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APPLICATION NUMBER:

204031Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	204-031
Priority or Standard	Priority
Submit Date	May 24, 2013
Received Date	May 28, 2013
PDUFA Goal Date	November 28, 2013
Division / Office	Anesthesia, Analgesia and Addiction
Reviewer Name	Elizabeth Kilgore, MD
Review Completion Date	October 27, 2013
Established Name	Oxycodone Hydrochloride (OC) 7.5mg and Acetaminophen (APAP) 325 mg
(Proposed) Trade Name	Xartemis XR
Therapeutic Class	Combination Product Opioid + Non-opioid
Applicant	Mallinckrodt, Inc.
Formulation(s)	Oral
Dosing Regimen	Two tablets every 12 hours
Indication(s)	(b) (4) Acute Pain
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Throughout this review, study drug may be referred to as MNK795, COV795, Oxycodone/APAP, Xartemis or Xartemis XR interchangeably.

The Applicant has submitted this NDA as a 505(b)(2) application which relies on the Agency's previous findings of safety and efficacy of two listed drugs:

- Roxicodone (NDA 021-011, Oxycodone, approved August 31, 2000)
- Ultracet (NDA 021-123, APAP/tramadol hydrochloride, approved August 15, 2001)

The Applicant's proposed Tradename for this product is Xartemis XR (extended-release) tablets.

Approval is recommended for Xartemis XR (Oxycodone/APAP) for the indication of management of (b) (4) acute pain where use of an opioid analgesic is appropriate.

This product is unique because it is an extended-release opioid being approved for the treatment of acute pain.

Efficacy was established by the findings of pain improvement in Xartemis-treated patients compared to placebo-treated patients in one adequate and well controlled clinical trial. There was an adequate number of patients exposed during clinical trials to inform the safety profile of Xartemis XR, and the adverse event profile appeared acceptable in the intended to-be-marketed dosage of two tablets (Oxycodone 7.5mg/APAP 325mg) every 12 hours. The profile of adverse events was consistent with a mu-opioid agonist and acetaminophen.

The dosing recommendations are acceptable based on the data from two Phase 3 studies.

1.2 Risk Benefit Assessment

The efficacy of Xartemis (Oxycodone/APAP) was demonstrated with a single, adequate and well-controlled clinical trial, Study 0182. This key efficacy clinical trial was conducted as a randomized, double-blind, placebo-controlled, parallel-arm multiple-dose study in post bunionectomy patients with acute pain who received a dosage of two tablets of Xartemis every 12 hours. The primary endpoint was the summed pain intensity difference over 48 hours ($SPID_{48}$). Statistical significance of the primary endpoint was shown using acceptable imputation methods. In general, the secondary

endpoints supported the primary endpoint. Therefore, Xartemis was found to be efficacious in the population studied.

From the perspective of risk, the safety data submitted were, overall, consistent with those of the opioid class of drugs and APAP. There were no deaths definitely or probably attributable to Xartemis and no unexpected or unusual adverse events of special interest were identified.

All opioids pose the risk of abuse and misuse. The Applicant maintains that Xartemis was formulated with abuse-deterrent properties. At this time, the review of the Applicant's abuse-deterrent findings is ongoing by the Agency's Controlled Substances Staff (CSS). This information will be updated in the Cross Discipline Team Leader (CDTL) Memo.

As an extended-release Schedule II opioid analgesic, the risks (including overdose, misuse and abuse) associated with this product appear similar to other opioids in this class. These risks, however, appear to be manageable with the labeling and REMS and should not preclude approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This product will be under the existing Extended Release/Long-Acting (ER/LA) class-wide opioid Risk Evaluation and Mitigation Strategy (REMS). Product specific language regarding Xartemis XR will be added to the REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

In order to comply with the Pediatric Research Equity Act (PREA), the Applicant submitted a pediatric study plan. Deferral of pediatric studies was requested based on the criteria that the drug is ready for approval for use in adults before the pediatric studies are complete.

A protocol for the initial pediatric study (b) (4): "A Phase 4, Open-Label Study of the PK and Safety of MNK795 (7.5mg Oxycodone HCL/325mg Acetaminophen) in Postsurgical Pediatric Subjects [Ages 12 to 17] with Moderate to Severe Acute Pain") has been submitted to IND 104,702. The timing and description of the Applicant's proposed pediatric protocols is summarized in Table 1 below.

Table 1. Applicant's Pediatric Plan Timeline Summary

Study Title	Protocol Submission	Study Completion	Final Report
Ages 12 to 17 years (Study #1) Open-label study of the PK and safety of MNK795 (7.5mg oxycodone HCl/325mg acetaminophen) in postsurgical pediatric adolescent patients (ages 12 to 17) with moderate to severe acute pain	Draft: 5/30/13 Final: 1/31/14	8/01/15	12/31/15
Ages 2 to 11 years (Study #2) Open-label study of the PK and safety of an age-appropriate formulation (7.5mg oxycodone HCL/325mg acetaminophen, solution/product) in pediatric children patients (ages 2 to 11) with moderate to severe acute pain	Final: 7/1/16 4/1/16*	12/31/17 10/01/17*	6/01/18 3/01/18*
Ages <2 years (Study #3) Pediatric PK, safety and efficacy study of an age-appropriate MNK795 (7.5mg oxycodone HCL/325mg acetaminophen, solution/product) in pediatric children patients (ages <2) with moderate to severe acute pain	Final: 1/31/19 6/01/18*	8/01/20 12/01/19*	12/31/20 4/01/20*

(Table, reviewer) *Denotes Applicant's revised timeline based upon discussion with the Division

The Applicant states that the PK profile of the product will be characterized, and a safety evaluation performed, in adults prior to initiating study 2, i.e., at least nine months before the first pediatric subject is scheduled to receive drug product. Prior to initiating study 3, the PK profile will be characterized and a safety evaluation performed in adults.

The pediatric plan and deferral request were reviewed by the Agency's Pediatric Review Committee (PeRC) on October 2, 3013 who were in agreement with the Applicant's proposed plan, however the PeRC recommended that the Division discuss the dates of the third study with the Applicant. Specifically, it does not appear necessary for the Applicant to wait six months after the study report for Study 2 is submitted to submit the protocol for Study 3. The Division held a telephone conference with the Applicant on October 18, 2013 at which time the Applicant was informed that the intervals must be shortened between the submission of final clinical study reports and the submission of final protocols for the subsequent studies. The Applicant submitted a revised pediatric study plan on October 22, 2013 which, essentially, shortens the intervals of Studies 2 and 3 by at least three months. The revised dates are shown in Table 1, above, denoted by asterisks.

Refer to the CDTL memo for additional post marketing requirements.

2 Introduction and Regulatory Background

2.1 Product Information

COV795 is a fixed-dose, opioid/non-opioid, immediate-release (IR)/extended-release (ER) analgesic product containing oxycodone (OC) and acetaminophen (APAP) for the proposed indication of management of (b) (4) acute pain.

The Applicant maintains that COV795 has been formulated with physiochemical characteristics which utilize Depomed's AcuForm™ gastrorententive (GR) drug delivery technology intended to impart both an immediate-release and extended-release component when administered orally every 12 hours and which may convey potential tamper- and abuse-deterrent properties to the product.

The Applicant states that the AcuForm technology allows tablets to be retained in the stomach (i.e., gastroretentive) delivering the drug to the site of absorption for an extended period of time without losing bioavailability. The dosage form is reportedly retained in the stomach by swelling to a size that promotes gastric retention within 30 minutes after administration and then maintains its swelled size for over (b) (4) hours in vivo. AcuForm technology utilizes polyethylene oxide to form a hydro-gel matrix system. Reportedly, the polyethylene oxide has the desired physical strength after hydration to maintain the integrity of the dosage form under the conditions of the stomach and which, according to the Applicant, may provide some abuse-deterrent properties.

COV795 multilayer tablet is, according to the Applicant, comprised of the IR layer and the gastrorententive ER layer. The IR layer contains (b) (4)% of the total OC and (b) (4)% of the total APAP dose, whereas the ER layer contains (b) (4)% of the total OC and (b) (4)% of the total APAP dose.

The IR and ER layer components and composition are shown below in Table 2.

Table 2. Components and Composition of COV795 by Layer

IR 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) (b) (4)	NF	Controlled Release Polymer		(b) (4)
(b) (4)				

(Applicant's figure, Section 2.3.01 Submission, p. 3)

2.2 Tables of Currently Available Treatments for Proposed Indications

Multiple products are available for the treatment of moderate-to-severe acute pain, including immediate and extended-release opioids, prescription strength NSAIDs, and tramadol.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients in this combination product are the opioid agonist, oxycodone and the non-opioid analgesic, APAP.

Single-entity oxycodone is available as an extended-release tablet, as immediate-release oral tablets and capsules, and as an oral solution. It is also available in combination with APAP as an immediate-release product. APAP is available as prescription injection (IV Ofirmev), in generic combination products with opioids and other drugs, and as an over-the-counter analgesic.

There are currently no approved abuse-deterrent oxycodone/APAP combination products.

2.4 Important Safety Issues With Consideration to Related Drugs

Opioids: The risks associated with the use of oxycodone/APAP appear similar to the risks of other immediate-release and extended release opioids. These risks would include death, respiratory depression, withdrawal, physical dependence, misuse, abuse, diversion and overdosage (intended or accidental). The class of opioids, in general, carry label warnings regarding concomitant use with CNS depressants such as alcohol, other opioids, anesthetic agents, sedative hypnotics and skeletal muscle relaxants which can potentiate respiratory depressant effects and increase the risk of adverse outcome. The Applicant conducted an analysis of AEs of special interest which included these possible risks, which were generally similar to those of other opioids.

APAP (acetaminophen): *The* Agency has recommended limiting the maximum amount of APAP to 325mg per tablet due to the risk of drug-induced liver injury (DILI). The proposed product is formulated with 325mg APAP per tablet which is consistent with the Agency recommendation. The dosing of Xartemis is two tablets every 12 hours, which would provide 15mg oxycodone and 650mg APAP per dose with a maximum daily dose of 30mg of oxycodone and 1,300 mg of APAP. This is within the guidelines of a maximum recommended daily limit of APAP of 4,000mg.

Gastroretentive Properties: According to the Applicant, the presence of food could potentially contribute to the gastrotentive (GR) and hence controlled release (CR) characteristics of the drug product, by resulting in longer retention in the stomach when administered following a high-fat meal, and/or by affecting the drug-release characteristics of the polyethylene oxide used in the GR layer of the formulation.

According to the labels, relevant GI-related AEs of other approved gastroretentive drugs are shown below:

- Glumetza (metformin HCl ER) Label: Serious GI disorders occurred in 1% of drug treated compared to 0% not treated. Pancreatitis was the only serious GI-related event which occurred in two drug-treated subjects. Treatment-emergent

adverse reactions reported by >5% of Glumetza plus glyburide compared to placebo plus glyburide were diarrhea (12.5%) in drug-treated compared to 5.6% in placebo and nausea (6.7%) in drug-treated compared to 4.2% placebo.

- Gralise (gabapentin) Label: Diarrhea occurred in 3.3% drug-treated compared to 2.7% placebo; dyspepsia occurred in 1.4% drug-treated compared to 0.8% placebo; and constipation 1.4% drug-treated compared to 0.3% placebo.
- Proquin XR (ciprofloxacin) ER tablets Label: GI disorders occurred in less than 1% of subjects and included abdominal pain, nausea, diarrhea, dyspepsia, aggravated irritable bowel syndrome, lower abdominal pain, and vomiting.

While GI-related adverse events were the most frequently occurring in the Xartemis-treated subjects, these findings were consistent with those seen in other opioid products and not necessarily a result of the gastroretentive properties of Xartemis.

PEO (Polyethylene Oxide or Polyox) Properties: As taken verbatim from the Applicant's submission, "Polyethylene oxide (Polyox) is a functional excipient that serves as the predominant GR technology component. Due to polyethylene oxide, COV795 expands when exposed to fluid and is retained in the stomach, thereby targeting the release of both APIs to the upper gastrointestinal tract…"

From a safety standpoint, polyethylene oxide has been reported to be associated with choking or swallowing difficulties in some postmarketing data for approved products using this formulation and resulted in labeling of those product(s) regarding the possibility of choking or difficulty swallowing the tablets. The Applicant conducted an analysis of AEs of special interest which included the possible risks of choking. No cases of choking or difficulty swallowing the tablets were reported in the Applicant's submission.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Sponsor had written and face-to-face interactions with the Agency on several occasions during the drug development under IND 104,702 with key interactions as follows:

- 5/19/10 – original IND was submitted
- 12/7/11 – Written responses were provided (in lieu of an End-of-Phase 1) [EOP1] meeting. The Sponsor was advised of the following:
    - A single adequate and well-controlled efficacy study and an open-label safety study would be acceptable to support filing an application for an acute pain indication.
    - Proposal to rely upon the Agency's prior findings of safety and efficacy for Roxicodone NDA and the Ultracet NDA was acceptable.
    - No new nonclinical pharmacology or toxicology studies were needed for oxycodone or acetaminophen drug substances to support a 505(b)(2) NDA for COV795.

  - Pediatric plan must be submitted with the NDA that includes requests and justifications for waivers and deferrals, the proposed study plan and a time line.
  - The $SPID_{48}$ is an acceptable primary endpoint for an acute pain indication. The timing for evaluation of $SPID_{48}$ must start from time zero.
- 12/13/12 – Type B PreNDA Meeting
  - The integrated safety analyses should focus on the clinical studies that used the intended commercial dose regimen of two COV795 tablets (15mg OC/650mg APAP) Q12 hours

2.6 Other Relevant Background Information

The Applicant conducted the following studies to support abuse-deterrent formulation properties of the product:

1. In vitro laboratory studies
2. Clinical human abuse liability study

See Dr. Jim Tolliver's CSS review for further discussion regarding these studies.

3 Ethics and Good Clinical Practice

3.1 Submission Quality and Integrity

The submission appeared to be of good quality. It was well organized and easily navigated. Three clinical information requests (IRs) were sent to the Applicant for clarification of hepatic safety information and detailed narratives. The Applicant responded to the IRs in a timely manner. There are no outstanding clinical information requests at the time of this review.

3.2 Compliance with Good Clinical Practices

The Applicant reported that all clinical studies in this application were conducted in accordance with applicable regulatory guidances and relevant sections of the International Conference on Harmonization guidelines.

