# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 204031Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 204-031 | Submission Date(s): May 28, 2013 |
| Brand Name (proposed) | Xartemis |
| Generic Name | Oxycodone (OC) and acetaminophen (APAP) extended-release (ER) tablets |
| Reviewer | Wei Qiu, Ph.D. |
| Team Leader | Yun Xu, Ph.D. |
| OCP Division | DCPII |
| OND division | DAAAP |
| Sponsor | Mallinckrodt |
| Relevant IND(s) | IND 104,702 |
| Submission Type | Original Submission; 505(b)(2) |
| Formulation; Strength(s) | Oral tablet; 7.5 mg Oxycodone and 325 mg acetaminophen |
| Indication | Management of (b) (4) acute pain where use of an opioid analgesic is appropriate |

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# 1 Executive Summary

## 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed this submission dated May 28, 2013 and finds it acceptable from clinical pharmacology perspective.

Optional Intra-Division Level OCP briefing was held on October 23, 2013.

## 1.2 Phase IV Commitments

None.

## 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Key clinical pharmacology findings:

1. Xartemis exhibited equivalent dose normalized Cmax and AUC values of oxycodone and acetaminophen in comparison to the respective listed drugs, Roxicodone (oxycodone HCl) and Ultracet (tramadol HCl/acetaminophen) tablets following both single dose and multiple dose administrations.
2. Both low fat and high fat foods do not have a significant effect on oxycodone and acetaminophen pharmacokinetics following the single dose administration of Xartemis; the product can be taken without regard to meals.
3. After multiple dosing of two Xartemis tablets every 12 hours, steady state plasma concentrations of oxycodone and acetaminophen were achieved following 1 day administration.
4. (b) (4)

Xartemis is an extended release (ER) combination oral tablet containing two active ingredients, oxycodone and acetaminophen. Mallinckrodt submitted a 505(b)(2) NDA 204-031 for Xartemis ER tablets for the management of (b) (4) acute pain where use of an opioid analgesic is appropriate. COV795 was used throughout the

clinical development process for Xartemis ER tablets so both COV795 and Xartemis are used in this review and they are interchangeable. Currently, there is no approved NDA product which contains both oxycodone and acetaminophen, either in immediate release or extended release formulation. (b) (4) However, the Agency agreed with sponsor's alternative proposal to rely on the Agency's previous finding of the safety and efficacy for Roxicodone (oxycodone) tablet (NDA 21-011) and Ultracet (tramadol/acetaminophen) tablet (NDA 21-123).

The clinical and clinical pharmacology database for this NDA consists of 11 PK studies, 1 abuse potential study (Study 244), and 2 Phase 3 studies (Studies 182 and 181). Earlier formulations and/or strengths were used in 6 PK studies (Studies 041, 043, 107, 045, 042, and 044). The final to-be-marketed tablet with debossed logos was used in pivotal single dose and multiple dose relative bioavailability studies (Studies 256 and 255), food effect study (Study 171), and a Phase 3 open-label study (Study 181). The final formulation was also used in two other relative bioavailability studies where listed drugs (Roxicodone and Ultracet tablets) were not included as references (Studies 170 and 172). The tablets without the debossed logos were used in the Phase 3 blinded study (Study 182) and human abuse liability study (Study 244). The sponsor used the comparative hardness and dissolution data to link these two formulations and it was considered acceptable by ONDQA/Biopharm reviewer (refer to ONDQA/Biopharm review for this assessment). The safety and efficacy of this proposed combination product was evaluated in pivotal Phase 3 clinical trials. This review will focus on the pivotal relative bioavailability studies (Studies 256 and 255), food effect study (Study 171), and PK data from human abuse liability study (Study 244).

**Relative Bioavailability of Xartemis in Comparison to the Listed Drugs ((Roxicodone tablet and Ultracet tablet)**

Single Dose:

After dose normalization, Xartemis exhibited equivalent systemic exposure to oxycodone in comparison to listed drug, Roxicodone tablet. The point estimate (90% CI) of the geometric mean ratio (Xartemis tablets/Roxicodone tablet) for dose normalized Cmax, AUCt, and AUCinf values of oxycodone are 92% (85 – 100%), 100% (96 – 105%), and

100% (96 – 105%), respectively. After dose normalization, Xartemis has equivalent systemic exposure to acetaminophen in comparison to listed drug, Ultracet tablet. The point estimates (90% CI) of the geometric mean ratios (Xartemis tablet/Ultracet tablet) for dose normalized Cmax, AUCt and AUCinf values of acetaminophen are 106% (98 – 115%), 96% (94 – 99%), and 98% (96 – 101%), respectively.

Multiple Doses:

After dose normalization, Xartemis exhibited equivalent systemic exposure to oxycodone in comparison to listed drug, Roxicodone tablet. The point estimate (90% CI) of the geometric mean ratio (Xartemis tablets/Roxicodone tablet) for dose normalized Cmaxss and AUC0-12ss are 107% (98 – 117%) and 110% (104 – 117%), respectively. After dose normalization, Xartemis has equivalent Cmax and AUC values to acetaminophen in comparison to listed drug, Ultracet tablet. The point estimates (90% CI) of the geometric mean ratios (Xartemis tablet/Ultracet tablet) for dose normalized Cmaxss and AUC0-12ss values of acetaminophen are 96% (85 – 107%) and 95% (91 – 99%), respectively.

**Multiple Dose PK of Xartemis:**

After multiple dosing of two Xartemis tablets every 12 hours, steady state plasma concentrations of oxycodone and acetaminophen were achieved following 1 day administration since the pre-dose concentration obtained on Days 2 through 5 were similar. The accumulation index calculated as the Cmin under steady state conditions divided by the Cmin after the first dose, drug accumulates 1.7 fold for oxycodone and 1.4 fold for acetaminophen.

**Food Effect**:

Low and high fat meals delayed median oxycodone Tmax by 1 and 2 hrs, respectively. On average, low fat and high fat meal increased AUCt and AUCinf by 15% but the 90% CIs for the geometric mean ratios (low fat fed/fasting or high fat fed/fasting) were within the no effect range of 80% to 125%. Low fat meal increased oxycodone Cmax by 25% and high fat increased oxycodone Cmax by 12%. The 90% CIs for the geometric mean ratios of Cmax values are 117 to 134% and 105 to 102%, for low fat fed/fasting and high fat fed/fasting, respectively. Low and high fat meals delayed median acetaminophen Tmax by 1.5 hours. Either low fat or high fat meal did not affect the AUC values of

acetaminophen. Low fat and high fat meals decreased acetaminophen Cmax values by 23 to 24%. These changes in Cmax and AUC values of oxycodone and acetaminophen are considered to be not significant and the product can be taken without regard to meals.

**Alcohol Effect:**

Refer to the ONDQA/Biopharm review for the In vitro alcohol effect on the dissolution of Xartemis. Per Pre-NDA meeting minutes, it was agreed that the results of dissolution testing do not indicate potential for dose-dumping in the presence of alcohol, and that an in vivo human alcohol interaction study will not be necessary. Sponsor did not conduct in vivo alcohol interaction study for Xartemis.

**Abuse Potential:**

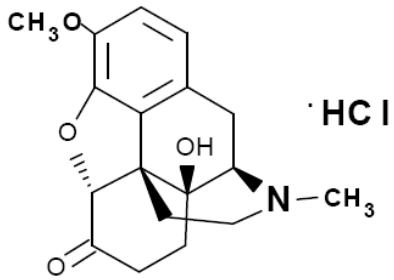
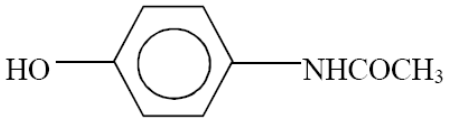
(b) (4)

## 2 Question Based Review

### 2.1 General Attributes of the Drug

***1. What are the highlights of the chemistry and physico-chemical properties of the drug substances, and the formulation of the drug product?***

**Table 1** Physical-Chemical Properties of Oxycodone Hydrochloride and Acetaminophen

| Drug Name | Oxycodone Hydrochloride | Acetaminophen |
|---|---|---|
| Chemical Name | 1) Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5α)-<br>2) 4,5 α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride | 1) N-acetyl-p-aminophenol<br>2) 4'-hydroxyacetanilide<br>3) p-hydroxyacetanilide<br>4) p-acetamidophenol<br>5) p-acetaminophenol<br>6) p-acetylaminophenol |
| Structure |  |  |
| Molecular Formulation | $C_{18}H_{21}NO_4 \cdot HCl$ | $C_8H_9NO_2$ |
| MW | 351.83 | 151.16 |
| Appearance | White to off-white, fine, crystalline powder. | White crystalline powder possessing a bitter taste. |

Xartemis is a multilayer tablet, comprised of an immediate release (IR) layer and a gastroretentive extended release (ER layer). Xartemis utilizes the AcuForm® delivery technology which is designed to swell in gastric fluid and gradually release the remainder of oxycodone and acetaminophen to the upper gastrointestinal tract. The IR layer contains (b) (4)% of the total oxycodone and (b) (4)% of the total acetaminophen dose, whereas the ER layer contains (b) (4)% of the total oxycodone and (b) (4)% of the total acetaminophen dose. The components and compositions of the drug product, Xartemis tablet, are listed in **Table 2**. The inactive ingredients include polyethylene oxide, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, polyvinyl alcohol, magnesium stearate, titanium dioxide, polyethylene glycol, colloidal silicon dioxide, talc, pregelatinized starch, FD&C Blue #2 aluminum lake, citric acid anhydrous powder, and edentate disodium.

**Table 2** Components and Composition of the to-be-marketed formulations for Xartemis tablet by layer

| | (b) (4) Layer | | | |
|---|---|---|---|---|
| **Ingredient** | **Grade** | **Role** | **mg in Tablet** | **w/w %** |
| Oxycodone HCl[1] | USP | Active | 1.875 | 0.197% |
| Acetaminophen | USP | Active | 162.500 | 17.073% |
| Hydroxypropyl Cellulose (b) (4) | NF | | | (b) (4) |
| Microcrystalline Cellulose (b) (4) | NF | | | |
| Croscarmellose Sodium (b) (4) | NF | | | |
| Colloidal Silicon Dioxide (b) (4) | NF | | | |
| Magnesium Stearate | NF | | | |
| Pregelatinized Starch (b) (4) | NF | | | |
| Citric Acid Anhydrous Powder | USP | | | |
| Edetate Disodium | USP | | | |
| | | | | (b) (4) |
| Polyethylene Oxide (Polyox) (b) (4) molecular weight = (b) (4) | NF | | | (b) (4) |
| | | | | (b) (4) |

***2. What are the proposed mechanism(s) of action and therapeutic indication(s)?***

Oxycodone HCl is a pure opioid agonist and is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia.

Acetaminophen is a non-opiate, non-salicylate analgesic, and antipyretic. The site and mechanism for the analgesic effect of acetaminophen has not been determined. The antipyretic effect of acetaminophen is accomplished through the inhibition of endogenous pyrogen action on the hypothalamic heat-regulating centers.

Xartemis is indicated for the management of [redacted] (b) (4) acute pain where the use of an opioid analgesic is appropriate.

***3. What are the proposed dosage(s) and route(s) of administration?***

Xartemis tablets contain both immediate release and extended-release layers of oxycodone and acetaminophen for oral administration. The recommended dose is 2 tablets every 12 hours administered with or without food.

2.2 General Clinical Pharmacology

***1. What is known about the PK characteristics of oxycodone and acetaminophen following the administration of the listed drugs, Roxicodone and Ultracet tablets?***

The oral bioavailability of oxycodone is approximately 60% to 87%. Food has small effect on the oral absorption of oxycodone. On average, oxycodone AUC values were increased by 27%. Food caused a delay in Tmax (1.25 to 2.54 hour). Dose proportionality was established over the dose range of 5 to 30 mg. Plasma protein binding at 37oC and a pH of 7.4 was about 45%. It takes approximately 18 to 24 hours to reach steady-state with Roxicodone. Oxycodone is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone. The formation of noroxycodone is mainly medicated by CYP3A4 and the formation of oxymorphone is mediated by CYP2D6. Oxycodone and its metabolites are excreted primarily via the kidney. Apparent elimination half-life of oxycodone is 3.5 to 4 hours.

The peak plasma concentrations of acetaminophen following the administration of Ultracet occur within 1 hour and are not affected by tramadol. Oral absorption of acetaminophen following administration of Ultracet occurs primarily in the small intestine. When Ultracet was administered with food, acetaminophen Tmax was delayed for approximately 1 hour for. However, Cmax and AUC values were not affected. Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein. Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: 1) conjugation with glucuronide; 2) conjugation with sulfate; and 3) oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a

reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2, and CYP3A4 as additional pathways. In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, Sulfate-, and glutathione-derived metabolites lack biologic activity. The half-life of acetaminophen is about 2 to 3 hours in adults. Acetaminophen is eliminated from the body in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

***2. Were the active moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?***

For oxycodone, the activity is primarily due to the parent compound oxycodone, which is measured in all PK studies. Acetaminophen was measured in all PK studies.

***3. How do oxycodone and acetaminophen accumulate following multiple dose administration of Xartemis?***

Multiple dose pharmacokinetics of oxycodone and acetaminophen following the administration of Xartemis were assessed in Study 255 where two Xartemis tablets (2 x 7.5 mg oxycodone/325 mg acetaminophen) were administered every 12 hours over 4.5 days in healthy subjects under fasted conditions. The multiple dose PK of Xartemis were also compared with the two listed drugs, Roxicodone (1 x 15 mg oxycodone) and Ultracet (1 x 37.5 mg tramadol/325 mg acetaminophen) administered orally every 6 hours over 4.5 days, as well as Percocet (1 x 7.5 mg oxycodone/325 mg acetaminophen) administered orally every 6 hours over 4.5 days.

After multiple dosing of two Xartemis tablets every 12 hours, steady state plasma concentrations of oxycodone and acetaminophen were achieved following 1 day administration since the pre-dose concentration obtained on Days 2 through 5 were similar. Steady state pharmacokinetic parameters for oxycodone and acetaminophen are summarized in **Table 3**. The mean half-life values were 5.4 hours for oxycodone and 6.9 hours for acetaminophen. The degree of fluctuation (DFL) of the plasma concentration was calculated as [100 x ($C_{max}^{ss}$ – $C_{min}^{ss}$)/$C_{avg}^{ss}$] where $C_{avg}^{ss}$ is the average observed plasma concentration during the dosing interval at steady state, calculated as ($AUC_{0\text{-}12h}^{ss}$)/12. The mean DFL was 83.89% for oxycodone and 169.13% for acetaminophen.

Comparison of the steady state Cmin and the Cmin values after the first dose suggested that oxycodone and acetaminophen accumulated 1.7-fold and 1.4-fold following the administration of Xartemis every 12 hours, respectively.

**Table 3** Steady-state pharmacokinetic parameters (mean (SD)) following administration of 2 Xartemis tablets (2 x 7.5 mg oxycodone/325 mg acetaminophen) every 12 hours for 4.5 days (Study 255)

| PK Parameters | Oxycodone (N = 24) | Acetaminophen (N = 24) |
|---|---|---|
| ***Day 1*** | | |
| AUC0-12h (ng.h/mL) | 136.14 (23.7) | 24924.32 (5667.48) |
| Cmax (ng/mL) | 16.04 (3.64) | 4857.50 (1066.47) |
| Cmin (ng/mL) | 6.90 (1.98) | 738.17 (227.04) |
| ***Days 2 through 5*** | | |
| Day 2 Cmin (ng/mL) | 11.10 (2.52) | 1146.25 (391.14) |
| Day 3 Cmin (ng/mL) | 11.01 (2.59) | 1037.92 (301.11) |
| Day 4 Cmin (ng/mL) | 12.32 (2.88) | 1105.88 (435.60) |
| Day 5 Cmin (ng/mL) | 11.68 (2.80) | 1052.00 (339.26) |
| ***Day 5*** | | |
| $AUC_{0\text{-}12h}^{SS}$ (ng.h/mL) | 208.34 (45.34) | 28160.40 (5807.09) |
| $C_{avg}^{SS}$ (ng/mL) | 17.36 (3.78) | 2346.70 (483.92) |
| $C_{max}^{SS}$ (ng/mL) | 24.00 (5.38) | 4792.50 (1132.40) |
| $C_{min}^{SS}$ (ng/mL) | 9.31 (2.39) | 852.75 (273.25) |
| DFL (%) | 83.89 (17.58) | 169.13 (39.83) |
| ***Days 5 through 6*** | | |
| Kel (1/h) | 0.1318 (0.0223) | 0.1072 (0.0285) |
| T1/2 (h) | 5.40 (0.87) | 6.90 (1.76) |

*data from Table 11-2 and 11-3 for Study 255

### *4. What is the abuse potential of Xartemis?*

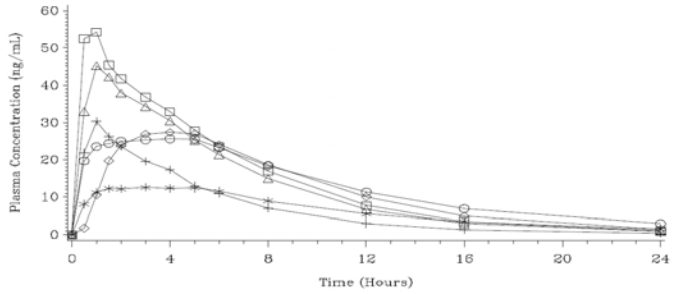
Abuse Potential Study 244 contains PK data besides drug liking data. This review will mainly focus on PK data. Also refer to the review conducted by Control Substance Staff (CSS).

(b) (4)


**Figure 1** shows the PK profiles and **Table 4** summaries the PK parameters of oxycodone. Oxycodone Cmax values of crushed COV795 tablets (30 mg OC/1300 mg APAP) in capsules were similar to intact COV795 tablets (30 mg OC/1300 mg APAP).

Median Tmax values of oxycodone were delayed by 1.5 hour. For the reference product, Percocet, the oxycodone PK profiles of crushed Percocet tablets (30 mg OC/1300 mg APAP) in capsules were similar to intact Percocet tablets (30 mg OC/1300 mg APAP) in capsules. Although mean oxycodone Cmax values were 16% lower for tampered IR-OC/APAP group, there was an overlap in Cmax values for intact and tampered IR-OC/APAP treatments. On average, oxycodone Cmax values of COV795 treatment groups (30 mg OC/1300 mg APAP) are approximately 50% less than that of IR-OC/APAP treatment groups (30 mg OC/1300 mg APAP), either intact or crushed. In addition, the median Tmax values of oxycodone of COV795 treatment groups (30 mg OC/1300 mg APAP) are 1 to 2 hours longer than that of IR-OC/APAP treatment groups (30 mg OC/1300 mg APAP).

**Figure 1** Mean Plasma Concentrations of Oxycodone over 24 Hours by Treatment




Treatment * = COV795 (15 mg OC/650 mg APAP)
Treatment o = COV795 (30 mg OC/1,300 mg APAP)
Treatment + = IR-OC/APAP (15 mg OC/650 mg APAP)
Treatment □ = IR-OC/APAP (30 mg OC/1,300 mg APAP)
Treatment ◊ = Tampered COV795 (30 mg OC/1,300 mg APAP)
Treatment Δ = Tampered IR-OC/APAP (30 mg OC/1,300 APAP)

**Table 4** Mean (SD) PK parameters for Oxycodone by Treatment (PK population)

| PK parameter | A COV795 (15 mg OC/650 mg APAP) N = 57 | B COV795 (30 mg OC/1300 mg APAP) N = 56 | C IR-OC/APAP (15 mg OC/650 mg APAP) N = 57 | D IR-OC/APAP (30 mg OC/1300 mg APAP) N = 58 | E Tampered COV795 (30 mg OC/1300 mg APAP) N = 58 | F Tampered IR-OC/APAP (30 mg OC/1300 mg APAP) N = 58 |
|---|---|---|---|---|---|---|
| Tmax (hr)* | 3.08 (0.58, 6.08) | 2.08 (0.55, 6.12) | 1.08 (0.42, 4.18) | 1.06 (0.52, 8.15) | 3.59 (1.10, 6.10) | 1.08 (0.52, 5.17) |
| Cmax (ng/mL) | 14.42 (3.60) | 31.36 (7.55) | 34.09 (9.71) | 66.15 (24.40) | 32.22 (8.51) | 55.11 (18.68) |
| AUCt (ng.hr/mL) | 153.04 (41.77) | 313.31 (84.70) | 163.72 (40.94) | 343.00 (101.2) | 276.71 (77.25) | 298.80 (80.63) |
| AUCinf (ng.hr/mL) | 167.76 (45.88) | 339.83 (94.71) | 166.35 (42.49) | 349.09 (105.6) | 286.54 (83.29) | 303.84 (83.41) |
| T1/2 (hr) | 6.46 (2.08) | 6.32 (2.29) | 3.92 (0.62) | 3.85 (0.57) | 4.18 (0.75) | 3.83 (0.56) |

Source of data: table 14.2.1-3 *Median (min, max)


2.3 Intrinsic Factors

***1. What is the pediatric plan?***

In line with the Agency's current policy with respect to pure opioids, sponsor would be required to conduct pharmacokinetics studies in all ages. Efficacy studies will be required in children up to 2 years of age. At this time, sponsor is requesting full deferral of pediatric studies and the request is granted because adult studies are completed and ready for approval.

2.4 General Biopharmaceutics

***1. What is the relative bioavailability of Xartemis related to the listed drugs, Roxicodone and Ultracet, following single dose and multiple administrations?***

Xartemis exhibited equivalent systemic exposure to oxycodone and acetaminophen after dose normalization in comparison to the respective listed drugs, Roxicodone and Ultracet tablets following single dose and multiple dose administrations. Although there was a mutual agreement that Percocet (7.5 mg oxycodone/325 mg acetaminophen) immediate release tablets are not appropriate to be used as a listed drug because it is an ANDA product, sponsor still included it in the single dose and multiple dose relative bioavailability studies. Results indicated that Xartemis had equivalent AUC but 28% lower Cmax for oxycodone and equivalent exposure for acetaminophen following single

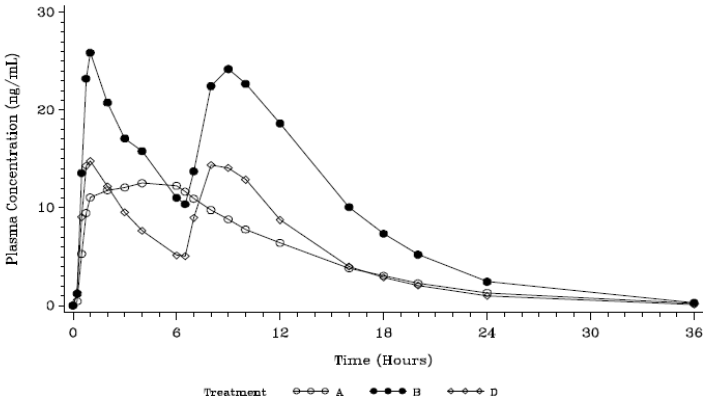
dose administration in comparison to Percocet. Equivalent exposures to oxycodone and acetaminophen were demonstrated following multiple dose administration between Xartemis and Percocet.

Single Dose Study 256

The relative bioavailability of oxycodone and acetaminophen following the administration of Xartemis tablets administered as a single dose of 2 x 7.5 mg oxycodone/325 mg acetaminophen in comparison to listed drugs, Roxicodone tablet administered as 1 x 15 mg dose every 6 hours for 2 doses, and Ultracet tablet administered as 1 x 37.5 mg tramadol/325 mg acetaminophen dose every 6 hours for 2 doses, were evaluated in a single dose, open-label, randomized, four-period cross-over study in healthy subjects under fasting condition. The immediate release Percocet administered as 1 x 7.5 mg oxycodone /325 mg acetaminophen every 6 hours for 2 doses was also included in this study. There was a minimum 7-day interval between the start of each period. Blood samples for the determination of plasma concentrations of oxycodone and acetaminophen were drawn before dosing and at 15, 30, and 45 minutes, and at 1, 2, 3, 4, 6, 6 hours 30 minutes, 7, 8, 9, 10, 12, 16, 18, 20, 24, and 36 hours after dosing.

The oxycodone plasma concentration-time profiles for Xartemis tablets and reference products are shown in **Figure 5**. PK parameters of oxycodone are summarized in **Table 5**. The statistical analysis results for the assessment of relative bioavailability based on dose normalized PK parameters of oxycodone are presented in the **Table 6**. The dose normalized oxycodone Cmax and AUC values for Xartemis tablets are equivalent to Roxicodone tablet since 90% CIs for the comparison of Cmax (85%, 100%), AUC0-t (96%, 105%) and AUC0-inf (96%, 105%) fell within the 80-125% bounds. The dose normalized oxycodone AUC values for Xartemis are equivalent to Percocet but Cmax values are 28% lower than Percocet. The shapes of oxycodone PK profiles following the administration of Xartemis ER tablets are different from the immediate release reference products.

**Figure 5** Mean Oxycodone plasma concentration time profiles (Study 256)




Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally 1 tablet at a time.
Treatment B: 1 tablet of, Roxicodone (15 mg OC) administered orally every 6 hours (Q6h) for 2 doses.
Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 2 doses.

**Table 5** Mean (SD) PK parameter of oxycodone following single oral administration of 2 x 7.5 mg oxycodone/325 mg acetaminophen tablets, 1 x 15 mg Roxicodone tablet administered Q6h for 2 doses, and 1 x Percocet 7.5 mg oxycodone/325 mg acetaminophen administered Q6h for 2 doses in healthy adult subjects under fasted condition (Study 256)

| Parameter | Treatment A COV795 (2 tablets once) (n = 29) | Treatment B Roxicodone (1 tablet twice) (n = 29) | Treatment D Percocet (1 tablet twice) (n = 29) |
|---|---|---|---|
| $AUC_{0-t}$ (ng•h/mL) | 167.90 (36.83) | 334.61 (62.46) | 169.85 (34.23) |
| $AUC_{0-inf}$ (ng•h/mL) | 169.34 (37.03) | 336.30 (62.77) | 171.53 (34.05) |
| $C_{max}$ (ng/mL) | 14.28 (2.94) | 31.27 (8.17) | 19.42 (4.62) |
| $T_{max}$ (h)[a] | 4.00 (0.75, 12.00) | 8.00 (0.75, 12.00) | 8.00 (0.50, 12.00) |
| $t_{lag}$ (h)[a] | 0.00 (0.00, 0.25) | 0.00 (0.00, 0.27) | 0.00 (0.00, 0.25) |
| $K_{el}$ ($h^{-1}$) | 0.1577 (0.0223) | 0.1796 (0.0141) | 0.1764 (0.0226) |
| $t_{1/2}$ (h) | 4.47 (0.58) | 3.88 (0.31) | 3.99 (0.48) |

Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally 1 tablet at a time.
Treatment B: 1 tablet of Roxicodone (15 mg OC) administered Q6h for 2 doses.
Treatment D: 1 tablet of IR-OC/APAP (7.5 mg OC/325 mg APAP) administered orally Q6h for 2 doses.
[a] For $T_{max}$ and $t_{lag}$, the median (minimum, maximum) values are presented.

**Table 6** Statistical Analysis of Plasma PK Parameters of Oxycodone (Study 256)

| Dose-Normalized Parameter | Treatment | N | Geometric LS Means | Treatment Comparison | Ratio of Geometric LS Means (%) | 90% CI of the Ratio |
|---|---|---|---|---|---|---|
| $AUC_{0-t}$/Dose (ng•h/mL/mg) | A | 29 | 10.971 | A/B | 100.122 | (95.571, 104.891) |
| | B | 29 | 10.958 | B/D | 97.878 | (93.453, 102.511) |
| | D | 29 | 11.195 | A/D | 97.997 | (93.546, 102.660) |
| $AUC_{0-inf}$/Dose (ng•h/mL/mg) | A | 29 | 11.071 | A/B | 100.517 | (95.997, 105.250) |
| | B | 29 | 11.014 | B/D | 97.356 | (93.003, 101.912) |
| | D | 29 | 11.314 | A/D | 97.859 | (93.463, 102.463) |
| $C_{max}$/Dose (ng/mL/mg) | A | 29 | 0.932 | A/B | 92.221 | (85.134, 99.897) |
| | B | 29 | 1.011 | B/D | 78.618 | (72.610, 85.122) |
| | D | 29 | 1.285 | A/D | 72.502 | (66.936, 78.531) |

Note: An analysis of variance was performed with the natural log-transformed dose-normalized PK parameters as the dependent variable and sequence, treatment, and period as fixed effects and subjects nested within sequences as a random effect.

