: B

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) |
|---|---|---|---|---|---|---|
| (b) (6) | | | | | | |
| | 20.98 | 22.89 | 3.83 | 0.50 | 0.2276 | 3.05 |
| | 23.11 | 24.60 | 4.14 | 0.50 | 0.2363 | 2.93 |
| | 27.21 | 30.81 | 4.18 | 3.00 | 0.1892 | 3.66 |
| | 35.42 | 38.66 | 5.68 | 2.00 | 0.2147 | 3.23 |
| | 23.75 | 25.52 | 3.93 | 2.00 | 0.2396 | 2.89 |
| | 31.29 | 36.03 | 5.01 | 1.00 | 0.1738 | 3.99 |
| | 28.71 | 32.69 | 4.32 | 1.00 | 0.1911 | 3.63 |
| | 44.52 | 48.10 | 7.44 | 2.02 | 0.2388 | 2.90 |
| | 50.03 | 57.04 | 7.03 | 2.50 | 0.1885 | 3.68 |
| | 45.75 | 49.80 | 8.26 | 1.50 | 0.2238 | 3.10 |
| | 40.31 | 44.69 | 6.24 | 1.50 | 0.2045 | 3.39 |
| | 37.01 | 41.00 | 6.21 | 2.00 | 0.2159 | 3.21 |
| | 44.74 | 46.90 | 8.68 | 1.50 | 0.2729 | 2.54 |
| | 54.55 | 62.92 | 7.62 | 2.50 | 0.1803 | 3.84 |
| | 23.91 | 25.29 | 5.34 | 0.50 | 0.2506 | 2.77 |
| | 28.46 | 30.22 | 5.24 | 1.05 | 0.2462 | 2.82 |
| | 38.48 | 41.97 | 7.72 | 1.00 | 0.2155 | 3.22 |
| | 23.13 | 24.52 | 4.90 | 1.00 | 0.2609 | 2.66 |
| | 63.57 | 68.70 | 10.8 | 2.00 | 0.2396 | 2.89 |
| | 28.06 | 30.37 | 5.20 | 1.50 | 0.2338 | 2.97 |
| | 55.41 | 63.77 | 8.00 | 1.02 | 0.1794 | 3.86 |
| | 34.84 | 39.56 | 5.25 | 1.50 | 0.1873 | 3.70 |
| | 20.94 | 24.42 | 3.23 | 1.50 | 0.1695 | 4.09 |
| | 32.97 | 37.42 | 5.05 | 2.00 | 0.1891 | 3.67 |
| | 34.85 | 37.33 | 5.91 | 1.50 | 0.2477 | 2.80 |
| | 31.64 | 34.20 | 5.44 | 1.00 | 0.2253 | 3.08 |
| | 9.97 | 10.88 | 1.52 | 1.50 | 0.2253 | 3.08 |
| | 42.16 | 44.76 | 7.25 | 1.00 | 0.2557 | 2.71 |
| | 30.30 | 32.43 | 6.34 | 1.00 | 0.2426 | 2.86 |

Treatment A : Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.);
Treatment B : Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).
Subjects (b) (6) and (b) (6) did not complete both treatments; Subject (b) (6) completed only Treatment B and Subject (b) (6) completed only Treatment A.

Treatment: B

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) |
|---|---|---|---|---|---|---|
| Descriptive Statistics (Safety Population) | | | | | | |
| N | 29 | 29 | 29 | 29 | 29 | 29 |
| Mean | 34.691 | 38.189 | 5.854 | 1.468 | 0.21949 | 3.214 |
| SD | 11.9976 | 13.5004 | 1.9018 | 0.6246 | 0.028878 | 0.4410 |
| Min | 9.97 | 10.88 | 1.52 | 0.50 | 0.1695 | 2.54 |
| Median | 32.972 | 37.329 | 5.440 | 1.500 | 0.22526 | 3.077 |
| Max | 63.57 | 68.70 | 10.8 | 3.00 | 0.2729 | 4.09 |
| CV% | 34.6 | 35.4 | 32.5 | 42.5 | 13.2 | 13.7 |
| Descriptive Statistics (Completers) | | | | | | |
| N | 28 | 28 | 28 | 28 | 28 | 28 |
| Mean | 34.914 | 38.474 | 5.876 | 1.483 | 0.21853 | 3.228 |
| SD | 12.1566 | 13.6594 | 1.9330 | 0.6308 | 0.028939 | 0.4422 |
| Min | 9.97 | 10.88 | 1.52 | 0.50 | 0.1695 | 2.54 |
| Median | 33.905 | 37.377 | 5.560 | 1.500 | 0.22452 | 3.087 |
| Max | 63.57 | 68.70 | 10.8 | 3.00 | 0.2729 | 4.09 |
| CV% | 34.8 | 35.5 | 32.9 | 42.5 | 13.2 | 13.7 |