The Division of Scientific Investigations (DSI) conducted routine inspections of three specific sites: Study 0181 (Site 166) and Study 0182 (Sites 001 and 203). The study sites were selected primarily based on the number of enrolled study subjects. Based upon the OSI report of Dr. John Lee, at all three sites, "Deficiency observations were limited to minor and/or isolated findings. The study data from all three sites for Studies 181 and 182 appear reliable as reported in the NDA". For two Sites (001 and 203) in Study 0182, the Establishment Inspection Report (EIR) has not been received from the field office and the outcome classification remains pending. Therefore, the observations are based on preliminary communication with the field investigator. Dr. Lee states that

"an addendum to the inspection summary will be forwarded from OSI to the Division if the outcome classification changes or if additional observations of clinical or regulatory significance are discovered after receipt and review of the final EIRs". Any updated information regarding the inspection sites will be covered in the CDTL memo.

3.3 Financial Disclosures

The Agency's Office of Scientific Investigations (OSI) has piloted a program using a risk-based model tool for identification of site selection. Part of that risk-based model tool includes information from the Applicant regarding financial disclosure. Initial internal communication between the Division and OSI and then subsequent communication between OSI and the Applicant confirmed that there were no substantial sums reported for clinical investigators.

The Applicant's submission included the completed Certification: Financial Interests and Arrangements of Clinical Investigators in compliance with 21CFR part 54. This certified that the Applicant had not entered into any financial arrangements with the listed clinical investigators, that each clinical investigator had no financial interests to disclose and that no investigator was the recipient of any other sorts of payments from the Applicant for studies 0171, 0182, 0244, 0255 and 0256.

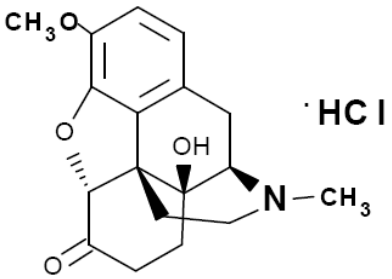
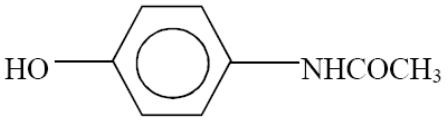
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemical properties of the active components of Xartemis, oxycodone (OC) and APAP are shown summarized below in Table 3.

Table 3. Chemical Properties of Oxycodone (OC) HCL and Acetaminophen (APAP)

Drug Name	Oxycodone Hydrochloride	Acetaminophen
Chemical Name	1) Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5α)- 2) 4,5 α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride	1) N-acetyl-p-aminophenol 2) 4'-hydroxyacetanilide 3) p-hydroxyacetanilide 4) p-acetamidophenol 5) p-acetaminophenol 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.

(Source: Sponsor's Figures, table modified by reviewer, NDA submission Drug Nomenclature Section 3.2.S.1.1 APAP p. 1/Oxycodone p. 1 and Drug Structure Section 3.2.S.1.2 APAP, p. 1 /Oxycodone, p. 1.)

The CMC review by Dr. Yong Hu is ongoing at this time. However, Dr. Hu has reported that the inactive ingredients of the product are acceptable and there are no approvability issues identified from the CMC perspective.

4.2 Clinical Microbiology

This product is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

According to Dr. Beth Bolan, the Division's Pharmacology/Toxicology reviewer, the Applicant plans to rely on the Agency's findings of safety and the pharmacology, pharmacokinetics and toxicology information in the labels of the listed products, Roxicodone (NDA 21-011) and Ultracet (NDA 21-123).

No new nonclinical studies with OC or APAP were required or submitted with this NDA submission.

Dr. Bolan has determined that the excipients in this formulation can be found in higher amounts in approved products and do not pose any toxicologic concerns. Further, she notes that all impurities/degradants in the drug substances and drug product are controlled at acceptable levels and there are no unique nonclinical issues with this product as compared to other oral formulations of its individual components, OC and APAP. She has recommended approvability with no post-marketing studies required from the pharm/toxicology perspective.

The reader is referred to Dr. Beth Bolan's review for the full preclinical pharmacology/toxicology discussion.

4.4 Clinical Pharmacology

As taken from Dr. Wei Qiu's Clinical Pharmacology review, the following are the 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.

4.4.1 Mechanism of Action

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.

4.4.2 Pharmacodynamics

The Applicant conducted PK studies to bridge to the listed drugs with no pharmcodynamic data collected aside from that in the abuse-liability clinical trial.

4.4.3 Pharmacokinetics

According to Dr. Qiu's review, after multiple dosing of two Xartemis tablets every 12 hours, steady state plasma concentrations of oxycodone and acetaminophen were

achieved following one 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 4 below. 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_{0-12h}^{ss})/12. The mean DFL was 83.89% for oxycodone and 169.13% for acetaminophen.

Comparison of the steady state C_{min} and the C_{min} 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 4. Steady-state PK Parameters of Two Xartemis Tablets

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_{0-12h}^{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

(Source: Dr. Wei Qiu's Clinical Pharmacology Review, p. 10)

5 Sources of Clinical Data

The Applicant reported that fourteen clinical studies have been conducted (12 Phase 1 studies and two Phase 3 studies) in a total of 705 patients, 469 healthy subjects and

107 healthy recreational drug users designed to support an indication of the management of (b) (4) acute pain where the use of an opioid analgesic is appropriate. The clinical study reports (CSRs) were previously submitted to IND 104,702. Study COV15000182 was the only double-blinded efficacy trial in the COV795 program, in accordance with prior Agency advice. According to the Applicant, there are no ongoing clinical studies with COV795 and final CSRs for each of the 14 clinical trials were included in the submission.

5.1 Tables of Studies/Clinical Trials

The Applicant's 14 studies included in the submission are summarized below.

Table 5. Table of Studies/Clinical Trials

Study Identifier	Type of Study and Study Objective (s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Total Number of Subjects Dosed; Healthy Subjects or Diagnosis of Patients	Duration of Treatment
COV01300107 (Study 0107)	PK; PK and BA of 1 and 2 tablets of COV795 vs Percocet	Randomized, open label, single dose, 3-period, crossover	COV795 (15 mg OC/650 mg APAP), 1 tablet PO, fed COV795 (15 mg OC/650 mg APAP), 2 tablets PO, fed Percocet (7.5 mg OC/325 mg APAP), 1 tablet Q6h for 2 doses, PO fed	42; Healthy subjects	Three separate single doses separated by at least 7 days
COV01300041 (Study 0041)	Bioequivalence, PK and BA of 3 formulations of COV795 vs Percocet	Randomized, open-label, single-dose, 4-period crossover	COV795 (15 mg OC/500 mg APAP), 1 tablet fast drug release, PO fed COV795 (15 mg OC/500 mg APAP), 1 tablet medium drug release, PO fed COV795 (15 mg OC/500 mg APAP), 1 tablet slow drug release, PO fed Percocet (7.5 mg OC/325 mg APAP), 1 tablet, 2 doses Q6h, PO fed	39; Healthy subjects	Each treatment administered once, separated by at least 7 days

COV01300043 (Study 0043)	Bioequivalence, PK and BA of 3 formulations of COV795 vs Percocet	Randomized, open-label, single-dose, 4-period crossover	COV795 (30 mg OC/500 mg APAP), 1 tablet, fast drug release, PO fed COV795 (30 mg OC/500 mg APAP), 1 tablet, medium drug release, PO fed COV795 (30 mg OC/500 mg APAP), 1 tablet, slow drug release, PO fed. Percocet (7.5 mg OC/325 mg APAP), 1 tablet, 2 doses Q6h, PO fed	40; Healthy subjects	Each treatment administered once, separated by at least 7 days
COV01300045 (Study 0045)	PK, PK and BA of COV795 vs Percocet	Randomized, open-label, multiple-dose, 3-period crossover	COV795 (15 mg OC/650 mg APAP), 1 tablet, Q12h for 4.5 days, PO fed COV795 (15 mg OC/650 mg APAP), 2 tablets, Q12h for 4.5 days, PO fed Percocet (7.5 mg OC/325 mg APAP), 2 tablets, Q6h for 4.5 days, PO fed	48; Healthy subjects	Multiple treatments administered Q12h (COV795) or Q6h (Percocet) over 4.5 days, treatment periods separated by 14 days
COV15000170 (Study 0170)	PK; PK and BA of COV795 or Percocet	Randomized, open-label, single-dose, 3-period crossover	COV795 (7.5 mg OC/325 mg APAP), 1 tablet, PO fasted COV795 (7.5 mg OC/325 mg APAP), 2 tablets, PO fasted Percocet (7.5 mg OC/325 mg APAP), 1 tablet, Q6h for 2 doses, PO fasted Percocet (7.5 mg OC/325 mg APAP), 2 tablets, Q6h for 2 doses, PO fasted	48; Healthy subjects	Four separate single doses separated by at least 7 days
COV15000172 (Study 0172)	PK; PK and BA of COV795 over 4.5 days vs Percocet	Randomized, open-label, multiple-dose, 3-period crossover	COV795 (7.5 mg OC/325 mg APAP), 1 tablet, Q12h for 4.5 days, PO fasted COV795 (7.5 mg OC/325 mg APAP), 2 tablets, Q12h for 4.5 days, PO fasted Percocet (7.5 mg OC/325 mg APAP), 1 tablet, Q6h for 4.5 days, PO fasted	48; Healthy subjects	Each treatment administered once, separated by 14 days

COV15000255 (Study 0255)	PK; PK and BA of COV795 over 4.5 days vs Roxicodone, Ultracet and Percocet	Randomized, open-label, multiple-dose, 4-period crossover	COV795 (7.5 mg OC/325 mg APAP), 2 tablets, Q12h for 4.5 days, PO fasted Roxicodone (15 mg OC), 1 tablet, Q6h for 4.5 days, PO fasted Ultracet (37.5 mg tramadol/325 mg APAP), 1 tablet, Q6h for 4.5 days, PO fasted Percocet (7.5 mg OC/325 mg APAP), 1 tablet, Q6h for 4.5 days, PO fasted	48; Healthy subjects	Multiple treatments administered Q12h (COV795) or Q6h (Percocet) over 4.5 days, treatment periods separated by at least 13 days
COV15000256 (Study 0256)	PK; PK and BA of COV795 vs Roxicodone, Ultracet and Percocet	Randomized, open-label, single-dose, 4-period crossover	COV795 (7.5 mg OC/325 mg APAP), 2 tablets taken 1 at a time, PO fasted Roxicodone (15 mg OC), 1 tablet, 2 doses Q6h, PO fasted Ultracet (37.5 mg tramadol/325 mg APAP), 1 tablet, 2 doses Q6h, PO fasted Percocet (7.5 mg OC/325 mg APAP), 1 tablet, 2 doses Q6h apart, PO fasted	48; Healthy subjects	Four separate single doses separated by at least 7 days
COV01300042 (Study 0042)	PK; PK and BA under fed and fasted conditions	Randomized, open-label, single-dose, 2-period, crossover	COV795 (15 mg OC/650 mg APAP), 1 tablet, PO fed COV795 (15 mg OC/650 mg APAP), 1 tablet, PO fasted	30; Healthy subjects	Two separate single doses separated by at least 7 days
COV01300044 (Study 0044)	PK; PK and BA under fed and fasted conditions	Randomized, open-label, single dose, 2-period, crossover	COV795 (15 mg OC/650 mg APAP), 2 tablets, PO fed COV795 (15 mg OC/650 mg APAP), 2 tablets, PO fasted	30; Healthy subjects	Each treatment administered once, separated by at least 7 days
COV15000171 (Study 0171)	PK; PK and BA under fed (high fat and low fat meals) and fasted conditions	Randomized, open-label, single-dose, 3-period, crossover	COV795 (7.5 mg OC/325 mg APAP), 2 tablets, PO fed, high-fat meal COV795 (7.5 mg OC/325 mg APAP), 2 tablets, PO fed, low-fat meal COV795 (7.5 mg OC/325 mg APAP), 2 tablets, fasted	48; Healthy subjects	Three separate single doses separated by at least 7 days
COV15000182 (Study 0182)	Efficacy; Demonstrate analgesic efficacy of COV795 vs placebo	Randomized, double blind, placebo-controlled, parallel-group	Blinded (2 days): • COV795 (7.5 mg OC/325 mg APAP), 2 tablets PO Q12h • Placebo, 2 tablets PO Q12h Open-label extension (up to 14 days): COV795 (7.5 mg OC/325 mg APAP), 2 tablets PO Q12h	329; Patients with postoperative bunionectomy pain	Double blind phase 2 days, open-label extension phase up to 14 days

COV15000181 (Study 0181)	Safety; Safety and tolerability of COV795 for up to 35 days	Open-label	COV795 (7.5 mg OC/325 mg APAP), 2 tablets PO Q12h for up to 35 days	376; Patients with osteoarthritis of the knee or hip, or patients with chronic lower back pain	Up to 35 days
(b) (4) (Study 0244)	Abuse liability; Compare the relative abuse potential of COV795 tablets to IR OC/APAP capsules	(b) (4)			

Abbreviations: APAP = acetaminophen, BA= bioavailability, IR = immediate release, NDA = New Drug Application, OC = oxycodone HCl, PK = Pharmacokinetic, PO = by mouth, Q6h = every 6 hours, Q12h = every 12 hours.
[a]A total of 107 subjects were in the Naloxone Challenge Test, 106 subjects were in the Drug Discrimination Test, and 61 subjects were randomized into the Treatment Phase.

(Source: Applicant's Tabular Listing of All Clinical Studies, Section 5.2, NDA Submission)

5.2 Review Strategy

Pertinent sections of the Phase 1 studies were reviewed for Section 7 of this review (Safety). The protocols and final reports of the Phase 3, double-blind key efficacy study (0182) and open-label safety study (0181) were reviewed in full for Section 6 of this review (Efficacy) as the Applicant plans to rely upon findings from these studies for primary and supportive efficacy and safety. The abuse liability study (0244) was reviewed for safety findings and discussed in Section 7. The Applicant's supporting efficacy and safety literature were also reviewed.

Review Organization: Phase 3 studies 0182 and 0181 are discussed in Section 5.3. Detailed efficacy results from key efficacy study 1082 are discussed in Section 6 (Efficacy). Overall efficacy results from Phase 3 supportive efficacy study 0181 are included in Section 5.3 after a description of the study. The safety findings from the Phase 1 and Phase 3 studies are summarized, as needed, in Section 7 (Safety).

5.3 Discussion of Individual Studies/Clinical Trials

I) Key Efficacy Study 0182

Overview: This was a multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 3 study followed by an open-label extension (OLE) phase to evaluate the efficacy and safety of the administration of multiple doses of COV795 in subjects who were undergoing uncomplicated unilateral bunionectomy. The blinded dosing phase of the study was designed to evaluate the safety and efficacy of COV795 versus placebo. Study subjects with acute postoperative pain of moderate to severe intensity following unilateral bunionectomy surgery were randomized and stayed at the study site for the duration of the 48-hour blinded dosing phase.