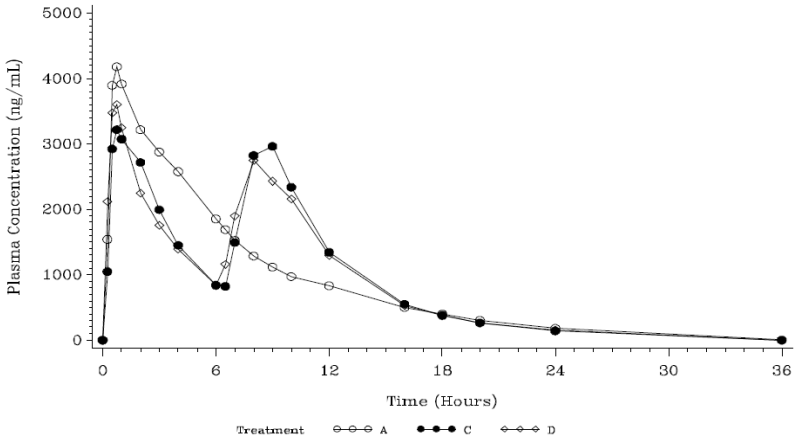
Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally 1 tablet at a time.

Treatment B: 1 tablet of Roxicodone (15 mg OC) administered orally Q6h for 2 doses.

Treatment D: 1 tablet of IR-OC/APAP (7.5 mg OC/325 mg APAP) administered orally Q6h for 2 doses.

The acetaminophen plasma concentration-time profiles for Xartemis tablets and the reference products are shown in **Figure 6**. PK parameters are summarized in **Table 7**. The Cmax and AUC values of Xartemis tablets are equivalent to Ultracet tablet with respect to the rate and extent of absorption of acetaminophen since the 90% CIs for the comparison of Cmax (98%, 115%), AUC0-t (94%, 99%) and AUC0-inf (96%, 101%) fell within the 80-125% bounds (**Table 8**). Acetaminophen Cmax and AUC values for Xartemis are equivalent to Percocet tablets. The shapes of the acetaminophen PK profiles are different from the immediate release reference products.

**Figure 6** Mean Acetaminophen plasma concentration time profiles (Study 256) (N = 24)




Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally 1 tablet at a time.
Treatment C: 1 tablet of, Ultracet (37.5 mg tramadol/325 mg APAP) administered orally Q6h for 2 doses.
Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 2 doses.

**Table 7** Mean (SD) PK parameter of acetaminophen following single oral administration of Xartemis tablets (2 x 7.5 mg oxycodone/325 mg acetaminophen), Ultracet tablet (1 x 37.5 mg tramadol/325 mg acetaminophen) administered every 6 hours for 2 doses, and Percocet (1 x 7.5 mg oxycodone/325 mg acetaminophen) administered every 6 hours for 2 doses in healthy adult subjects under fasted condition (Study 256)

| Parameter | Treatment A COV795 (2 tablets once) (n = 29) | Treatment C Ultracet (1 tablet twice) (n = 29) | Treatment D Percocet (1 tablet twice) (n = 29) |
|---|---|---|---|
| $AUC_{0-t}$ (ng•h/mL) | 29064.91 (6851.20) | 29934.67 (6577.90) | 29192.56 (6892.03) |
| $AUC_{0-inf}$ (ng•h/mL) | 30759.04 (7000.49) | 30989.26 (6759.41) | 30367.98 (7290.82) |
| $C_{max}$ (ng/mL) | 4653.79 (1360.28) | 4255.52 (1004.33) | 4387.24 (1326.26) |
| $T_{max}$ (h)[a] | 0.75 (0.50, 2.00) | 2.00 (0.50, 9.00) | 0.75 (0.25, 12.00) |
| $t_{lag}$ (h)[a] | 0.00 (0.00, 0.25) | 0.00 (0.00, 0.50) | 0.00 (0.00, 0.25) |
| $K_{el}$ ($h^{-1}$) | 0.1328 (0.0375) | 0.1780 (0.0399) | 0.1684 (0.0435) |
| $t_{1/2}$ (h) | 5.75 (2.07) | 4.12 (1.08) | 4.41 (1.24) |

Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally 1 tablet at a time.
Treatment C: 1 tablet of Ultracet (37.5 mg tramadol/325 mg APAP) administered orally every 6 hours (Q6h) for 2 doses.
Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 2 doses.
[a] For $T_{max}$ and $t_{lag}$, the median (minimum, maximum) values are presented.

**Table 8** Statistical Analysis of Plasma PK Parameters of Acetaminophen (Study 256)

| Dose-Normalized Parameter | Treatment | N | Geometric LS Means | Treatment Comparison | Ratio of Geometric LS Means (%) | 90% CI of the Ratio |
|---|---|---|---|---|---|---|
| **$AUC_{0-t}$/Dose (ng•h/mL/mg)** | A | 29 | 42.902 | A/C | 96.302 | (93.538, 99.147) |
| | C | 29 | 44.549 | C/D | 102.418 | (99.464, 105.460) |
| | D | 29 | 43.498 | A/D | 98.630 | (95.783, 101.562) |
| **$AUC_{0-inf}$/Dose (ng•h/mL/mg)** | A | 29 | 45.482 | A/C | 98.498 | (95.612, 101.470) |
| | C | 29 | 46.175 | C/D | 102.161 | (99.154, 105.260) |
| | D | 29 | 45.198 | A/D | 100.626 | (97.662, 103.681) |
| **$C_{max}$/Dose (ng/mL/mg)** | A | 29 | 6.782 | A/C | 106.018 | (97.572, 115.194) |
| | C | 29 | 6.397 | C/D | 99.423 | (91.466, 108.074) |
| | D | 29 | 6.434 | A/D | 105.406 | (96.962, 114.586) |

Note: An analysis of variance was performed with the natural log-transformed dose-normalized PK parameters as the dependent variable and sequence, treatment, and period as fixed effects and subjects nested within sequences as a random effect.

Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally 1 tablet at a time.

Treatment C: 1 tablet of Ultracet (37.5 mg tramadol/325 mg APAP) administered orally Q6h for 2 doses.

Treatment D: 1 tablet of IR-OC/APAP (7.5 mg OC/325 mg APAP) administered orally Q6h for 2 doses.

Multiple Dose Study (255)

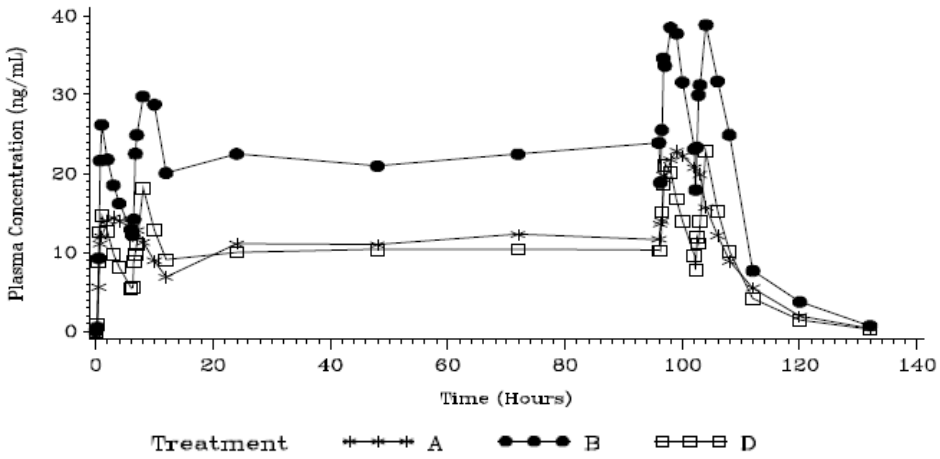
The relative bioavailability of oxycodone and acetaminophen following the administration of Xartemis tablets administered as 2 x 7.5 mg oxycodone/523 mg acetaminophen dose every 12 hours for 4.5 days in comparison to listed drugs, Roxicodone tablet administered as 1 x 15 mg dose every 6 hours for 4.5 days, and Ultracet tablet administered as 1 x 37.5 mg tramadol/325 mg acetaminophen dose every 6 hours for 4.5 days, were evaluated in a multiple dose, open-label, randomized, four-period cross-over study (Study 255) in healthy subjects under fasting condition. The immediate release Percocet administered as 1 x 7.5 mg oxycodone/325 mg acetaminophen tablet every 6 hours for 4.5 days was also used as a reference in this study.

The oxycodone plasma concentration-time profiles for Xartemis tablets, Roxicodone tablets, and Percocet are shown in **Figure 7**. **Table 9** summarized the PK parameters. The statistical analysis results for the assessment of relative bioavailability based on dose normalized PK parameters of oxycodone are presented in the **Table 10**. Dose normalized oxycodone Cmax and AUC values of Xartemis tablets are equivalent to Roxicodone tablets with respect to the rate and extent of absorption of oxycodone since

the 90% CIs for the comparison of Cmax/Dose (98%, 117%), AUC0-12hss/Dose (104%, 117%) fell within the 80-125% bounds. The dose normalized oxycodone Cminss values and DFL (%) of Xartemis tablets are equivalent to Roxicodone tablets.

In addition, dose normalized oxycodone Cmax and AUC values of Xartemis tablets are equivalent to Percocet tablets since the 90% CIs for the comparison of Cmaxss/Dose (84%, 100%), AUC0-12hss/Dose (103%, 116%) fell within the 80-125% bounds.

**Figure 7** Mean oxycodone plasma concentration time profiles (Study 255)




Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally, 1 tablet at a time, every 12 hours for 4.5 days (9 doses).
Treatment B: 1 tablet of Roxicodone (15 mg OC) administered orally every 6 hours (Q6h) for 4.5 days (18 doses).
Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

**Table 9** Mean (SD) PK parameter of oxycodone following multiple dose administration of 2 tablets of Xartemis (7.5 mg oxycodone/325 mg acetaminophen) Q12H for 4.5 days, 1 tablet of Roxicodone (15 mg oxycodone) Q6H for 4.5 days, and 1 tablet of Percocet (7.5 mg oxycodone/325 mg acetaminophen) Q6H for 4.5 days in healthy adult subjects under fasted condition (Study 255)

| Parameter | Treatment A COV795 (2 tablets Q12h) (n = 24) | Treatment B Roxicodone (1 tablet Q6h) (n = 24) | Treatment D IR-OC/APAP (1 tablet Q6h) (n = 24) |
|---|---|---|---|
| Day 1 | | | |
| $AUC_{0\text{-}12h}$ (ng•h/mL) | 136.14 (23.7) | 242.56 (19.9) | 132.45 (22.8) |
| $C_{max}$ (ng/mL) | 16.04 (3.64) | 34.78 (8.64) | 19.83 (5.07) |
| $C_{min}$ (ng/mL) | 6.90 (1.98) | 20.05 (4.66) | 9.08 (2.38) |
| $T_{max}$ (h)[a] | 3.00 (0.50, 8.00) | 7.00 (0.75, 10.00) | 8.00 (0.50, 10.00) |
| $t_{lag}$ (h)[a] | 0.00 (0.00, 0.27) | 0.00 (0.00, 0.25) | 0.00 (0.00, 0.25) |
| Days 2 through 5 | | | |
| Day 2 $C_{min}$ (ng/mL) | 11.10 (2.52) | 22.49 (6.56) | 10.00 (2.81) |
| Day 3 $C_{min}$ (ng/mL) | 11.01 (2.59) | 20.94 (7.47) | 10.39 (3.21) |
| Day 4 $C_{min}$ (ng/mL) | 12.32 (2.88) | 22.45 (6.78) | 10.40 (2.69) |
| Day 5 $C_{min}$ (ng/mL) | 11.68 (2.80) | 23.92 (6.03) | 10.30 (2.86) |
| Day 5 | | | |
| $AUC_{0\text{-}12h}^{ss}$ (ng•h/mL) | 208.34 (45.34) | 376.88 (83.90) | 191.54 (42.81) |
| $C_{avg}^{ss}$ (ng/mL) | 17.36 (3.78) | 31.41 (6.99) | 15.96 (3.57) |
| $C_{max}^{ss}$ (ng/mL) | 24.00 (5.38) | 45.15 (10.54) | 26.32 (6.18) |
| $C_{min}^{ss}$ (ng/mL) | 9.31 (2.39) | 19.91 (4.93) | 8.81 (2.40) |
| DFL (%) | 83.89 (17.58) | 79.94 (19.83) | 110.90 (33.39) |
| swing | 1.65 (0.58) | 1.32 (0.50) | 2.13 (0.94) |
| $T_{max}^{ss}$ (h)[a] | 3.00 (1.00, 5.92) | 3.00 (1.00, 12.00) | 7.25 (0.50, 8.13) |
| Days 5 through 6 | | | |
| $K_{el}$ (1/h) | 0.1318 (0.0223) | 0.1525 (0.0206) | 0.1517 (0.0205) |
| $t_{1/2}$ (h) | 5.40 (0.87) | 4.62 (0.59) | 4.65 (0.62) |

Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally, 1 tablet at a time, Q12h for 4.5 days (9 doses).

Treatment B: 1 tablet of Roxicodone (15 mg OC) administered orally Q6h for 4.5 days (18 doses).

Treatment D: 1 tablet of IR-OC/APAP (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

[a]For $T_{max}$ and $t_{lag}$, the median (minimum, maximum) values are presented.

The degree of fluctuation (DFL) = [100 x ($C_{max}^{ss}$ – $C_{min}^{ss}$)/$C_{avg}^{ss}$]

**Table 10** Statistical Analysis of Plasma PK Parameters of Oxycodone on Day 5 (Study 255)

| Dose-Normalized Parameter | Treatment | N | Geometric LS Means | Treatment Comparison | Ratio of Geometric LS Means (%) | 90% CI of the Ratio |
|---|---|---|---|---|---|---|
| $AUC_{0-12}^{ss}$/Dose (ng•h/mL/mg) | A | 24 | 13.823 | A/B | 110.226 | (103.596, 117.281) |
| | B | 24 | 12.541 | B/D | 99.179 | (93.153, 105.595) |
| | D | 24 | 12.645 | A/D | 109.322 | (102.771, 116.290) |
| $C_{max}^{ss}$/Dose (ng/mL/mg) | A | 24 | 1.605 | A/B | 106.898 | (97.581, 117.103) |
| | B | 24 | 1.501 | B/D | 85.559 | (78.029, 93.817) |
| | D | 24 | 1.755 | A/D | 91.461 | (83.520, 100.157) |
| $C_{avg}^{ss}$/Dose (ng/mL/mg) | A | 24 | 1.152 | A/B | 110.226 | (103.596, 117.281) |
| | B | 24 | 1.045 | B/D | 99.179 | (93.153, 105.595) |
| | D | 24 | 1.054 | A/D | 109.322 | (102.771, 116.290) |
| $C_{min}^{ss}$/Dose (ng/mL/mg) | A | 24 | 0.596 | A/B | 91.164 | (83.557, 99.463) |
| | B | 24 | 0.654 | B/D | 115.912 | (106.144, 126.579) |
| | D | 24 | 0.564 | A/D | 105.670 | (96.886, 115.251) |
| DFL (%) | A | 24 | 84.883 | A/B | 108.305 | (97.008, 120.918) |
| | B | 24 | 78.374 | B/D | 71.363 | (63.846, 79.765) |
| | D | 24 | 109.825 | A/D | 77.289 | (69.257, 86.253) |
| swing | A | 24 | 1.641 | A/B | 130.952 | (110.609, 155.036) |
| | B | 24 | 1.253 | B/D | 61.061 | (51.485, 72.418) |
| | D | 24 | 2.052 | A/D | 79.960 | (67.583, 94.604) |

Note: An analysis of variance was performed with the natural log-transformed dose-normalized PK parameters ($AUC_{0-12}^{ss}$, $C_{max}^{ss}$, $C_{min}^{ss}$, and $C_{avg}^{ss}$) or natural log-transformed PK parameters (DFL and swing) as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequences as a random effect.

Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally, 1 tablet at a time, Q12h for 4.5 days (9 doses).

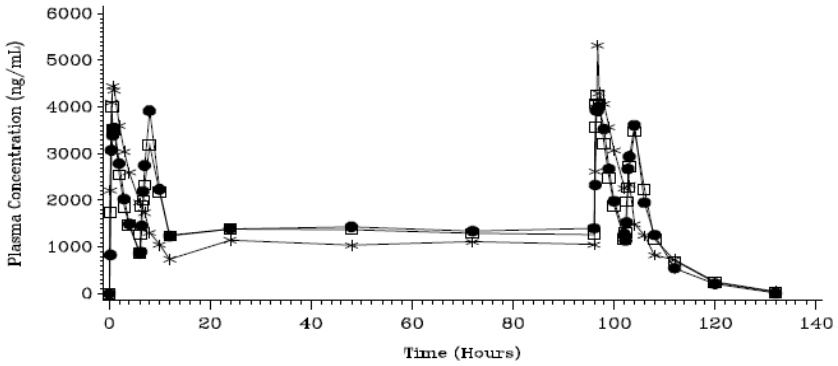
Treatment B: 1 tablet of Roxicodone (15 mg OC) administered orally Q6h for 4.5 days (18 doses).

Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

The acetaminophen plasma concentration-time profiles for Xartemis tablets, Ultracet, and Percocet are shown in **Figure 8**. PK parameters are summarized in **Table 11**. Statistical analysis results are shown in **Table 12**. Dose normalized acetaminophen Cmax and AUC values of Xartemis tablets are equivalent to Ultracet tablets with respect to the rate and extent of absorption of acetaminophen since the 90% CIs for the comparison of Cmax/Dose (85%, 107%), AUC0-12hss/Dose (91%, 99%) fell within the 80-125% bounds. The dose normalized acetaminophen Cminss values for Xartemis tablets are 21% lower than Ultracet tablets. DFL values for Xartemis tablets are equivalent to Ultracet tablets.

In addition, dose normalized acetaminophen Cmax and AUC values of Xartemis tablets are equivalent to Percocet tablets since the 90% CIs for the comparison of Cmaxss/Dose (88%, 110%), AUC0-12hss/Dose (92%, 100%) fell within the 80-125% bounds.

**Figure 8** Mean acetaminophen plasma concentration time profiles (Study 255)




Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally, 1 tablet at a time, every 12 hours for 4.5 days (9 doses).
Treatment C: 1 tablet of Ultracet (37.5 mg tramadol/325 mg APAP) administered orally every 6 hours (Q6h) for 4.5 days (18 doses).
Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

**Table 11** Mean (SD) PK parameter of acetaminophen following multiple dose administration of 2 tablets of Xartemis (7.5 mg oxycodone/325 mg acetaminophen) Q12H for 4.5 days, 1 tablet of Ultracet (37.5 mg tramadol/325 mg acetaminophen) Q6H for 4.5 days, and 1 tablet of Percocet (7.5 mg oxycodone/325 mg acetaminophen) Q6H for 4.5 days in healthy adult subjects under fasted condition (Study 255)

| Parameter | Treatment A COV795 (2 tablets Q12h) (n = 24) | Treatment C Ultracet (1 tablet Q6h) (n = 24) | Treatment D Percocet (1 tablet Q6h) (n = 24) |
|---|---|---|---|
| Day 1 | | | |
| $AUC_{0\text{-}12h}$ (ng•h/mL) | 24924.32 (5667.48) | 26342.76 (4721.38) | 25093.74 (5085.04) |
| $C_{max}$ (ng/mL) | 4857.50 (1066.47) | 4567.92 (975.62) | 4317.92 (1006.30) |
| $C_{min}$ (ng/mL) | 738.17 (227.04) | 1234.92 (345.20) | 1242.21 (289.86) |
| $T_{max}$ (h)[a] | 1.00 (0.50, 4.00) | 6.75 (0.50, 8.20) | 0.53 (0.50, 8.00) |
| $t_{lag}$ (h)[a] | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.30) | 0.00 (0.00, 0.00) |
| Days 2 through 5 | | | |
| Day 2 $C_{min}$ (ng/mL) | 1146.25 (391.14) | 1389.38 (428.81) | 1389.92 (418.59) |
| Day 3 $C_{min}$ (ng/mL) | 1037.92 (301.11) | 1435.92 (425.85) | 1375.50 (351.41) |
| Day 4 $C_{min}$ (ng/mL) | 1105.88 (435.60) | 1338.88 (409.82) | 1289.71 (384.79) |
| Day 5 $C_{min}$ (ng/mL) | 1052.00 (339.26) | 1400.21 (442.85) | 1258.63 (340.40) |
| Day 5 | | | |
| $AUC_{0\text{-}12h}^{ss}$ (ng•h/mL) | 28160.40 (5807.09) | 29711.92 (5427.37) | 29284.22 (5477.73) |
| $C_{avg}^{ss}$ (ng/mL) | 2346.70 (483.92) | 2475.99 (452.28) | 2440.35 (456.48) |
| $C_{max}^{ss}$ (ng/mL) | 4792.50 (1132.40) | 5078.33 (1189.70) | 4876.67 (1383.08) |
| $C_{min}^{ss}$ (ng/mL) | 852.75 (273.25) | 1070.92 (367.35) | 1069.13 (291.83) |
| DFL (%) | 169.13 (39.83) | 163.90 (47.17) | 155.25 (38.77) |
| swing | 5.08 (2.07) | 4.22 (2.14) | 3.81 (1.63) |
| $T_{max}^{ss}$ (h)[a] | 1.00 (0.50, 4.00) | 0.88 (0.25, 8.00) | 0.75 (0.25, 8.00) |
| Days 5 through 6 | | | |
| $K_{el}$ (1/h) | 0.1072 (0.0285) | 0.1355 (0.0279) | 0.1201 (0.0338) |
| $t_{1/2}$ (h) | 6.90 (1.76) | 5.32 (1.10) | 6.21 (1.79) |

Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally, 1 tablet at a time, Q12h for 4.5 days (9 doses).
Treatment C: 1 tablet of Ultracet (37.5 mg tramadol/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).
Treatment D: 1 tablet of IR-OC/APAP (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).
[a] For $T_{max}$ and $t_{lag}$, the median (minimum, maximum) values are presented.

**Table 12** Statistical Analysis of Plasma PK Parameters of Acetaminophen on Day 5 (Study 255)

| Dose-Normalized Parameter | Treatment | N | Geometric LS Means | Treatment Comparison | Ratio of Geometric LS Means (%) | 90% CI of the Ratio |
|---|---|---|---|---|---|---|
| $AUC_{0-12h}^{ss}$/Dose (ng•h/mL/mg) | A | 24 | 42.567 | A/C | 94.975 | (90.822, 99.317) |
| | C | 24 | 44.819 | C/D | 100.845 | (96.496, 105.389) |
| | D | 24 | 44.444 | A/D | 95.777 | (91.631, 100.110) |
| $C_{max}^{ss}$/Dose (ng/mL/mg) | A | 24 | 7.256 | A/C | 95.619 | (85.302, 107.183) |
| | C | 24 | 7.588 | C/D | 102.668 | (91.739, 114.899) |
| | D | 24 | 7.391 | A/D | 98.170 | (87.681, 109.914) |
| $C_{avg}^{ss}$/Dose (ng/mL/mg) | A | 24 | 3.547 | A/C | 94.975 | (90.822, 99.317) |
| | C | 24 | 3.735 | C/D | 100.845 | (96.496, 105.389) |
| | D | 24 | 3.704 | A/D | 95.777 | (91.631, 100.110) |
| $C_{min}^{ss}$/Dose (ng/mL/mg) | A | 24 | 1.214 | A/C | 79.144 | (73.365, 85.377) |
| | C | 24 | 1.534 | C/D | 99.093 | (91.957, 106.784) |
| | D | 24 | 1.548 | A/D | 78.426 | (72.757, 84.537) |
| DFL (%) | A | 24 | 168.239 | A/C | 106.322 | (93.865, 120.433) |
| | C | 24 | 158.235 | C/D | 102.150 | (90.341, 115.503) |
| | D | 24 | 154.904 | A/D | 108.609 | (96.007, 122.865) |
| swing | A | 24 | 4.915 | A/C | 127.590 | (106.047, 153.509) |
| | C | 24 | 3.852 | C/D | 103.956 | (86.629, 124.747) |
| | D | 24 | 3.706 | A/D | 132.637 | (110.451, 159.278) |

Note: An analysis of variance was performed with the natural log-transformed dose-normalized PK parameters ($AUC_{0-12}^{ss}$, $C_{max}^{ss}$, $C_{min}^{ss}$, and $C_{avg}^{ss}$) or natural log-transformed PK parameters (DFL and swing) as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequences as a random effect.

Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally, 1 tablet at a time, Q12h for 4.5 days (9 doses).

Treatment C: 1 tablet of Ultracet (37.5 mg tramadol/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

Treatment D: 1 tablet of IR-OC/APAP (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

***2. Does food affect the bioavailability of oxycodone or acetaminophen from the Xartemis tablets?***

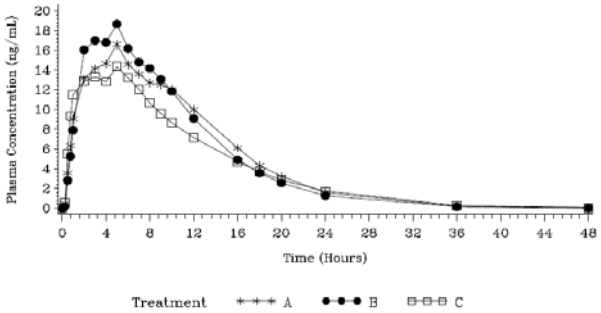
The effect of low fat and high fat meals on the bioavailability of oxycodone and acetaminophen following the administration of the to-be-marketed formulation of Xartemis was evaluated in a single dose, open-label, three-period crossover study (**Study 171**) in healthy subjects.

Oxycodone and acetaminophen concentration-time profiles following a single dose administration of two tablets of Xartemis (7.5 mg oxycodone/325 mg acetaminophen) under fasting and low fat and high fat fed conditions are shown in the following **Figure 9**. PK parameters are summarized in **Table 13**. Statistical analysis is presented in **Table 14**.

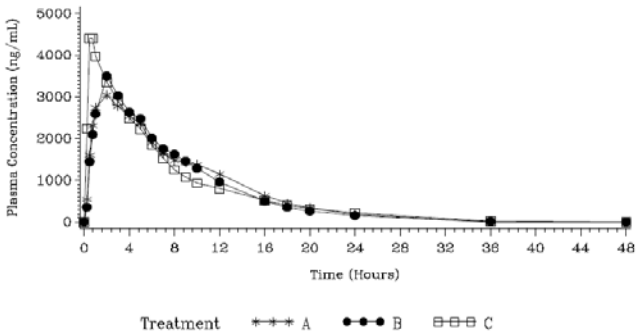
Following a single dose administration of Xartemis tablet, low and high fat meals delayed median oxycodone Tmax by 1 and 2 hrs, respectively. Mean AUC values were increased by 15% to 16%, however, 90% CIs for the geometric mean ratios of AUC values (high fat fed/fasting or low fat fed/fasting) were within the no effect range of 80% to 125%. Peak concentrations were 12% to 25% higher with food. The extent of food effect is similar to the listed drug, Roxicodone tablets. According to Roxicodone labeling, high fat meal increased oxycodone Tmax values from 1.25 to 2.54 hours, did not affect Cmax, increased AUC values by 27%.

Low and high fat meals delayed median acetaminophen Tmax by 1.5 hours. Either low fat or high fat meal did not affect the AUC values of acetaminophen. Low fat and high fat meals decreased acetaminophen Cmax values by 23 to 24%. According to Ultracet labeling, food delay Tmax values of acetaminophen by 1 hr but did not affect AUC and Cmax values of acetaminophen.

**Figure 9** Oxycodone (upper panel) and acetaminophen (lower panel) plasma concentration time course following single oral doses of 2 tablets of Xartemis (7.5 mg oxycodone/325 mg acetaminophen) (Study 171)




Note: Pharmacokinetic Analysis Population = Study completers (N = 31 Subjects).
Note: Treatment A: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (HF meal);
Treatment B: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (LF meal);
Treatment C: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fasted conditions.




Note: Pharmacokinetic Analysis Population = Study completers (N = 31 Subjects).
Treatment A: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (HF meal);
Treatment B: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (LF meal);
Treatment C: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fasted conditions.