3. Plasma Pharmacokinetic Parameters and Descriptive Statistics of Acetaminophen glucuronide by Treatment

Treatment: A

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) |
|---|---|---|---|---|---|---|
| (b) (6) | 145.77 | 177.53 | 25.8 | 3.50 | 0.1571 | 4.41 |
| | 112.09 | 121.55 | 19.7 | 2.00 | 0.2188 | 3.17 |
| | 111.35 | 125.11 | 18.5 | 2.00 | 0.2049 | 3.38 |
| | 114.44 | 128.35 | 21.2 | 3.00 | 0.2020 | 3.43 |
| | 141.60 | 156.08 | 22.9 | 2.00 | 0.2224 | 3.12 |
| | 80.05 | 91.32 | 12.6 | 2.50 | 0.1935 | 3.58 |
| | 118.19 | 135.04 | 18.4 | 2.67 | 0.1993 | 3.48 |
| | 138.88 | 150.15 | 23.5 | 2.00 | 0.2404 | 2.88 |
| | 161.46 | 178.75 | 24.8 | 2.00 | 0.2192 | 3.16 |
| | 133.45 | 149.22 | 20.5 | 2.00 | 0.2099 | 3.30 |
| | 193.29 | 218.79 | 29.3 | 2.50 | 0.2000 | 3.46 |
| | 166.80 | 183.92 | 26.1 | 2.50 | 0.2249 | 3.08 |
| | 152.36 | 159.75 | 27.8 | 2.50 | 0.2894 | 2.40 |
| | 61.58 | 70.20 | 8.88 | 3.00 | 0.2006 | 3.45 |
| | 110.08 | 115.68 | 20.0 | 1.50 | 0.2819 | 2.46 |
| | 132.28 | 146.79 | 25.3 | 1.50 | 0.2096 | 3.31 |
| | 180.17 | 191.29 | 30.9 | 2.55 | 0.2697 | 2.57 |
| | 101.58 | 108.62 | 17.5 | 1.50 | 0.2631 | 2.63 |

| (b) (6) | | | | | | |
|---|---|---|---|---|---|---|
| | 130.73 | 141.96 | 22.4 | 3.00 | 0.2387 | 2.90 |
| | 80.04 | 93.32 | 10.8 | 2.50 | 0.1852 | 3.74 |
| | 143.73 | 173.58 | 20.4 | 3.00 | 0.1646 | 4.20 |
| | 149.36 | 170.83 | 22.5 | 2.00 | 0.1910 | 3.63 |
| | 169.49 | 195.09 | 25.3 | 2.00 | 0.1871 | 3.70 |
| | 143.13 | 157.77 | 23.0 | 2.52 | 0.2267 | 3.06 |
| | 126.24 | 141.37 | 19.2 | 2.50 | 0.2069 | 3.35 |
| | 195.58 | 211.60 | 33.2 | 2.00 | 0.2440 | 2.84 |
| | 128.78 | 138.48 | 23.0 | 2.00 | 0.2435 | 2.85 |
| | 128.65 | 137.59 | 20.6 | 3.00 | 0.2571 | 2.70 |
| | 115.48 | 120.55 | 22.7 | 2.00 | 0.2958 | 2.34 |

Treatment A : Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.);
Treatment B : Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).
Subjects (b) (6) and (b) (6) did not complete both treatments; Subject (b) (6) completed only Treatment B and Subject (b) (6) completed only Treatment A.

Treatment: A

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) |
|---|---|---|---|---|---|---|
| Descriptive Statistics (Safety Population) | | | | | | |
| N | 29 | 29 | 29 | 29 | 29 | 29 |
| Mean | 133.332 | 147.941 | 21.96 | 2.336 | 0.22233 | 3.193 |
| SD | 31.7781 | 35.5568 | 5.3928 | 0.5087 | 0.035287 | 0.5030 |
| Min | 61.58 | 70.20 | 8.88 | 1.50 | 0.1571 | 2.34 |
| Median | 132.284 | 146.786 | 22.50 | 2.500 | 0.21879 | 3.168 |
| Max | 195.58 | 218.79 | 33.2 | 3.50 | 0.2958 | 4.41 |
| CV% | 23.8 | 24.0 | 24.6 | 21.8 | 15.9 | 15.8 |
| Descriptive Statistics (Completers) | | | | | | |
| N | 28 | 28 | 28 | 28 | 28 | 28 |
| Mean | 133.499 | 148.311 | 22.01 | 2.312 | 0.22109 | 3.211 |
| SD | 32.3482 | 36.1525 | 5.4853 | 0.5015 | 0.035283 | 0.5029 |
| Min | 61.58 | 70.20 | 8.88 | 1.50 | 0.1571 | 2.34 |
| Median | 132.867 | 148.003 | 22.60 | 2.250 | 0.21435 | 3.235 |
| Max | 195.58 | 218.79 | 33.2 | 3.50 | 0.2958 | 4.41 |
| CV% | 24.2 | 24.4 | 24.9 | 21.7 | 16.0 | 15.7 |