Subjects who were enrolled prior to Amendment 2 were initially given a single dose and then continued with dosing every 12 hours (Q12h) at the time a second dose was requested. These subjects are referred to as Cohort 1. Subjects who enrolled at Amendment 2 or later started the trial with 12-hour dosing and are referred to as Cohort 2.

During the blinded dosing phase, subjects were administered study drug within 30 minutes of randomization and received a total of four doses of study drug Q12 hours over 2 days. Subjects who did not enter the OLE phase were discharged from the clinic and returned 7 (±2) days from last dose of study drug to complete end of treatment evaluations.

Study Title: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Evaluation of the Safety and Analgesic Efficacy of COV795 (Oxycodone HCL/Acetaminophen) ER Tablets in Moderate to Severe Post-Operative Bunionectomy Pain followed by an Open-Label Extension

Protocol Number: COV15000182US

Study Dates: November 14, 2011 to August 22, 2012; conducted by five investigators at five U.S. sites

Report Date: March 26, 2012

Amendments: There were a total of four amendments over the course of the study. Major changes included Amendment 2, which removed the single-dose time to remedication phase. Thus, the 26 subjects enrolled under the original protocol/Amendment 1 were identified as Cohort 1 (received a single dose, then Q12 hour if repeat doses were requested). The remaining 303 subjects enrolled under Amendment 2, or later, were identified as Cohort 2, where subjects started with Q12 hour dosing.

A full listing and discussion of all amendments to the protocol are discussed later in this review.

Study Population: Subjects undergoing uncomplicated, unilateral first metatarsal bunionectomy

Number Subjects: 320 subjects were to have been randomized and dosed; 303 subjects were included in the modified intent-to-treat (mITT) population and 146 subjects enrolled in the OLE phase.

Duration: Approximately 54 days if the subject participated in both Double-blind and Open Label Extension parts of the study:

- Double-blind study duration was to have been up to 40 days, including a screening period of up to 30 days, a surgical period of one day, a blinded dosing phase of 2 days and, for those not entering the OLE phase, a follow-up period of 7 days (±2 days)

- Open Label Extension (OLE) phase lasted up to 17 days, followed by a telephone call 7 days (±2 days) later

Study Drugs:

- Active test product - 7.5mg oxycodone HCL(OC)/325mg acetaminophen (APAP); 2 tablets Q12 hours, orally

- Reference product – Matching placebo tablets (blinded dosing phase only); 2 tablets Q12 hours, orally

Sponsor's Dose Selection Rationale:

- Subjects who received COV795 during the blinded dosing phase received a total daily dose of 30 mg OC/1,300 mg APAP. The approved dosage range for Percocet 7.5 mg OC/325 mg APAP for the management of moderate to severe pain is 1 tablet Q6h to a maximum daily dose of 8 tablets (60 mg OC/2,600 mg APAP). Thus, COV795 is being developed in the lower range of approved OC/APAP doses, intended to confer greater patient safety within the efficacious and therapeutic dose range.

- The COV795 dose regimen used in this study (7.5 mg OC/325 mg APAP, 2 tablets Q12h) was representative of the intended commercial regimen. From a safety perspective, the total dose of COV795 (30 mg OC/1,300 mg APAP) was half the maximum dosage of Percocet (60 mg OC/2,600 mg APAP). The overall dose of APAP within all treatments (1,300 mg) was below the maximum recommended daily limit of 4,000 mg.

Rescue Medication: Ibuprofen 400mg (i.e., two 200mg tablets) could have been taken

up to six times per day (2,400mg/day) during both the double-blind and OLE phases. Rescue medication use was monitored during both phases.

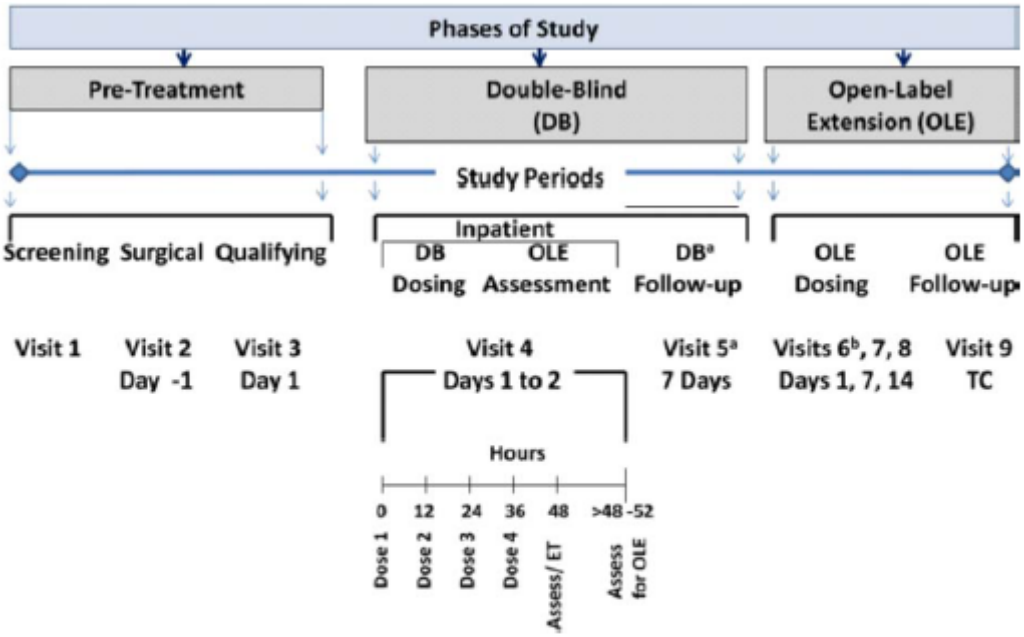
Primary Objective: The primary objective of this study was to have been demonstration of the analgesic efficacy of repeated doses of COV795 versus placebo, using the summed pain intensity difference over the first 48 hours ($SPID_{48}$) after the first dose of study medication in subjects with acute moderate to severe pain following unilateral bunionectomy.

Secondary Objectives:

- Determine the safety and tolerability of COV795 as evaluated by physical examinations, vital signs, pulse oximetry, electrocardiograms (ECGs), clinical laboratory tests, and adverse events (AEs)
- Evaluate onset of analgesia of COV795 versus placebo using onset of confirmed perceptible pain relief and time to peak pain intensity difference (PID)
- Evaluate the analgesic effects of COV795 versus placebo using the following:
    - Pain intensity scores, PIDs, and summed pain intensity differences (SPIDs)
    - Pain relief scores and total pain relief (TOTPAR)
    - Percentage of responders
    - Mean dosing (rescue) interval
    - Use of rescue medication
    - Global assessment of subject satisfaction with study drug

Study Design Schematic
The study design is shown schematically in Figure 1, below:

Figure 1. Design Schematic Study 0182



ET = early termination; TC = telephone call.
[a] Only for subjects not participating in the OLE phase.
[b] Subjects who met the OLE eligibility criteria received study treatment/rescue medication for up to 14 days with 2 scheduled visits (Visits 7 and 8), and a telephone follow-up (Visit 9).

(Source: CSR, Study 0182, p. 24)

Key Inclusion Criteria:

1. Generally good health
2. Aged 18 to 75 years, inclusively at Screening
3. Were scheduled for a primary unilateral first metatarsal bunionectomy (with no collateral procedures)
4. Had a body mass index ≤33 kg/m^2
5. Females: Non pregnant, non-lactating, surgically sterile or using adequate birth control
6. Males: Sterile (biologically or surgically) or using reliable method of birth control
7. Classified as PS-1 or PS-2 by the American Society of Anesthetists Physical Status (PS) Classification System
8. Randomization criteria: Must have experienced a postoperative pain intensity score of ≥ 4 on a 0 to 10 numerical pain rating scale (NPRS) for more than 1 hour and less than 9 hours after discontinuing the nerve block and at least 30 minutes after the last ice pack had been removed (if used).

Key Exclusion Criteria

1. Had an uncontrolled medical condition, serious intercurrent illness, clinically significant general health condition, or extenuating circumstance
2. Clinically significant abnormal ECG at Screening
3. Clinically significant abnormality on clinical laboratory values
4. A known allergy or hypersensitivity to any of the drugs used in the study
5. History of intolerance to short term opioid use
6. History of substance or alcohol abuse within 2 years prior to Screening
7. Positive quantitative urine drug test at Screening for alcohol, illicit drugs, or controlled substances other than those prescribed medications
8. Randomization criteria: Had surgical complications that could have compromised the safety of the subject or confounded the results of the trial.

Key Procedures: The summary of procedures for the Blinded Dosing Phase is shown in the Applicant's Table 6 below, and for the OLE phase in Table 7, following.

<u>Blinded Dosing Phase</u>

Table 6. Study 0182 Schedule

Study Phase	Pretreatment Phase					Blinded Dosing Phase																									
Study Visit	Visit 1	Visit 2			Visit 3	Visit 4																									Visit 5[a]
Timeline		Day -1			Day 1	Days 1 to 2																									
Study Period	Screening	Surgical			Qual[b]	Blinded Dosing																								OLE Assessment	Blinded Follow-up
Procedures	Screening: 2 to 30 days before Day 1	Admit to clinic	Presurgery	Bunion surgery and post-op anesthesia	Qualify Pain Scores Randomization[c]	Predose	0 h – Dose 1	15 min	30 min	45 min	1 h	1.5 h	2 h	4 h	8 h	12 h – Dose 2	14 h	16 h	20 h	24 h – Dose 3	26 h	28 h	32 h	36 h – Dose 4	38 h	40 h	44 h	48 h	Early termination[d]	> 48 h to 52 h	7 days (± 2 days) Postfinal Dose and Discharge
Informed consent(s)	X																														
Inclusion/exclusion criteria	X	X			X																										
Medical/surgical history	X																														
Demographics (weight and height)	X																														
Physical examination	X																											X	X		X
HIV, hepatitis B and C tests	X																														
Pregnancy test	X[e]	X[f]																													X[f]
Alcohol/drug screen	X																														
Clinical laboratory tests	X																											X	X		X
Vital signs and pulse oximetry	X		X		X						X			X	X	X		X	X	X		X	X	X		X	X	X	X		X
ECG	X																											X	X		
Administration of study medication							X									X				X				X							
Pain Intensity (0 to 10) NPRS score[g]					X	X		X	X	X	X	X	X	X	X	X[h]	X	X	X	X[h]	X	X	X	X[h]	X	X	X	X	X		
Pain Relief (0 to 4) categorical scale[g]								X	X	X	X	X	X	X	X	X[h]	X	X	X	X[h]	X	X	X	X[h]	X	X	X	X	X		
Global Assessment of Subject Satisfaction																												X	X		X
Open-Label assessment[i]																														X	
Double stop watch							◄— X —►																								
Concomitant therapy	◄— X —►																														X
Adverse events[j]	◄— X —►																														X

AE = adverse event; ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; NPRS = numerical pain rating scale; OLE = open-label extension; SAE = serious adverse event.
[a] Visit 5 marked the end of the blinded follow-up, and AE/SAE collection and follow-up assessments for subjects not entering the OLE phase.
[b] Qualification.
[c] After the subject awoke and was alert, they were assessed periodically and asked about their pain, until their pain level at rest was ≥ 4, at which point they were randomly assigned study treatment; vital signs and oxygen saturation were measured and recorded.
[d] Early termination procedures were only needed for those subjects who received at least 1 dose of study drug. Subjects that failed Screening or had a surgery complication and did not receive drug did not need ET procedures.
[e] Female subjects of child bearing potential had a serum pregnancy test.
[f] Female subjects of child bearing potential had a urine pregnancy test.
[g] Assessment must have been taken just prior to each administration of rescue medication.
[h] Assessment must have been taken just prior to administration of study drug.
[i] For subjects that met all the OLE assessment criteria, this was marked as the end of the blinded dosing phase. They did not go onto Visit 5 but followed the schedule outlined in Table 9.5.3.3-2.
[j] For subjects that failed Screening and that had an AE during Screening, or during or immediately after surgery, AE information was recorded in the source documents.

(Source: CSR, Study 0182, p. 37-38)

Open-label Extension Phase:

In order to participate in the OLE phase, subjects must have met the following criteria:

1. Signed an OLE phase informed consent form (ICF) before surgery;
2. Completed the blinded dosing period of the study;
3. Reached a pain intensity score ≥ 3 after the blinded dosing period but no later than 52 hours after the first dose; and
4. Agreed to participate in the OLE phase.

During the OLE phase, subjects who met OLE eligibility criteria were given study drug with instructions to take 2 tablets Q12h until medication was no longer needed.

End-of-treatment evaluations were conducted within 3 days of stopping medication, at Visit 7 or 8. Subjects received a follow-up telephone call 7 (± 2) days after the last dose of study drug to check on the subject's general condition, to monitor the subject for new or spontaneously reported or ongoing AEs/serious AEs (SAEs), and to check on the use of concomitant medication.

Table 7. Study 0182 Schedule (OLE)

Study Phase	OLE Phase			
Study Period	OLE Dosing Period			OLE Follow-up Period
Study Visit	Visit 6[a]	Visit 7[b] (EOT)	Visit 8[b] (EOT)	Visit 9
Timeline (Study Days within corresponding Period or Phase)	Discharge/OLE Transition	7-Day Clinic Visit	14-Day Clinic Visit	Telephone Call
Procedures Timeline (Study Days of This Period)	1	7 (± 1 day)	14 (± 1 day)	7 (± 2 days) After last dose
Clinic visit	X	X	X	
Inclusion/exclusion criteria	X			
Physical examination		X	X	
Pregnancy test[c]		X	X	
Clinical laboratory tests		X	X	
Vital signs	X	X	X	
Pulse oximetry	X	X	X	
Retrieve unused drug and/or bottles		X	X	
Dispense study medications[d]	X	X		
COV795 dosing[e]	X			
Drug accountability		X	X	
Global Assessment of Subject Satisfaction	X	X	X	
Concomitant therapy	← X →			X
Collect AEs/SAEs	← X →			X

EOT = end of treatment.

[a] Discharge from site was at least 49 hours after Dose 1 and at least 13 hours after Dose 4. Subjects were administered their first dose of open-label medication and evaluated for 1 hour at the site prior to discharge to assess tolerability. If the subject initially could not tolerate study drug (exemplified by moderate to severe nausea and vomiting), the subject was discontinued from the study, and Visit 7 procedures were performed (note: clinical laboratory tests were not completed at this time), and routine standards for postsurgical care were followed. All subjects must have had arranged rides home.