**Table 13** Mean (SD) Plasma Pharmacokinetic Parameters of oxycodone and acetaminophen following single oral administration of two tablets of the to-be-marketed formulation of Xartemis (7.5 mg oxycodone/325 mg acetaminophen) under fasted and low fat and high fat fed conditions in healthy subjects (Study 171)

| Parameter | Treatment A High Fat COV795 Mean (SD) (N = 31) | Treatment B Low Fat COV795 Mean (SD) (N = 31) | Treatment C Fasted COV795 Mean (SD) (N = 31) |
|---|---|---|---|
| **Oxycodone** | | | |
| $AUC_{0-t}$ (ng•h/mL) | 219.41 (54.07) | 219.49 (57.29) | 190.70 (50.03) |
| $AUC_{0-inf}$ (ng•h/mL) | 221.00 (54.14) | 221.38 (56.95) | 192.63 (49.69) |
| $C_{max}$ (ng/mL) | 17.90 (4.25) | 19.94 (4.66) | 15.91 (3.43) |
| $T_{max}$ (h)[a] | 5.00 (1.00 – 12.00) | 4.00 (1.00 – 5.00) | 3.00 (0.75 – 8.00) |
| $K_{el}$ (1/h) | 0.1682 (0.0298) | 0.1693 (0.0321) | 0.1502 (0.0269) |
| $t_{lag}$ (h)[a] | 0.25 (0.00 – 1.00) | 0.25 (0.00 – 0.75) | 0.00 (0.00 – 0.25) |
| $t_{1/2}$ (h) | 4.26 (0.83) | 4.26 (0.91) | 4.76 (0.87) |
| **Acetaminophen** | | | |
| $AUC_{0-t}$ (ng•h/mL) | 29617.96 (7765.99) | 29346.82 (7869.75) | 29763.19 (7592.89) |
| $AUC_{0-inf}$ (ng•h/mL) | 31457.06 (7973.16)[b] | 30550.48 (8051.47) | 31807.70 (7923.30)[b] |
| $C_{max}$ (ng/mL) | 3774.52 (949.84) | 3862.90 (978.08) | 5175.48 (1731.31) |
| $T_{max}$ (h)[a] | 2.00 (0.50 - 5.00) | 2.00 (0.50 - 5.00) | 0.53 (0.23 - 5.00) |
| $K_{el}$ (1/h) | 0.1564 (0.0363)[b] | 0.1593 (0.0408) | 0.1146 (0.0360)[b] |
| $t_{lag}$ (h)[a] | 0.00 (0.00 - 1.00) | 0.25 (0.00 - 0.50) | 0.00 (0.00 - 0.25) |
| $t_{1/2}$ (h) | 4.66 (1.08)[b] | 4.71 (1.60) | 6.63 (1.99)[b] |

Note: Treatment A: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (high-fat meal); Treatment B: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (low-fat meal); Treatment C: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fasted conditions.

[a]Median (minimum - maximum). [b]N=29.

**Table 14** Geometric LS Means Ratios and 90% CIs for the Comparison of COV795 under Fed and Fasted Conditions (Study 171)

| Parameter | Geometric LS Means Ratio (%) (90% CI) | Geometric LS Means Ratio (%) (90% CI) | Geometric LS Means Ratio (%) (90% CI) |
|---|---|---|---|
| | Treatment A/C High Fat/Fasted | Treatment B/C Low Fat/Fasted | Treatment A/B High Fat/Low Fat |
| **Oxycodone** | | | |
| $AUC_{0-inf}$ (ng•h/mL)[a] | 115.41 (110.63, 120.41) | 115.09 (110.38, 120.01) | 100.28 (96.18, 104.55) |
| $AUC_{0-t}$ (ng•h/mL)[a] | 115.85 (111.00, 120.90) | 115.30 (110.54, 120.27) | 100.47 (96.34, 104.79) |
| $C_{max}$ (ng/mL)[a] | 112.11 (104.61, 120.16) | 125.16 (116.88, 134.03) | 89.57 (83.67, 95.90) |
| **Acetaminophen** | | | |
| $AUC_{0-inf}$ (ng•h/mL)[b] | 98.60 (95.75, 101.54) | 96.56 (93.80, 99.39) | 102.12 (99.20, 105.11) |
| $AUC_{0-t}$ (ng•h/mL)[a] | 99.88 (97.31, 102.52) | 98.79 (96.27, 101.37) | 101.10 (98.54, 103.74) |
| $C_{max}$ (ng/mL)[a] | 76.00 (70.49, 81.94) | 77.18 (71.65, 83.13) | 98.48 (91.45, 106.05) |

Note: Treatment A: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (high-fat meal); Treatment B: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (low-fat meal); Treatment C: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fasted conditions.

[a]N = 31, [b]N=27.

## 2.5 Analytical Method and Validation

***1. What bioanalytical methods are used to assess concentrations?***

Validated LC-MS/MS method was used for the determination of oxycodone and acetaminophen in human plasma throughout the development program. Table summarizes inter-day assay precision and accuracy for individual studies.

**Table 15** Summary of Assay Performance: Precision and Accuracy of Standards and Quality Control Samples for the measurement of oxycodone and acetaminophen in plasma from each study

| | | All Standards (N = 8 standards/run) | | | | QCs (N = 5 controls/run) | | |
|---|---|---|---|---|---|---|---|---|
| Study[a] | Analyte | Concentration Range (ng/mL) | # of Runs | Inter Day Precision (%CV) Range | Inter Day Accuracy (%Actual) | Concentration Range (ng/mL) | Inter Day Precision (%CV) Range | Inter Day Accuracy (%Actual) |
| 0041 | OC | 0.100 - 100 | 28 | 2.80 – 7.53 | −1.12 - 1.04[b] | 0.300 – 75.0 | 3.73 – 14.0 | 1.40 – 7.12[b] |
| 0042 | OC | 0.100 - 100 | 11 | 2.96 – 9.38 | 94.6 - 105 | 0.300 – 75.0 | 4.44 – 6.68 | 98.0 - 107 |
| 0043 | OC | 0.100 - 100 | 26 | 2.63 – 7.39 | 98.6 - 101 | 0.300 – 75.0 | 3.37 – 6.11 | 101 - 106 |
| 0044 | OC | 0.100 - 100 | 9 | 2.77 – 6.45 | 98.6 - 101 | 0.300 – 75.0 | 3.35 – 6.82 | 99.6 - 102 |
| 0045 | OC | 0.100 - 100 | 25 | 3.26 – 7.91 | 97.2 - 103 | 0.300 – 75.0 | 4.49 – 6.27 | 98.0 - 102 |
| 0107 | OC | 0.100 - 100 | 18 | 3.14 – 10.5 | 94.7 - 104 | 0.300 – 75.0 | 5.09 – 13.8 | 99.1 - 104 |
| 0170 | OC | 0.100 - 100 | 38 | 2.85 – 9.78 | 94.5 - 104 | 0.300 – 75.0 | 3.35 – 9.65[c] | 98.1 – 104[c] |
| 0171 | OC | 0.100 - 100 | 24 | 2.68 – 10.1 | 96.4 - 104 | 0.300 – 75.0 | 2.98 – 5.25 | 99.0 - 104 |
| 0172 | OC | 0.100 - 100 | 46 | 2.74 – 9.74 | 94.4 - 104 | 0.300 – 75.0 | 3.42 – 9.55[e] | 98.4 – 105[e] |
| 0244 | OC | 0.100 - 100 | 60 | 4.02 – 6.64 | −4.98 – 2.70[b] | 0.300 – 75.0 | 4.82 – 9.50 | −7.03 – 3.17[b] |
| 0255 | OC | 0.100 - 100 | 29 | 4.00 – 7.58 | 93.6 - 104 | 0.300 – 75.0 | 4.48 – 6.89 | 93.6 - 104 |
| 0256 | OC | 0.100 - 100 | 27 | 3.70 – 7.76 | 94.1 - 104 | 0.300 – 75.0 | 4.18 – 5.76 | 91.6 - 103 |
| 0041 | APAP | 100 – 50,000 | 28 | 3.62 – 5.43 | −2.28 – 1.57[b] | 250 – 37,500 | 3.47 – 14.2 | −0.372 – 2.73[b] |
| 0042 | APAP | 100 – 50,000 | 11 | 2.82 – 4.87 | 96.0 - 103 | 250 – 37,500 | 3.60 – 5.07 | 99.5 - 105 |
| 0043 | APAP | 100 – 50,000 | 26 | 3.45 – 6.47 | 98.2 - 102 | 250 – 37,500 | 3.99 – 7.03 | 99.1 - 102 |
| 0044 | APAP | 100 – 50,000 | 9 | 3.38 – 5.69 | 98.7 - 101 | 250 – 37,500 | 3.22 – 6.45 | 100 - 103 |
| 0045 | APAP | 100 – 50,000 | 25 | 2.80 – 5.69 | 98.4 - 101 | 250 – 37,500 | 4.40 – 5.19 | 101 - 102 |
| 0107 | APAP | 100 – 50,000 | 18 | 3.81 – 5.97 | 98.2 - 102 | 250 – 37,500 | 6.21 – 13.0 | 98.5 - 102 |
| 0170 | APAP | 100 – 50,000 | 38 | 2.71 – 5.41 | 96.0 - 103 | 250 – 37,500 | 3.42 – 8.85[d] | 97.4 – 105[d] |

| | | All Standards (N = 8 standards/run) | | | | QCs (N = 5 controls/run) | | |
|---|---|---|---|---|---|---|---|---|
| Study[a] | Analyte | Concentration Range (ng/mL) | # of Runs | Inter Day Precision (%CV) Range | Inter Day Accuracy (%Actual) | Concentration Range (ng/mL) | Inter Day Precision (%CV) Range | Inter Day Accuracy (%Actual) |
| 0171 | APAP | 100 – 50,000 | 24 | 3.25 – 6.45 | 96.5 - 103 | 250 – 37,500 | 3.38 – 7.53 | 97.9 - 105 |
| 0172 | APAP | 100 – 50,000 | 46 | 3.15 – 4.98 | 96.5 - 102 | 250 – 37,500 | 3.33 – 9.01[f] | 97.8 – 104[f] |
| 0244 | APAP | 100 – 50,000 | 60 | 3.67 – 5.47 | −1.52 – 1.29[b] | 250 – 37,500 | 4.01 – 6.86 | −0.827 – 1.05[b] |
| 0255 | APAP | 100 – 50,000 | 29 | 3.69 – 6.16 | 98.9 - 101 | 250 – 37,500 | 4.01 – 6.07 | 98.8 - 101 |
| 0256 | APAP | 100 – 50,000 | 27 | 3.35 – 5.73 | 98.4 - 101 | 250 – 37,500 | 3.88 – 5.74 | 98.0 - 101 |

[a] Source: Final bioanalytical reports are located in NDA Section 5.3.1.4.
[b] % difference from theoretical.
[c] Excludes 1 outlier, with outlier, upper limits of %CV = 35.0 (b) (4)
[d] Excludes 1 outlier, with outlier, upper limits of %CV = 26.6
[e] Excludes 1 outlier, with outlier, upper limits of %CV = 89.7
[f] Excludes 1 outlier, with outlier, upper limits of %CV = 86.5

## 3 Labeling Recommendations

It is ongoing.

## 4 Appendix

### 4.1 Clinical Pharmacology Filing Memo

| Office of Clinical Pharmacology<br>*New Drug Application Filing and Review Form* | | | |
|---|---|---|---|
| *General Information About the Submission* | | | |
| | **Information** | | **Information** |
| NDA/BLA Number | 204031 | Proposed Brand Name | Xartemis |
| OCP Division (I, II, III, IV, V) | II | Generic Name | Oxycodone and acetaminophen (b) (4)-release tablets |
| Medical Division | DAAAP | Drug Class | An opioid agonist and a non-opiate, non-salicylate analgesic and antipyretic |
| OCP Reviewer | Wei Qiu, Ph.D. | Indication(s) | Management of (b) (4) acute pain |
| OCP Team Leader | Yun Xu, Ph.D. | Dosage Form, Strength | (b) (4) release oral tablet, 7.5 mg oxycodone and 325 mg acetaminophen |
| Pharmacometrics Reviewer | N/A | Dosing Regimen | 2 tablets every 12 hours |
| Date of Submission | 5/28/13 | Route of Administration | Oral |
| Primary Review Goal Date (GRMP) | 11/1/2013 | Sponsor | Mallinckrodt |
| | | Priority Classification | Priority |
| PDUFA Due Date | 11/28/13 (assuming priority review, 6-mo clock) | Relevant INDs | IND 104702 |

| *Clin. Pharm. and Biopharm. Information* | | | | |
|---|---|---|---|---|
| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | x | | | |
| Tabular Listing of All Human Studies | x | | | |
| HPK Summary | x | | | |
| Labeling | x | | | |
| Reference Bioanalytical and Analytical Methods | x | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers- | | | | |
| single dose: | x | 8 | | Pivotal studies: 171 and 256 |
| multiple dose: | x | 2 | | Pivotal study: 255 |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| PD - | | | | |
| Phase 1: | x | 1 | | Abuse liability study 244 (with PK measurement) |

| | | | | |
|---|---|---|---|---|
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | x | 4 | | **Pivotal studies 256 and 255** |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | x | 3 | | **Pivotal study: 171** |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | 12 | | |

## 4.2 Individual Study Synopsis

This section includes study synopsis from 4 studies, Study 171 food effect, Study 256 single dose relative BA, Study 255 multiple dose relative BA, and Study 244 abuse liability.

### Study 171 (food effect)

| | | |
|---|---|---|
| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen | |
| **Indication:** | Management of (b) (4) acute pain | |
| **Phase:** | Phase 1 | |
| **Title of Study:** | An Open-Label, Randomized, Three-Period Crossover Study to Evaluate the Pharmacokinetics, Bioavailability and Safety of Two Tablets of a Multi-Layer Extended-Release Formulation, COV795 (7.5 mg Oxycodone Hydrochloride/325 mg Acetaminophen), Administered as a Single Dose in Normal, Healthy Subjects Under Fed (High- and Low-Fat Meal) and Fasted Conditions | |
| **REPORT DETAILS** | | |
| **Report Date:** | Original clinical study report: 24 Feb 2012<br>Amendment 1 to the original clinical study report: 27 Aug 2012 | |
| **Period of Study:** | 25 Jun 2011 to 25 Jul 2011 | |
| **Protocol and Amendment:** | Original Protocol: 27 Apr 2011<br>Protocol Amendment 1: 16 Jun 2011 | |
| **Principal Investigator:** | Aziz L. Laurent, MD | |
| **Study Centers:** | (b) (4) | |
| **OBJECTIVES** | | |
| **Primary**:<br>• To determine the pharmacokinetics (PK) and bioavailability of COV795 under fed (high- and low-fat) and fasted conditions in normal, healthy subjects<br>**Secondary**:<br>• To examine the safety of COV795 under fed and fasted conditions in normal, healthy subjects | | |
| **METHODOLOGY** | | |
| **Study Design:** | This was an open-label, single-center, randomized, single-dose, 3-period, 6 sequence, crossover design | |
| **Treatments:** | **Treatment A**: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally, 1 at a time, under fed conditions (high-fat with approximately 50% of calories from fat and a total of 1000 ± 100 calories in the meal)<br>**Treatment B**: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally, 1 at a time, under fed conditions (low-fat with approximately 25% to 30% of calories from fat and a total of 800 ± 80 calories in the meal)<br>**Treatment C**: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally, 1 at a time, under fasted conditions | |

| | | |
|---|---|---|
| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen | |
| **Treatment Duration:** | The study duration included a screening visit up to 45 days prior to Period 1 check-in, 3 confinement periods of approximately 60 hours each, 2 intervals with a minimum of 7 days between the start of each period and a follow-up visit at least 7 days following the conclusion of the study for subjects with ongoing adverse events (AEs)/serious adverse events (SAEs). The total study duration, including a follow-up period of up to 28 days following the last dose of study drug for all SAEs, was approximately 13 weeks. | |
| **Study Drug and Formulation:** | **Study Drug**: COV795, an ER formulation of 7.5 mg OC/325 mg APAP | |
| **Product Codes and Lot Numbers:** | **Treatment A, B, and C**: COV795 lot number A78056 | |
| **Dose and Route of Administration:** | **Treatment A**: COV795 (7.5 mg OC/325 mg APAP), 2 tablets (total dose 15 mg OC/650 mg APAP) administered orally under fed conditions (high-fat meal)<br>**Treatment B**: COV795 (7.5 mg OC/325 mg APAP), 2 tablets (total dose 15 mg OC/650 mg APAP) administered orally under fed conditions (low-fat meal)<br>**Treatment C**: COV795 (7.5 mg OC/325 mg APAP), 2 tablets (total dose 15 mg OC/650 mg APAP) administered orally under fasted conditions | |
| **Concomitant and Excluded Therapy:** | The use of over-the-counter (OTC) or prescription medications, vitamins, herbal therapies or nutritional supplements, other than the study drug treatments, was not permitted starting at 14 days prior to Period 1 check-in and for the duration of the study. Medications were permitted during the study for the treatment of AEs. The use of OC- and/or APAP-containing products for the treatment of AEs was not permitted. | |
| **SUBJECT POPULATION** | | |
| **Number of Subjects (Planned and Analyzed):** | Up to 48 healthy subjects were planned for enrollment. A total of 48 subjects were enrolled. Data from 31 subjects were evaluated for the pharmacokinetic (PK) analysis, and all 48 subjects were included in the safety analysis. | |
| **Inclusion Criteria:** | Subjects met all the following criteria for inclusion in the study:<br>1. Subjects must have been males or nonpregnant, nonlactating females, between 18 and 55 years of age, inclusive, at the time of screening.<br>2. Subjects must have had a body mass index (BMI) $\geq 19$ and $\leq 30$ kg/m$^2$ with a minimum weight of 130 pounds at the time of screening.<br>3. Female subjects must have had a negative serum pregnancy test at screening and check-in to each period. All subjects who were biologically capable of having children must have agreed and committed to the use of 2 acceptable methods of birth control which included nonhormonal forms of contraception, condoms, or diaphragms with spermicidal foam, 30 days prior to Period 1 check-in and for the duration of study participation. Unacceptable methods of birth control included abstinence, hormone-containing intrauterine devices (IUDs), uterine ablation, hormonal methods, rhythm, and withdrawal.<br>4. Postmenopausal subjects must have been amenorrheic for at least 12 consecutive months prior to screening.<br>5. Subjects must have had a health status of "normal healthy" assessed by the investigator at screening and check-in assessments.<br>6. Subjects must have been able to communicate effectively with study personnel.<br>7. Subjects must have been able and willing to follow all protocol requirements and study restrictions. | |

| | | |
|---|---|---|
| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen | |
| | 8. Subjects must have been able to consume the entire standardized Food and Drug Administration (FDA) high-fat or a low-fat meal in 30 minutes or less prior to study drug dosing at Hour 0.<br>9. Subjects must have been able and willing to return for all periods of the study. | |
| **Exclusion Criteria:** | Subjects were ineligible for the study if they met any of the following criteria:<br>1. Subjects from vulnerable populations, as defined by the Code of Federal Regulations (CFR) Title 45, Part 46, Section 46.111(b), including employees of the sponsor and clinical site.<br>2. Subjects with electrocardiogram (ECG) abnormalities, including but not limited to atrioventricular block and bundle branch blocks, axis deviations, corrected QT interval prolongations, ischemia or injury patterns, or clinically significant arrhythmias at screening. Subjects with clinically insignificant ECG abnormalities and/or ECG values outside the protocol defined ranges did not qualify without investigator comments and sponsor approval prior to participation in the study.<br>3. Subjects with screening laboratory test results that fell outside the upper or lower normal limits of the clinical laboratory's reference range did not qualify without sponsor approval. Exceptions to the lower limit requirement included the following: aspartate transaminase (AST), total bilirubin, alanine transaminase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), uric acid, lactate dehydrogenase (LDH), creatinine, and gamma-glutamyl transpeptidase (GGT). Urinalysis interpretation for subject entry into the study was at the investigator's discretion.<br>4. Subjects with positive test results for human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening.<br>5. Subjects with screening and check-in pulse oximetry readings of < 95% while awake.<br>6. Subjects with positive urine test results for drugs of abuse (opioids, barbiturates, cannabinoids, benzodiazepines, cocaine, and amphetamine), alcohol, and/or cotinine at either screening and/or check-in to each period.<br>7. Subjects with a history of abuse or treatment for alcohol, drugs of abuse, or narcotic addiction.<br>8. Subjects who had used marijuana or illicit drugs within 2 years prior to Period 1 check-in.<br>9. Subjects who had smoked or used nicotine-containing products within 6 months prior to Period 1 check-in.<br>10. Subjects who planned to participate in another clinical trial while enrolled in this study and/or who had received an investigational drug and/or device within 30 days prior to Period 1 check-in.<br>11. Subjects who had donated or had significant loss of whole blood (480 mL or more) within 30 days or plasma within 14 days prior to Period 1 check-in, or planned to donate blood or plasma during the course of the study.<br>12. Subjects who had taken prescription drugs or OTC medications, including nutritional supplements, vitamins, and herbal therapies, including hormonal contraception or hormone replacement therapy, antihistamines, H2 blockers, proton pump inhibitors, or antacids within 14 days prior to Period 1 check-in as well as those subjects who needed medications during the course of the study.<br>13. Subjects with an acute illness within 14 days prior to Period 1 check-in. | |

| | | |
|---|---|---|
| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen | |
| | 14. Subjects who had undergone abdominal and/or pelvic surgery (including but not limited to appendectomy, laparoscopic surgery, cesarean [C]-section, and hysterectomy) within 1 year prior to Period 1 check-in.<br>15. Subjects who had previous cholecystectomy.<br>16. Subjects who had a previous gastric bypass or gastric band surgery.<br>17. Subjects who had a previous cardiothoracic surgery.<br>18. Subjects with a history of anxiety, tension, agitation, psychiatric disorders, psychosis or depression requiring hospitalization, psychotherapy and/or medication within 3 years prior to Period 1 check-in.<br>19. Subjects with acute or chronic gastrointestinal disease, including, but not limited to, peptic ulcer, diverticulitis, bowel obstructions, adhesions, ileus, malabsorption, gastritis, or diarrhea.<br>20. Subjects with a history of any condition that may have interfered with the absorption, distribution, metabolism, or excretion of the study drug.<br>21. Subjects with a history of seizures or diagnosis of epilepsy or other seizure disorder.<br>22. Subjects with a history or laboratory evidence of bleeding or clotting disorders or conditions.<br>23. Subjects with a history of malignancy (other than basal cell carcinoma or adequately treated carcinoma-in-situ of the cervix), stroke, diabetes, cardiac, renal, liver, or chronic pulmonary disease.<br>24. Subjects with abnormal screening thyroid-stimulating hormone results.<br>25. Subjects with a history of conditions that might have been specifically contraindicated or required caution while using OC or APAP, per the Investigator's Brochure.<br>26. Subjects with a history of any drug allergy, hypersensitivity, or intolerance, including OC, APAP, or excipients, or any opioid drug product, which in the opinion of the investigator, would have placed the subject at particular risk and compromised the safety of the subject in the study.<br>27. Subjects who had participated in a previous Mallinckrodt COV795 study within 6 months prior to Period 1 dosing.<br>28. Subjects who had a history of hay fever or seasonal allergies requiring OTC or prescription medications 14 days prior to Period 1 check-in and/or during the study. | |
| **ASSESSMENTS** | | |
| **Pharmacokinetics:** | One blood sample was collected up to 60 minutes prior to the first dose, 15, 30, and 45 minutes and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 18, 20, 24, 36, and 48 hours postdose for determining plasma concentrations of OC and APAP.<br>The following PK parameters for OC and APAP were determined using noncompartmental methods:<br>$AUC_{0-t}$: Area under the plasma concentration curve from time 0 to the last quantifiable concentration calculated by the linear trapezoidal rule for all treatments:<br>$AUC_{0-t} = \sum_{i=1}^{n} \frac{(C_i + C_{i-1})}{2}(t_i - t_{i-1})$<br>$AUC_{0-inf}$: Area under the plasma concentration curve from time 0 extrapolated to infinity, calculated as $AUC_{0-inf} = AUC_{0-t} + C_{last}/Kel$ where $C_{last}$ is the last quantifiable plasma concentration. Percent extrapolation $\leq 20\%$ and $r^2 > 0.90$ are needed to retain $AUC_{0-inf}$.<br>$C_{max}$: Maximum observed plasma concentration. | |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen | |
| | $T_{max}$: Time to achieve maximum observed plasma concentration.<br>$t_{lag}$: Time prior to the first measurable (nonzero) concentration.<br>$K_{el}$: Apparent first order terminal elimination rate constant, calculated using linear regression on the terminal portion of the ln-concentration versus time curve. At least 3 time points (excluding $C_{max}$) and $r^2 > 0.90$ are required to calculate and retain $K_{el}$ and its associated parameters ($AUC_{0\text{-}inf}$, $t_{1/2}$).<br>$t_{1/2}$: Apparent plasma terminal elimination half-life, calculated as $t_{1/2} = \ln(2)/K_{el}$ | |
| **Safety:** | Subjects underwent screening evaluation within 45 days before check-in to Period 1 (screening) and further evaluations during the study, and at the conclusion of the study or early termination. The safety of 2 tablets of 7.5 mg OC/325 mg APAP administration was monitored by the following procedures:<br>1. Adverse events and SAEs were collected and monitored from the time of signing of the informed consent form (ICF) through the conclusion of the study (Period 3, Hour 48), or at early termination. Additionally, a follow-up visit via telephone was performed for subjects who had ongoing AEs/SAEs at the conclusion of the study, or at early termination. Serious adverse events were followed up to 28 days after last dose of study medication or until resolution.<br>2. Clinical laboratory tests (hematology, clinical chemistry, and urinalysis) were done at screening and at the conclusion of the study or early termination.<br>3. Vital signs (blood pressure, pulse rate, and respiratory rate) and pulse oximetry were evaluated at screening, check-in, predose, and 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 hours postdose in each treatment period after the subject had been seated for at least 5 minutes.<br>4. Oral temperature was taken at screening and at check-in and predose for each period.<br>5. Physical examinations were performed at screening and at the conclusion of the study or early termination.<br>6. A 12-lead ECG was obtained for all subjects at screening and at the conclusion of the study or early termination.<br>7. Impaired judgment evaluation (lightheadedness, dizziness, sedation, confusion, visual disturbances, weakness, or uncoordinated muscle movements) was performed prior to each period check-out from the study site at the conclusion of each period, or at early termination. | |
| **STATISTICAL METHODS AND ANALYSIS** | | |
| **Efficacy:** | Not applicable. | |
| **Pharmacokinetics** | Individual plasma concentration versus time data was used to estimate the PK parameters of OC and APAP by standard noncompartmental methods using Phoenix WinNonlin Version 6.1 for each completer in each treatment. Plasma concentrations that were below the limit of quantitation (BLQ) were set to 0 before $T_{max}$, with the exception that if BLQ occurs between measurable concentrations it was set to missing. Values that were BLQ were set to missing after $T_{max}$.<br>The SAS mixed effect linear model procedure (PROC MIXED) was used to perform an analysis of variance (ANOVA) with the natural log-transformed PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $C_{max}$) as the dependent variable with sequence, treatment and period as fixed effects, and subject nested within sequence as a random effect. Treatment A (fed condition [high-fat meal]) was compared to Treatment C (fasted condition), Treatment B (fed condition [low-fat]) was compared to Treatment C (fasted condition), and Treatment A (fed condition [high-fat meal]) was compared to Treatment B (fed condition [low-fat meal]). A 90% CI of the | |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen | |
| | geometric LS means ratio fully contained within 80% to 125% will conclude no difference between treatments. Geometric LS Means, % Ratio of geometric LS means, and corresponding 90 % CI of the ratio, intrasubject variability (CV%) and the *P*-value for testing the fixed effects were provided.<br>The SAS mixed effect linear model procedure (PROC MIXED) was used to perform ANOVA with the un-transformed PK parameters ($K_{el}$, $t_{1/2}$) as the dependent variable with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. Treatment A (fed condition [high-fat meal]) was compared to Treatment C (fasted condition), Treatment B (fed condition [low-fat meal]) was compared to Treatment C (fasted condition), and Treatment A (fed condition [high-fat meal]) was compared to Treatment B (fed condition [low-fat meal]). A 90% CI of the difference that contains 0 was used to conclude no difference between treatments ($\alpha = 0.1$). Least squares means, the difference of LS means, the 90% CI of the difference, intrasubject variability (CV%), and the *P*-value for testing the fixed effects was provided.<br>The Wilcoxon signed-rank test was performed on the untransformed PK parameters $T_{max}$ and $t_{lag}$ and the P-value for the difference was provided. A *P*-value $\leq 0.05$ was considered a significant difference between treatments.<br>Outliers were evaluated using Grubbs' test and the Likelihood Distance Test on natural log-transformed PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and $C_{max}$). | |
| **Safety:** | **Adverse Events**:<br>Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 13.1. All AEs are presented in a data listing.<br>Treatment-emergent AEs (TEAEs), treatment-related TEAEs, severity of TEAEs, and TEAEs leading to early discontinuation were summarized by system organ class (SOC) and preferred term for all dosed subjects at the treatment level and overall. All TEAEs leading to early discontinuation are presented in data listings.<br>Treatment-emergent AEs generated from clinically significant changes in laboratory test results, physical examination findings, and ECG findings were not assigned to a treatment. These TEAEs are summarized at the study level. Treatment-emergent AEs or findings from the impaired judgment evaluations were assigned to the most recently administered study treatment.<br>**Clinical Laboratory Tests**:<br>Screening and study exit results and changes from baseline (screening visit) for hematology and serum chemistry test results were summarized at the study level.<br>**Electrocardiograms**:<br>Screening and exit results and changes from baseline (screening visit) for the ECG measures were summarized at the study level. Clinically significant changes from baseline are summarized within the TEAE study level summary table.<br>**Physical Examinations**:<br>Physical examination results are presented in a data listing. Clinically significant changes from baseline (screening visit) in physical examination findings were summarized within the TEAE study level summary.<br>**Vital Signs and Pulse Oximetry**:<br>Actual values and changes from baseline (predose) for vital signs (systolic blood pressure, diastolic blood pressure, respiratory rate, and pulse rate) and pulse oximetry are summarized at the treatment level for each time point. Clinically significant changes from baseline are summarized within the TEAE treatment level summary tables. | |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen | |
| | **Impaired Judgment Evaluation**:<br>Clinically significant findings in the impaired judgment evaluation were summarized within the TEAE treatment level summary tables. | |
| **STUDY POPULATION RESULTS** | | |
| **Treatment and Disposition:** | Forty-eight subjects enrolled and received study drug and were included in the safety analysis. A total of 31 subjects were included in the PK analysis. Seventeen subjects terminated early (14 subjects due to TEAEs and 3 subjects met withdrawal criteria) and were not part of the PK population as defined in the analysis plan.<br>The majority of all dosed subjects enrolled in the study were white (32 of 48 subjects; 66.7%), with another 31.3% (15 of 48 subjects) being black or African American and 2.1% (1 of 48 subjects) being multiracial. The majority (32 of 48 subjects; 66.7%) were not Hispanic or Latino in ethnicity. Subjects ranged in age from 18 to 52 years, and had a mean BMI of 25.84 $kg/m^2$. There were more male than female subjects (25 of 48 subjects; 52.1%).<br>The demographic characteristics of the 31 subjects that completed the study (completers) were comparable to the 48 enrolled subjects, although a greater percentage were male (67.7%, 21 of 31 subjects). | |
| **Treatment Terminations:** | Of the 17 subjects (35.4%) who discontinued early 14 subjects (29.2%) discontinued because of the TEAE of vomiting (5 subjects in the Treatment A group, 5 subjects in the Treatment B group, and 4 subjects in the Treatment C group). Three subjects (6.3%) met withdrawal criteria. | |
| **PHARMACOKINETIC RESULTS** | | |
| **Pharmacokinetics:** | Mean total exposures of OC were similar between the subjects in the fed (high-fat and low-fat meal) conditions when each were compared to subjects in the fasted condition. A 25% increase in mean peak exposure was observed in subjects in the fed condition (low-fat meal) compared to subjects in the fasted condition. Mean peak and total exposures were similar between subjects in the fed condition (high-fat and low-fat meal). Mean total exposures of APAP were similar between subjects in the fed and fasted conditions, and 23% to 24% reductions were observed in mean peak exposure in subjects under the fed conditions (high- and low-fat meals) compared to subjects in the fasted condition, respectively. A significant increase in the median $T_{max}$ of OC was observed in subjects in the fed condition (high-fat meal) compared to subjects in the fasted condition, and a significant increase in median $T_{max}$ of APAP was observed in subjects under each fed condition compared to subjects in the fasted condition.<br>For OC subjects under the fed (high-fat meal) compared to subjects in the fasted condition, the 90% CIs of the ratios of geometric LS means for $AUC_{0\text{-}inf}$ (110.63% to 120.41%), $AUC_{0\text{-}t}$ (111.00% to 120.90%), and $C_{max}$ (104.61% to 120.16%) were entirely contained within the predefined no-effect range of 80% to 125%, indicating that food did not affect the extent of exposure (Table S1).<br>For OC in subjects under the fed condition (low-fat meal) compared to subjects in the fasted condition, the 90% CIs of the ratios of geometric LS means for $AUC_{0\text{-}inf}$ (110.38% to 120.01%) and $AUC_{0\text{-}t}$ (110.54% to 120.27%) were entirely contained within the predefined no-effect range of 80% to 125%. The 90% CI for $C_{max}$ (116.88% to 134.03%) was partially contained within the no-effect range. Exposures were similar between subjects in the fed condition (high-fat and low-fat meal). | |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen | |

**Table S1: Oxycodone Geometric LS Means Ratios and 90% CIs for the Comparison of COV795 Under Fed and Fasted Conditions**

| Parameter | Geometric LS Means Ratio (%) (90% CI) Treatment A/C High Fat/Fasted | Geometric LS Means Ratio (%) (90% CI) Treatment B/C Low Fat/Fasted | Geometric LS Means Ratio (%) (90% CI) Treatment A/B High Fat/Low Fat |
|---|---|---|---|
| $AUC_{0-inf}$ (ng•h/mL)[a] | 115.41 (110.63, 120.41) | 115.09 (110.38, 120.01) | 100.28 (96.18, 104.55) |
| $AUC_{0-t}$ (ng•h/mL)[a] | 115.85 (111.00, 120.90) | 115.30 (110.54, 120.27) | 100.47 (96.34, 104.79) |
| $C_{max}$ (ng/mL)[a] | 112.11 (104.61, 120.16) | 125.16 (116.88, 134.03) | 89.57 (83.67, 95.90) |

Note: Treatment A: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (high-fat meal); Treatment B: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (low-fat meal); Treatment C: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fasted conditions.

[a]N = 31.

For APAP comparison of subjects in the fed condition (high-fat meal) compared to subjects in the fasted condition, the 90% CIs of the ratios of geometric LS means for $AUC_{0-inf}$ (95.75% to 101.54%) and $AUC_{0-t}$ (97.31% to 102.52%) were entirely contained within the predefined no-effect range of 80% to 125%. The 90% CI for $C_{max}$ (70.49% to 81.94%) was partially contained within the no-effect range (Table S2).

For APAP comparison of subjects in the fed condition (low-fat meal) compared to subjects in the fasted condition, the 90% CIs of the ratios of geometric LS means for $AUC_{0-inf}$ (93.80% to 99.39%) and $AUC_{0-t}$ (96.27% to 101.37%) were entirely contained within the predefined no-effect range of 80% to 125%. The 90% CI for $C_{max}$ (71.65% to 83.13%) was partially contained within the no-effect range. Exposures were similar between the subjects fed high-fat and low-fat meals.

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| **Name of Sponsor:** | Mallinckrodt Inc |
| **Name of Test Drug:** | COV795 |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen |

**Table S2: Acetaminophen Geometric LS Means Ratios and 90% CIs for the Comparison of COV795 Under Fed and Fasted Conditions**

| Parameter | Geometric LS Means Ratio (%) (90% CI) Treatment A/C High Fat/Fasted | Geometric LS Means Ratio (%) (90% CI) Treatment B/C Low Fat/Fasted | Geometric LS Means Ratio (%) (90% CI) Treatment A/B High Fat/Low Fat |
|---|---|---|---|
| $AUC_{0-inf}$ (ng•h/mL)[a] | 98.60 (95.75, 101.54) | 96.56 (93.80, 99.39) | 102.12 (99.20, 105.11) |
| $AUC_{0-t}$ (ng•h/mL)[b] | 99.88 (97.31, 102.52) | 98.79 (96.27, 101.37) | 101.10 (98.54, 103.74) |
| $C_{max}$ (ng/mL)[b] | 76.00 (70.49, 81.94) | 77.18 (71.65, 83.13) | 98.48 (91.45, 106.05) |

Note: An appropriate terminal phase could not be determined for Subject 109 (Treatment C), Subject 116 (Treatment A), Subject 124 (Treatment A), and Subject 145 (Treatment C).
Treatment A: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (high-fat meal); Treatment B: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fed conditions (low-fat meal); Treatment C: Two tablets of COV795 (7.5mg OC/325 mg APAP) administered orally under fasted conditions.
[a]N = 27.
[b]N = 31.

**SAFETY RESULTS**

| | |
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| **Extent of Exposure:** | Forty-eight subjects received at least 1 of the 3 treatments. Thirty-one of the 48 dosed subjects (64.6%) received all scheduled treatments, and completed all 3 periods of the study. |
| **All AEs:** | Overall, 33 subjects (68.8%) reported at least 1 TEAE. The majority of the TEAEs were considered treatment related by the investigator. The highest percentage of subjects reported TEAEs classified by SOC as gastrointestinal disorders (52.1%) and nervous system disorders (35.4%). Although statistical comparisons were not performed there were no notable differences in the overall incidence of TEAEs between the treatment groups (Treatment A 43.2%, Treatment B 44.7%, and Treatment C 38.5%).<br>The most frequently reported TEAEs were nausea (21 subjects; 43.8%), vomiting (15 subjects; 31.3%), and dizziness (10 subjects; 20.8%).<br>Fourteen of the 15 subjects who experienced moderate vomiting were discontinued early from the study based on the protocol requirement for subjects experiencing this AE. One female subject (Subject 114) was dosed in Period 1 and completed the period. She experienced moderate vomiting before dosing in Period 2 and was discontinued because she met withdrawal criteria (failure to consume entire breakfast). Five subjects in each treatment group experienced the TEAE of moderate vomiting.<br>Overall 35.4% of the subjects experienced TEAEs that were mild and 33.3% experienced TEAEs that were of moderate intensity. No TEAEs were severe and no SAEs or deaths occurred in the study. No symptoms of impaired judgment were recorded as a TEAE by the |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen | |
| | investigator. | |
| **Deaths and Other Serious AEs:** | No deaths or SAEs were reported during the study. | |
| **Laboratory Results:** | Most individual hematology and serum chemistry values were within the reference range for the testing laboratory. All changes that were noted as abnormal were considered by the investigator to not be clinically significant, except for the urinalysis results for Subject 112 who had an increase in urinary white blood cells. The AE was considered mild and unlikely related to study drug.<br>No clinically significant trends or changes in mean values for clinical laboratory test results were noted. | |
| **Vital Signs, Pulse Oximetry, and ECGs:** | None of the changes in individual vital sign values that were outside of the protocol defined normal ranges were considered by the investigator to be clinically significant. Two subjects had oxygen saturation measurements below the protocol defined range of < 95%. These oxygen saturation measurements were not considered clinically significant.<br>No clinically significant trends or changes in mean values for vital signs were noted.<br>None of the abnormalities in ECGs and changes in individual ECG values were considered by the investigator to be clinically significant.<br>Mean 12-lead ECG values were summarized by overall change from baseline (screening) to study exit. There were no clinically significant trends or changes in mean ECG measurements from mean baseline (screening) values.<br>There were no apparent trends in mean oxygen saturation values for any treatment group over the assessment period. | |
| **CONCLUSIONS** | | |
| **Pharmacokinetics:** | • The 90% CIs of the ratios of the geometric LS means for mean total exposure (AUC) of OC and APAP were within the no-effect range of 80% to 125% when COV795 was administered to subjects under high- and low-fat fed conditions, each compared with subjects under the fasted condition. This suggests that food does not have an effect on total exposure of OC and APAP.<br>• The 90% CI of the ratio of the geometric LS means for mean peak exposure ($C_{max}$) of OC was within the no-effect range of 80% to 125% when COV795 was administered to subjects under the high-fat fed condition. However, an increase of 25% was observed when COV795 was administered to subjects under the low-fat fed condition compared with the fasted condition and the 90% CI of the ratio of the geometric LS mean was partially contained within the no-effect range.<br>• The 90% CIs of the ratios of the geometric LS means for $C_{max}$ of APAP were outside the no-effect boundary, indicating that food decreased peak exposure by 23% to 24% for subjects under the high- and low-fat fed conditions compared with the fasted condition, respectively.<br>• The median $T_{max}$ of OC was significantly delayed ($P$-value < 0.02) by 2 hours when COV795 was administered to subjects under high-fat fed condition compared to the fasted condition, while the median $T_{max}$ of APAP was significantly delayed ($P$-value < 0.001) by 1.5 hours in subjects under fed conditions (high- and low-fat meal) compared to the fasted conditions.<br>• The median $t_{lag}$ for OC and APAP after administration of COV795 to subjects under fed conditions were slightly, but significantly ($P$-value < 0.02), prolonged by up to | |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | 7.5 mg Oxycodone hydrochloride/325 mg acetaminophen | |
| | 15 minutes compared to subjects under fasted conditions. | |
| **Safety:** | • Thirty-three subjects (68.8%) experienced at least 1 TEAE. The majority of subjects (31 subjects, 64.6%) experienced TEAEs that were considered treatment-related by the investigator. There were no notable differences in the overall incidence of TEAEs between the treatment groups (Treatment A 43.2%, Treatment B 44.7%, and Treatment C 38.5%).<br>• The most frequently reported TEAEs overall were nausea (21 subjects; 43.8%), vomiting (15 subjects; 31.3%), and dizziness (10 subjects; 20.8%).<br>• Fourteen subjects were discontinued early from the study as required by the protocol for experiencing the AE of vomiting. One subject experienced the TEAE of moderate vomiting prior to dosing and also met withdrawal criteria (failure to consume the entire breakfast before dosing) so was not considered discontinued due to an AE. Five subjects in each treatment group experienced the TEAE of moderate vomiting.<br>• One subject had a clinically significant change in a clinical laboratory test result with an increase in urinary white blood cells. The AE was considered mild and unlikely related to study drug.<br>• All changes in vital signs that were outside of the protocol defined normal range were considered by the investigator to not be clinically significant.<br>• All changes in oxygen saturation that were outside of the protocol defined normal range were considered by the investigator to not be clinically significant.<br>• Abnormalities in ECGs and changes in individual ECG values that were outside of the protocol defined normal ranges were not considered by the investigator to be clinically significant.<br>• Physical examination results were normal for all subjects with the exception of 1 subject who had a cast on his left arm as a result of a hand fracture that was considered not related to study drug.<br>• Overall, the safety profile of COV795 in this single dose food-effect study was consistent with expectations for a low-dose opioid treatment and comparable to Percocet. There were no significant safety differences observed between the high-fat fed, low-fat fed, and fasted treatment groups. | |

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| **Name of Sponsor/Company**:<br>Mallinckrodt Inc | **Individual Study Table Referring to Part of the Dossier**<br><br>**Volume**:<br><br>**Page**: | **(For National Authority Use Only)** |
| **Name of Finished Product**:<br>COV795 | | |
| **Name of Active Ingredient**:<br>Oxycodone hydrochloride/ acetaminophen | | |
| **Title of study**: An Open-Label, Randomized, Single-Dose, Four-Period Crossover Study to Evaluate the Pharmacokinetics, Bioavailability and Safety of COV795 Compared to Immediate-Release Roxicodone®, Ultracet® and Percocet® Administered Q6h for Two Doses in Normal Healthy Human Subjects Under Fasted Conditions | | |
| **Investigator**: Aziz L. Laurent, MD | | |
| **Study site**: (b) (4) | | |
| **Publication (reference)**: None | | |
| **Studied period**:<br>12 May 2012 (first subject, first dose) to<br>09 June 2012 (last subject, last dose) | **Phase of development**: 1 | |

**Objectives**:

**Primary Objective:**

The primary objective was to evaluate the single-dose pharmacokinetics (PK) and bioavailability (BA) of oxycodone hydrochloride (OC) and acetaminophen (APAP) following dosing of COV795 (7.5 mg OC/325 mg APAP) administered orally as 2 tablets compared with the listed drugs (LDs), 1 tablet of Roxicodone (15 mg OC) and 1 tablet of Ultracet (37.5 mg tramadol/325 mg APAP), administered orally every 6 hours (Q6h) for 2 doses in normal, healthy subjects under fasted conditions.

**Secondary Objectives:**

The secondary objectives were:

- To compare the single-dose PK and BA of COV795 (OC and APAP) and the PK and BA of OC from 1 tablet of Roxicodone and of APAP from 1 tablet of Ultracet with that of Percocet (7.5 mg OC/325 mg APAP) administered Q6h for 2 doses.
- To evaluate the relative safety of 2 tablets of COV795 compared with Roxicodone, Ultracet, and Percocet.

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| Name of Finished Product:<br>COV795 | | |
| Name of Active Ingredient:<br>Oxycodone hydrochloride/ acetaminophen | | |

**Methodology**: This was a single-center, open-label, randomized, single-dose, 4-period crossover, 4-sequence, PK, BA, and safety study in normal healthy male and nonpregnant, nonlactating female subjects 18 to 55 years old, inclusive. Attempts were made to enroll equal numbers of male and female subjects.

Subjects underwent screening evaluations to determine eligibility within 30 days of Check-in to Period 1. Subjects who met all of the inclusion and none of the exclusion criteria were randomly assigned to 1 of 4 treatment sequences: A/D/B/C, B/A/C/D, C/B/D/A, or D/C/A/B. Treatments A, B, C, and D were as follows:

- Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally under fasted conditions, 1 tablet at a time, at Hour 0 on Day 1 of the period
- Treatment B: 1 tablet of the LD, Roxicodone (15 mg OC) administered orally under fasted conditions at Hour 0 and Hour 6 on Day 1 of the period
- Treatment C: 1 tablet of the LD, Ultracet (37.5 mg tramadol/325 mg APAP) administered orally under fasted conditions at Hour 0 and Hour 6 on Day 1 of the period
- Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally under fasted conditions at Hour 0 and Hour 6 on Day 1 of the period

Each period started at Check-in and ended at Check-in to the subsequent period. There was a minimum 7-day interval between the start of each period. Subjects entered the clinic the evening before dosing in each period and were released from the clinic after the 48-hour postdose assessments. They received their assigned study drug treatment beginning on Hour 0 of Day 1. In all 4 periods, subjects fasted for at least 10 hours before study drug administration at Hour 0. For Treatments B, C, and D, subjects also fasted for at least 1 hour before the Hour 6 study drug administration.

During each period, blood samples were collected at designated times before dosing and up to 36 hours after dosing for PK analysis of OC and APAP. Standard safety assessments included monitoring of adverse events (AEs) and serious AEs (SAEs) from signing of the study-specific informed consent form to the end of the study or early termination, clinical laboratory tests (urinalysis, serum chemistry, hematology, and serum pregnancy tests for female subjects), vital sign (systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature) and pulse oximetry measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings. In addition, impaired judgment

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| **Name of Active Ingredient**:<br>Oxycodone hydrochloride/ acetaminophen | **Page**: | |

evaluations were performed at the completion of each period before the subjects were released from the clinic or at early termination.

**Number of subjects (planned and analyzed):** Forty-eight subjects were planned, 48 subjects (29 males and 19 females) were enrolled, and 30 subjects (22 males and 8 females) completed the 4 periods of the study. Forty-eight subjects who received study drug were included in the safety analysis, and 29 of the 30 subjects who completed the 4 periods were included in the PK analyses.

**Diagnosis and main criteria for inclusion:** Eligible subjects who provided written informed consent were normal, healthy males or nonpregnant, nonlactating females between 18 and 55 years of age, inclusive, with a body mass index (BMI) of at least 19 to less than 30 $kg/m^2$, inclusive, with a minimum body weight of 130 pounds.

**Test product, dose and mode of administration, batch number:**

Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally, 1 tablet at a time, under fasted conditions, lot number A78056.

**Reference therapy, dose and mode of administration, batch number**:

Treatment B: 1 tablet of the LD, Roxicodone (15 mg OC) administered orally Q6h for 2 doses under fasted conditions, lot number 159815A.

Treatment C: 1 tablet of the LD, Ultracet (37.5 mg tramadol/325 mg APAP) administered orally Q6h for 2 doses under fasted conditions, lot number 1JG073.

Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 2 doses under fasted conditions, lot number 402452NV.

**Duration of treatment:** The study duration included a screening visit up to 30 days before Period 1 Check-in, 4 confinement periods of approximately 48 hours each, and 3 minimum 7-day intervals between the start of each period. The total study duration was approximately 8 weeks.

**Criteria for evaluation:**

Pharmacokinetics: Blood samples for the determination of plasma concentrations of OC and APAP were drawn before dosing and at 15, 30, and 45 minutes, and 1, 2, 3, 4, 6, 6 hours 30 minutes, 7, 8, 9, 10, 12, 16, 18, 20, 24, and 36 hours after dosing.

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The following PK parameters were calculated for OC and APAP using standard noncompartmental methods: area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable concentration ($AUC_{0-t}$), AUC from time 0 extrapolated to infinity ($AUC_{0-inf}$), maximum observed plasma concentration ($C_{max}$), time of observed $C_{max}$ ($T_{max}$), lag time ($t_{lag}$), apparent first-order terminal elimination rate constant ($K_{el}$), and apparent plasma terminal elimination half-life ($t_{1/2}$).

Safety: Safety parameters included AEs/SAEs monitored constantly throughout the study from the time the study-specific informed consent was signed through the conclusion of the study or early termination; clinical laboratory tests, ECG measurements, and physical examinations performed at Screening and the conclusion of Period 4 or early termination; vital sign and pulse oximetry measurements performed at Screening, Check-in to each period, before dosing, and at selected times during each period; and impaired judgment evaluations performed 48 hours after dosing for each period or at early termination.

**Statistical methods**:

Pharmacokinetics: The SAS® mixed linear model procedure (PROC MIXED, SAS Institute, Inc, Cary, North Carolina) was used to perform an analysis of variance (ANOVA) with the natural log-transformed dose-normalized PK parameters ($AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$) as the dependent variable with sequence, treatment, and period as fixed effects and subjects nested within sequences as a random effect. Treatment A was compared with Treatment B (A/B), Treatment A was compared with Treatment C (A/C), Treatment A was compared with Treatment D (A/D), Treatment B was compared with Treatment D (B/D), and Treatment C was compared with Treatment D (C/D). Geometric least squares (LS) means, ratio of geometric LS means, the corresponding 90% confidence interval (CI) of the ratio, intrasubject variability (coefficient of variation), and *P*-values for testing the fixed effects were summarized. A 90% CI of the geometric LS mean ratio fully contained within 80% to 125% concluded no difference between treatments.

The SAS PROC MIXED procedure was used to perform an ANOVA with the nontransformed PK parameters ($K_{el}$ and $t_{1/2}$) as the dependent variables with sequence, treatment, and period as fixed effects and subjects nested within sequences as a random effect. Least squares means, difference of LS means (Treatment A/Treatment B [A–B], Treatment A/Treatment C [A–C], Treatment A/Treatment D [A–D], Treatment B/Treatment D [B–D], and Treatment C/Treatment D [C–D]), the 90% CI of the difference, and *P*-values for testing the fixed effects were presented. The Wilcoxon

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signed-rank test was performed to determine the statistical significance of the median difference (A–B, A–C, A–D, B–D, and C–D) for $T_{max}$ and $t_{lag}$. A *P*-value $\leq 0.05$ was considered a significant difference between treatments.

The $C_{max}$ and AUC for all treatments were tested for outliers using Grubb's test and the Likelihood Distance test. Outliers were evaluated using Grubb's test and the Likelihood Distance test on natural log-transformed dose-normalized PK parameters ($AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$). A subject was considered an outlier at a 5% level of significance if the corresponding *P*-value for the likelihood distance was $\leq 0.05$.

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 14.1. Treatment-emergent AEs (TEAEs), treatment-related TEAEs, severity of TEAEs, and TEAEs leading to early discontinuation were summarized by system organ class and preferred term for all dosed subjects by treatment and overall. The TEAEs generated from physical examination findings, clinically significant changes in laboratory test results, and ECG findings were summarized overall for all dosed subjects. All AEs, SAEs, and TEAEs leading to early discontinuation were presented in data listings.

Actual results and changes from Baseline for hematology and serum chemistry test results, vital sign and pulse oximetry measurements, and ECG results were summarized by treatment for all dosed subjects. All hematology, serum chemistry, urinalysis, vital signs and pulse oximetry, physical examination, and 12-lead ECG results were presented in data listings.

**RESULTS**:

Overall, the majority of all dosed subjects enrolled in the study were white (32 of 48 subjects; 66.7%), and the remainder were black or African American (16 of 48 subjects, 33.3%). The majority (29 of 48 subjects; 60.4%) were not of Hispanic or Latino ethnicity. Subjects ranged in age from 18 to 53 years and had a mean BMI of 26.56 $kg/m^2$. There were more male subjects (29 subjects, 60.4%) than female subjects (19 subjects, 39.6%) enrolled. This difference was more apparent in subjects that completed the study; of completers, 22 subjects (73.3%) were male and 8 subjects (26.7%) were female. There were no apparent differences in demographics and baseline characteristics for all dosed subjects compared with study completers.

Pharmacokinetic results:

**Oxycodone:** The plasma concentrations of OC rose rapidly (median $t_{lag} = 0$) after

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administration of COV795, similar to that observed with Roxicodone. The median $T_{max}$ of OC from COV795 (4 hours) was shorter than that for Roxicodone as the median $T_{max}$ for Roxicodone was observed 2 hours after the second dose (8 hours); this difference was not significant ($P = 0.065$). Conversely, the median $T_{max}$ of OC from COV795 was significantly earlier than median $T_{max}$ from Percocet (8 hours; $P = 0.004$).

Mean plasma OC levels from COV795 were approximately 45% of the peak plasma concentration by 12 hours after dosing. Mean plasma concentrations of OC from COV795, Roxicodone, and Percocet were detectable in all subjects through 24 hours after initial dosing and were detectable in most of the subjects through 36 hours after initial dosing. Mean plasma OC levels declined monoexponentially to approximately 5% to 9% of the peak plasma concentration by 24 hours after initial dosing.

The results from the statistical analysis of the PK parameters for OC are presented in Table 1. The dose-normalized total exposures of OC were comparable across treatment groups. The 90% CIs of the ratios of geometric LS means for $AUC_{0-t}$ and $AUC_{0-inf}$ were fully contained within the predefined no-difference range of 80% to 125% for OC, indicating that the dose-normalized drug total exposures for the 3 treatment groups were equivalent. The 90% CIs of the ratios of geometric LS means for $AUC_{0-t}$ of OC were (95.571% to 104.891%), (93.453% to 102.511%), and (93.546% to 102.660%) for comparisons of COV795 vs Roxicodone, Roxicodone vs Percocet, and COV795 vs Percocet, respectively. For $AUC_{0-inf}$ of OC, the 90% CIs of the ratios of geometric LS means were (95.997% to 105.250%), (93.003% to 101.912%), and (93.463% to 102.463%) for comparisons of COV795 vs Roxicodone, Roxicodone vs Percocet, and COV795 vs Percocet, respectively.

For dose-normalized $C_{max}$ of OC, the 90% CI of the ratio of geometric LS means for COV795 vs Roxicodone was fully contained within the predefined no-difference range of 80% to 125% (85.134% to 99.897%), indicating that the dose-normalized $C_{max}$ from COV795 was equivalent to that of Roxicodone. However, the percent ratios of geometric LS means with 90% CIs were 78.618% (72.610% to 85.122%) and 72.502% (66.936% to 78.531%) for comparisons of Roxicodone vs Percocet and COV795 vs Percocet, respectively, indicating that dose-normalized $C_{max}$ values of OC from Roxicodone and COV795 were approximately 21% and 27% lower than that for Percocet, respectively.