Treatment: B

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) |
|---|---|---|---|---|---|---|
| (b) (6) | | | | | | |
| | 125.03 | 138.75 | 19.5 | 4.50 | 0.2296 | 3.02 |
| | 117.82 | 127.11 | 21.5 | 3.00 | 0.2295 | 3.02 |
| | 113.09 | 131.65 | 18.3 | 3.00 | 0.1821 | 3.81 |
| | 118.82 | 130.27 | 19.3 | 2.00 | 0.2191 | 3.16 |
| | 151.87 | 167.23 | 24.2 | 2.00 | 0.2174 | 3.19 |
| | 73.85 | 84.28 | 11.4 | 3.00 | 0.1966 | 3.53 |
| | 130.27 | 145.75 | 19.1 | 3.50 | 0.2113 | 3.28 |
| | 148.33 | 161.38 | 25.4 | 2.02 | 0.2315 | 2.99 |
| | 183.95 | 214.74 | 27.5 | 2.50 | 0.1835 | 3.78 |
| | 129.11 | 141.43 | 20.6 | 2.50 | 0.2264 | 3.06 |
| | 203.75 | 227.92 | 31.4 | 2.00 | 0.2076 | 3.34 |
| | 180.40 | 199.92 | 28.7 | 2.00 | 0.2233 | 3.10 |
| | 154.86 | 163.02 | 28.7 | 3.00 | 0.2856 | 2.43 |
| | 59.83 | 69.53 | 8.66 | 3.00 | 0.1844 | 3.76 |
| | 131.52 | 141.03 | 24.0 | 1.50 | 0.2460 | 2.82 |
| | 124.31 | 133.03 | 20.1 | 3.07 | 0.2545 | 2.72 |
| | 130.73 | 146.45 | 21.7 | 2.00 | 0.2042 | 3.39 |
| | 175.85 | 187.32 | 29.9 | 1.50 | 0.2676 | 2.59 |
| | 94.56 | 99.25 | 18.2 | 2.00 | 0.2898 | 2.39 |
| | 127.72 | 138.63 | 22.4 | 2.00 | 0.2402 | 2.89 |
| | 83.83 | 95.33 | 12.3 | 2.58 | 0.1990 | 3.48 |
| | 146.54 | 173.72 | 20.3 | 2.50 | 0.1729 | 4.01 |
| | 159.79 | 182.47 | 23.8 | 2.50 | 0.1927 | 3.60 |
| | 175.92 | 202.65 | 26.8 | 2.00 | 0.1848 | 3.75 |
| | 171.44 | 184.14 | 27.4 | 3.00 | 0.2559 | 2.71 |
| | 121.29 | 131.52 | 20.6 | 2.50 | 0.2328 | 2.98 |
| | 180.16 | 200.58 | 28.0 | 3.00 | 0.2170 | 3.19 |
| | 133.72 | 142.26 | 23.0 | 2.00 | 0.2613 | 2.65 |
| | 122.57 | 128.51 | 27.2 | 1.50 | 0.2829 | 2.45 |

Treatment A : Acetaminophen Injection (1000 mg IV infusion; B.Braun Medical Inc.);
Treatment B : Ofirmev (1000 mg IV infusion; Mallinckrodt Pharmaceuticals).
Subjects (b) (6) and (b) (6) did not complete both treatments; Subject (b) (6) completed only Treatment B and Subject (b) (6) completed only Treatment A.

Treatment: B

| Subject | AUC0-t (h*ug/mL) | AUC0-inf (h*ug/mL) | Cmax (ug/mL) | tmax (h) | kel (/h) | t1/2 (h) |
|---|---|---|---|---|---|---|
| Descriptive Statistics (Safety Population) | | | | | | |
| N | 29 | 29 | 29 | 29 | 29 | 29 |
| Mean | 136.928 | 151.374 | 22.41 | 2.471 | 0.22516 | 3.141 |
| SD | 34.2100 | 38.7303 | 5.5135 | 0.6692 | 0.032806 | 0.4496 |
| Min | 59.83 | 69.53 | 8.66 | 1.50 | 0.1729 | 2.39 |
| Median | 130.728 | 142.258 | 22.40 | 2.500 | 0.22335 | 3.103 |
| Max | 203.75 | 227.92 | 31.4 | 4.50 | 0.2898 | 4.01 |
| CV% | 25.0 | 25.6 | 24.6 | 27.1 | 14.6 | 14.3 |
| Descriptive Statistics (Completers) | | | | | | |
| N | 28 | 28 | 28 | 28 | 28 | 28 |
| Mean | 137.379 | 152.029 | 22.50 | 2.450 | 0.22411 | 3.156 |
| SD | 34.7500 | 39.2770 | 5.5963 | 0.6714 | 0.032911 | 0.4505 |
| Min | 59.83 | 69.53 | 8.66 | 1.50 | 0.1729 | 2.39 |
| Median | 131.122 | 144.004 | 22.70 | 2.500 | 0.22124 | 3.133 |
| Max | 203.75 | 227.92 | 31.4 | 4.50 | 0.2898 | 4.01 |
| CV% | 25.3 | 25.8 | 24.9 | 27.4 | 14.7 | 14.3 |

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DAVID J LEE
09/01/2017

YUN XU
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