[b] Depending on when the subject stopped taking study drug, either Visit 7 or Visit 8 served as the final in-clinic visit. End-of-treatment procedures were performed. For example, in some cases, such as stopping medication on Day 2 of the OLE phase, Visit 8 was not necessary.

[c] Female subjects of childbearing potential had a urine pregnancy test.

[d] Study drug was dispensed only if subject was still dosing.

[e] First dose in clinic under supervision for first hour, and after discharge was to be self-administered, up to every 12 hours for up to 14 days.

(Source: Applicant's table, CSR, Study 0182, p. 39)

Outcome Measures Assessments (all data was to have been collected according to Time and Events as per Tables 6 and 7 above)

- Efficacy Assessments:
    - Pain intensity (PI) over time, Pain Relief over time, Time to Perceptible and Meaningful Pain Relief and subject's Global Assessment
    - Frequency and amount of rescue medication taken were to have been recorded
    - Derived endpoints were to have been analyzed for SPID, TOTPAR and responder analyses

- Safety Assessments: Safety was to have been assessed during both the double-blind and OLE phases by conducting physical examinations, measuring vital signs (sitting blood pressure, pulse oximetry, pulse rate, respiratory rate, and temperature), performing 12-lead ECGs (during the blinded dosing period only), conducting clinical laboratory tests (chemistry, hematology, and urinalysis), pregnancy testing, and recording AEs at the times indicated in the study schedule shown in Tables 6 and 7 of this review.

- Pharmacokinetic Assessments: none performed during this study

- Pharmacogenomics: none performed during this study

- Other Evaluations: Possible Abuse and Diversion was to have been documented via accountability for investigational product (IP) Irregularities Plan that detailed handling and reporting of incorrect study drug administration, lost or missing study drug, or suspected misuse and diversion.

Efficacy Endpoints:

- *Primary* – $SPID_{48}$ after the first dose (i.e., during the blinded dosing phase). The PID was the simple difference in baseline pain intensity score (predose pain score) minus pain intensity score at the time point of interest. The SPID was the sum of time-weighted PID scores over a given period of time.

- *Secondary – (blinded phase)*

    - Time from initial dose of study drug to onset of perceptible, meaningful, and confirmed perceptible pain relief measured using the double stop watch method. *Method:* Immediately after administration of the first dose of study drug, clinic personnel were to have started 2 stop watches, both with faces masked. The first watch was to have been given to the subject and instructed to stop when perceptible pain relief occurred. When the subject stopped the first watch, clinic personnel collected it, recorded the data, and gave the second watch to the subject. The subject was to have stopped the second watch when he or she had meaningful pain relief. If the watch was not stopped within 4 hours of study drug administration, the second watch was not to have been given to the subject, and ≥ 4 hours was entered for meaningful pain relief. Onset of confirmed perceptible pain relief was to have been defined as the onset of the perceptible pain relief for only those subjects who experienced pain relief within the first 4 hours and did not require rescue medication prior to the onset time of the meaningful pain relief.

- Time to peak PID – time associated with the first maximum observed PID
- Maximum observed PID within each dosing interval – the largest observed PID that occurred prior to any use of rescue mediation within the given dosing interval
- Pain intensity scores at specified time points
- PIDs associated with each pain intensity score
- SPIDs over 0 to 4, 0 to 12, 0 to 24, 0 to 36, 12 to 24, 24 to 36, and 36 to 48 hours
- Pain relief scores at specified time points – using a categorical scale where 0=no pain relief; 1=slight pain relief; 2=moderate pain relief; 3=good pain relief; and 4=complete pain relief
- TOTPAR for 0 to 4, 0 to 12, 0 to 24, 0 to 36, 0 to 48, 12 to 24, 24 to 36, and 36 to 48 hours
- Proportion of responders at each pain assessment time point*. Methods*: Two levels of responders, 30% and 50% reduction in pain intensity score, were to have been defined with the following 3 variations of responders with respect to rescue medication usage: 1) responders who had no prior use of rescue medication; 2) responders who had no prior use of rescue medication within a dosing interval; and 3) responders who may or may not have had prior use of rescue medication at any time
- Cumulative responders at each pain assessment time point
- Mean dosing (rescue) intervals between the first and second doses, the second and third doses, the third and fourth doses, and 12 hours after the fourth dose*. Methods:* The rescue interval was to have been defined as the time between dose and the time of first rescue medication administration within the interval of interest
- Rescue medication usage was determined for both percentage of subjects who took rescue medication and the amount of rescue mediation taken. Rescue medication usage was to have been summarized for the entire blinded dosing period and with each dosing interval.
- Time to first rescue medication use
- Global assessment of subject satisfaction with study drug. *Methods*: at 48 hours or early termination for blinded dosing phase and at each clinic visit for the OLE phase. A global assessment of subject satisfaction questionnaire assessed the impression of drug efficacy on a categorical scale with the choices of very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied.

Subject completion/withdrawal:
A subject may have discontinued or have withdrawn from the study because of lack of efficacy, an AE, subject request, investigator request, discontinuation of the study by the sponsor, protocol violation, or failure to return for clinic visits (lost to follow-up). If a subject discontinued or was withdrawn from the study after receiving at least 1 dose of study drug, the investigator notified the sponsor's designee and, when possible, performed the procedures indicated for the early termination procedures (Visit 4 of the double-blind period or Visit 7 or 8 of the OLE phase).

Statistical methods: For the primary efficacy analysis, multiple imputation (MI) methods were to have been applied to obtain estimates of intermittent and monotonic (due to early withdrawal) missing PIDs needed for the calculation of the $SPID_{48}$. The PIDs measured within 6 hours after rescue medication use were censored and also estimated using MI. Mean treatment differences were compared using the analyst's model with $SPID_{48}$ as the dependent variable and treatment as the fixed effect and baseline pain intensity score and site as covariates along with the treatment-by-site interaction term.

Please see the Agency's statistical review by Dr. Feng Li for full discussion of the statistical methods and efficacy analyses.

Primary Efficacy Analyses
The primary efficacy analysis was changed with Amendment 4 of the protocol. The primary analysis was conducted on Cohort 2, and a limited number of efficacy analyses were performed on the overall population (combined cohorts).

The combining process was to have consisted of assigning Cohort 1 data to match up with the time points for Cohort 2. The Applicant states that since the primary efficacy measure started with the first dose for both cohorts, the timing difference of the second dose greatly impacted the alignment of efficacy assessments when the cohorts were combined. Additionally, the number of doses a subject received for a given efficacy assessment varied between subjects. The misalignment of efficacy measures and the varying amounts of drug exposure for a given assessment made combining both cohorts for the efficacy analysis problematic and difficult to interpret, and thus the primary analysis population included only Cohort 2. The number of subjects in Cohort 1 was not sufficient enough to perform efficacy analyses on this cohort alone.

The primary efficacy analysis used the modified intent-to-treat (mITT) population. Any pain intensity score that was not collected because a subject withdrew before the planned 48-hour blinded dosing period time point was classified as monotonic missing. Any planned pain intensity score within 6 hours following rescue dosing that was not replaced by the rescue medication pain score was censored (i.e., the value was not used in the analysis). The PIDs were calculated for all nonmissing/noncensored pain scores for each planned time point as defined in Amendment 2.

Sensitivity Analyses:
The Applicant used several different methods of imputing missing data before inferential analysis. See Dr. Li's review and further discussion of Sensitivity Analyses results in Section 6 of this review.

Secondary Efficacy Analyses
The following secondary endpoints were to have been estimated using the Kaplan-Meier method and group comparison were analyzed using the log-rank test.

- Time-to-event statistics for time to onset of perceptible, meaningful and confirmed perceptible pain relief
- Time to peak PID
- Time to first use of rescue medication

Safety Analyses: As per the Applicant, in general, separate summaries were to have been created for the blinded dosing phase and the OLE phase. For both phases, Baseline was defined as the last available observation before dosing in the blinded dosing phase. For any safety measures repeated after the first dose of study drug, the original safety measure was used as the postbaseline measure. Repeat postbaseline safety measurements were not used in any safety analyses unless otherwise stated.

Interim Analysis: not applicable

AdHoc Analyses: Additional Ad Hoc Tables and Figures were provided after unblinding, according to the Applicant, "to further the understanding of the trial results and fulfill regulatory agency requests". Refer to the Agency's statistical (biometrics) review by Dr. Feng Li for further details. In general, Dr. Li has stated that these ad hoc analyses did not affect the primary efficacy analysis.

PostHoc Analyses: According to Dr. Li's review, "at the pre-NDA meeting in December 2012, the Applicant stated that a method to assign bad outcomes to subjects who discontinued due to adverse events would be conducted as a post-hoc analysis as the study had been unblinded". See Dr. Li's review for discussion.

Protocol Amendments
The key changes contained in the 4 protocol amendments are summarized below in Table 8.

Table 8. Protocol Amendments to Study 0182

#	Date	Key Changes
1	10/18/11	• Clarified prohibited medications. • Clarified criteria for whether patient was tolerating study drug.
2	1/26/12	• Increased planned number of subjects from 250 to 270.

		• Eliminated the Single Dose (first dose [0 hour] to request for second dose) and Multiple Dosing (second dose to 48 hours after second dose) Periods in the Blinded Dosing Phase and created a single Blinded Dosing Period (0 to 48 hours from first dose). During the new blinded dosing period, subjects were to receive a total of 4 doses of study drug in place of 5 doses as in the old Blinded Dosing Periods, which were administered at a fixed 12-hour dosing regimen for all doses. The open-label extension assessment visit was incorporated into the Blinded Dosing Phase as the open-label assessment period clarified requirements for each period. • Defined subjects that required rescue medication within 1 hour of cessation of nerve block, regardless of administration of first dose of study drug, as screen failures. • Defined subjects enrolled under Amendment 1 as Cohort 1 and subjects enrolled under Amendment 2 as Cohort 2.
3	4/13/12	• Changed randomization criteria to include subject pain intensity of moderate to severe. • Further specified determination of screen failure.
4	6/4/12	• Changed planned number of subjects from 270 to 320 to increase the absolute number of subjects with minimal censor/missing pain scores from 40 to about 60, which added to the robustness of the estimates used to impute the censored/missing values.

(Table, reviewer)

Of these amendments, changes were made which affected the sample size, populations analyzed, changes in study conduct and statistical analysis. However, overall, these amendments should not have affected the primary efficacy outcome and analysis as the amendments were adequately taken into account with the final primary endpoint analysis, as discussed below:

Sample size determination – In Amendment 4, the study sample size was increased based on the criteria specified in the original protocol, namely, that >35% of the scores were “missing” (mostly due to censoring after the first use of rescue medication). The sample size increase from 244 to 294 subjects in Cohort 2 was based on only 34% of subjects (43 of the first 126 enrolled) having a minimal number of censored or missing pain intensity scores (i.e., ≤2 censored/missing scores out of 21 measures). The additional 50 subjects increased the absolute number of subjects with minimal censored/missing pain scores from 43 to about 60 (a 40% increase), which added to the robustness of the estimates used to impute the censored/missing values.

Populations analyzed: Amendments 2 and 3 amended the definition of screen failure. Specifically, if rescue medication (ibuprofen 400mg every 4 hours as needed up to 6 times daily) was required after termination of nerve block before randomization, the

subject was considered a screen failure. Subjects with surgical complications were also considered screen failures.

Reviewer comment: These amendments should not have affected the primary efficacy outcome as they increased the robustness of the statistical estimates and identified patients with a pain level more likely to be consistent with (b) (4) *pain, the proposed indication of the drug.*

Changes in study conduct: Amendment 2 eliminated the Single Dose (first dose [0 hour] to request for second dose) and Multiple Dosing (second dose to 48 hours after second dose) Periods in the Blinded Dosing Phase and created a single Blinded Dosing Period (0 to 48 hours from first dose).

Due to the small number of subjects in Cohort 1, these differences were not deemed sufficient enough by the Applicant to perform safety analyses on Cohort 1 alone (although the safety population included all dose subjects).

Reviewer comment: Due to the small number of subjects involved, this should not have affected the primary efficacy outcome results.

Changes in Planned Analyses – The primary efficacy analysis was changed with Amendment 4. Originally, all planned pain intensity scores collected after the first use of rescue medication were to be censored and their PIDs estimated using multiple imputation (MI) techniques. However, preliminary blinded safety data showed that a large proportion of subjects used rescue medication at least once, resulting in too many censored PIDs. To reduce the confounding effects of rescue medication use and the incidence of censored scores (unusable pain scores), the primary analysis was modified to use 6-hour censoring for rescue medication use as described below. Also, the initial MI step was performed separately on the PIDs of the subjects who took rescue medication and those who did not. This modification to the primary analysis was agreed upon with the FDA prior to the database lock (FDA Written Response, IND 104,702, August 14, 2012).

The primary efficacy analysis used the modified intent-to-treat (mITT) population. Any pain intensity score that was not collected because a subject withdrew before the planned 48-hour blinded dosing period time point was classified as monotonic missing. Any planned pain intensity score within 6 hours following rescue dosing that was not replaced by the rescue medication pain score was censored (ie, the value was not used in the analysis). The PIDs were calculated for all nonmissing/noncensored pain scores for each planned time point as defined in Amendment 2. See the review of Dr. Feng Li, Agency statistical reviewer, for further details.

Reviewer comment: Because this change was made prior to unblinding, efficacy results should not have been affected.

See Section 6 for a detailed discussion of the efficacy results of Study 0182.

II) Supportive Efficacy and Safety Study 0181

Overview: This was a multicenter, open-label, Phase 3 study designed to collect safety data on the short-term use of COV795 in populations who frequently use low-dose opioids for short periods of time, similar to the treatment of acute pain, and to obtain supportive efficacy data. It was planned to enroll approximately 400 subjects who were transitioning from Step 1 of the World Health Organization (WHO) pain scale (nonsteroidal anti-inflammatory drugs [NSAIDs] and other nonopioid medications to control pain) to Step 2 of the WHO pain scale (needing to escalate to opioid combinations, lower dose opioids, etc., plus NSAIDs to control pain). Subjects were treated with 2 tablets of COV795 every Q12h for up to 35 days. Enrollment was stopped when at least 250 subjects had completed 10 or more days of exposure at the COV795 dose of 2 tablets Q12h (15 mg OC/650 mg APAP Q12h).