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**Table 1 Statistical Analysis of Plasma PK Parameters of OC**

| Dose-Normalized Parameter | Treatment | N | Geometric LS Means | Treatment Comparison | Ratio of Geometric LS Means (%) | 90% CI of the Ratio | Intrasubject Coefficient of Variation | *P*-Value | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Sequence | Treatment | Period |
| $AUC_{0-t}$/Dose (ng•h/mL/mg) | A | 29 | 10.971 | A/B | 100.122 | (95.571, 104.891) | 10.43 | 0.833 | 0.686 | 0.059 |
| | B | 29 | 10.958 | B/D | 97.878 | (93.453, 102.511) | | | | |
| | D | 29 | 11.195 | A/D | 97.997 | (93.546, 102.660) | | | | |
| $AUC_{0-inf}$/Dose (ng•h/mL/mg) | A | 29 | 11.071 | A/B | 100.517 | (95.997, 105.250) | 10.31 | 0.826 | 0.585 | 0.064 |
| | B | 29 | 11.014 | B/D | 97.356 | (93.003, 101.912) | | | | |
| | D | 29 | 11.314 | A/D | 97.859 | (93.463, 102.463) | | | | |
| $C_{max}$/Dose (ng/mL/mg) | A | 29 | 0.932 | A/B | 92.221 | (85.134, 99.897) | 18.02 | 0.476 | < 0.001 | 0.023 |
| | B | 29 | 1.011 | B/D | 78.618 | (72.610, 85.122) | | | | |
| | D | 29 | 1.285 | A/D | 72.502 | (66.936, 78.531) | | | | |

Note: An analysis of variance was performed with the natural log-transformed dose-normalized pharmacokinetic parameters as the dependent variable and sequence, treatment, and period as fixed effects and subjects nested within sequences as a random effect.

Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally 1 tablet at a time.

Treatment B: 1 tablet of Roxicodone (15 mg OC) administered orally every 6 hours (Q6h) for 2 doses.

Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 2 doses.

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Acetaminophen: The plasma concentrations of APAP rose rapidly after administration of COV795 (median $t_{lag} = 0$), similar to that observed with Ultracet. Peak plasma levels of APAP after administration of COV795 were observed at 45 minutes (median $T_{max}$) after dosing and were significantly different ($P < 0.001$) from the $T_{max}$ for Ultracet, which occurred at approximately 2 hours after dosing (range 30 minutes to 9 hours [3 hours after the second dose]). The median $T_{max}$ for Percocet was observed at 45 minutes postdose and was not significantly different from the $T_{max}$ for COV795 or Ultracet. Plasma APAP levels for COV795 fell below those for Ultracet and Percocet by 8 hours after dosing. Mean plasma APAP levels from COV795 were approximately 18% of the peak plasma concentration by 12 hours after dosing. Mean plasma concentrations of APAP from COV795, Ultracet, and Percocet were detectable through 24 hours after initial dosing in most subjects but were detectable in only 1 subject at 36 hours after initial dosing. Mean plasma APAP levels were approximately 4% of the peak plasma concentration by 24 hours after dosing.

The results from the statistical analysis for the PK parameters of APAP are presented in Table 2. The dose-normalized total exposures of APAP were comparable across treatment groups. The 90% CIs of the ratios of geometric LS means for $AUC_{0-t}$ and $AUC_{0-inf}$ were fully contained within the predefined no-difference range of 80% to 125% for APAP, indicating that the dose-normalized drug total exposures for the 3 treatment groups were equivalent. The 90% CIs of the ratios of geometric LS means for $AUC_{0-t}$ of APAP were (93.538% to 99.147%), (99.464% to 105.460%), and (95.783% to 101.562%) for comparisons of COV795 vs Ultracet, Ultracet vs Percocet, and COV795 vs Percocet, respectively. For $AUC_{0-inf}$ of APAP, the 90% CIs of the ratios of geometric LS means were (95.612% to 101.470%), (99.154% to 105.260%), and (97.662% to 103.681%) for comparisons of COV795 vs Ultracet, Ultracet vs Percocet, and COV795 vs Percocet, respectively.

Similar results were observed for the dose-normalized $C_{max}$ of APAP. The 90% CI of the ratios of geometric LS means were fully contained within the predefined no-difference range of 80% to 125% for APAP, indicating that the dose-normalized mean $C_{max}$ values for the 3 treatment groups were equivalent. The 90% CIs of the ratios of geometric LS means for $C_{max}$ of APAP were (97.572% to 115.194%), (91.466% to 108.074%), and (96.962% to 114.586%) for comparisons of COV795 vs Ultracet, Ultracet vs Percocet, and COV795 vs Percocet, respectively.

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**Table 2 Statistical Analysis of Plasma PK Parameters of APAP**

| Dose-Normalized Parameter | Treatment | N | Geometric LS Means | Treatment Comparison | Ratio of Geometric LS Means (%) | 90% CI of the Ratio | Intrasubject Coefficient of Variation | *P*-Value | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Sequence | Treatment | Period |
| $AUC_{0-t}$/Dose (ng•h/mL/mg) | A | 29 | 42.902 | A/C | 96.302 | (93.538, 99.147) | 6.55 | 0.403 | 0.100 | 0.032 |
| | C | 29 | 44.549 | C/D | 102.418 | (99.464, 105.460) | | | | |
| | D | 29 | 43.498 | A/D | 98.630 | (95.783, 101.562) | | | | |
| $AUC_{0-inf}$/Dose (ng•h/mL/mg) | A | 29 | 45.482 | A/C | 98.498 | (95.612, 101.470) | 6.69 | 0.444 | 0.472 | 0.028 |
| | C | 29 | 46.175 | C/D | 102.161 | (99.154, 105.260) | | | | |
| | D | 29 | 45.198 | A/D | 100.626 | (97.662, 103.681) | | | | |
| $C_{max}$/Dose (ng/mL/mg) | A | 29 | 6.782 | A/C | 106.018 | (97.572, 115.194) | 18.83 | 0.757 | 0.437 | 0.085 |
| | C | 29 | 6.397 | C/D | 99.423 | (91.466, 108.074) | | | | |
| | D | 29 | 6.434 | A/D | 105.406 | (96.962, 114.586) | | | | |

Note: An analysis of variance was performed with the natural log-transformed dose-normalized pharmacokinetic parameters as the dependent variable and sequence, treatment, and period as fixed effects and subjects nested within sequences as a random effect.
Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally 1 tablet at a time.
Treatment C: 1 tablet of Ultracet (37.5 mg tramadol/325 mg APAP) administered orally every 6 hours (Q6h) for 2 doses.
Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 2 doses.

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Safety results:

Overall, 29 of 48 subjects (60.4%) reported at least 1 TEAE. More subjects reported TEAEs after receiving Roxicodone (25 of 43 subjects, 58.1%) than after receiving Percocet (15 of 40 subjects, 37.5%), COV795 (9 of 39 subjects, 23.1%), or Ultracet (8 of 36 subjects, 22.2%). This was expected because of the higher dose of OC in Roxicodone (1 tablet containing 15 mg OC administered Q6h for 2 doses, 30 mg total dose) compared with Percocet (1 tablet containing 7.5 mg OC administered Q6h for 2 doses, 15 mg total dose) and COV795 (2 tablets containing 7.5 mg OC, 15 mg total dose).

Overall, the highest percentage of subjects reported TEAEs classified as gastrointestinal disorders (25 of 48 subjects, 52.1%) followed by nervous system disorders (23 of 48 subjects, 47.9%).

Overall, the most frequently reported TEAEs (that occurred in more than 10% of the total number of subjects) were nausea (43.8%), dizziness (33.3%), vomiting (27.1%), and headache (20.8%); somnolence, feeling hot, and pruritus were each reported by 10.4% of subjects.

With the exception of 1 reported TEAE of hiccups, all TEAEs reported after subjects received COV795 were considered treatment-related (possibly related or related). The majority of TEAEs reported after Roxicodone, Ultracet, and Percocet were also considered treatment-related.

Fifteen subjects (31.3%) reported at least 1 moderate TEAE, and 14 subjects (29.2%) reported only mild TEAEs. There were no severe TEAEs reported.

No deaths or SAEs were reported during the study. Thirteen subjects (27.1%) experienced TEAEs of vomiting and were withdrawn from the study as required by the protocol: 10 subjects after receiving Roxicodone (23.3%) and 1 subject each after receiving COV795 (2.6%), Ultracet (2.8%), and Percocet (2.5%).

All TEAEs were considered resolved or resolving by the end of the study. No abnormalities in laboratory tests, ECGs, vital signs or pulse oximetry, or physical examinations were recorded as a TEAE.

**CONCLUSIONS**:

Pharmacokinetics:

- The dose-normalized $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$ of OC from COV795 were equivalent

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to those from Roxicodone.

- The dose-normalized $AUC_{0-t}$ and $AUC_{0-inf}$ of OC from COV795 and Roxicodone were equivalent to those from Percocet. Dose-normalized $C_{max}$ values of OC from Roxicodone and COV795 were approximately 21% and 27% lower than that for Percocet, respectively.
- There was no significant difference in median $T_{max}$ of OC between COV795 and Roxicodone. In addition, there was no significant difference between Roxicodone and Percocet; however, median $T_{max}$ of OC from COV795 occurred earlier than median $T_{max}$ from Percocet ($P = 0.004$).
- There was no lag (median $t_{lag} = 0$) in plasma OC levels for any treatment and there was no significant difference across treatment groups.
- The dose-normalized $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$ of APAP from COV795 were equivalent to those from Ultracet. Furthermore, the dose-normalized $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$ of APAP from COV795 and Ultracet were equivalent to those from Percocet.
- Median $T_{max}$ of APAP from COV795 occurred significantly earlier than median $T_{max}$ for Ultracet ($P < 0.001$). There was no significant difference in median $T_{max}$ of APAP from COV795 when compared with Percocet.
- There was no lag (median $t_{lag} = 0$) in plasma APAP levels for any treatment and there was no significant difference across treatment groups.
- There were no outliers identified in terms of dose-normalized AUC and $C_{max}$ by either the Likelihood Distance test or Grubb's test for OC or APAP.
- Overall, the comparable PK findings between treatment groups in this study support further product development of COV795 for acute pain and provide extended exposure data over the proposed 12-hour dosing interval.

Safety:

- Overall, 29 subjects (60.4%) reported at least 1 TEAE. More subjects reported TEAEs after receiving Roxicodone (58.1%), than after receiving Percocet (37.5%), COV795 (23.1%), or Ultracet (22.2%).
- The most frequently reported TEAEs (that occurred in more than 10% of the total number of subjects) were nausea (43.8%), dizziness (33.3%), vomiting (27.1%), and

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headache (20.8%); somnolence, feeling hot, and pruritus were each reported by 10.4% of subjects. The majority of TEAEs reported were considered treatment-related. Fifteen subjects (31.3%) reported at least 1 moderate TEAE, and 14 subjects (29.2%) reported only mild TEAEs. There were no severe TEAEs reported.

- There were no deaths or SAEs.
- Thirteen subjects (27.1%) experienced TEAEs of vomiting and were withdrawn from the study as required by the protocol: 10 subjects after receiving Roxicodone (23.3%) and 1 subject each after receiving COV795 (2.6%), Ultracet (2.8%), and Percocet (2.5%).
- No apparent clinically significant treatment-related trends were observed in clinical laboratory test results, vital sign and pulse oximetry measurements, 12-lead ECG results, or physical examination findings.
- COV795 demonstrated the anticipated tolerability and safety profile for a low-dose opioid/APAP treatment. As expected, fewer subjects reported TEAEs after receiving COV795 (15 mg total OC dose) than Roxicodone (30 mg total OC dose). The safety profile of COV795 was comparable to Ultracet and Percocet.
- Overall, the comparable safety findings between treatment groups in this study support further product development and suggest that COV795 can be safely administered to patients for the management of (b) (4) acute pain.

**Date of report:** 11 December 2012

Study 255 (Multiple Dose Relative Bioavailability)

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**Title of study**: An Open-Label, Randomized, Multiple-Dose, Four-Period, Crossover Study to Evaluate the Steady-State Pharmacokinetics, Bioavailability and Safety of COV795 Administered Q12h Compared to Immediate-Release Roxicodone®, Ultracet® and Percocet® Administered Q6h in Normal, Healthy Subjects

**Investigator**: Aziz L. Laurent, MD

**Study site**: (b) (4)

**Publication (reference)**: None

| | |
|---|---|
| **Studied period**:<br>03 May 2012 (first subject, first dose) to<br>01 July 2012 (last subject, last dose) | **Phase of development**: 1 |

**Objectives**:

**Primary Objective:**

The primary objective of this study was to evaluate the steady-state pharmacokinetics (PK) and bioavailability (BA) after dosing of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally as 2 tablets every 12 hours (Q12h) over 4.5 days compared with 1 tablet of Roxicodone (15 mg OC) and 1 tablet of Ultracet (37.5 mg tramadol/325 mg APAP) administered orally every 6 hours (Q6h) over 4.5 days in normal, healthy subjects under fasted conditions.

**Secondary Objectives:**

The secondary objectives were:

- To compare the multiple-dose PK and BA of COV795 (OC and APAP) and the PK and BA of OC from 1 tablet of Roxicodone and of APAP from 1 tablet of Ultracet with that of 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered Q6h for 4.5 days.
- To evaluate the relative safety of 2 tablets of COV795 compared with Roxicodone, Ultracet, and Percocet.

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**Methodology**: This was a single-center, open-label, randomized, multiple-dose, 4-period, 4-sequence, crossover, PK, BA, and safety study in normal healthy male and nonpregnant, nonlactating female subjects 18 to 55 years old, inclusive.

Subjects underwent screening evaluations to determine eligibility within 30 days of Check-in to Period 1. Subjects who met all of the inclusion and none of the exclusion criteria were randomly assigned to 1 of 4 treatment sequences: A/D/B/C, B/A/C/D, C/B/D/A, or D/C/A/B. Treatments A, B, C, and D were as follows:

- Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally, 1 tablet at a time, Q12h for 4.5 days (9 doses).
- Treatment B: 1 tablet of the listed drug (LD), Roxicodone (15 mg OC) administered orally Q6h for 4.5 days (18 doses).
- Treatment C: 1 tablet of the LD, Ultracet (37.5 mg tramadol/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).
- Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

Treatment A: At Hour 0 on Day 1 and Hour 96 on Day 5, subjects received 2 tablets of COV795 after an overnight fast of at least 10 hours. Subjects received subsequent doses of COV795 administered Q12h at Hours 12, 24, 36, 48, 60, 72, and 84 after a fast of at least 1 hour.

Treatments B, C, and D: At Hour 0 on Day 1 and Hour 96 on Day 5, subjects received 1 tablet of Roxicodone, Ultracet, or Percocet after an overnight fast of at least 10 hours. Subjects received subsequent doses of Roxicodone, Ultracet, or Percocet administered Q6h at Hours 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 102 after a fast of at least 1 hour.

Subjects were confined at the clinic through Day 7 of each period. There was an interval of at least 13 days between the start of each period.

During each period, serial blood samples for PK analysis of OC and APAP were collected before dosing and up to 12 hours after dosing. For steady-state analysis, blood samples were

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collected on Days 2 through 4 before the morning dose of study drug and on Day 5 before dosing and through 132 hours (Day 6).

Standard safety assessments included monitoring adverse events (AEs) and serious AEs (SAEs) from the time the informed consent form was signed through the end of the study or early termination, clinical laboratory test results (hematology, serum chemistry, urinalysis, and serum pregnancy tests for female subjects), vital sign (systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature) and pulse oximetry measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings. In addition, impaired judgment evaluations were performed at the end of each period before the subjects were released from the clinic or at early termination.

**Number of subjects (planned and analyzed)**: Forty-eight subjects were planned, 48 subjects (27 males and 21 females) were enrolled, and 24 subjects (17 males and 7 females) completed the 4 periods of the study. Forty-eight subjects who received study drug were included in the safety analysis, and 24 subjects who completed the 4 periods were included in the PK analyses.

**Diagnosis and main criteria for inclusion**: Eligible subjects who provided written informed consent were normal, healthy males or nonpregnant, nonlactating females between 18 and 55 years of age, inclusive, with a body mass index (BMI) at least 19 to less than 30 $kg/m^2$, inclusive, with a minimum body weight of 130 pounds.

**Test product, dose and mode of administration, batch number**:

Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally, 1 tablet at a time, Q12h for 4.5 days (9 doses) under fasted conditions, lot number A78056.

**Reference therapy, dose and mode of administration, batch number**:

Treatment B: 1 tablet of the LD, Roxicodone (15 mg OC), administered orally Q6h for 4.5 days (18 doses) under fasted conditions, lot number 159815A.

Treatment C: 1 tablet of the LD, Ultracet (37.5 mg tramadol/325 mg APAP), administered orally Q6h for 4.5 days (18 doses) under fasted conditions, lot number 1JG073.

Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses) under fasted conditions, lot number 402452NV.

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**Duration of treatment**: The study duration included a screening visit within 30 days of Period 1 Check-in, 4 confinement periods of approximately 7 days each, and 3 intervals of at least 13 days between the start of each period. The total study duration was approximately 11 weeks.

**Criteria for evaluation**:

Pharmacokinetics: While operating according to the original protocol, dated 08 March 2012, blood samples for the determination of plasma concentrations of OC and APAP were drawn on Day 1 before dosing and at 15, 30, 45 minutes, 1, 2, 3, 4, 6 hours, 6 hours 15 minutes (Treatments B, C, and D only), 6 hours 30 minutes (Treatments B, C, and D only), 6 hours 45 minutes (Treatments B, C, and D only), 7, 8, 10, and 12 hours after dosing. On Days 2 through 4, blood samples were drawn before the morning dose of study drug at 24 (Day 2), 48 (Day 3), and 72 (Day 4) hours. On Days 5 through 6, blood samples were drawn before dosing at 96 hours (Day 5) and at 96 hours 15 minutes, 96 hours 30 minutes, 96 hours 45 minutes, 97, 98, 99, 100, 102 hours, 102 hours and 15 minutes (Treatments B, C, and D only), 102 hours and 30 minutes (Treatments B, C, and D only), 102 hours and 45 minutes (Treatments B, C, and D only), 103, 104, 106, 108, 112, 120 (Day 6), and 132 hours. Blood was collected according to this schedule during Period 1 for Cohort 1 and for blood samples up to 96 hours after dosing during Period 2 for Cohort 1 and Period 1 for Cohort 2.

The protocol was amended to reduce the frequency of blood draws in order to meet the Food and Drug Administration recommendation of collecting only 550 mL blood every 8 weeks (communicated to Mallinckrodt on 17 May 2012). While operating according to the protocol amendment, dated 18 May 2012, blood samples for the determination of plasma concentrations of OC and APAP were drawn on Day 1 before dosing and at 30 minutes, 1, 2, 3, 4, 6 hours, 6 hours and 30 minutes (Treatments B, C, and D only), 8, and 12 hours after dosing. On Days 2 through 4, blood samples were drawn before the morning dose of study drug at 24 (Day 2), 48 (Day 3), and 72 (Day 4) hours. On Days 5 through 6, blood samples were drawn before dosing at 96 hours (Day 5) and at 96 hours and 30 minutes, 97, 98, 99, 100, 102 hours, 102 hours and 30 minutes (Treatments B, C, and D only), 104, 108, 120 (Day 6), and 132 hours. This schedule was followed for all cohorts and periods other than those blood samples collected during Period 1 for Cohort 1 and for blood samples up to 96 hours after dosing during Period 2 for Cohort 1 and Period 1 for Cohort 2, which were collected while operating under the original protocol, as described above.

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The following PK parameters were calculated for OC and APAP using standard noncompartmental methods:

Day 1 (0 to 12 hours):

| | |
|---|---|
| $AUC_{0-12h}$ | Area under the plasma concentration-time curve from time 0 to 12 hours |
| $C_{max}$ | Maximum observed plasma concentration after dosing |
| $C_{min}$ | Plasma concentration obtained at 12 hours after dosing on Day 1 |
| $T_{max}$ | Time of $C_{max}$ |
| $t_{lag}$ | Lag time; the time before the first measurable concentration |

Day 2 through Day 5 (24, 48, 72, and 96 hours):

| | |
|---|---|
| $C_{min}$ | Plasma concentration obtained before dosing on Days 2 to 5 |

Day 5 (0 to 12 hours at steady state):

| | |
|---|---|
| $AUC_{0-12h}^{ss}$ | Area under the plasma concentration-time curve from time 0 to 12 hours at steady state |
| $C_{max}^{ss}$ | Maximum observed plasma concentration after dosing at steady state (0 to 12 hours) |
| $C_{min}^{ss}$ | Minimum observed plasma concentration at steady state (0 to 12 hours) |
| $C_{avg}^{ss}$ | Average observed plasma concentration during the dosing interval at steady state |
| DFL | Degree of fluctuation of the plasma concentration |
| swing | Swing of plasma concentrations, defined as: $(C_{max}^{ss} - C_{min}^{ss})/C_{min}^{ss}$ |
| $T_{max}^{ss}$ | Time of $C_{max}$ at steady state |

Day 5 through Day 6:

| | |
|---|---|
| $K_{el}$ | Apparent first-order terminal elimination rate constant |
| $t_{1/2}$ | Apparent plasma terminal elimination half-life |

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Safety: Safety parameters included AEs monitored constantly throughout the study from the time the informed consent form was signed through the end of the study or early termination; clinical laboratory tests and ECG measurements performed at Screening, Check-in to each period, and at the end of each period or early termination; physical examinations performed at Screening and the end of Period 4 or at early termination; vital sign and pulse oximetry measurements performed at Screening, Check-in to each period, before dosing, and at selected times during each period, including overnight continuous pulse oximetry and pulse rate monitoring on Days 1 through 5 of each period; and impaired judgment evaluations performed at the end of each period or at early termination.

**Statistical methods**:

Pharmacokinetics:

Steady-state attainment analysis (Days 1 [12 hour] through 5): The SAS® mixed effect linear model procedure (PROC MIXED; SAS Institute, Inc, Cary, North Carolina) was used to perform an analysis of variance (ANOVA) with the natural log-transformed PK parameter ($C_{min}$) as the dependent variable with day and sequence as fixed effects and subjects nested within sequence as a random effect for each treatment separately. Helmert transformation was used for comparing the geometric mean concentration of the corresponding study day to the geometric mean concentration pooled over all remaining days within treatment. Comparison continued until the day comparison was not statistically significant at $\alpha = 0.05$. The earliest study day that included a nonsignificant contrast was considered as the study day on which steady state was attained. Geometric least squares (LS) means, the percent ratio of the geometric LS means, and the corresponding 90% confidence interval (CI) of the ratio were presented and *P* values were used for comparison testing.

Analysis at steady state (Day 5): The SAS PROC MIXED procedure was used to perform an ANOVA with the natural log-transformed, dose-normalized PK parameters ($C_{max}^{ss}$, $C_{min}^{ss}$, $C_{avg}^{ss}$, and $AUC_{0\text{-}12h}^{ss}$) or natural log-transformed PK parameters (DFL and swing) as the dependent variable with sequence, treatment, and period as fixed effects and subjects nested within sequences as a random effect. Treatment A was compared with Treatment B (A/B), Treatment A was compared with Treatment C (A/C), Treatment A was compared with Treatment D (A/D), Treatment B was compared with Treatment D (B/D), and Treatment C was compared with Treatment D (C/D). Geometric LS means, percent ratio of the geometric LS means, and the corresponding 90% CI of the ratio were presented. A 90% CI of the

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geometric LS means ratio fully contained within 80% to 125% concluded no difference between treatments. Intrasubject coefficient of variation and *P* values for testing the fixed effects were also presented.

The SAS PROC MIXED procedure was also used to perform an ANOVA with the nontransformed PK parameter ($K_{el}$ and $t_{1/2}$) as the dependent variable and sequence, treatment, and period as fixed effects and subjects nested within sequences as a random effect. Least squares means, the difference of the LS means (Treatment A–Treatment B [A-B], Treatment A–Treatment C [A–C], Treatment A–Treatment D [A–D], Treatment B-Treatment D [B–D], and Treatment C–Treatment D [C–D],), the 90% CI of the difference, and *P* values for testing the fixed effects were presented. The Wilcoxon signed-rank test was used to determine the statistical significance of the median difference (A–B, A–C, A–D, B–D, and C–D) for $T_{max}^{ss}$. A *P* value of $\leq 0.05$ was considered a significant difference between treatments.

Outlier analysis (Day 5): Outliers were evaluated using Grubb's test and the Likelihood Distance test on natural log-transformed, dose-normalized PK parameters ($C_{max}^{ss}$, $C_{min}^{ss}$, and $AUC_{0\text{-}12h}^{ss}$). A subject was considered an outlier at a 5% level of significance if the corresponding *P* value for the likelihood distance was $\leq 0.05$.

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 14.1. Treatment-emergent AEs (TEAEs), treatment-related TEAEs, severity of TEAEs, and TEAEs leading to early discontinuation were summarized by system organ class and preferred term for all dosed subjects by treatment and overall. The TEAEs generated from physical examination findings were summarized overall for all dosed subjects. All AEs, SAEs, and TEAEs leading to early discontinuation were presented in data listings.

Actual results and changes from Baseline for hematology and serum chemistry test results, vital sign and pulse oximetry measurements, and ECG results were summarized by treatment for all dosed subjects. All hematology, serum chemistry, urinalysis, vital sign and pulse oximetry, physical examination, and 12-lead ECG results were presented in data listings.

**RESULTS**:

Overall, the majority of all dosed subjects enrolled in the study were white (33 of 48 subjects; 68.8%), and the remainder were black or African American (15 of 48 subjects, 31.3%).

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Subjects ranged in age from 18 to 51 years and had a mean BMI of 25.45 $kg/m^2$. There were slightly more male subjects (27 subjects, 56.3%) than female subjects (21 subjects, 43.8%) enrolled. This difference was more apparent in subjects that completed the study; of completers, 17 subjects (70.8%) were male and 7 subjects (29.2%) were female. There were no apparent differences in demographics and baseline characteristics for all dosed subjects compared with study completers.

Pharmacokinetic results:

Oxycodone: Steady-state plasma concentrations were reached by Day 1 for Roxicodone and Day 2 for COV795 and Percocet. On Day 5 under steady-state conditions, mean plasma concentrations of OC increased rapidly after administration of COV795, similar to that observed for Roxicodone. Peak plasma levels of OC on Day 5 after administration of COV795 and Roxicodone were observed at 3 hours (median $T_{max}^{ss}$) after dosing, whereas the peak plasma level of OC after administration of Percocet was observed at approximately 7.25 hours (about 1.25 hours after the second dose). However, the $T_{max}^{ss}$ for OC from COV795 was significantly different from both Roxicodone and Percocet ($P < 0.05$). Mean plasma OC levels for COV795 were approximately 37% of the peak plasma concentration by 12 hours after dosing. Mean plasma concentrations of OC from COV795, Roxicodone, and Percocet were detectable in all subjects through 24 hours after the initial Day 5 (96 hour) dosing and were detectable in most of the subjects through 36 hours after this dose. Mean plasma OC levels declined monoexponentially to approximately 8% of the peak plasma concentration by 24 hours after the first Day 5 dose of COV795. The pattern of the PK profiles of OC from Roxicodone and Percocet were very similar except that $C_{max}$ (Day 1) and $C_{max}^{ss}$ (Day 5) values from Roxicodone were higher than that of Percocet, as expected.

The results from the statistical analysis of the PK parameters for OC on Day 5 are presented in Table 1. A comparison of the geometric LS means of dose-normalized exposure within the first 12 hours at steady state ($AUC_{0\text{-}12h}^{ss}$) of OC and the dose-normalized average plasma concentration during the dosing interval at steady state ($C_{avg}^{ss}$) of OC did not show a significant difference among COV795, Roxicodone, and Percocet; the 90% CIs of the ratios of the geometric LS means for the treatment comparisons were fully contained within the predefined no-difference range of 80% to 125%. The ratios of geometric LS means and 90% CIs of the ratios for dose-normalized $AUC_{0\text{-}12h}^{ss}$ were 110.23% (103.60%, 117.28%), 99.18% (93.15%, 105.60%), and 109.32% (102.77%, 116.29%) for comparisons of COV795

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and Roxicodone (A/B), Roxicodone and Percocet (B/D), and COV795 and Percocet (A/D), respectively. The ratios of geometric LS means and 90% CIs of the ratios for dose-normalized $C_{avg}^{ss}$ were the same as $AUC_{0\text{-}12h}^{ss}$, as $C_{avg}^{ss}$ was equal to $AUC_{0\text{-}12h}^{ss}/\tau$, where $\tau$ was the dosing interval. The 90% CI of the geometric LS means ratios for dose-normalized $C_{max}^{ss}$ and $C_{min}^{ss}$ were completely contained within the no-difference range for the comparison between COV795 and Roxicodone (A/B) and COV795 and Percocet (A/D); however, a decrease of 14% for $C_{max}^{ss}$ and an increase of 16% for $C_{min}^{ss}$ were observed between Roxicodone and Percocet (B/D), and the corresponding 90% CIs of the ratios of the geometric LS means were not completely contained within the no-difference range of 80% to 125%. The ratios of geometric LS means and 90% CIs of the ratios for dose-normalized $C_{max}^{ss}$ of OC were 106.90% (97.58%, 117.10%), 85.56% (78.03%, 93.82%), and 91.46% (83.52%, 100.16%) for comparisons of COV795 and Roxicodone (A/B), Roxicodone and Percocet (B/D), and COV795 and Percocet (A/D), respectively. The ratios of geometric LS means and 90% CIs of the ratios for dose-normalized $C_{min}^{ss}$ of OC were 91.16% (83.56%, 99.46%), 115.91% (106.14%, 126.58%), and 105.67% (96.89%, 115.25%) for comparisons of COV795 and Roxicodone (A/B), Roxicodone and Percocet (B/D), and COV795 and Percocet (A/D), respectively.

A comparison of the geometric LS means for the DFL of OC revealed no significant difference between COV795 and Roxicodone (A/B). However, decreases of 29% and 23% were observed between Roxicodone and Percocet (B/D) and COV795 and Percocet (A/D), respectively. The ratios of geometric LS means and 90% CIs of the ratios for the DFL of OC were 108.31% (97.01%, 120.92%), 71.36% (63.85%, 79.77%), and 77.29% (69.26%, 86.25%) for comparisons of COV795 and Roxicodone (A/B), Roxicodone and Percocet (B/D), and COV795 and Percocet (A/D), respectively.

A 31% higher geometric LS means for swing of OC was observed for COV795 compared with Roxicodone (A/B); the 90% CIs of the ratios of the geometric LS means were not completely contained within the no-difference range. Moreover, a 39% and 20% lower swing of OC was observed for Roxicodone compared with Percocet (B/D) and COV795 compared with Percocet (A/D), respectively. The ratios of geometric LS means and 90% CIs of the ratios for the swing of OC were 130.95% (110.61%, 155.04%), 61.06% (51.49%, 72.42%), and 79.96% (67.58%, 94.60%) for comparisons of COV795 and Roxicodone (A/B), Roxicodone and Percocet (B/D), and COV795 and Percocet (A/D), respectively.

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**Table 1 Statistical Analysis of Plasma PK Parameters of OC on Day 5 (Completers)**

| Dose-Normalized Parameter | Treatment | N | Geometric LS Means | Treatment Comparison | Ratio of Geometric LS Means (%) | 90% CI of the Ratio |
|---|---|---|---|---|---|---|
| $AUC_{0-12}^{ss}$/Dose (ng•h/mL/mg) | A | 24 | 13.823 | A/B | 110.226 | (103.596, 117.281) |
| | B | 24 | 12.541 | B/D | 99.179 | (93.153, 105.595) |
| | D | 24 | 12.645 | A/D | 109.322 | (102.771, 116.290) |
| $C_{max}^{ss}$/Dose (ng/mL/mg) | A | 24 | 1.605 | A/B | 106.898 | (97.581, 117.103) |
| | B | 24 | 1.501 | B/D | 85.559 | (78.029, 93.817) |
| | D | 24 | 1.755 | A/D | 91.461 | (83.520, 100.157) |
| $C_{avg}^{ss}$/Dose (ng/mL/mg) | A | 24 | 1.152 | A/B | 110.226 | (103.596, 117.281) |
| | B | 24 | 1.045 | B/D | 99.179 | (93.153, 105.595) |
| | D | 24 | 1.054 | A/D | 109.322 | (102.771, 116.290) |
| $C_{min}^{ss}$/Dose (ng/mL/mg)[a] | A | 24 | 0.596 | A/B | 91.164 | (83.557, 99.463) |
| | B | 24 | 0.654 | B/D | 115.912 | (106.144, 126.579) |
| | D | 24 | 0.564 | A/D | 105.670 | (96.886, 115.251) |
| DFL (%) | A | 24 | 84.883 | A/B | 108.305 | (97.008, 120.918) |
| | B | 24 | 78.374 | B/D | 71.363 | (63.846, 79.765) |
| | D | 24 | 109.825 | A/D | 77.289 | (69.257, 86.253) |
| swing | A | 24 | 1.641 | A/B | 130.952 | (110.609, 155.036) |
| | B | 24 | 1.253 | B/D | 61.061 | (51.485, 72.418) |
| | D | 24 | 2.052 | A/D | 79.960 | (67.583, 94.604) |

Note: An analysis of variance was performed with the natural log-transformed dose-normalized pharmacokinetic (PK) parameters ($AUC_{0-12}^{ss}$, $C_{max}^{ss}$, $C_{min}^{ss}$, and $C_{avg}^{ss}$) or natural log-transformed PK parameters (DFL and swing) as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequences as a random effect.

Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally, 1 tablet at a time, every 12 hours for 4.5 days (9 doses).

Treatment B: 1 tablet of Roxicodone (15 mg OC) administered orally every 6 hours (Q6h) for 4.5 days (18 doses).

Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

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Acetaminophen: Steady-state plasma concentrations were reached by Day 2 for COV795 and Roxicodone and by Day 1 for Percocet. On Day 5 under steady-state conditions, mean plasma concentrations of APAP increased rapidly after administration of COV795, similar to that observed with Ultracet. Peak plasma levels of APAP after administration of COV795 were observed at 1 hour (median $T_{max}^{ss}$) after dosing; likewise, the peak levels of APAP after administration of Ultracet and Percocet were observed at approximately 1 hour after dosing (range 15 minutes to 8 hours [2 hours after the second dose]). Plasma APAP levels for COV795 fell below those of Ultracet and Percocet by 7 hours after the initial Day 5 (96 hour) dosing and were 17% of $C_{max}^{ss}$ by 12 hours after dosing. Mean plasma concentrations of APAP from COV795, Ultracet, and Percocet were detectable through 24 hours in most subjects after the initial (96 hour) dosing on Day 5, while less than half of the subjects had detectable concentrations by 36 hours after this dose. Mean plasma APAP levels were approximately 5% of the peak plasma concentration by 24 hours after dosing of COV795 on Day 5. The pattern of the PK profiles of APAP from Ultracet and Percocet were similar with comparable peak concentrations.

The results from the statistical analysis for the PK parameters of APAP on Day 5 are presented in Table 2. A comparison of the geometric LS means of dose-normalized exposure within the first 12 hours at steady state ($AUC_{0-12h}^{ss}$), dose-normalized peak exposure ($C_{max}^{ss}$), and the dose-normalized average plasma concentration during the dosing interval at steady state ($C_{avg}^{ss}$) of APAP did not show a difference among COV795, Ultracet, and Percocet; the 90% CIs of the ratios of the geometric LS means for all treatment comparisons were fully contained within the predefined no-difference range of 80% to 125% for APAP. The ratios of geometric LS means and 90% CIs of the ratios for dose-normalized $AUC_{0-12h}^{ss}$ were 94.98% (90.82%, 99.32%), 100.85% (96.50%, 105.39%), and 95.78% (91.63%, 100.11%) for comparisons of COV795 and Ultracet (A/C), Ultracet and Percocet (C/D), and COV795 and Percocet (A/D), respectively. The ratios of geometric LS means and 90% CIs of the ratios for dose-normalized $C_{max}^{ss}$ were 95.62% (85.30%, 107.18%), 102.67% (91.74%, 114.90%), and 98.17% (87.68%, 109.91%) for comparisons of COV795 and Ultracet (A/C), Ultracet and Percocet (C/D), and COV795 and Percocet (A/D), respectively. The ratios of geometric LS means and 90% CIs of the ratios for dose-normalized $C_{avg}^{ss}$ were the same as $AUC_{0-12h}^{ss}$, as $C_{avg}^{ss}$ was equal to $AUC_{0-12h}^{ss}/\tau$, where $\tau$ was the dosing interval. Decreases of 21% and 22% for $C_{min}^{ss}$ were observed between COV795 and Ultracet (A/C) and COV795 and Percocet (A/D). However, the 90% CI of the geometric LS means ratio for dose-normalized

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$C_{min}^{ss}$ was completely contained within the no-difference range for the comparison between Ultracet and Percocet (C/D). The ratios of geometric LS means and 90% CIs of the ratios for dose-normalized $C_{min}^{ss}$ of APAP were 79.14% (73.37%, 85.38%), 99.09% (91.96%, 106.78%), and 78.43% (72.76%, 84.54%) for comparisons of COV795 and Ultracet (A/C), Ultracet and Percocet (C/D), and COV795 and Percocet (A/D), respectively.

A comparison of the geometric LS means for the DFL of APAP revealed no significant difference in the DFL among COV795, Ultracet, and Percocet. The ratios of geometric LS means and 90% CIs of the ratios for the DFL of APAP were 106.32% (93.87%, 120.43%), 102.15% (90.34%, 115.50%), and 108.61% (96.01%, 122.87%) for comparisons of COV795 and Ultracet (A/C), Ultracet and Percocet (C/D), and COV795 and Percocet (A/D), respectively.

There were 28% and 33% higher geometric LS means for the swing of APAP observed for COV795 compared with Ultracet and Percocet, respectively; the 90% CIs of the ratios of the geometric LS means were not completely contained within the no-difference range. However, there was no significant difference in the swing of APAP between Ultracet and Percocet. The ratios of geometric LS means and 90% CIs of the ratios for the swing of APAP were 127.59% (106.05%, 153.51%), 103.96% (86.63%, 124.75%), and 132.64% (110.45%, 159.28%) for comparisons of COV795 and Ultracet (A/C), Ultracet and Percocet (C/D), and COV795 and Percocet (A/D), respectively.

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**Table 2 Statistical Analysis of Plasma PK Parameters of APAP on Day 5 (Completers)**

| Dose-Normalized Parameter | Treatment | N | Geometric LS Means | Treatment Comparison | Ratio of Geometric LS Means (%) | 90% CI of the Ratio |
|---|---|---|---|---|---|---|
| $AUC_{0-12}^{SS}$/Dose (ng•h/mL/mg) | A | 24 | 42.567 | A/C | 94.975 | (90.822, 99.317) |
| | C | 24 | 44.819 | C/D | 100.845 | (96.496, 105.389) |
| | D | 24 | 44.444 | A/D | 95.777 | (91.631, 100.110) |
| $C_{max}^{SS}$/Dose (ng/mL/mg) | A | 24 | 7.256 | A/C | 95.619 | (85.302, 107.183) |
| | C | 24 | 7.588 | C/D | 102.668 | (91.739, 114.899) |
| | D | 24 | 7.391 | A/D | 98.170 | (87.681, 109.914) |
| $C_{avg}^{SS}$/Dose (ng/mL/mg) | A | 24 | 3.547 | A/C | 94.975 | (90.822, 99.317) |
| | C | 24 | 3.735 | C/D | 100.845 | (96.496, 105.389) |
| | D | 24 | 3.704 | A/D | 95.777 | (91.631, 100.110) |
| $C_{min}^{SS}$/Dose (ng/mL/mg)[a] | A | 24 | 1.214 | A/C | 79.144 | (73.365, 85.377) |
| | C | 24 | 1.534 | C/D | 99.093 | (91.957, 106.784) |
| | D | 24 | 1.548 | A/D | 78.426 | (72.757, 84.537) |
| DFL (%) | A | 24 | 168.239 | A/C | 106.322 | (93.865, 120.433) |
| | C | 24 | 158.235 | C/D | 102.150 | (90.341, 115.503) |
| | D | 24 | 154.904 | A/D | 108.609 | (96.007, 122.865) |
| swing | A | 24 | 4.915 | A/C | 127.590 | (106.047, 153.509) |
| | C | 24 | 3.852 | C/D | 103.956 | (86.629, 124.747) |
| | D | 24 | 3.706 | A/D | 132.637 | (110.451, 159.278) |

Note: An analysis of variance was performed with the natural log-transformed dose-normalized pharmacokinetic (PK) parameters ($AUC_{0-12}^{SS}$, $C_{max}^{SS}$, $C_{min}^{SS}$, and $C_{avg}^{SS}$) or natural log-transformed PK parameters (DFL and swing) as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequences as a random effect.

Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally, 1 tablet at a time, every 12 hours for 4.5 days (9 doses).

Treatment C: 1 tablet of Ultracet (37.5 mg tramadol/325 mg APAP) administered orally every 6 hours (Q6h) for 4.5 days (18 doses).

Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

| Name of Sponsor/Company:<br><br>Mallinckrodt Inc | Individual Study Table Referring to Part of the Dossier<br><br>Volume: | (For National Authority Use Only) |
|---|---|---|
| Name of Finished Product:<br><br>COV795 | | |
| Name of Active Ingredient:<br><br>Oxycodone hydrochloride/ acetaminophen | Page: | |

Safety results: Overall, 44 of 48 subjects (91.7%) reported at least 1 TEAE. More subjects reported TEAEs during treatment with Roxicodone (28 of 34 subjects, 82.4%) than during treatment with Percocet (20 of 31 subjects, 64.5%), COV795 (15 of 33 subjects, 45.5%) or Ultracet (12 of 28 subjects, 42.9%). This was expected because of the higher dose of OC in Roxicodone (1 tablet containing 15 mg OC administered Q6h for 4.5 days; 60 mg OC daily dose) compared with Percocet (1 tablet containing 7.5 mg OC administered Q6h for 4.5 days; 30 mg OC daily dose) and COV795 (2 tablets each containing 7.5 mg OC administered Q12h for 4.5 days; 30 mg OC daily dose).

The highest percentage of subjects reported TEAEs classified as gastrointestinal disorders (70.8%), nervous system disorders (58.3%), and skin and subcutaneous tissue disorders (41.7%).

The most frequently reported TEAEs overall were nausea (54.2%), vomiting (45.8%), pruritus (39.6%), dizziness (39.6%), and headache (29.2%). The majority of TEAEs were considered related to study drug.

Twenty subjects (41.7%) reported at least 1 mild TEAE and 24 subjects (50.0%) reported at least 1 moderate TEAE; there were no severe TEAEs reported.

No deaths or SAEs were reported during the study. Twenty-two subjects (45.8%) experienced TEAEs of vomiting and were withdrawn from the study as required by the protocol. Of the 22 subjects who vomited, 8 subjects (23.5%) vomited during Roxicodone treatment, 7 subjects (21.2%) vomited during COV795 treatment, 5 subjects (16.1%) vomited during Percocet treatment, and 2 subjects (7.1%) vomited during Ultracet treatment.

Seven subjects had TEAEs that were either resolving or not resolved at the last study visit.

No vital sign, pulse oximetry, ECG, or physical examination abnormality was recorded as a TEAE; 2 subjects had clinically significant laboratory abnormalities that were reported as TEAEs (elevated liver enzymes and trichomoniasis).

**CONCLUSIONS**:

Pharmacokinetics:

- The dose-normalized $AUC_{0\text{-}12h}^{SS}$, $C_{max}^{SS}$, $C_{min}^{SS}$, and $C_{avg}^{SS}$ of OC for COV795 were equivalent to those for Roxicodone.
- Median $T_{max}^{SS}$ of OC was significantly shorter for COV795 compared with Roxicodone

| Name of Sponsor/Company:<br><br>Mallinckrodt Inc | Individual Study Table Referring to Part of the Dossier<br><br>Volume:<br><br>Page: | (For National Authority Use Only) |
|---|---|---|
| Name of Finished Product:<br><br>COV795 | | |
| Name of Active Ingredient:<br><br>Oxycodone hydrochloride/ acetaminophen | | |

($P < 0.05$).

- The dose-normalized $AUC_{0\text{-}12h}^{SS}$, $C_{max}^{SS}$, $C_{min}^{SS}$, and $C_{avg}^{SS}$ of OC for COV795 were equivalent to those for Percocet.
- The dose-normalized $AUC_{0\text{-}12h}^{SS}$ and $C_{avg}^{SS}$ of OC for Roxicodone were equivalent to those for Percocet.
- The dose-normalized $C_{max}^{SS}$ and $C_{min}^{SS}$ of OC for Roxicodone was approximately 14% lower and 16% higher than those for Percocet, respectively.
- Median $T_{max}^{SS}$ was significantly shorter for COV795 compared with Percocet ($P < 0.05$), but no significant difference in $T_{max}^{SS}$ was observed for OC between Roxicodone and Percocet.
- Steady state was attained for OC by Day 2 after administration of COV795, Roxicodone, and Percocet.
- There was no significant difference between the DFL of plasma OC concentrations for COV795 and Roxicodone.
- DFL values were 29% and 23% lower for Roxicodone compared with Percocet and for COV795 compared with Percocet, respectively.
- Swing value of OC from COV795 was 31% higher compared with Roxicodone.
- Swing value of OC from COV795 and Roxicodone was 20% and 39% lower compared with Percocet, respectively.
- The dose-normalized $AUC_{0\text{-}12h}^{SS}$, $C_{avg}^{SS}$, and $C_{max}^{SS}$ of APAP for COV795 were equivalent to those for Ultracet.
- The dose-normalized $C_{min}^{SS}$ of APAP for COV795 was approximately 21% lower than for Ultracet.
- The dose-normalized $AUC_{0\text{-}12h}^{SS}$, $C_{avg}^{SS}$, and $C_{max}^{SS}$ of APAP for COV795 and Ultracet were equivalent to those for Percocet.
- The dose-normalized $C_{min}^{SS}$ of APAP for COV795 was approximately 22% lower than that for Percocet, whereas the dose-normalized $C_{min}^{SS}$ of APAP for Ultracet was equivalent to that for Percocet.

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- No significant difference in $T_{max}^{ss}$ was observed for APAP between COV795, Ultracet, and Percocet.
- Steady state was attained for APAP on Day 1 for Percocet and on Day 2 for both COV795 and Ultracet.
- There was no significant difference in the DFL of plasma APAP concentrations across treatment groups.
- The swing value of APAP for COV795 was 28% higher than for Ultracet.
- The swing value of APAP for COV795 was 33% higher than for Percocet. There was no significant difference between the swing value of APAP for Ultracet and Percocet.
- Overall, the comparable PK findings between treatment groups in this study support further product development of COV795 for acute pain and provide extended exposure data over the proposed 12-hour dosing interval at steady state.

Safety:

- Overall, 44 subjects (91.7%) reported at least 1 TEAE. More subjects reported TEAEs during treatment with Roxicodone (82.4%) than during treatment with Percocet (64.5%), COV795 (45.5%) or Ultracet (42.9%).
- The most frequently reported TEAEs overall were nausea (54.2%), vomiting (45.8%), pruritus (39.6%), dizziness (39.6%), and headache (29.2%). The majority of TEAEs were considered related to study drug. Twenty subjects (41.7%) reported at least 1 mild TEAE and 24 subjects (50.0%) reported at least 1 moderate TEAE; there were no severe TEAEs reported.
- There were no deaths or SAEs.
- Twenty-two subjects (45.8%) experienced TEAEs of vomiting and were withdrawn from the study as required by the protocol. Of the 22 subjects who vomited, 8 subjects (23.5%) vomited during Roxicodone treatment, 7 subjects (21.2%) vomited during COV795 treatment, 5 subjects (16.1%) vomited during Percocet treatment, and 2 subjects (7.1%) vomited during Ultracet treatment.
- No apparent clinically significant treatment-related trends were observed in clinical laboratory test results, vital sign and pulse oximetry measurements, 12-lead ECG results,

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| **Name of Finished Product**:<br><br>COV795 | | |
| **Name of Active Ingredient**:<br><br>Oxycodone hydrochloride/ acetaminophen | | |

or physical examination findings.

- COV795 demonstrated the anticipated tolerability and safety profile for a low-dose opioid/APAP treatment. As expected, fewer subjects reported TEAEs after receiving COV795 (30 mg daily OC dose) than Roxicodone (60 mg daily OC dose). The safety profile of COV795 was comparable to Ultracet and Percocet.
- Overall, the comparable safety findings between treatment groups in this study support further product development and suggest that COV795 can be safely administered to patients for the management of (b) (4) acute pain.

**Date of report:** 11 December 2012

Study 244 (Abuse Liability Study)

| | |
|---|---|
| **Name of Sponsor:** | Mallinckrodt Inc |
| **Name of Test Drug:** | COV795 |
| **Name of Active Ingredient:** | Oxycodone hydrochloride/acetaminophen |
| **Indication:** | Management of (b) (4) acute pain |
| **Phase:** | Phase 1 |
| **Title of Study:** | A Randomized, Double-Blind, Double-Dummy, Active- and Placebo-Controlled Study to Assess the Relative Abuse Potential of COV795 (Oxycodone Hydrochloride/Acetaminophen) vs Immediate-Release Oxycodone Hydrochloride/Acetaminophen Tablets in Non-Dependent, Recreational Opioid Users |
| **REPORT DETAILS** | |
| **Report Date:** | 11 March 2013 |
| **Period of Study:** | (b) (4) |
| **Protocol:** | (b) (4) |
| **Protocol Amendment:** | (b) (4) |
| **Principal Investigator:** | (b) (4) |
| **Study Centers:** | |
| **OBJECTIVES** | |
| **Primary:** (b) (4) | |
| **Secondary:** (b) (4) | |
| • To assess the safety and pharmacokinetics (PK) of COV795. | |
| **Exploratory:** | |
| • To determine the relationship between PK and pharmacodynamic (PD) parameters of COV795. | |
| (b) (4) | |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | Oxycodone hydrochloride/acetaminophen | |
| | [redacted] | |
| **Treatments:** | A) [redacted] COV795 (7.5 mg OC/325 mg APAP for a total dose of 15 mg OC/650 mg APAP) plus [redacted] placebo tablets for COV795 plus [redacted] placebo capsules for IR-OC/APAP<br>B) [redacted] COV795 (7.5 mg OC/325 mg APAP for a total dose of 30 mg OC/1,300 mg APAP) plus [redacted] placebo capsules for IR-OC/APAP<br>C) [redacted] IR-OC/APAP (7.5 mg OC/325 mg APAP for a total dose of 15 mg/650 mg OC/APAP) plus [redacted] placebo capsules for IR-OC/APAP plus [redacted] placebo tablets for COV795<br>D) [redacted] IR-OC/APAP (7.5 mg OC/325 mg APAP for a total dose of 30 mg OC/1,300 mg APAP) plus [redacted] placebo capsules for IR-OC/APAP plus [redacted] placebo tablets for COV795<br>E) Tampered COV795: [redacted] COV795 (7.5 mg OC/325 mg APAP for a total dose of 30 mg OC/1,300 mg APAP) crushed [redacted] plus [redacted] placebo tablets for COV795<br>F) Tampered IR-OC/APAP: [redacted] IR-OC/APAP (7.5 mg OC/325 mg APAP for a total dose of 30 mg OC/1,300 mg APAP) crushed [redacted] plus [redacted] placebo capsules for IR-OC/APAP plus [redacted] placebo tablets for COV795<br>G) [redacted] COV795 and [redacted] placebo capsules for IR-OC/APAP | |
| **Treatment Duration:** | The Treatment Phase consisted of 7 treatment periods. During each treatment period subjects received a single treatment with 1 of the 7 study drugs; study periods were separated by a 72 (± 2) h washout. | |
| [redacted] | | |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | Oxycodone hydrochloride/acetaminophen | |
| | (b) (4) | |
| **Dose and Route of Administration:** | Study tablets and capsules were administered orally with 240 mL of room temperature water. Subjects were permitted to use more water if necessary to consume the capsules and tablets with the amount of any additional water documented. All dosing procedures were to be completed within 5 minutes. | |
| **Concomitant and Excluded Therapy:** | No opioids or analgesics including APAP or APAP-containing products; benzodiazepines or other hypnotics or anxiolytics; antidepressants; muscle relaxants; or any other medications that may have a PK or PD interaction with study drugs were permitted during this study. Ibuprofen could be given as needed during the study except for the 72-hour period prior to Day -1. Thereafter, ibuprofen could be given as needed as rescue medication to treat headaches or other adverse events (AEs). | |
| | (b) (4) | |

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|---|---|---|
| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | Oxycodone hydrochloride/acetaminophen | |
| | (b) (4) | |
| **Pharmacokinetics:** | • Pharmacokinetic blood sampling: 5 mL collections in pre-chilled vacuum blood collection tubes containing $K_3$EDTA as the anticoagulant<br>• Sampling times: T = predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 h post-dose<br>• Volume: A total of 492 mL blood was to be collected per subject, 455 mL for PK blood samples and approximately 37 mL for safety samples<br>• Plasma samples were analyzed for oxycodone and acetaminophen by liquid chromatography with tandem mass spectrometry detection<br>• $AUC_{0\text{-}1h}$, $AUC_{0\text{-}2h}$, $AUC_{0\text{-}4h}$, $AUC_{0\text{-}8h}$, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $C_{max}$, $T_{max}$, $t_{lag}$, $K_{el}$, and $t_{1/2}$ for oxycodone and acetaminophen were determined by non-compartmental methods. Plasma concentrations that were below the limit of quantitation (BLQ) were set to 0 before $T_{max}$, with the exception that a BLQ value occurring between measurable concentrations was set to missing. Values that were BLQ were set to missing after $T_{max}$. | |
| **Safety:** | Safety was evaluated by treatment-emergent AEs, oxygen saturation measured by pulse oximetry, ECGs, vital signs, impaired judgment, physical examinations, and clinical laboratory tests. The occurrence of AEs was evaluated by incidence, severity, relatedness, and seriousness. | |
| | (b) (4) | |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | Oxycodone hydrochloride/acetaminophen | |
| | (b) (4) | |
| **Pharmacokinetics:** | Pharmacokinetic analyses were based on the double-blind PK population that included all randomized subjects who received at least 1 dose of study drug and had post-dose PK sample collection up to at least 1 h during any treatment period completed in the Treatment phase. Individual plasma concentration versus actual time data was used to estimate the PK parameters by a non-compartmental approach. Actual sampling times were used to calculate the PK parameters; however, nominal sampling times were used for concentration versus time graphs and summary statistical tables.<br>Plasma concentration was summarized by treatment using descriptive statistics. Mean and individual plasma concentration versus time profiles were presented on both linear and semilogarithmic scales. Descriptive statistics were used to summarize all PK parameters. A linear mixed model with the natural log-transformed dose-normalized PK parameters as the dependent variable with sequence, treatment, and period as fixed effects and subjects nested within sequences as a random effect was used to analyze $AUC_{0\text{-}1h}$, $AUC_{0\text{-}2h}$, $AUC_{0\text{-}4\,h}$, $AUC_{0\text{-}8\,h}$, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and $C_{max}$. Geometric LS means along with 90% CIs were provided for each treatment. The geometric LS mean ratio (test/reference) along with 90% CI was calculated for all treatment comparisons of interest excluding comparisons with placebo. A linear mixed model with the non-transformed PK parameters as the dependent variable with sequence, treatment, and period as fixed effects and subjects nested within sequences as a random effect was used to analyze $K_{el}$ and $t_{1/2}$. The LS means along with 90% CIs were provided for each treatment. The LS mean difference (test - reference) along with 90% CI was calculated for all treatment comparisons of interest excluding comparisons with placebo. The Wilcoxon signed-rank test was performed on the medians of $T_{max}$ and $t_{lag}$ to determine a difference between treatment groups. The distribution of each PK parameter was examined to determine whether substantial departures from normality were apparent using the Shapiro-Wilk test. If the data were inconsistent with the assumptions of ANOVA, a nonparametric model, Wilcoxon signed-rank test was used to evaluate differences among treatment groups.<br>(b) (4) |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | Oxycodone hydrochloride/acetaminophen | |
| | (b) (4) | |
| **PHARMACOKINETIC RESULTS** | | |
| **Pharmacokinetics:** | Oxycodone: All IR-OC/APAP treatments produced higher peak concentrations than corresponding doses of all COV795 treatments. COV795 treatments had a more gradual | |

| Name of Sponsor: | Mallinckrodt Inc | |
|---|---|---|
| Name of Test Drug: | COV795 | |
| Name of Active Ingredient: | Oxycodone hydrochloride/acetaminophen | |

ascent to peak plasma concentration than the IR-OC/APAP treatments, even for the tampered COV795. (b) (4)-

Geometric mean (CV%) $C_{max}$ with high dose of IR-OC/APAP compared with the corresponding dose of COV795 was 62 ng/mL (37%) vs 31 ng/mL (24%) (Ratio of Geometric LS mean [90% CI] was 49.5 [46.3, 52.9]). Median $T_{max}$ was shorter with high dose of IR-OC/APAP than the comparable dose of COV795 ($p < 0.001$). $AUC_{0-2h}$ for high dose IR-OC/APAP was more than double that of the high dose of COV795 (Ratio of Geometric LS mean [90% CI] was 46.3 [42.2, 50.8]). Comparisons of low dose of IR-OC/APAP to low dose COV795 were similar to findings described for the higher doses with $AUC_{0-2h}$ and $C_{max}$ more than double with IR-OC/APAP. Comparisons of the tampered IR-OC/APAP and tampered COV795 revealed an $AUC_{0-2h}$ that was more than 3 times higher with IR-OC/APAP than COV795 (63 ng·h/mL [38.9%] vs 17 ng·h/mL [54%]). $AUC_{0-1h}$ was considerably higher for intact COV795 compared with tampered COV795 and $AUC_{0-2h}$ was twice as high for intact COV795 compared with tampered. $C_{max}$ was similar for the intact and tampered formulations, however median $T_{max}$ was shorter for the intact formulation (2.08 vs 3.59 h). It is noteworthy that the higher dose of COV795 produced slightly lower $AUC_{0-1h}$, $AUC_{0-2}$, and $C_{max}$ values than the lower dose of IR-OC/APAP. $AUC_{0-8h}$ for the higher dose of COV795 was higher than for the lower dose of IR-OC/APAP. Median $T_{max}$ was significantly shorter with the lower dose IR-OC/APAP than the higher dose of COV795 (1.08 h vs 2.08, $p < 0.001$).