Title: An Open-Label Safety Study of COV795 in Subjects with Osteoarthritis or Chronic Low Back Pain

Protocol Number: COV15000181

Study Dates: September 20, 2011 to June 18, 2012

Amendments: There were a total of four amendments. Prior to Amendment 3 of the protocol, subjects began with a dose titration. On the initial day of dosing, subjects received 1 tablet of COV795, followed by a second tablet after a 2-hour delay for safety assessments between tablets. Subjects could then proceed to a 2-tablet regimen or continue on the 1-tablet regimen for the first week. Ninety-one subjects enrolled and initiated dosing prior to Amendment 3 of the protocol; all but 4 of these subjects proceeded onto the 2-tablet regimen for the first week of study dosing. The 4 subjects who were to receive the 1-tablet regimen for the first week discontinued the study after the first day of dosing (3 subjects discontinued after taking the first tablet, and 1 subject discontinued after taking the second tablet).

Primary Objective: The primary objective was to demonstrate the safety and tolerability of COV795 with up to 35 days of use as evaluated by physical examination, vital signs, pulse oximetry, clinical laboratory tests, and adverse events (AEs).

Secondary Objectives:

- Evaluate changes from pretreatment in pain using the pain intensity items of the modified Brief Pain Inventory short form (mBPI-sf) questionnaire for all subjects.

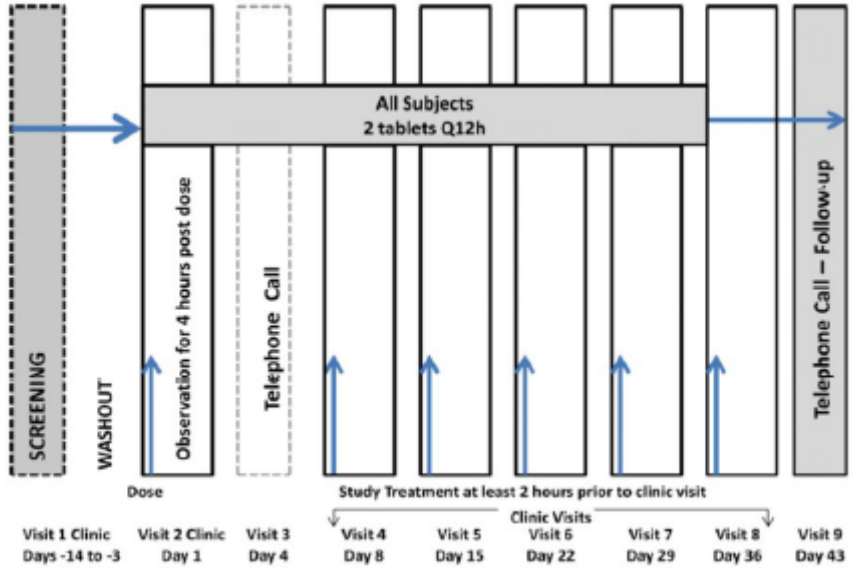
- Evaluate pain relief using the pain relief item of the mBPI-sf for all subjects.

- Evaluate the pain-related quality of life using the pain interference subscale of the mBPI-sf for all subjects.

- Evaluate changes from pretreatment in disease-specific quality of life using the Western Ontario and McMaster Universities Arthritis index (WOMAC) questionnaire (48-hour version) for subjects with osteoarthritis (OA) of the hip or knee or the Roland-Morris Low Back Pain and Disability Questionnaire for subjects with chronic low back pain (CLBP), as appropriate.

Study Design
The study design is shown schematically in Figure 2, below:

Figure 2. Design Schematic Study 0181



Note: Blue arrows indicate dosing.
(Sponsor's figure, CSR 0181, p. 19)

Duration: Each subject participated in the study for up to 57 days. This included a screening period of up to 14 days, a treatment period of up to 36 ± 1 days, and a follow-up phone call at Day 43(± 2 days).

Methods:
- After screening, subjects on pain medication of any kind underwent a 3-day washout period before Visit 2 (Day 1).

- At Visit 2, all subjects meeting inclusion criteria completed baseline pain assessments and received the first dose of study drug. After receiving study drug

at Visit 2, subjects were observed for opioid tolerability symptoms for 4 hours. Subjects who experienced emesis of any severity or moderate to severe AEs, including nausea, within 4 hours of dosing were discontinued from the study.

- Ongoing subjects were provided with rescue medication of 200 mg ibuprofen, with instructions to take 2 tablets orally as needed every 4 to 6 hours for breakthrough pain (up to 2,400 mg/day).
- On Day 4, subjects were contacted by telephone to check on their well-being.

The schedule of events is shown below in Table 9.

Table 9. Schedule of Events Study 0181

	Screening Visit[a]	Treatment Period							Follow-up
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8/EOT**	**V9**
Week	**-2 to -1**	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Day	**-14 to -3**	**1**	**4 ± 1**	**8 ± 1**	**15 ± 1**	**22 ± 1**	**29 ± 1**	**36 ± 1**	**43 ± 2**
Clinic visit (Cl)/telephone (T)	**Cl**	**Cl**	**T**	**Cl**	**Cl**	**Cl**	**Cl**	**Cl**	**T**
Informed consent	X								
Medical/surgical history	X								
Demographic information; height and weight	X								
Urine drug screen	X								
Serum pregnancy test[b]	X								
Urine pregnancy test[b]	X	X		X	X	X	X	X	
Full clinical laboratory tests[c]	X							X	
HIV and hepatitis B and C	X								
Abbreviated clinical laboratory tests[d]				X	X	X	X		
Physical examination	X							X	
ECG (12-lead)	X								
Hospital Anxiety and Depression Scale	X								
ACR criteria for OA of knee or hip	X								
Quebec Task Force Classification (CLBP subjects)	X								
Vital signs (blood pressure, pulse rate, respiratory rate, oral temperature)	X	X		X	X	X	X	X	
Pulse oximetry	X	X		X	X	X	X	X	
Review inclusion/exclusion criteria	X	X							
Instructions for 3-day washout	X								
Treatment with COV795		←----------			X			----------→	

Dispense (D)/collect (C) study and rescue medication		D		C/D	C/D	C/D	C/D	C	
mBPI-sf	X	X[e]	X[f]	X	X	X	X	X	
Average dosing times question			X	X	X	X	X	X	
Query use of rescue medication			X						
WOMAC (OA subjects)		X[e]		X	X	X	X	X	
Roland-Morris (CLBP subjects)		X[e]		X	X	X	X	X	
Prior/concomitant medications	←----------X----------→								
AEs[g]	←----------X----------→								

Abbreviations: EOT= end of treatment (procedures done for subjects who discontinued early); HIV = human immunodeficiency virus; V = visit.
[a] Includes 3-day washout from all opioids, NSAIDs, APAP, and aspirin (except as noted in low doses for heart function).
[b] Females of childbearing potential.
[c] Full clinical laboratory tests = hematology, clinical chemistry and urinalysis.
[d] Abbreviated clinical laboratory tests included liver function tests (see text for list).
[e] Baseline assessments for study.
[f] Question 3 only.
[g] Collection of AEs began with subject's signing of the informed consent form, continued throughout the trial, and ended 7 days following the last dose of study drug, or at early termination. Adverse events were reported during Visit 9 for subjects not terminating early.

(Sponsor's table, CSR 0181, p. 26-27)

Key Inclusion Criteria

1. Were in good general health at the screening visit, other than OA or CLBP, based on results of medical and surgical history, vital signs, pulse oximetry, physical examination, clinical laboratory tests, and electrocardiogram (ECG)
2. Male or female ≥ 18 years of age at the time of screening
3. If female, were not pregnant (negative serum pregnancy test at screening); not lactating; not planning to become pregnant in the next 2 months, surgically sterile, at least 2 years postmenopausal, or were practicing an acceptable form of birth control for > 2 month before screening and committed to the use of an acceptable form of birth control for the duration of the study and for 1 week after the last dose of COV795
4. If male and biologically capable of having children, were committed to the use of a reliable birth control method for the duration of the study and for 1 week after the last dose of COV795. (Surgical sterilization of a subject's monogamous partner qualified as adequate birth control.)
5. Had a clinical diagnosis of 1 of the following:
    a. OA of the knee or hip for at least 1 year based on American College of Rheumatology (ACR) criteria with moderate to severe mean daily pain intensity despite chronic use of stable doses of NSAIDs or other nonsteroidal, nonopioid therapies, or with therapies including opioids;
    b. Moderate to severe CLBP (ie, pain that occurs in an area with boundaries between the lowest rib and the crease of the buttocks) present for at least several hours a day for a minimum of 3 months, not due to known malignancy, classified as nonneuropathic, neuropathic, or symptomatic for more than 6 months after surgery for lower back pain based on the Quebec Task Force Classification of Spinal Disorders

6. Had an average in-clinic pain score ≥ 3 on the 11-point (0 to 10) numerical rating scale (NRS) for the last 24 hours at Visit 1
7. Had an average pain intensity score ≥ 4 on NRS for the last 24 hours at Visit 2

Key Exclusion Criteria

1. Had any clinically significant condition or unstable inter-current illness that would, in the opinion of the investigator, preclude study participation or interfere with assessment of pain and other symptoms of CLBP or OA or would increase the risk of opioid or NSAID-related AEs
2. Had uncontrolled or poorly controlled major psychiatric condition or had clinically significant anxiety or depression as indicated by a Hospital Anxiety and Depression Scale (HADS) score of > 12 in either depression or anxiety subscales at screening visit
3. Had a surgical procedure for back pain within 6 months prior to screening.
4. Had a nerve or plexus block, including epidural steroid injections or facet blocks, for CLBP within 1 month prior to screening or botulinum toxin injection in the lower back region within 3 months prior to screening or joint injection of the OA study joint within 1 month of screening
5. Had gastric reduction surgery
6. Taking opioid equivalents > 20 mg OC or > 40 mg morphine sulfate orally per day or taking opioid medications ≥ 4 days/week
7. Had alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), or total bilirubin > 2 times the upper limit of normal (ULN) or creatinine > 1.5 times the ULN

Selection and Timing of Dose for Each Subject

- The first dose of study drug was given to subjects on Day 1 under clinic supervision. Each subject was monitored for 4 hours after the first dose for emesis and nausea or other AEs**.** If subjects tolerated the first dose, they continued a regimen of 2 tablets Q12h for the duration of the study. Subjects were instructed that doses of COV795 should be taken every 12 ± 1 hours, and were to be taken orally with water, with or without food.

- Prior to Amendment 3 of the protocol, subjects began with a dose titration. On the initial day of dosing, subjects received 1 tablet of COV795, followed by a second tablet after a 2-hour delay for safety assessments between tablets. Subjects could then proceed to a 2-tablet regimen or continue on the 1-tablet regimen for the first week.

- Ninety-one subjects enrolled and initiated dosing prior to Amendment 3 of the protocol; all but 4 of these subjects proceeded onto the 2-tablet regimen for the first week of study dosing. The 4 subjects who were to receive the 1-tablet regimen for the first week discontinued the study after the first day of dosing (3 subjects discontinued after taking the first tablet, and 1 subject discontinued after taking the second tablet).

Primary Endpoint: The primary endpoint was safety and tolerability of COV795 administered Q12h for up to 35 days. This endpoint was evaluated by using the following measures and assessments:

- Time to discontinuation
- Changes in physical examination findings from baseline to end of treatment
- Changes from baseline in vital signs (sitting blood pressure, pulse rate, respiratory rate, oral temperature) at each visit
- Changes from baseline in pulse oximetry at each visit
- Changes in clinical laboratory test results (chemistry, hematology, and urinalysis) from baseline to end of treatment
- Liver function test results (ALT, AST, alkaline phosphatase [ALP], lactate dehydrogenase [LDH], GGT, and total and direct bilirubin) at Visits 4 through 7
- Treatment-emergent adverse events (TEAEs)

Secondary Endpoints:
Efficacy measures were secondary endpoints. Efficacy measure questionnaires were completed by subjects directly on an electronic tablet at the study site. These endpoints were:

- Mean changes from pretreatment in the worst, least, average, and current pain using the corresponding pain intensity items of the modified Brief Pain Inventory (mBPI-sf) (Questions 1 to 4). The mBPI-sf questionnaire uses a numerical rating scale, with 0 being “no pain” and 10 being “pain as bad as you can imagine.”
- Pain relief using the pain relief item of the mBPI-sf (Question 5).
- Pain-related quality of life using the pain interference subscale of the mBPI-sf. The mBPI-sf assesses the degree to which pain interferes with mood, physical activity, work, social activity, relations with others, and sleep, with 0 being “no interference” and 10 being “interferes completely.”
- Mean changes from pretreatment in disease-specific quality of life using the WOMAC questionnaire (48-hour version) for subjects with OA of the hip or knee. The WOMAC assesses 3 dimensions of pain, stiffness, and physical function using 24 questions. Each question is rated 0 to 4, where 0 = none; 1 = slight; 2 = moderate; 3 = severe; and 4 = extreme.

- Mean changes from pretreatment in disease-specific quality of life using the Roland-Morris CLBP and Disability Questionnaire for subjects with CLBP. In this questionnaire, subjects mark which of 24 statements

Protocol Amendments
There were a total of four amendments to the study protocol summarized in Table 10 below:

Table 10. Protocol Amendments to Study 0181

#	Date	Key Changes
1	7/11/11	• Made prior to screening. • Clarification of procedures for titration subjects.
2	12/2/11	• No major changes. • Clarification of exclusion criteria.
3	1/23/12	• Clarification of dosing for rescue medication. • Revision of the study design schematic. • Addition of time to discontinuation to primary endpoint and addition of specific information regarding the primary endpoint. • Revision of secondary endpoint to include mean changes in worst, least, average, and current pain.
4	4/19/12	• Clarification of the impact of Amendment on statistical summaries.

(Table, reviewer)

Study 0181 Efficacy Results:
The primary safety population consisted of all subjects enrolled in the study. This primary safety population was summarized as originally planned. Because this is an open-label study, all efficacy assessments are merely descriptive in nature.

Study Disposition: 285 of 376 subjects (75.8%) completed the study and 91 of 376 subjects (24.2%) discontinued the study. According to the Applicant, the most common reason for study discontinuation (71 subjects, 18.9%) was a treatment-emergent adverse event (TEAE). Nausea and vomiting were the most common AEs that led to discontinuation. Eight subjects (2.1%) withdrew consent and 3 subjects (0.8%) each discontinued for lack of efficacy, physician's decision, and lost to follow-up.

Applicant's Efficacy Results (Study 0181)

- Several measures of pain control and relief were demonstrated in patients with either OA or CLBP. Pain intensity scores (mean score change) all decreased from baseline pain to the end of treatment for worst pain in the last 24 hours (47% decrease), least pain in the last 24 hours (57%), average pain in the last 24 hours (52%), and current pain (60%). The improvements in pain scores occurred by Day 8 and persisted throughout the study, with the largest improvement occurring at Day 36.

- Percent pain relief increased from baseline through Day 36 (mean improvement of 55%), seen in Table 11.

Table 11. Modified Brief Pain Inventory-SF from Medication

	Percent Pain Relief[a]		
Time Point	Mean (SD)	Median	Minimum, maximum
Baseline (n = 376)	13.2 (21.93)	0.0	0, 90
End of treatment (n = 359)	67.7 (28.47)	80.0	0, 100
Change from baseline	54.5 (35.32)	60.0	–80, 100

Source: Table 14.2.1.
[a] Percentages range from 0% = no relief to 100% = complete relief.

(Source: Applicant's table, CSR 0181, p. 46)

- Pain-related quality of life, as measured by the Modified Brief Pain Inventory-Short Form (mBPI-SF) pain interference score, improved at each visit. The changes in pain intensity mBPI scores from baseline to end of treatment are shown in Table 12 below:

Table 12. Modified Brief Pain Inventory Pain Intensity Scores

	Score[a]		
mBPI-sf Item	Mean (SD)	Median	Minimum, maximum
Worst pain in last 24 hours			
Baseline (n = 376)	7.6 (1.32)	8.0	4, 10
End of treatment (n = 359)	4.0 (2.58)	4.0	0, 10
Change from baseline	–3.7 (2.69)	–4.0	–10, 3
Least pain in last 24 hours			
Baseline (n = 376)	5.6 (1.94)	6.0	0, 10
End of treatment (n = 359)	2.4 (2.13)	2.0	0, 10
Change from baseline	–3.2 (2.45)	–3.0	–10, 3
Average pain in the last 24 hours			
Baseline (n = 376)	6.7 (1.38)	7.0	4, 10
End of treatment (n = 359)	3.2 (2.25)	3.0	0, 10
Change from baseline	–3.5 (2.43)	–3.0	–10, 3
Pain right now			
Baseline (n = 376)	6.7 (1.64)	7.0	2, 10
End of treatment (n = 359)	2.8 (2.36)	2.0	0, 10
Change from baseline	–4.0 (2.60)	–4.0	–10, 2

Source: Table 14.2.1.
[a] Scores range from 0 = no pain to 10 = pain as bad as you can imagine.

(Source: CSR 0181, p. 45)

- WOMAC pain scores and Roland-Morris scores both improved from baseline to end of treatment, by 46% (mean total score, OA) and 45% (mean score, CLBP),

respectively. Tables 13 and 14, below, display the changes in WOMAC and Roland-Morris scores from baseline to end-of treatment, respectively.

Table 13. Changes in WOMAC Scores in Subjects with Osteoarthritis

	OA Hip		OA Knee		All OA	
Domain/Time Point	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Pain[a]						
Baseline	12	12.50 (3.090)	128	11.66 (2.962)	140	11.74 (2.971)
End of treatment	12	7.08 (4.420)	122	6.13 (3.983)	134	6.22 (4.016)
Change from baseline		–5.42 (4.522)		–5.70 (4.653)		–5.68 (4.625)
Stiffness[b]						
Baseline	12	5.75 (1.288)	128	4.86 (1.228)	140	4.94 (1.254)
End of treatment	12	3.50 (1.732)	122	2.77 (1.705)	134	2.84 (1.713)
Change from baseline		–2.25 (1.603)		–2.11 (1.804)		–2.12 (1.781)
Physical function[c]						
Baseline	12	40.33 (10.369)	128	38.83 (9.847)	140	38.96 (9.863)
End of treatment	12	24.17 (13.272)	122	21.02 (13.192)	134	21.30 (13.180)
Change from baseline		–16.17 (14.115)		–18.17 (14.629)		–17.99 (14.543)
Total score[d]						
Baseline	12	58.58 (13.655)	128	55.35 (13.234)	140	55.63 (13.251)
End of treatment	12	34.75 (18.767)	122	29.92 (18.440)	134	30.35 (18.450)
Change from baseline		–23.83 (19.591)		–25.98 (20.485)		–25.79 (20.344)

Source: Table 14.2.2.
[a] Pain score ranges from 0 to 20, with higher scores representing worse pain.
[b] Stiffness score ranges from 0 to 8, with higher scores representing worse stiffness.
[c] Physical function score ranges from 0 to 68, with higher scores representing worse functional limitations.
[d] Total score ranges from 0 to 96, with higher scores representing worse pain/disability.

(Source: Applicant's table, CSR 0181, p. 47)

Table 14. Roland-Morris Low Back Pain and Disability Scores for Subjects with Chronic LBP

	Roland-Morris Score[a]		
Time point	**Mean (SD)**	**Median**	**Minimum, Maximum**
Baseline (n = 235)	10.9 (5.27)	11.0	3, 24
End of treatment (n = 224)	6.1 (5.75)	5.0	0, 23
Change from baseline	–4.9 (5.83)	–4.0	–22, 9

Source: Table 14.2.3.
[a] Scores ranged from 0 to 24, with higher scores representing greater disability.

(Source: Applicant's table, CSR0181, p. 48)

Statistical Analyses

The safety population was used for efficacy analyses. The primary safety population consisted of all subjects enrolled in the study.

Descriptive statistics included the number of subjects with data to be summarized (n), mean, SD, median, minimum, and maximum. All categorical/qualitative data are

presented using frequency counts and percentages. Data were summarized for subjects with < 10 days of exposure and ≥ 10 days of exposure, as well as by titration class and indication, where appropriate. Summary statistics were provided for time to discontinuation.

No adjustments for covariates were made and no imputation was done for missing data, with the exception of AE onset dates and times and concomitant medications start and stop dates and times.

Subgroup Analyses
Certain analyses were conducted for the following subgroups of the safety population:

- Length of exposure: < 10 days or ≥ 10 days.
- Titration class: subjects who enrolled before protocol Amendment 3 (titration subjects; these subjects received 1 tablet of study drug followed by another tablet 2 hours later) or after Amendment 3 (nontitration subjects; these subjects took an initial dose of 2 tablets).
- Indication: OA of the hip, OA of the knee, OA all, or CLBP

Applicant's Efficacy Conclusions (Study 0181)

- Scores for worst pain in the last 24 hours, least pain in the last 24 hours, average pain in the last 24 hours, and current pain all decreased over the course of the study.
- The improvements in pain scores occurred by Visit 4 (Day 8) and persisted throughout the study, with the largest decreases occurring at Visit 8 (Day 36).
- Percent pain relief increased from baseline through Visit 8 (Day 36).
- Pain-related quality of life, as measured by the mBPI-sf pain interference score improved at each visit.
- WOMAC pain scores and Roland-Morris scores both improved from baseline to end of treatment.

Reviewer's Comments: Since this is an open-label study and there was no placebo group for comparison, limited efficacy conclusions can be drawn. However, based upon the Applicant's findings, there appears to be general supportive efficacy of study drug in the studied population. The Applicant is not proposing any efficacy claims in the label based upon results from Study 0181.

6 Review of Efficacy

Efficacy Summary

According to the Applicant, overall, COV795 subjects reported less pain, greater pain relief, less need for rescue medication, and rated COV795 more highly as a pain reliever. Pain relief was rapid, peaked consistently in magnitude after each dose of COV795, and had a duration that lasted over the 12-hour dosing interval in subjects with acute moderate to severe pain following unilateral bunionectomy.

> *Section 14. Proposed Label:* Efficacy was demonstrated in one multicenter, randomized, double-blind, placebo-controlled, parallel-arm, multiple-dose clinical trial comparing XARTEMIS XR and placebo in patients with acute pain following a unilateral first metatarsal bunionectomy. A total of (b) (4) patients with a mean age of 43 (range 18 to 73) years, meeting criteria for randomization (pain intensity ≥4 on a 0 to 10 numerical pain rating scale) and receiving a fixed-dose of (b) (4) XARTEMIS XR, 7.5 mg oxycodone hydrochloride and 325 mg acetaminophen tablets (b) (4) every 12 hours over 48 hours were (b) (4) Mean baseline pain intensity scores were 6.2 in the XARTEMIS XR group (b) (4) and 6.0 in the placebo group (b) (4)

In general, I agree with the Applicant's efficacy conclusions, although the Applicant's proposal for Section 14 of the label will be edited by the Division in order to include the appropriate and relevant language based on the study results.

6.1 Indication

COV795 (Oxycodone/APAP) is indicated for the management of (b) (4) acute pain where use of an opioid analgesic is appropriate.

6.1.1 Methods

The Applicant has conducted one Phase 3 study, COV15000182 (hereafter referred to as Study 0182), to be used as the key efficacy study to assess the safety and efficacy of

study drug oxycodone/APAP in the treatment of moderate to severe acute pain. Study 0182 evaluated the use of 7.5mg oxycodone/325mg APAP multilayer, extended-release tablets with repeated dosing in postoperative bunionectomy patients.

This section of the review will report the efficacy findings of Study 0182 in detail. The other Phase 3 study, 0181, was an OL study which the Applicant proposes to use for supportive efficacy. Major efficacy findings from Study 0181 have been summarized in Section 5.3.

Study 0182 planned to randomize and dose 320 subjects; 303 subjects were included in the modified intent to treat (mITT) population and 146 subjects enrolled in the OLE phase.

6.1.2 Demographics

Treatment groups were comparable in this study in terms of demographic and baseline characteristics. Overall, approximately 85% of subjects were female with the mean subject age of 43 years. The majority (59.4%) were white. The placebo group was slightly older (median age 46 years vs 42 years in study drug) and slightly more Caucasians were in the placebo than study drug, but these differences were unlikely to be clinically meaningful. The demographic data are summarized in Table 15, below.

Table 15. Demographics (mITT Population) Study 0182

	COV795 n (%)[a] (N = 150)	Placebo n (%)[a] (N = 153)	All Subjects n (%)[a] (N = 303)	*P* value[a]
Age (years)				
n	150	153	303	0.158
Mean (SD)	41.9 (13.13)	44.1 (14.01)	43.0 (13.61)	
Median	42.5	46.0	44.0	
Minimum, Maximum	18, 70	18, 73	18, 73	
Gender				0.334
Male	19 (12.7)	26 (17.0)	45 (14.9)	
Female	131 (87.3)	127 (83.0)	258 (85.1)	
Race[b]				0.464
American Indian or Alaska Native	3 (2.0)	0	3 (1.0)	
Asian	13 (8.7)	11 (7.2)	24 (7.9)	
Black or African American	48 (32.0)	45 (29.4)	93 (30.7)	
Native Hawaiian or Other Pacific Islander	0	1 (0.7)	1 (0.3)	
White or Caucasian	85 (56.7)	95 (62.1)	180 (59.4)	
Other	1 (0.7)	1 (0.7)	2 (0.7)	
Ethnicity				0.793
Hispanic or Latino	37 (24.7)	40 (26.1)	77 (25.4)	
Not Hispanic or Latino	113 (75.3)	113 (73.9)	226 (74.6)	
Weight (kg)				
n	150	153	303	0.196
Mean (SD)	70.26 (13.134)	72.19 (12.751)	71.23 (12.957)	
Median	69.95	71.80	70.70	
Minimum, Maximum	42.2, 105.7	45.5, 112.0	42.2, 112.0	
Body Mass Index (kg/m^2)				
n	150	153	303	0.088
Mean (SD)	25.64 (3.986)	26.39 (3.676)	26.02 (3.845)	
Median	26.00	26.90	26.40	
Minimum, Maximum	15.9, 33.0	18.0, 33.0	15.9, 33.0	

(Source: Study 0182 CSR, p. 71)

Baseline Pain Intensity (PI) Scores

Baseline PI score was summarized with descriptive statistics for the mITT, combined cohort mITT, and Cohort 1 populations. By-site summarizations were produced for these populations.

The Applicant reported that mean baseline pain intensity scores were 6.2 in the study drug treatment group (max: 10) and 6.0 in the placebo group (max: 10).

Prior and Concomitant Medications

All subjects (100%) in the blinded safety population used at least one prior medication and at least one concomitant medication. Due to the surgical entry criteria, the most common prior medications used by ≥ 5% of subjects overall were anesthetics (general and local) and antiemetics/antinauseants which were used essentially equally between

the treatment groups. Other classes of drugs used as prior medications by approximately 50% of subjects in each group were anti-inflammatory/antirheumatic products/non-steroidals; hypnotics and sedatives; IV solutions; beta-lactam antibacterials and oxygen.

Concomitant medication classes used by ≥50% of subjects included anesthetics and anti-inflammatory/antirheumatic products/non-steroidals. Of note, antiemetics and antinauseants (ondansetron) were used by approximately 16% of drug-treated compared to only 6% placebo.

6.1.3 Subject Disposition

A total of 329 subjects (164 COV795 at 7.5mgOC/325mg APAP and 165 placebo) were enrolled under Amendments 1-4, randomized, and received at least one dose of study drug during the blinding dosing phase.

According to the Applicant, 293 of 329 subjects (89.1%) completed the blinded dosing period, 180 of 183 subjects (98.4%) completed the blinded follow-up, and 129 of 146 (88.4%) in the open-label safety population completed the open-label extension phase. Two subjects (201-120 and 204-098) were randomized to placebo but actually received study drug. Per the Applicant, both instances occurred because the incorrect kit was dispensed.

The first 26 subjects were enrolled under Amendment 1. Based upon interactions with the FDA, Amendment 2 eliminated the Single Dose (first dose [0 hour] to request for second dose) and Multiple Dosing (second dose to 48 hours after second dose) Periods in the Blinded Dosing Phase and created a single Blinded Dosing Period (0 to 48 hours from first dose). Protocol Amendment 2 defined subjects enrolled under Amendment 1 as Cohort 1; the 303 subjects enrolled under Amendments 2 to 4 were defined as Cohort 2. The modified intent-to-treat (mITT) population consisted of all subjects from Cohort 2 who received at least 1 dose of study drug, and was the primary efficacy population.

As per the Applicant, each of the study populations included all subjects from both cohorts who received at least 1 dose of study drug. The study populations comprised the combined cohort mITT population, the overall safety population (subjects who received at least 1 dose of study drug [COV795 or placebo]), the blinded safety population (data from the open-label extension phase were not included), and the open-label extension safety population (data from the blinded dosing phase were not included). Treatment group assignments in both the blinded and open-label safety populations were based on the actual treatment received during the blinded dosing phase.