Table 2.3 summarizes the PK parameters for OC following each treatment.

**Table 2-3: PK Parameters for Oxycodone (PK Population)**

| | Treatment | | | | | |
|---|---|---|---|---|---|---|
| Parameter | A Low Dose COV795 | B High Dose COV795 | C Low Dose IR-OC/ APAP | D High Dose IR-OC/ APAP | E Tampered COV795 | F Tampered IR-OC/ APAP |
| $AUC_{0-1h}$ (ng•h/mL)[a] | 5.74 | 13.00 | 14.17 | 31.94 | 1.94 | 19.33 |
| $AUC_{0-2h}$ (ng•h/mL)[a] | 17.53 | 36.73 | 41.37 | 79.22 | 17.31 | 62.65 |
| $AUC_{0-4h}$ (ng•h/mL)[a] | 41.83 | 86.24 | 81.78 | 152.73 | 68.01 | 131.01 |
| $AUC_{0-8h}$ (ng•h/mL)[a] | 85.11 | 175.76 | 126.54 | 248.42 | 162.70 | 217.72 |
| $AUC_{0-12h}$ (ng•h/mL)[a] | 112.18 | 232.31 | 145.07 | 293.18 | 217.14 | 257.94 |
| $AUC_{0-inf}$ (ng•h/mL)[a] | 161.77 | 327.16 | 161.21 | 332.06 | 275.04 | 292.42 |
| $AUC_{0-t}$ (ng•h/mL)[a] | 147.66 | 302.42 | 158.85 | 326.86 | 266.25 | 287.90 |
| $C_{max}$ (ng/mL)[a] | 13.99 | 30.50 | 32.81 | 61.85 | 31.10 | 52.27 |
| $T_{max}$ (h)[b] | 3.08 | 2.08 | 1.08 | 1.06 | 3.59 | 1.08 |
| $t_{lag}$ (h)[b] | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| $K_{el}$ (/h)[c] | 0.1159 | 0.1236 | 0.1813 | 0.1841 | 0.1707 | 0.1844 |
| $t_{1/2}$ (h)[c] | 6.46 | 6.32 | 3.92 | 3.85 | 4.18 | 3.83 |

[a]Geometric mean (CV%); [b]Median (CV%); [c]Arithmetic mean (CV%) for $K_{el}$ and $t_{1/2}$

| | | |
|---|---|---|
| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | Oxycodone hydrochloride/acetaminophen | |
| | APAP: Peak plasma concentrations of acetaminophen were highest for the intact and tampered IR-OC/APAP treatments, followed by high dose COV795. In general, when comparing the high dose of IR-OC/APAP with the high dose of COV795 and the low dose of IR-OC/APAP with the low dose of COV795, the findings for APAP were similar to findings for oxycodone, although the magnitude of the differences between the treatments was not as great. $AUC_{0-2h}$ and $C_{max}$ were higher for IR-OC/APAP than for the corresponding doses of COV795. Of note, $AUC_{0-2h}$ and $C_{max}$ were notably higher with tampered IR-OC/APAP than tampered COV795. $T_{max}$ for the high and low doses of intact IR-OC/APAP and COV795 and for tampered IR-OC/APAP were approximately 0.6 h. $T_{max}$ for the tampered COV795 was considerably longer (3.1 h). (b) (4) | |

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| **Name of Sponsor:** | Mallinckrodt Inc | |
| **Name of Test Drug:** | COV795 | |
| **Name of Active Ingredient:** | Oxycodone hydrochloride/acetaminophen | |
| | (b) (4) | |
| **Pharmacokinetics:** | PK results were consistent with the PD analyses.<br>• COV795, when compared with equivalent doses of IR-OC/APAP, had a lower $C_{max}$, a delay in $T_{max}$, and lower initial AUC values; AUC values for COV795 approached the IR-OC/APAP AUC values as the interval extended to infinity.<br>• AUC values were lower and $T_{max}$ was longer for tampered COV795 relative to intact COV795.<br>• (b) (4)<br>• COV795 and IR-OC/APAP treatments appeared to be dose proportional. | |
| (b) (4) | | |

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| BIOPHARMACEUTICS REVIEW<br>Office of New Drug Quality Assessment | | | |
|---|---|---|---|
| **Application No.:** | NDA 204031 SN-000 | **Reviewer:** Sandra Suarez Sharp, Ph.D. | |
| **Division:** | DAAAP | | |
| **Applicant:** | Mallinckrodt, Inc. | **Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D. | |
| **Trade Name:** | Xartemis | **Biopharmaceutics Supervisory Lead (acting)**: Richard Lostritto, Ph.D | |
| **Generic Name:** | Oxycodone hydrochloride (OC) and acetaminophen (APAP) (b) (4) -release tablets | **Date Assigned:** | June 28, 2013 |
| **Indication:** | Management of (b) (4) (b) (4) acute pain | **Date of Review:** | October 21, 2013 |
| **Formulation/ Strength** | Extended release Tablets/ 7.5 mg OC/325 mg APAP | | |
| **Route of Administration** | Oral | | |

| **SUBMISSIONS REVIEWED IN THIS DOCUMENT** | | |
|---|---|---|
| **Submission dates** | **Date of informal/Formal Consult** | **Primary Review Due in DARRTS** |
| May 24, 2013<br>Oct 4, 2013 | June 28, 13 | Oct 28, 2013 |
| **Type of Submission:** | 505 (b) (2) | |
| **Review focus:** | ▪ Dissolution Method and Acceptance Criteria<br>▪ Extended Release Designation Claim<br>▪ IVIVR<br>▪ In vitro Alcohol Dose Dumping<br>▪ Dissolution testing supporting the "in process" and proposed drug product specification limits<br>▪ Dissolution data supporting debossing manufacturing change | |

**SUMMARY OF BIOPHARMACEUTICS FINDINGS:**

This 505 (b) (2) NDA for OC/APAP (b) (4) Release Tablets, 7.5 mg/325 mg , also refer in this document as COV795, relies on the FDA's previous findings of safety and efficacy of Roxicodone® (15 mg OC oral tablets, NDA 021011; Mallinckrodt) and Ultracet® (325 mg APAP/37.5 mg tramadol hydrochloride oral tablets, NDA 021123; Janssen Pharms). COV795 is a multilayer oral formulation (IR/ER) providing extended release of OC and APAP and has been developed using the Depomed AcuForm® gastroretentive (GR) drug delivery technology. It is intended to be administered as 2 tablets every 12 hours (15 mg OC/650 mg APAP total dose) for the management of (b) (4) acute pain. According to the Applicant the delivery system also conveys abuse-deterrent properties to the product. The nomenclature, (b) (4) release, is under review by the CMC review team.

The development program supporting this NDA consist of several BA/BE studies conducted under fed and fasted conditions and three Phase 3 Efficacy and Safety and abuse liability trials. All the BA/BE studies are being reviewed by OCP. The Biopharmaceutics review focuses on the

acceptability of the dissolution method and acceptance criteria, the extended release designation claim, the In Vitro In Vivo Relationship supporting the clinical relevance of the dissolution method, the in vitro alcohol dose-dumping studies, the use of dissolution to support "in process" and proposed drug product specifications (e.g. (b) (4) viscosity ranges) and debossing manufacturing change.

## 1. DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

The following dissolution method and acceptance criteria are deemed acceptable and have agreed upon with the Applicant (refer to submission dated Oct 4, 2013):

| USP Apparatus | Spindle Rotation | Media Volume | Temp | Medium |
|---|---|---|---|---|
| Paddles, with 316 stainless steel sinker | 100 rpm | 900 mL | 37 C | 0.1N HCl |

| APAP | Target | Minimum | Maximum |
|---|---|---|---|
| 0.5 hours | | | (b) (4) |
| 2 hours | | | |
| 4 hours | | | |
| 6 hours | | | |

| OC | Target | Minimum | Maximum |
|---|---|---|---|
| 0.5 hours | | | (b) (4) |
| 2 hours | | | |
| 4 hours | | | |
| 6 hours | | | |

## 2. IN VITRO IN VIVO RELATIONSHIP

A physiologically-based pharmacokinetic (PBPK) relationship was developed that integrated human anatomical and physiological parameters, physicochemical properties of OC and APAP, and formulation properties of COV795 with the PK behavior of each drug substance using GastroPlus software. The IVIVR was constructed using in vitro and in vivo data from one formulation tested in Phase III trials. The relationship was validated and tested using in vitro data from three formulations with different release rate characteristics. Virtual bioequivalence (BE) tests were conducted between the faster or slower formulation and the clinical formulation using the population simulation module of GastroPlus. The Applicant used this virtual BE analysis as the basis for establishing the in vitro in vivo relationships for both APAP and OC. The Applicant believes that the utility of the IVIVR in predicting the PK behavior of COV795 products from dissolution data replaces the need for BE studies, when minor changes are made to the COV795 drug product. Upon review of the information, the Applicant was informed on Sep 20, 2013 and Oct 04, 2013, that the proposed IVIV relationship is not acceptable (b) (4)

## 3. EXTENDED RELEASE DESIGNATION CLAIM

Based on the PK performance with acceptable and consistent variability among subjects, the

absence of dose-dumping in the presence of food, the prolonged Tmax in relation to the listed drugs, and similar degree of fluctuation and swing compared to the selected listed drugs, the proposed product meets the requirements for an extended release designation claim.

**4. IN VITRO ALCOHOL DOSE DUMPING**

The potential for dose dumping was evaluated in vitro settings using ethanolic media at different concentrations (0%, 5%, 10%, 20% and 40%) with N=12 tablets of COV795 (7.5 mg OC/325 mg APAP). There were no signs of in vitro dose dumping in the presence of alcohol when tested in the QC media and in phosphate buffer pH 6.8 On the contrary, dissolution rate was decreased in the presence of 40% alcohol for both OC and APAP.

**5. DISOLUTION TESTING SUPPORTIG THE PRODUCT SPECIFICATION RANGES**

COV795 uses Polyox (b) (4), which has an approximate molecular weight of (b) (4), as a rate controlling polymer. The viscosity of polyethylene oxide was determined to be a critical material attribute, since the release rate of the drug product is directly impacted by the viscosity of the polymer. Tablets were manufactured using polyethylene oxide grades with viscosities below the lower viscosity limit, at the lower viscosity limit, in the middle of the viscosity range, at the upper viscosity limit, and above the upper viscosity limit. The dissolution profiles were assessed using the proposed dissolution method. The dissolution of APAP and OC in all formulations (using polyethylene oxide at the extremes and outside the viscosity specifications) was within the dissolution specifications for the drug product. Assuming that the change in polymer molecular weight does not change the mechanism of drug release, then it appears that, in the ranges of viscosity tested, the drug product meets the recommended dissolution acceptance criteria. Under these assumptions, the proposed viscosity specification limits are acceptable (e.g. (b) (4)).

**RECOMMENDATION:**

The ONDQA-Biopharmaceutics team has reviewed NDA 204031 and its amendments submitted on May 24, 2013 and Oct 04, 2013. Biopharmaceutics has the following comments for the CMC Team.

**Comments to the CMC Review Team**

*Based on ICH Q6A, the need for (b) (4) depends on the known physicochemical properties of the forms such as solubility, melting point, etc. From the solubility perspective, OC forms seem to be similar; however, there was no information provided for APAP. According to the CMC reviewer, Dr. Hu, only (b) (4) for APAP is being used during manufacturing. Although from the biopharmaceutics perspective, no dissolution data were provided as a function of different (b) (4) solubility, this lack of information is no an issue because it appears to be similar solubility (b) (4). Therefore, it will be the CMC review team's purview to agree with the Applicant's control strategy to determine the need for implementing a quality control specification for monitoring the different (b) (4) of the proposed drug product.*

From the Biopharmaceutics perspective, NDA 204031 for Xartemis (7.5 mg OC/325 mg APAP) is recommended for **Approval**.

**Sandra Suarez Sharp, Ph. D.**
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

**Angelica Dorantes, Ph. D.**
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

cc: RLostritto

## BIOPHARMACEUTICS ASSESSMENT

### INTRODUCTION

COV795 is a fixed-dose, opioid/non-opioid (bimodal), immediate-release (IR)/extended release (ER) (biphasic), analgesic product containing oxycodone (OC) and acetaminophen (APAP). Oxycodone is a semisynthetic opioid analgesic derived from the opium alkaloid thebaine. Acetaminophen, 4 is a nonopiate, nonsalicylate analgesic and antipyretic.

This 505 (b) (2) relies on the FDA's previous findings of safety and efficacy of Roxicodone® (15 mg OC oral tablets, NDA 021011; Mallinckrodt) and Ultracet® (325 mg APAP/37.5 mg tramadol hydrochloride oral tablets, NDA 021123; Janssen Pharms). COV795 has been developed using the Depomed AcuForm® gastroretentive (GR) drug delivery technology. The product is intended to be administered as 2 tablets every 12 hours (15 mg OC/650 mg APAP total dose) for the management of (b) (4) acute pain. According to the Applicant the delivery system also conveys abuse-deterrent properties to the product. The proposed "(b) (4) release" nomenclature, is being reviewed by the CMC team. Based on the assessment of the DMEPA-CMC reviewers the terminology "(b) (4) Release" tablet should not be used as a dosage form nomenclature.

The development program supporting this NDA consist of several BA/BE studies conducted under fed and fasted conditions and three Phase 3 Efficacy and Safety and abuse liability trials. All the BA/BE studies are being reviewed by OCP.

The Biopharmaceutics review focuses on the acceptability of the dissolution method and acceptance criteria, the extended release designation claim, the proposed In Vitro-In Vivo Relationship supporting the clinical relevance of the dissolution method, the in vitro alcohol dose-dumping studies, the dissolution testing supporting the "in process" and proposed drug product specification ranges, and evaluation of the dissolution data supporting a manufacturing change (debossing).

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### DRUG SUBSTANCE

#### Oxycodone Hydrochloride

OC is a weak base and has a pKa of 8.894. The solubility of OC is 1 g in 10 mL water at 25 °C. It is freely soluble in water and slightly soluble in alcohol. At pH 7.6, the solubility of OC is 3.64 mg/mL. The solubility of OC increases at pH values below the neutral pH of water (Figure 1).

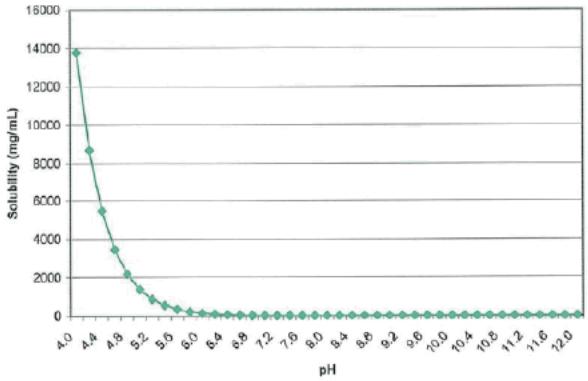


**Figure 1.** Overall solubility profile of OC.

The Applicant states that OC is known to have different solvates/hydrates. However, since the different crystalline forms of OC are all readily soluble (180-190 mg/mL), changes in crystalline form due to drug product manufacturing are not expected to be a significant factor on the bioavailability of OC from the dosage form.

***Reviewer's Comments***

*On Sep 20, 2013, the Applicant was requested to provide solubility differences among the crystalline forms of oxycodone hydrochloride and acetaminophen as a function of pH.*

***The Applicant responded to this inquiry on Oct 04, 2013, stating that for OC the bulk drug substance has been observed to contain*** (b) (4) :

**Table 1.** Solubility Data of Forms (b) (4) – Oxycodone at pH's 2, 4, 7 and 10

| Crystalline Form | pH | Solubility (mg/mL) |
|---|---|---|
| Form (b) (4) | 2 | 276 |
| Form | 4 | 335 |
| Form | 7 | 294 |
| Form | 10 | 0.5 |
| Form | 2 | 315 |
| Form | 4 | 315 |
| Form | 7 | 320 |
| Form | 10 | 0.5 |
| Form | 2 | 282 |
| Form | 4 | 320 |
| Form | 7 | 328 |
| Form | 10 | 0.6 |

*Based on the results provided on Table 1, one can conclude that there are no significant differences in the solubility of Forms* (b) (4) .

*However, no information was provided for Form* (b) (4) *in terms of solubility differences and percentage contribution on the drug product. Based on email communications with the CMC reviewer, since the oxycodone for* (b) (4)

**Acetaminophen**

APAP is weakly acidic and has a pKa of 9.44. The solubility of APAP is 1.39 g in 100 mL water at 25˚C. The solubility of APAP remains essentially constant (14.95 to 15.17 mg/mL) in the pH range of 2.0 to 7.6 (Figure 2).

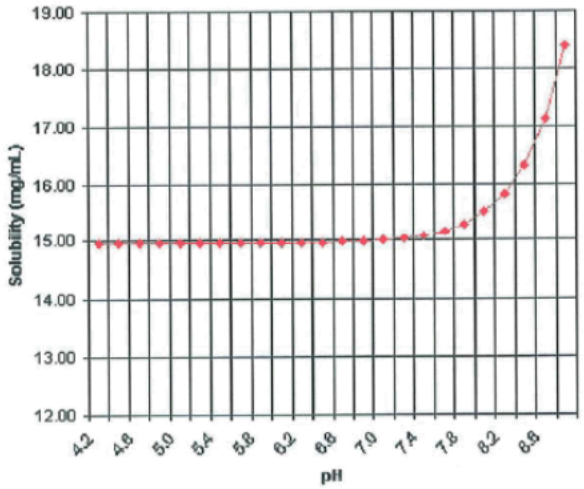


**Figure 2.** Overall solubility profile of OC.

The Applicant states that APAP is present in the stable, (b) (4) and due to its low in vivo permeability, the particle size of APAP is not expected to be a significant factor on the bioavailability of APAP from the dosage form.

***Reviewer's Comments***

*The Applicant response to the inquiry sent on Sep20, 2013 in relation to APAP's solubility difference among its* (b) (4) *is summarized as follows:*

***APAP exhibits*** (b) (4) ***although only the*** (b) (4) ***is produced in the drug substance manufacturing process. A summary of the crystalline forms is provided in Table 2. The Applicant concluded that the crystalline form of APAP does not need to be considered as a variable in APAP bioavailability from the drug product.***

**Table 2.** APAP Crystalline Forms

(b) (4)

*Based on email communications with the CMC reviewer Dr. Yong Hu, the Applicant states that Form (b) (4) is the thermodynamically stable form and only Form (b) (4) produced in the drug substance manufacturing process. In addition, the drug substance DMF was reviewed and deemed adequate for ANDAs.*

***Reviewer's Conclusion*** (b) (4)
***Based on ICH Q6A, the need for*** (b) (4) ***control depends on the known physicochemical properties of the forms such as solubility, melting point etc. From solubility perspective, OC forms seems to be similar; however, there is no information provided for APAP. According to the CMC reviewer, Dr. Hu, only Form*** (b) (4) ***for APAP is being used during manufacturing. From biopharmaceutics perspective, although no dissolution data were provided as a function of different*** (b) (4) ***forms and solubility, this lack of information is no an issue because it appears to be similar solubility among the forms. Therefore, it will be the CMC review team's decision to agree with the Applicant's control strategy to determine the need for implementing a quality control specification for monitoring the different*** (b) (4) ***of the proposed drug product.***

## DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCTS

***Product Description****:*

According to the Applicant, COV795 utilizes Depomed's AcuForm™ technology to target drug release to the upper gastrointestinal tract over an extended period of time. The tablets contain high molecular weight polyethylene oxide (Polyox®) as the swellable release-controlling polymer, which imparts gastroretentive (GR) properties to the dosage form. The controlled release tablets are composed of an immediate release (IR) and a GR ER layer with both layers (IR/ER) containing OC ((b) (4)%) and APAP ((b) (4)%). The Applicant claims that the GR delivery system also conveys abuse-deterrent properties to the product and that the ER properties (b) (4) The Applicant states that COV795 is designed to be retained in the stomach, slowly releasing OC and APAP into the upper gastrointestinal tract by diffusion and erosion where APAP absorption is optimal. The composition of COV795 is shown in Table 3.

**Table 3.** Composition of COV795 ER Tablets

| (b) (4) | | | | |
|---|---|---|---|---|
| **Ingredient** | **Grade** | **Role** | **mg in Tablet** | **w/w %** |
| Oxycodone HCl[a] | USP | Active | 1.875 | 0.197% |
| Acetaminophen | USP | Active | 162.500 | 17.073% |
| Hydroxypropyl Cellulose (b) (4) | NF | (b) (4) | | |
| Microcrystalline Cellulose (b) (4) | NF | | | |
| Croscarmellose Sodium (b) (4) | NF | | | |
| Colloidal Silicon Dioxide (b) (4) | NF | | | |

| | | | |
|---|---|---|---|
| Magnesium Stearate | NF | | (b) (4) |
| Pregelatinized Starch (b) (4) | NF | | |
| Citric Acid Anhydrous Powder | USP | | |
| Edetate Disodium | USP | | |
| | | | (b) (4) |
| Polyethylene Oxide (Polyox (b) (4), molecular weight = (b) (4)) | NF | Controlled Release Polymer | (b) (4) |
| | | | (b) (4) |

## 1. DISSOLUTION METHOD

The following in vitro dissolution testing conditions are being proposed for quality control purposes (release and stability testing) of COV795 ER Tablets:

| USP Apparatus | Spindle Rotation | Media Volume | Temp | Medium |
|---|---|---|---|---|
| Paddles, with 316 stainless steel sinker | 100 rpm | 900 mL | 37°C | 0.1N HCl |

**Dissolution Method Development**

In vitro testing investigated the effects of media volume, media pH and composition, apparatus type, and paddle speeds on the dissolution of COV795 formulations to determine the optimal dissolution conditions.

(b) (4)

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(b) (4)

## 2. DISSOLUTION ACCEPTANCE CRITERIA

**Applicant's Originally Proposed Dissolution Acceptance Criteria**

The proposed dissolution acceptance criteria for the proposed ER product are as follows:

| APAP | Target | Minimum | Maximum |
|---|---|---|---|
| 0.5 hours | (b) (4) | | |
| 2 hours | | | |
| 4 hours | | | |
| (b) (4) | | | |

| OC | Target | Minimum | Maximum |
|---|---|---|---|
| 0.5 hours | (b) (4) | | |
| 2 hours | | | |
| 4 hours | | | |
| (b) (4) | | | |

The typical dissolution profiles for APAP and OC are summarized in Figures 7 and 8, respectively.

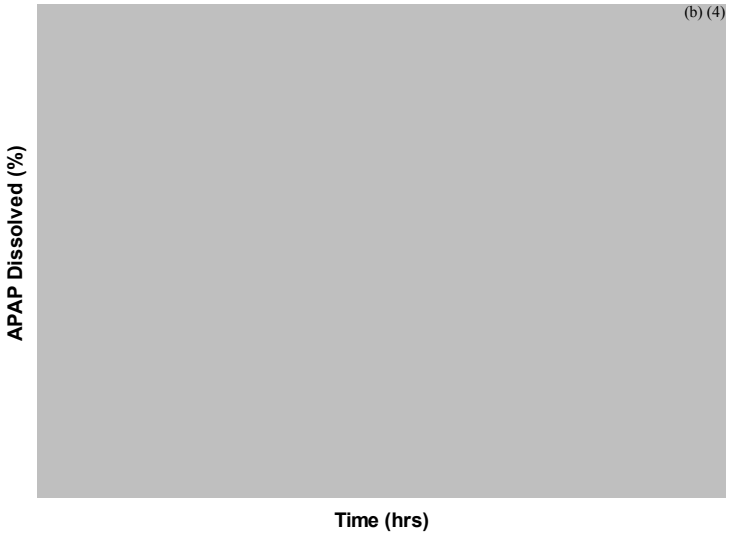


**Figure 7.** Mean dissolution profiles of APAP for representative commercial and phase 3 batches. Generated using Applicant's provided data.

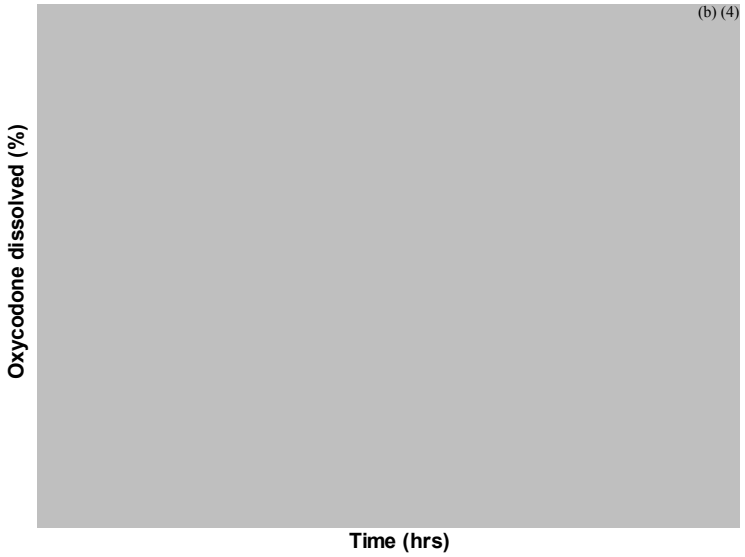


**Figure 8.** Mean dissolution profiles of OC for representative commercial and phase 3 batches. Generated using Applicant's provided data.

***Reviewer's Comments***

*The IR part of the tablet contains* (b) (4) *% APAP and* (b) (4) *% of OC. Therefore, an early interval (0.5 hrs) is appropriate to assure dissolution of the immediate release layer and to ensure that the product does not release prematurely (dose dump). Since this product contains both an immediate and an extended release component, a two sided criteria are*

*acceptable. Based on the mean values observed in pivotal batches and the time to achieve* (b) (4) *% release (Figures 7 and 8), the following comments were conveyed to the Applicant on Sep 20, 2013, as part of the 74-day letter:*

- *The provided dissolution data do not support the selection of* (b) (4) (b) (4) *this time point is not acceptable. Implement the following dissolution acceptance criteria for your proposed product and provide the updated specification tables for your product at batch release and on stability with the revised dissolution criteria.*

| APAP | Target | Minimum | Maximum |
|---|---|---|---|
| 0.5 hours | (b) (4) | | |
| 2 hours | | | |
| 4 hours | | | |
| 6 hours | | | |

| OC | Target | Minimum | Maximum |
|---|---|---|---|
| 0.5 hours | (b) (4) | | |
| 2 hours | | | |
| 4 hours | | | |
| 6 hours | | | |

*On Oct 04, 2013, Applicant accepted the recommended dissolution acceptance criteria listed above.*

## 3. EXTENDED RELEASE DESIGNATION CLAIM

According to 21 CFR 320.25(f) the following information should be included to support the extended release designation:

1. The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.
2. The drug product's steady-state performance is equivalent to a currently marketed non-extended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.
3. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

Data from multiple dose study 255 demonstrated that the PK profile for the proposed drug product rules out the occurrence of dose dumping, and that its steady state performance (q12 hrs) is equivalent to three listed Immediate-Release products,

Roxicodone®, Ultracet® and Percocet® Administered Q6h in Normal (refer to OCP review for details).