Details regarding the subjects disposition are shown are Sponsor's Table 16 and Figure 3, respectively, below:

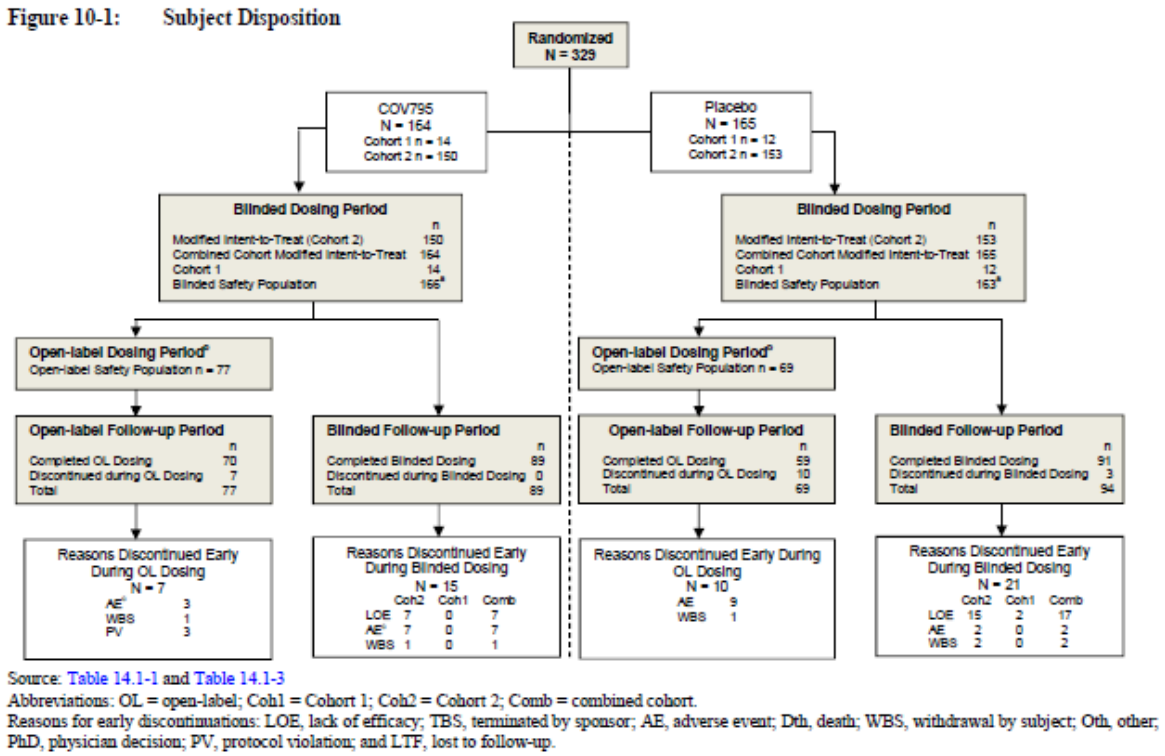
Table 16. Subject Disposition (All Randomized Subjects)

	COV795 n (%)	Placebo n (%)	All Subjects n (%)
All randomized[a]	164	165	329
Modified Intent-to-Treat Population (Cohort 2)[b]	150 (91.5)	153 (92.7)	303 (92.1)
Combined cohort mITT Population[b]	164 (100)	165 (100)	329 (100)
Cohort 1[b]	14 (8.5)	12 (7.3)	26 (7.9)
Blinded Safety Population	166	163	329
Completed blinded dosing period[a,c]	151 (91.0)	142 (87.1)	293 (89.1)
Discontinued early during blinded dosing period[c]	15 (9.0)	21 (12.9)	36 (10.9)
Subjects who entered blinded follow-up safety period[c]	89 (53.6)	94 (57.7)	183 (55.6)
Completed blinded follow-up[d]	89 (100)	91 (96.8)	180 (98.4)
Did not complete blinded follow-up[d]	0	3 (3.2)	3 (1.6)
Open-label Safety Population[e]	77 (46.4)	69 (42.3)	146 (44.4)
Completed open-label dosing period[e]	70 (90.9)	59 (85.5)	129 (88.4)
Discontinued early during open-label dosing period[e]	7 (9.1)	10 (14.5)	17 (11.6)

[a] Subjects 201-120 and 204-098 were randomized to placebo but were dispensed the wrong kits and actually received COV795.
[b] Percentages were based on the number of randomized subjects in each treatment group.
[c] Percentages were based on the number of subjects in each treatment group who were within the blinded safety population.
[d] Percentages were based on the number of subjects in each treatment group who did not enter the OLE phase.
[e] Percentages were based on the number of subjects in each treatment group who continued to the OLE phase.

(Source: Sponsor's table, Clinical Study Report, Study 0182, p. 57)

Figure 3. Subject Disposition Study 0182



Source: Table 14.1-1 and Table 14.1-3
Abbreviations: OL = open-label; Coh1 = Cohort 1; Coh2 = Cohort 2; Comb = combined cohort.
Reasons for early discontinuations: LOE, lack of efficacy; TBS, terminated by sponsor; AE, adverse event; Dth, death; WBS, withdrawal by subject; Oth, other; PhD, physician decision; PV, protocol violation; and LTF, lost to follow-up.

(Source: Applicant's Figure, CSR, p.

Discontinuations

The most common reasons for early discontinuation (≥3% in any treatment group) were lack of efficacy, AEs, and subject's withdrawal of consent.

According to the Applicant, in the mITT population, 22 of 303 subjects (7.3%) discontinued during the blinded dosing period because of lack of efficacy. Of those 22 subjects, 7 subjects (4.7%) were taking COV795 and 15 subjects (9.8%) were taking placebo. In the combined cohort mITT, two additional subjects taking placebo were withdrawn because of lack of efficacy, for a total of 24 of 329 subjects (7.3%) who discontinued because of lack of efficacy.

During the blinded dosing period, 9 subjects (3.0%; 7 COV795, 2 placebo; 7 during double-blind dosing, 2 during double-blind follow-up) experienced AEs and were withdrawn from the study and 3 subjects (1.0%) withdrew consent. One of the subjects taking COV795 discontinued because of an AE that was not treatment-emergent (Subject 202-046 had an event of nausea that started before dosing and led to discontinuation during the double-blind dosing phase). Overall, 19 subjects (5.8%) discontinued the study due to a TEAE. Safety reasons for discontinuation are discussed further in Section 7 of this review (Safety).

For the open-label safety population, treatment group assignment was based on what randomized subjects received during the blinded dosing period. Twelve of 146 subjects (8.2%) discontinued because of an AE; 3 subjects (3.9%) from the COV795 group and 9 subjects (13.0%) from the placebo group. One of the subjects (COV795 group) discontinued because of an AE that was not treatment-emergent (Subject 201-033 had an event of hypertension that started before dosing and the subject was discontinued during the OLE phase).

During the OLE phase the AEs that led to discontinuation in subjects from the COV795 group were: hypertension (Subject 201-033), nausea (Subject 201-076), and deep-vein thrombosis (Subject 201-127).

Overall, these findings show that more subjects discontinued in the placebo group due to lack of efficacy, as would be expected, and more subjects in the drug-treated group discontinued due AEs in the double-blind phase of the study. More subjects in placebo group discontinued due to AEs in the OL (13%) compared to drug treated (3.9%).

Specific reasons for early discontinuation for double-blind and open-label phases of the study are summarized below in Table 17.

Table 17. Reason for Early Discontinuation

	COV795 n (%)[a]	Placebo n (%)[a]	All Subjects n (%)[a]	*P* value[b]
Randomized	164	165	329	
Discontinuations prior to dosing	0	0	0	
Cohort 1	14	12	26	
Discontinuations prior to dosing	0	0	0	
Cohort 2	150	153	303	
Discontinuations prior to dosing	0	0	0	
Modified Intent-to-Treat	150	153	303	
Discontinuations during blinded dosing period	15 (10.0)	19 (12.4)	34 (11.2)	0.586
Lack of efficacy	7 (4.7)	15 (9.8)	22 (7.3)	
Adverse event	7 (4.7)	2 (1.3)	9 (3.0)	
Withdrawal by subject	1 (0.7)	2 (1.3)	3 (1.0)	
Combined cohort Modified Intent-to-Treat	164	165	329	
Discontinuations during blinded dosing period	15 (9.1)	21 (12.7)	36 (10.9)	0.378
Lack of efficacy	7 (4.3)	17 (10.3)	24 (7.3)	
Adverse event	7 (4.3)	2 (1.2)	9 (2.7)	
Withdrawal by subject	1 (0.6)	2 (1.2)	3 (0.9)	
Cohort 1	14	12	26	
Discontinuations during blinded dosing period	0	2 (16.7)	2 (7.7)	0.203
Lack of efficacy	0	2 (16.7)	2 (7.7)	
Blinded Safety Population	166	163	329	
Discontinuations during blinded dosing period	15 (9.0)	21 (12.9)	36 (10.9)	0.293
Lack of efficacy	7 (4.2)	17 (10.4)	24 (7.3)	
Adverse event[c]	7 (4.2)	2 (1.2)	9 (2.7)	
Withdrawal by subject	1 (0.6)	2 (1.2)	3 (0.9)	
Open-label Safety Population[d]	77	69	146	
Discontinuations during open-label dosing period	7 (9.1)	10 (14.5)	17 (11.6)	0.439
Lack of efficacy	0	0	0	
Adverse event[c]	3 (3.9)	9 (13.0)	12 (8.2)	
Withdrawal by subject	1 (1.3)	1 (1.4)	2 (1.4)	
Protocol violation	3 (3.9)	0	3 (2.1)	

Source: Table 14.1-3
[a] Percentages were based on the indicated population group size (*N*).
[b] *P* values were obtained from Fisher's exact test.
[c] Two subjects discontinued because of an AE that was not treatment-emergent. Subject 202-046 had an event of nausea that started before dosing and led to discontinuation during the double-blind dosing phase. Subject 201-033 had an event of hypertension that started before dosing and the subject was discontinued during the OLE phase.
[d] Treatment group assignment was based on what randomized subjects received during the blinded dosing period.

(Source: Applicant's table, CSR 0182, p. 61)

Protocol Deviations and Violations

The Applicant reported that major protocol deviations and violations recorded for the study included visit procedure deviations, noncompliance, drug compliance and dispensing deviations. Also, dosing errors, study and rescue medication noncompliance and incomplete return of study medication at study conclusion were listed.

Dosing Regimen Deviations/Violations: Most of the major protocol deviations or violations associated with dosing regimen occurred during the OLE phase of the study. Specifically, for the major protocol deviations and violations associated with the dosing regimen, there were five subjects during the blinded phase compared to 13 during the OLE phase. Of those five subjects, three were in the drug-treated group and two in placebo group. The type of protocol violation or deviation in the blinded phase group is shown below in Table 18.

None of these violations or deviations should have resulted in a major impact on the overall efficacy findings and results due to the small number of subjects involved.

Table 18. Major Protocol Deviations and Violations Associated with Dosing Regimen, Blinded Treatment Phase

Subject ID	Issue/Category[a]	Study Phase[b]/ Treatment[c]	Issue Description
201120	Deviation/ Other	Blinded/ COV795	Subject was randomized and assigned kit #70468 (Placebo) at Visit 4 (20 Jun 2012). The site staff dispensed/administered kit #70648 (COV795) in error.
203015	Violation/ Other	Blinded/ Placebo	Rescue medication was administered from an incorrect rescue medication bottle at the treatment site at Visit 4 (19 Nov 2011). The site dispensed 2 doses (4 tablets) of rescue medication to Subject 203-015 from the bottle that was assigned to Subject 203-006. The site created a Corrective Action Plan, which was immediately implemented. Subject 203-006 study drug was dispensed properly.
203046	Deviation/ Noncompliance	Blinded/ COV795	Rescue medication was administered less than 4 hours (21:04; 31 Mar 2012, 2h after the second dose of study medication) after the previous dose of rescue medication (17:58) at Visit 4.
204098	Deviation/ Dosing	Blinded/ COV795	Subject was randomized and assigned kit #70221 (Placebo) at Visit 4 (19 Jun 2012). The site staff dispensed/administered kit #70201 (COV795) in error.
204142	Deviation/ Dosing	Blinded/ Placebo	Rescue medication doses were given less than 4 hours apart at Visit 4 (10:36 AM and 12:19 PM; on 31 Jul 2012).

(Source: CSR 1082, Applicant's table, modified by reviewer, p. 63)

a. Categories include discrepancy of dosing, noncompliance, and other.
b. Study Phase describe when the discrepancy occurred, either in the blinded phase or the open label extension (OLE) phase of treatment.
c. Treatment actually received: active (COV795), or placebo.
d. Order of presentation of data is first by the blinded phase, followed by the OLE phase, both in ascending order by site.

Missing Pain Scores or Pain Scores Recorded at the Incorrect Time

Although there were numerous protocol deviations for this outcome assessment in the blinded portion of the study, the fact that the deviations were fairly equally distributed between placebo (19) and drug-treated groups (15) most likely negates their impact between groups. There was only subject who experienced a protocol deviation for this category in the OLE portion of the study.

Compliance

Compliance was summarized separately for the blinded dosing phase and the OLE phase. For the blinded dosing phase, a subject was considered compliant if he or she

received between 80% to 120% of the expected number of doses. For the OLE phase, a subject was considered compliant if he or she returned between 80% to 120% of the pills expected to be taken based on medication dispensed and returned. Counts and percentages were displayed for compliance categories; percentages were based on the group sizes within each population.

Fisher's exact test was used to compare proportions of compliant subjects between treatment groups.

The Applicant reported that during the blinded dosing period, 297 of 303 subjects (98.0%) in the mITT population received 100% of expected doses, and 6 subjects (2.0%) received < 80% of expected doses.

During the open-label dosing period, 57 of 146 subjects (39.0%) received 100% of expected doses, and 20 subjects (13.7%) received < 80% of expected doses.

The low percentage of subjects who were compliant during the OL dosing period is concerning, but would not have affected the blinded efficacy outcome which is the basis for efficacy determination.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable was SPID48 based on 0 to 10 NPRS pain intensity score at each time point. The MI results for SPID 48 with 6-hour censoring for rescue medication use in the mITT population are shown below in Table 19.

Primary Efficacy Findings
According to the Applicant, subjects treated with COV795 had less pain than the placebo-treated subjects. The $SPID_{48}$ was greater in the COV795 group than placebo with the MI mean $SPID_{48}$ of 114.9 for study drug and 66.9 for placebo. The treatment difference in MI mean $SPID_{48}$ values (48.0) was statistically significant ($p<0.001$), as shown below in Table 19.