Study 255 was a single-center, open-label, randomized, multiple-dose, 4-period, 4-sequence, crossover, PK, BA, and safety study in 24 normal healthy male and nonpregnant, nonlactating female subjects 18 to 55 years old, inclusive. The following treatments were administered:

- Treatment A: 2 tablets of COV795 (7.5 mg OC/325 mg APAP) administered orally, 1 tablet at a time, Q12h for 4.5 days (9 doses).
- Treatment B: 1 tablet of the listed drug (LD), Roxicodone (15 mg OC) administered orally Q6h for 4.5 days (18 doses).
- Treatment C: 1 tablet of the LD, Ultracet (37.5 mg tramadol/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).
- Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

Tables 5 and 6 show the mean PK and statistical for OC, respectively following multiple administration of the treatments. Likewise, Tables 7 and 8 show the mean PK and statistical for APAP, respectively following multiple administration of the treatments.

**Table 5.** Mean (SD) Plasma PK Parameters of OC by Treatment

| Parameter | Treatment A COV795 (2 tablets Q12h) (n = 24) | Treatment B Roxicodone (1 tablet Q6h) (n = 24) | Treatment D Percocet (1 tablet Q6h) (n = 24) |
|---|---|---|---|
| Day 1 | | | |
| $AUC_{0\text{-}12h}$ (ng•h/mL) | 136.14 (23.7) | 242.56 (19.9) | 132.45 (22.8) |
| $C_{max}$ (ng/mL) | 16.04 (3.64) | 34.78 (8.64) | 19.83 (5.07) |
| $C_{min}$ (ng/mL) | 6.90 (1.98) | 20.05 (4.66) | 9.08 (2.38) |
| $T_{max}$ (h)[a] | 3.00 (0.50, 8.00) | 7.00 (0.75, 10.00) | 8.00 (0.50, 10.00) |
| $t_{lag}$ (h)[a] | 0.00 (0.00, 0.27) | 0.00 (0.00, 0.25) | 0.00 (0.00, 0.25) |
| Days 2 through 5 | | | |
| Day 2 $C_{min}$ (ng/mL) | 11.10 (2.52) | 22.49 (6.56) | 10.00 (2.81) |
| Day 3 $C_{min}$ (ng/mL) | 11.01 (2.59) | 20.94 (7.47) | 10.39 (3.21) |
| Day 4 $C_{min}$ (ng/mL) | 12.32 (2.88) | 22.45 (6.78) | 10.40 (2.69) |
| Day 5 $C_{min}$ (ng/mL) | 11.68 (2.80) | 23.92 (6.03) | 10.30 (2.86) |
| Day 5 | | | |
| $AUC_{0\text{-}12h}^{SS}$ (ng•h/mL) | 208.34 (45.34) | 376.88 (83.90) | 191.54 (42.81) |
| $C_{avg}^{SS}$ (ng/mL) | 17.36 (3.78) | 31.41 (6.99) | 15.96 (3.57) |
| $C_{max}^{SS}$ (ng/mL) | 24.00 (5.38) | 45.15 (10.54) | 26.32 (6.18) |
| $C_{min}^{SS}$ (ng/mL) | 9.31 (2.39) | 19.91 (4.93) | 8.81 (2.40) |
| DFL (%) | 83.89 (17.58) | 79.94 (19.83) | 110.90 (33.39) |
| swing | 1.65 (0.58) | 1.32 (0.50) | 2.13 (0.94) |
| $T_{max}^{SS}$ (h)[a] | 3.00 (1.00, 5.92) | 3.00 (1.00, 12.00) | 7.25 (0.50, 8.13) |
| Days 5 through 6 | | | |
| $K_{el}$ (1/h) | 0.1318 (0.0223) | 0.1525 (0.0206) | 0.1517 (0.0205) |
| $t_{1/2}$ (h) | 5.40 (0.87) | 4.62 (0.59) | 4.65 (0.62) |

Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally, 1 tablet at a time, every 12 hours for 4.5 days (9 doses).

Treatment B: 1 tablet of Roxicodone (15 mg OC) administered orally every 6 hours (Q6h) for 4.5 days (18 doses).

Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

[a] For $T_{max}$ and $t_{lag}$, the median (minimum, maximum) values are presented.

**Table 6.** Statistical Analysis of Plasma PK Parameters of OC on Day 5

| Dose-Normalized Parameter | Treatment | N | Geometric LS Means | Treatment Comparison | Ratio of Geometric LS Means (%) | 90% CI of the Ratio |
|---|---|---|---|---|---|---|
| $AUC_{0-12}^{ss}$/Dose (ng•h/mL/mg) | A | 24 | 13.823 | A/B | 110.226 | (103.596, 117.281) |
| | B | 24 | 12.541 | B/D | 99.179 | (93.153, 105.595) |
| | D | 24 | 12.645 | A/D | 109.322 | (102.771, 116.290) |
| $C_{max}^{ss}$/Dose (ng/mL/mg) | A | 24 | 1.605 | A/B | 106.898 | (97.581, 117.103) |
| | B | 24 | 1.501 | B/D | 85.559 | (78.029, 93.817) |
| | D | 24 | 1.755 | A/D | 91.461 | (83.520, 100.157) |
| $C_{avg}^{ss}$/Dose (ng/mL/mg) | A | 24 | 1.152 | A/B | 110.226 | (103.596, 117.281) |
| | B | 24 | 1.045 | B/D | 99.179 | (93.153, 105.595) |
| | D | 24 | 1.054 | A/D | 109.322 | (102.771, 116.290) |
| $C_{min}^{ss}$/Dose (ng/mL/mg) | A | 24 | 0.596 | A/B | 91.164 | (83.557, 99.463) |
| | B | 24 | 0.654 | B/D | 115.912 | (106.144, 126.579) |
| | D | 24 | 0.564 | A/D | 105.670 | (96.886, 115.251) |

**Table 7.** Mean (SD) Plasma PK Parameters of APAP by Treatment

| Parameter | Treatment A COV795 (2 tablets Q12h) (n = 24) | Treatment C Ultracet (1 tablet Q6h) (n = 24) | Treatment D Percocet (1 tablet Q6h) (n = 24) |
|---|---|---|---|
| Day 1 | | | |
| $AUC_{0-12h}$ (ng•h/mL) | 24924.32 (5667.48) | 26342.76 (4721.38) | 25093.74 (5085.04) |
| $C_{max}$ (ng/mL) | 4857.50 (1066.47) | 4567.92 (975.62) | 4317.92 (1006.30) |
| $C_{min}$ (ng/mL) | 738.17 (227.04) | 1234.92 (345.20) | 1242.21 (289.86) |
| $T_{max}$ (h)[a] | 1.00 (0.50, 4.00) | 6.75 (0.50, 8.20) | 0.53 (0.50, 8.00) |
| $t_{lag}$ (h)[a] | 0.00 (0.00, 0.00) | 0.00 (0.00, 0.30) | 0.00 (0.00, 0.00) |
| Days 2 through 5 | | | |
| Day 2 $C_{min}$ (ng/mL) | 1146.25 (391.14) | 1389.38 (428.81) | 1389.92 (418.59) |
| Day 3 $C_{min}$ (ng/mL) | 1037.92 (301.11) | 1435.92 (425.85) | 1375.50 (351.41) |
| Day 4 $C_{min}$ (ng/mL) | 1105.88 (435.60) | 1338.88 (409.82) | 1289.71 (384.79) |
| Day 5 $C_{min}$ (ng/mL) | 1052.00 (339.26) | 1400.21 (442.85) | 1258.63 (340.40) |
| Day 5 | | | |
| $AUC_{0-12h}^{ss}$ (ng•h/mL) | 28160.40 (5807.09) | 29711.92 (5427.37) | 29284.22 (5477.73) |
| $C_{avg}^{ss}$ (ng/mL) | 2346.70 (483.92) | 2475.99 (452.28) | 2440.35 (456.48) |
| $C_{max}^{ss}$ (ng/mL) | 4792.50 (1132.40) | 5078.33 (1189.70) | 4876.67 (1383.08) |
| $C_{min}^{ss}$ (ng/mL) | 852.75 (273.25) | 1070.92 (367.35) | 1069.13 (291.83) |
| DFL (%) | 169.13 (39.83) | 163.90 (47.17) | 155.25 (38.77) |
| swing | 5.08 (2.07) | 4.22 (2.14) | 3.81 (1.63) |
| $T_{max}^{ss}$ (h)[a] | 1.00 (0.50, 4.00) | 0.88 (0.25, 8.00) | 0.75 (0.25, 8.00) |
| Days 5 through 6 | | | |
| $K_{el}$ (1/h) | 0.1072 (0.0285) | 0.1355 (0.0279) | 0.1201 (0.0338) |
| $t_{1/2}$ (h) | 6.90 (1.76) | 5.32 (1.10) | 6.21 (1.79) |

Treatment A: 2 tablets of COV795 (7.5 mg oxycodone hydrochloride [OC]/325 mg acetaminophen [APAP]) administered orally, 1 tablet at a time, every 12 hours for 4.5 days (9 doses).

Treatment C: 1 tablet of Ultracet (37.5 mg tramadol/325 mg APAP) administered orally every 6 hours (Q6h) for 4.5 days (18 doses).

Treatment D: 1 tablet of Percocet (7.5 mg OC/325 mg APAP) administered orally Q6h for 4.5 days (18 doses).

[a] For $T_{max}$ and $t_{lag}$, the median (minimum, maximum) values are presented.

**Table 8.** Statistical Analysis of Plasma PK Parameters of OC on Day 5

| Dose-Normalized Parameter | Treatment | N | Geometric LS Means | Treatment Comparison | Ratio of Geometric LS Means (%) | 90% CI of the Ratio |
|---|---|---|---|---|---|---|
| $AUC_{0\text{-}12h}^{SS}$/Dose (ng•h/mL/mg) | A | 24 | 42.567 | A/C | 94.975 | (90.822, 99.317) |
| | C | 24 | 44.819 | C/D | 100.845 | (96.496, 105.389) |
| | D | 24 | 44.444 | A/D | 95.777 | (91.631, 100.110) |
| $C_{max}^{SS}$/Dose (ng/mL/mg) | A | 24 | 7.256 | A/C | 95.619 | (85.302, 107.183) |
| | C | 24 | 7.588 | C/D | 102.668 | (91.739, 114.899) |
| | D | 24 | 7.391 | A/D | 98.170 | (87.681, 109.914) |
| $C_{avg}^{SS}$/Dose (ng/mL/mg) | A | 24 | 3.547 | A/C | 94.975 | (90.822, 99.317) |
| | C | 24 | 3.735 | C/D | 100.845 | (96.496, 105.389) |
| | D | 24 | 3.704 | A/D | 95.777 | (91.631, 100.110) |
| $C_{min}^{SS}$/Dose (ng/mL/mg) | A | 24 | 1.214 | A/C | 79.144 | (73.365, 85.377) |
| | C | 24 | 1.534 | C/D | 99.093 | (91.957, 106.784) |
| | D | 24 | 1.548 | A/D | 78.426 | (72.757, 84.537) |

According to the Applicant, overall the COV795 product has displayed a robust and consistent PK performance with minimal variability across subjects. No outliers have been detected for total and peak exposures to OC or APAP in studies utilizing the 7.5 mg OC/325 mg APAP COV795 formulation by the Likelihood Distance Test and only a few outliers (N = 3) have been detected using the Grubb's test.

Because of the previously demonstrated impact of food on the pharmacokinetic profile of marketed products that use the Depomed's Acuform GR technology (b) (4) (b) (4) a thorough characterization of the impact of diet upon the PK of COV795 was performed, including the investigation of various fed conditions (high- and low-fat diets) in comparison to the fasted condition with the to-be-marketed COV795 formulation and dosage strength. The Applicant claims that unlike other products that utilize the Depomed GR formulation, food had minimal effect on the rate and extent of absorption of OC and APAP from COV795. There was no dose-dumping and little to no lag in absorption of OC or APAP from COV795 in the presence or absence of food (refer to ClinPharm review for more details).

***Reviewer's Comments***

*Tables 5 shows that the Tmax for OC was significantly reduced following the administration of COV795 (Tmax= 3 hrs) compared to the ones observed after Roxicodone (Tmax= 7 hrs) and Percocet (Tmax= 8 hrs). In addition, the degree of fluctuation (DFL= [(Cmax-Cmin)/Cav] and swing [(Cmax-Cmin)/Cmin] for OC following administration of COV795 (DFL=84%; swing=1.65) were similar to those for Roxicodone (DFL=80%; swing=1.32) and smaller than those for Percocet (DFL=110.9%; swing=2.13). The 90% CI of the ratio for Cmax, Cmin, and AUC were within the 80-125 goal post for BE for the comparisons of COV795 to the two references (A vs B and A vs. D; Table 6). These data support the extended release properties of COV795 for the OC component.*

*Tables 7 shows that the Tmax for APAP was significantly reduced following the administration of COV795 (Tmax= 1 hrs) compared to the one observed after Ultracet (Tmax= 7 hrs) but about similar when compared to Percocet (Tmax= 0.53 hrs). In addition, the degree of fluctuation and swing for OC following administration of COV795 (DFL=169%; swing=5.1) were similar to those for Ultracet (DFL=164%; swing=4.22). Percocet showed less variability with respect to the other two comparators (DFL=155 %; swing=3.8). These results may be explained by the fact that* (b) (4) *% of the APAP dose is formulated as IR. The 90% CI of the ratio for Cmax, and AUC for APAP were within the 80-125 goal post for BE for the comparison of COV795 vs. Ultracet (Table 8). However, Cmin failed the lower bound for the comparison with both Ultracet and Percocet (refer to ClinPharm review for the clinical relevance of this outcome). However, since the lower bound are not too far apart [(73.365, 85.377; 72.757, 84.537)], this failing appears not to be of clinical relevance since the Efficacy studies support the approval of the product at the proposed dosing regimen (refer to MO review for more details.*

*In conclusion, based on the PK performance with minimal variability across subjects, the absence of dose-dumping in the presence of food, the prolonged Tmax, and similar degree of fluctuation and swing compared to the selected listed drug, the extended release designation claim for COV795 is acceptable.*

4. **IN VITRO IN VIVO RELATIONSHIP**

A physiologically-based pharmacokinetic (PBPK) relationship was developed, that,according to the Applicant integrated human anatomical and physiological parameters, physicochemical properties of OC and APAP and formulation properties of COV795 with the PK behavior of each drug substance using GastroPlus software (Version 8.0). The IVIVR was constructed using in vitro and in vivo data from one formulation tested in Phase III trials. The relationship was validated and tested to establish an IVIVR with utility in predicting the PK behavior of COV795 products from dissolution data, and according to the Applicant, obviates the need for BE studies when minor changes are made to the COV795 drug product.

(b) (4)

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(b) (4)

***Reviewer's Comments***

*The IVIVR is not acceptable due to the following deficiencies:*

*1.* (b) (4)

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## 5. EVALUATION OF THE DATA PROVIDED TO SUPPORT THE MANUFACTURING CHANGE (DEBOSSING)

Debossed tablets are proposed for the commercial product and have been used in the Phase I pharmacokinetic studies and Phase III open-label studies. Non-debossed tablets were used in the Phase III blinded clinical studies and human abuse liability study. The debossing is made on the IR layer of the tablet. According to the Applicant, tablet hardness and friability are similar between the debossed and non-debossed tablets. Comparative dissolution profiles in 0.1 N HCl, pH 1.2 HCl buffer, simulated gastric fluid without enzymes, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, (b) (4) were generated using debossed (lot A78056) and non-debossed (lot A79956) tablets using the proposed QC method (Paddles, 100 rpm, stainless steel sinker). No differences were observed in the dissolution profiles of debossed and non-debossed tablets in all media tested as shown by f2 values higher than 50 (Table 12, Figure 13).

**Table 12.** Calculated f2 Values for Comparison of OC and APAP Release Profiles from Debossed and Non-Debossed Tablets in Different Media

| | (b) (4) |
|---|---|
| OC | |
| APAP | |

(b) (4)

## 6. IN VITRO ALCOHOL DOSE DUMPING STUDIES

To assess the potential for dose dumping when taken with alcohol, dissolution testing was conducted in ethanolic media with N=12 tablets of COV795 (7.5 mg OC/325 mg APAP) from lot # A78056 using the conditions listed in Table 13. The results indicate no signs of in vitro dose dumping in the presence of alcohol (Figures 14-15). On the contrary, dissolution rate was decreased in the presence of 40% alcohol for both OC and APAP.

**Table 13.** Ethanolic Dissolution Testing Conditions for COV795 (7.5 mg OC/325 mg APAP)

| Media | Media Volume | Apparatus | Paddle Speed | Media Temperature | Intervals | Sample Count | Other |
|---|---|---|---|---|---|---|---|
| 100% 0.1 N HCl | 900 mL | Apparatus II (Paddles) | 100 RPM | 37 C | 15, 30, 45, 60, 75, 90, 105, 120, 240, and 480 minutes | n=12 | 316 Stainless Steel Sinker |
| 5% v/v ethanol / 95% v/v 0.1N HCl | | | | | | | |
| 20% v/v ethanol / 80% v/v 0.1N HCl | | | | | | | |
| 40% v/v ethanol / 60% v/v 0.1N HCl | | | | | | | |
| 40% v/v ethanol / 60% v/v pH 6.8 Phosphate Buffer | | | | | | | |

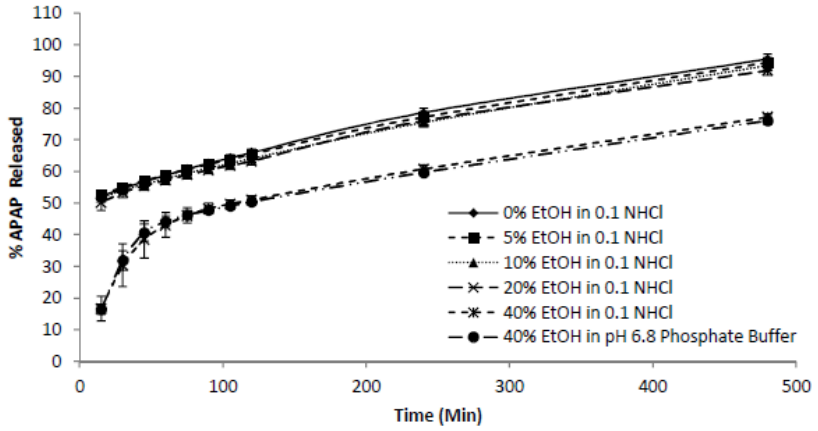


**Figure 14.** Mean APAP dissolution profiles in 0%, 5%, 20% and 40% ethanol for COV795 (7.5 mg OC/325 mg APAP), lot A78056 (n=12).

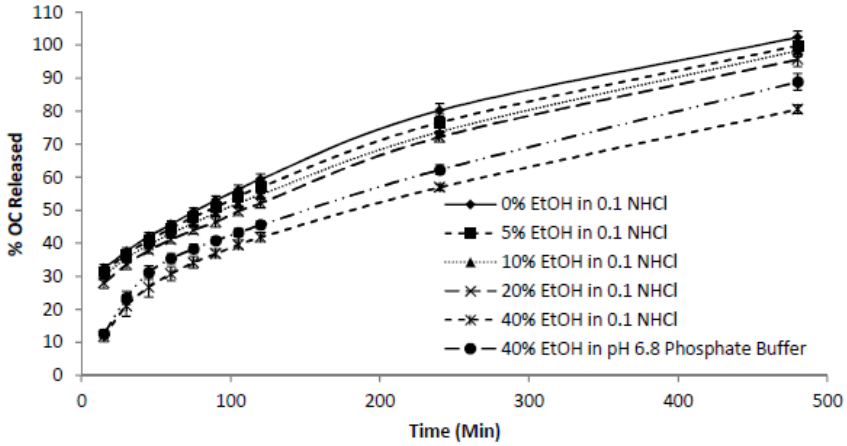


**Figure 15.** Mean OC dissolution profiles in 0%, 5%, 20% and 40% ethanol for COV795 (7.5 mg OC/325 mg APAP), lot A78056 (n=12).

## 7. DISSOLUTION TESTING IN SUPPORT OF IN PROCESS PRODUCT SPECIFICATION RANGES

According to the Applicant, COV795 product development utilized a systematic process to build a thorough process and formulation understanding and critical material attributes were identified based on formulation knowledge and manufacturing observations. These attributes were evaluated for their impact on the drug product specifications, which correlate to product performance and ultimately the quality target product profile. OC assay, APAP assay and polyethylene oxide viscosity were identified as critical material attributes. All other attributes were considered non-critical.

**Effect of Polyethylene Oxide Viscosity of Dissolution**

COV795 uses Polyox (b) (4), which has an approximate molecular weight of (b) (4) (b) (4), as a rate controlling polymer. The viscosity of polyethylene oxide was determined to be a critical material attribute, since the release rate of the drug product is directly impacted by the viscosity of the polymer. Each polyethylene oxide grade has a range of acceptable viscosities, as specified by the manufacturer, so the impact of viscosity on the dissolution release profiles was investigated. Tablets were manufactured using polyethylene oxide grades with viscosities below the lower viscosity limit, at the lower viscosity limit, in the middle of the viscosity range, at the upper viscosity limit, and above the upper viscosity limit (Table 14). The dissolution profiles were assessed using the current dissolution method (apparatus II, 900mL of 0.1N HCl, 100 rpm paddle speed). The dissolution of APAP and OC in all formulations (using polyethylene oxide at the extremes and outside the viscosity specifications) was within the dissolution specifications for the drug product (Figures 16 and 17).

**Table 14.** Viscosity Summary of Polyethylene Oxide Grades

| Polyethylene Oxide Grade | Approximate Molecular Weight (Daltons) | Viscosity Range (cP) | Measured Viscosity (cP) |
|---|---|---|---|
| (b) (4) | | | |


**Figure 16.** APAP dissolution release profiles of tablets (n=6) manufactured with different polyethylene oxide viscosities.


**Figure 17.** OC dissolution release profiles of tablets (n=6) manufactured with different polyethylene oxide viscosities.

***Reviewer's Comments***

*Assuming that the change in polymer does not change the mechanism of drug release, then it appears base on the data presented on Figures 16 and 17 that in the ranges of viscosity tested, the drug product meets the recommended dissolution acceptance criteria. Under these assumptions, the proposed viscosity specification limits are acceptable.*

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/s/

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SANDRA SUAREZ
10/25/2013

ANGELICA DORANTES
10/25/2013

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

## Office of Clinical Pharmacology

*New Drug Application Filing and Review Form*

*General Information About the Submission*

| | Information | | Information |
|---|---|---|---|
| **NDA/BLA Number** | **204031** | **Proposed Brand Name** | **Xartemis** |
| **OCP Division (I, II, III, IV, V)** | **II** | **Generic Name** | **Oxycodone and acetaminophen (b) (4) -release tablets** |
| **Medical Division** | **DAAAP** | **Drug Class** | **An opioid agonist and a non-opiate, non-salicylate analgesic and antipyretic** |
| **OCP Reviewer** | **Wei Qiu, Ph.D.** | **Indication(s)** | **Management of (b) (4) acute pain** |
| **OCP Team Leader** | **Yun Xu, Ph.D.** | **Dosage Form, Strength** | **(b) (4) release oral tablet, 7.5 mg oxycodone and 325 mg acetaminophen** |
| **Pharmacometrics Reviewer** | **N/A** | **Dosing Regimen** | **2 tablets every 12 hours** |
| **Date of Submission** | **5/28/13** | **Route of Administration** | **Oral** |
| **Primary Review Goal Date (GRMP)** | **11/1/2013** | **Sponsor** | **Mallinckrodt** |
| | | **Priority Classification** | **Priority** |
| PDUFA Due Date | **11/28/13 (assuming priority review, 6-mo clock)** | **Relevant INDs** | **IND 104702** |

*Clin. Pharm. and Biopharm. Information*

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **x** | | | |
| **Tabular Listing of All Human Studies** | **x** | | | |
| **HPK Summary** | **x** | | | |
| **Labeling** | **x** | | | |
| **Reference Bioanalytical and Analytical Methods** | **x** | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **Healthy Volunteers-** | | | | |
| single dose: | **x** | **8** | | **Pivotal studies: 171 and 256** |
| multiple dose: | **x** | **2** | | **Pivotal study: 255** |
| **Patients-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD -** | | | | |
| Phase 1: | x | 1 | | Abuse liability study 244 (with PK measurement) |

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

| | | | | |
|---|---|---|---|---|
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | **x** | **4** | | **Pivotal studies 256 and 255** |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | **x** | **3** | | **Pivotal study: 171** |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | **12** | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | | √ | To be marketed formulation was used in pivotal PK studies 255 and 256 and the Phase 3 open-label studies. The tablets without the debossed logos were used phase III studies and human abuse liability study. Sponsor will use comparative hardness and dissolution data to link these two formulations (defer to ONDQA/Biopharm Team). |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | | √ | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | √ | | | Relative BA studies was conducted with the list drugs, Roxicodone (NDA 21-011) and Ultracet (21-123) |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | √ | | | |
| 5 | Has a rationale for dose selection been submitted? | | | √ | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA | √ | | | |

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

| | | | | | |
|---|---|---|---|---|---|
| | organized, indexed and paginated in a manner to allow substantive review to begin? | | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | √ | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | √ | | | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | √ | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | √ | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | √ | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | √ | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | | √ | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | √ | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | √ | Pediatric plan was to request deferral of pediatric studies in all age groups at this time. There was no plan to submit a Proposed Pediatric Study Request or seek a Written Request. The study protocol for initial pediatric study was submitted to IND 104,702. |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | √ | See above |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | √ | | | |

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

| | General | | | | |
|---|---|---|---|---|---|
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | √ | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | √ | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**
**___YES_____**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**There are no comments for sponsor at this time.**

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

**Background:**

On May 28, 2013, Mallinckrodt submitted a 505(b)(2) NDA 204031 for Xartemis (oxycodone and acetaminophen) (b) (4) release oral tablets for the management of (b) (4) acute pain. This 505(b)(2) NDA relies on the agency's findings of safety and efficacy of 2 listed drugs, Roxicodone (NDA 21-011) and Ultracet (NDA 21-123) (acetaminophen portion).

The overall clinical and clinical pharmacology program consist 11 PK studies, 1 abuse potential study (Study 244), and 2 Phase 3 studies (Studies 182 and 181). Earlier formulations were used in 6 PK studies (Studies 041, 043, 107, 045, 042, and 044).

The final formulation was used in pivotal single dose and multiple dose relative bioavailability studies (Study 256 and 255), food effect study (Study 171), and a Phase 3 open-label study (181). The final formulation was also used in two other relative bioavailability studies where listed drugs were not included as references (Studies 170 and 172). The tablets without the debossed logos were used in the Phase 3 blinded study (182) and human abuse liability study (244). The sponsor proposed to use the comparative hardness and dissolution data to link these two formulations. The safety and efficacy of the product was evaluated in pivotal Phase 3 clinical trial. The clinical pharmacology studies are not considered pivotal so no OSI inspection on these studies will be requested.

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

This review will focus on the pivotal relative bioavailability studies (Studies 256 and 255), food effect study (171), and PK data from human abuse liability study (244).

Sponsor's summary on relative bioavailability of COV795 in comparison to the list drugs (Roxycodone and Ultracet):

- COV795 exhibited equivalent Cmax and AUC values of oxycodone and acetaminophen in comparison to the respective listed drugs following single and multiple dose administrations.
- COV795 exhibited equivalent AUC but 28% lower Cmax for oxycodone in comparison to Percocet; equivalent AUC and Cmax in terms of acetaminophen exposure following single dose administration.
- COV795 exhibited equivalent AUC and Cmax values for both oxycodone and acetaminophen in comparison to Percocet following multiple dose administration.
- Food has no effect on the AUC values of oxycodone and acetaminophen from COV795. With food, oxycodone Cmax was 25% higher and acetaminophen Cmax was 24% lower.

Please find the attached filing slides for more details.

## NDA 204031: Xartemis (Oxycodone and APAP (b) (4) tablets)

- **Sponsor:** Mallinckrodt
- **Strengths:** 7.5 mg OC/325 mg APAP
- **Dosage regimen**: two 7.5 mg OC/325 mg APAP tablets Q12H
- **Route of administration**: Oral (b) (4) tablets
- **Proposed indication**: management of (b) (4) (b) (4) acute pain
- **505(b)(2) NDA**
- **Listed drugs**: (b) (4) to 2 NDA products: Roxicodone (NDA 21011) and Ultracet (NDA 21-123)

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## Formulation

- Depomed AcuForm gastroretentive (GR) drug delivery technology
- Bilayer includes an IR layer and an ER layer
- (b) (4)

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

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06/28/2013

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