Table 19. Primary Analysis - 6 Hour Rescue Medication Use Censoring (mITT Population)

Statistic (number of imputations = 50)	COV795 (N = 150)	Placebo (N = 153)	95% Confidence Interval	*P* value[a]
MI Mean $SPID_{48}$ (SE)[b]	114.9 (7.64)	66.9 (7.60)		
MI Mean $SPID_{48}$ Treatment Difference (SE)[c]	48.0 (10.54)		27.3 to 68.6	< 0.001

Source: Table 14.2-2.1
n = number of subjects with data available; SE = standard error.
[a] The *P* values were generated from SAS MI Analyze Procedure using the analyst model with $SPID_{48}$ as the dependent variable and baseline pain intensity score as covariate with factors for treatment, site, and treatment-by-site interaction.
[b] Mean $SPID_{48}$ generated from the MI analyst model described in footnote a.
[c] Mean $SPID_{48}$ treatment differences (COV795 – placebo) from the MI analyst model described in footnote a.

(Source: Sponsor's table, Study Report , p. 76)

The analysis of the primary endpoint with regard to missing data is summarized below:

> According to the Applicant: "For the efficacy analyses, the primary analysis was conducted on Cohort 2, and a limited number of efficacy analyses were performed on the overall population (combined cohorts).
>
> The combining process consisted of assigning Cohort 1 data to match up with the time points for Cohort 2. Since the primary efficacy measure started with the first dose for both cohorts, the timing difference of the second dose greatly impacted the alignment of efficacy assessments when the cohorts were combined. Additionally, the number of doses a subject received for a given efficacy assessment varied between subjects. The misalignment of efficacy measures and the varying amounts of drug exposure for a given assessment made combining both cohorts for the efficacy analysis problematic and difficult to interpret, and thus the primary analysis population included only Cohort 2. The Applicant determined that the number of subjects in Cohort 1 was not sufficient to perform efficacy analyses on this cohort alone.
>
> The primary efficacy analysis was changed with Amendment 4 of the protocol. Originally, all planned pain intensity scores collected after the first use of rescue medication were to be censored (i.e., missing) and their PIDs estimated using multiple imputation (MI) techniques. However, preliminary blinded safety data showed that a large proportion of subjects used rescue medication at least once, resulting in too many censored PIDs. To reduce the confounding effects of rescue medication use and the incidence of censored scores (unusable pain scores), the primary analysis was modified to use 6-hour censoring for rescue medication use as described below. Also, the initial MI step was performed

> separately on the PIDs of the subjects who took rescue medication and those who did not. This modification to the primary analysis was agreed upon with the FDA prior to the database lock.
>
> The primary efficacy analysis used the modified intent-to-treat (mITT) population. Any pain intensity score that was not collected because a subject withdrew before the planned 48-hour blinded dosing period time point was classified as monotonic missing. Any planned pain intensity score within 6 hours following rescue dosing that was not replaced by the rescue medication pain score was censored (ie, the value was not used in the analysis). The PIDs were calculated for all nonmissing/noncensored pain scores for each planned time point as defined in Amendment 2."

According to the Applicant, since most missing values resulted from the use of rescue medication, the similarity of results across imputation techniques indicates that the use of rescue medication did not appreciably affect the findings.

Refer to Dr. Li Feng's Agency statistical review for further discussion of the analysis of the primary endpoint.

Sensitivity Analyses: The Applicant reported that the SPID48 cofactors' sensitivity analyses support the primary analyses.

The Applicant maintains that since most missing values resulted from the use of rescue medication, the similarity of results across imputation techniques indicates that the use of rescue medication did not appreciably affect the findings. They further state that in addition, the homogeneity of results across study sites and baseline pain severity was indicated by the lack of statistically significant interactions of these factors with treatment.

The Applicant found that least squares mean SPID48 treatment difference was statistically significantly greater ($P < 0.001$) for COV795 compared with placebo for all sensitivity analyses populations (i.e., combined cohort mITT population, mITT population with 8-hour rescue medication censoring, mITT population including scores after rescue medication use, and mITT population with last observation carried forward/baseline observation carried forward imputation).

The frequency of missing and censored pain relief scores within 6 hours after rescue medication use in the mITT population was analyzed by the Applicant. For each time point, the following data were presented: intermittent missing, monotonic missing due to AE, monotonic missing due to lack of efficacy, monotonic missing due to other, and censored due to rescue medication use. The Applicant reported that, in general, the frequency of intermittent missing, monotonic missing due to an AE, monotonic missing due to lack of efficacy, and monotonic missing due to other reason was low (< 10%) for both treatment groups at each time point. For the duration of the double-blind phase,

there were no censored pain scores due to rescue medication in either treatment group for the first 1.5 hours and with the exception of Hour 14, the frequency of censored pain scores due to rescue medication was lower for the COV795 group than the placebo group. At Hour 14, the frequency of censored pain scores due to rescue medication use was 54 (36.0%) for the COV795 group and 51 (33.3%) for the placebo group. The summed PI over the first 48 hours is shown below in Table 20.

Table 20. Summed Pain Intensity over First 48 Hours

Sensitivity Analysis (Number of imputations = 50) Statistic	COV795 (N = 150)	Placebo (N = 153)	95% Confidence Interval	*P* value[a]
Combined Cohort mITT population and 6-hour RM censoring				
MI Mean $SPID_{48}$ (SE)[b]	113.5 (7.35)	64.0 (7.40)		
MI Mean $SPID_{48}$ Treatment Difference (SE)[c]	49.4 (10.31)		29.2 to 69.6	< 0.001
mITT population and 8-hour RM censoring				
MI Mean $SPID_{48}$ (SE)[b]	111.2 (7.65)	60.4 (7.74)		
MI Mean $SPID_{48}$ Treatment Difference (SE)[c]	50.8 (10.49)		30.2 to 71.3	< 0.001
mITT population and including Post-RM Pain Scores				
MI Mean $SPID_{48}$ (SE)[b]	119.3 (7.46)	76.0 (7.49)		
MI Mean $SPID_{48}$ Treatment Difference (SE)[c]	43.4 (10.36)		23.1 to 63.7	< 0.001

Source: Table 14.2-2.3
RM = rescue medication; SE = standard error.
[a] The *P* values generated from the SAS MIXED procedure and combined using the MI Analyze procedure using the analyst model with $SPID_{48}$ as the dependent variable and baseline pain intensity score as covariate with factors for treatment, site and treatment-by-site interaction.
[b] Least squares means and standard errors obtained from SAS PROC MIXED from all 50 imputations and combined estimates from SAS PROC MIANALYZE.
[c] Differences (COV795 – placebo) in least squares means, standard errors, and confidence intervals obtained from SAS PROC MIXED from all 50 imputations and combined estimates from SAS PROC MIANALYZE.

(Source: Applicant's table, Study Report, p. 77).

6.1.5 Analysis of Secondary Endpoints(s)

Time-to-event statistics for time to onset of perceptible, meaningful, and confirmed perceptible pain relief; time to peak PID; and time to first use of rescue medication were estimated using the Kaplan-Meier method, and group comparisons were analyzed using the log-rank test. For time to onset of pain relief statistics, the number and percentage of subjects censored due to use of rescue medication and due to the 4-hour limit were presented. For time to peak PID, data were analyzed within the first 12 hours. This analysis was done both with and without censoring of PID values after the first use of rescue medication.

Descriptive statistics and plots by treatment were presented for pain intensity scores and pain intensity differences, the number and percentage of responders at various time

points, the number and percentage of subjects using rescue medication for each dosing interval, and global assessment of subject satisfaction at 48 hours and during the OLE phase.

For the percentage of responders, proportions were analyzed using the Cochran-Mantel-Haenszel (CMH) test with study site as the stratification variable. Data for this assessment did not use imputed values and were observed cases only. Summed pain intensity difference over 0 to 4, 0 to 12, 0 to 24, and 0 to 36 hours was analyzed using the same MI methodology as for the primary endpoint.

Mean dosing (rescue) interval between sequential doses was displayed by treatment. The overall interval between the first and last doses was also assessed. One mean value was calculated per subject for all doses, and overall descriptive statistics are provided by treatment. Data were inferentially assessed using analysis of variance (ANOVA) with treatment, site, and treatment-by-site interaction as factors. Only observed cases were used for this analysis.

The proportion of subjects using at least one dose of rescue medication was inferentially assessed using CMH statistics, stratifying by study site.

Secondary Endpoints Results

Applicant's proposed labeling claim: (b) (4)

Because there was no correction for multiple endpoints, the results of the secondary endpoint analyses and associated p-values are descriptive. Table 21, below, summarizes the key findings of the secondary endpoints.

Table 21. Secondary Endpoints Key Findings Study 0182

Pain Relief
Confirmed Perceptible Pain Relief (PPR) • More subjects in study drug group (86 of 150 [57%] than placebo group (57 of 153 [33%]) experienced confirmed perceptible PR. • The study drug group median time was shorter (47.95 minutes) compared with placebo group median time, which could not be estimated due to less than half of the subjects having confirmed PPR. The difference in time to confirmed PPR resulted in $p<0.001$
Perceptible Pain Relief (PPR) • More subjects in the COV795 treatment group (122 of 150; 81.3%) than in the placebo group (94 of 153; 61.4%) had perceptible pain relief following the first dose of study drug. • The median time subjects reached perceptible pain relief were 33.56 minutes and

43.63 minutes for COV795 and placebo groups, respectively, with P=0.002

Meaningful Pain Relief (MPR)

• More subjects in the COV795 group (86 of 150; 57.3%) than the placebo group (50 of 153; 32.7%) experienced meaningful pain relief after the first dose of study drug.
• Median time to meaningful pain relief was 92.25 minutes for COV795, while a value could not be estimated for the placebo group due to less than half the subjects experiencing meaningful pain relief with P<0.001.

Applicant's Overall Summary Pain Relief

• Twice as many scores were censored due to rescue medication use for subjects taking placebo as for COV795. Onset of pain relief for COV795 occurred within 1 hour of administration as demonstrated by the times to perceptible pain relief (33.56 minutes, P=0.002) and confirmed perceptible pain relief (47.95 minutes, P<0.001) compared to placebo.
• Statistically significantly more subjects in the COV795 treatment group than in the placebo group had perceptible (81.3% vs 61.4%), meaningful (57.3% vs 32.7%), and confirmed perceptible (52.3% vs 32.6%) pain relief following the first dose of study drug.

Time to Peak PID and Mean Max PID

Mean PID over Time

•The separation in PIDs between the groups was seen from the first dose and sustained throughout the 48-hour blinded dosing period, with COV795 mean PIDs remaining greater than placebo over the entire dosing interval.
•Mean PIDs increased in both treatment groups for approximately 2 hours (after the first dose), and up to 4 hours with each subsequent dose of COV795, the point at which the maximum mean PID was observed.
• After the first dose, at the earliest time point (15 min) and at each time point thereafter in the blinded evaluation period, the mean PID for COV795 was numerically superior to placebo; this difference became statistically significant at 30 minutes after the first dose.

SPID

•The mean change in $SPID_{0-4}$ for the COV795 group was greater than the placebo group, 8.1 versus 1.7, respectively, with a treatment difference of 6.5 ($P < 0.001$).
•The mean $SPID_{0-12}$ was greater in the COV795 group compared to the placebo group (15.5 vs 2.5, respectively) indicating a continuation of pain reduction over the first 12-hour dosing interval (treatment difference 13.0, $P < 0.001$).
• A consistent and comparable improvement in pain reduction was observed with subsequent doses of COV795 compared to placebo, as illustrated by the cumulative improvement in pain (i.e., $SPID_{0-24}$ [treatment difference 27.7, $P < 0.001$] and $SPID_{0-36}$ [treatment difference 39.7; $P < 0.001$]).
•The MI means were statistically significantly higher for COV795 compared with placebo at every SPID interval (all $P < 0.001$). These findings are summarized in the following table:

Summed PID Over 0-4, 0-12, 0-24, and 0-36 Hrs, Secondary Analyses Using MI Primary Analysis Methods, 6-hour Rescue Medication Use Censoring (mITT

Population)

SPID Interval	Statistic[a] (Number of Imputations = 50)	COV795 (N = 150)	Placebo (N = 153)	95% Confidence Interval	*P* value
0-4 hours	MI Mean (SE)	8.1 (0.76)	1.7 (0.78)		
	MI Mean Treatment Difference (SE)	6.5 (1.08)		4.4 to 8.6	< 0.001
0-12 hours	MI Mean (SE)	15.5 (1.94)	2.5 (1.90)		
	MI Mean Treatment Difference (SE)	13.0 (2.70)		7.7 to 18.2	< 0.001
0-24 hours	MI Mean (SE)	41.0 (3.86)	13.2 (3.83)		
	MI Mean Treatment Difference (SE)	27.7 (5.37)		17.2 to 38.2	< 0.001
0-36 hours	MI Mean (SE)	76.0 (5.75)	36.2 (5.76)		
	MI Mean Treatment Difference (SE)	39.7 (7.96)		24.1 to 55.3	< 0.001

Source: Table 14.2-3.1
SE = standard error.
[a] Multiple imputation mean, mean treatment differences, 95% confidence interval, and *P* values were generated from SAS MI Analyze Procedure using the analyst model with the indicated SPID ($SPID_{0-4}$, $SPID_{0-12}$,$SPID_{0-24}$, or $SPID_{0-36}$) as the dependent variable and baseline pain intensity score as covariate with factors for treatment, site and treatment-by-site interaction.

The MI means were statistically significantly higher for COV795 compared to placebo at every SPID dosing interval (all p<0.05), shown below.

SPID Interval	Statistic[a] (Number of Imputations = 50)	COV795 (N = 150)	Placebo (N = 153)	95% Confidence Interval	*P* Value
12 to 24 h	MI Mean (SE)	25.5 (2.37)	10.7 (2.50)		
	MI Mean Treatment Difference (SE)	14.8 (3.32)		8.3 to 21.3	< 0.0001
24 to 36 h	MI Mean (SE)	35.0 (2.32)	23.0 (2.37)		
	MI Mean Treatment Difference (SE)	12.0 (3.18)		5.8 to 18.3	0.0002
36 to 48 h	MI Mean (SE)	38.9 (2.40)	30.7 (2.33)		
	MI Mean Treatment Difference (SE)	8.3 (3.28)		1.8 to 14.7	0.0118

Source: Table 14.2-3.3
SE = standard error.
[a] Multiple imputation mean, mean treatment difference, 95% confidence interval, and *P* values were generated from SAS MI Analyze Procedure using the analyst model with the indicated SPID ($SPID_{12-24}$, $SPID_{24-36}$, or $SPID_{36-48}$) as the dependent variable and baseline pain intensity score as covariate with factors for treatment, site and treatment-by-site interaction.

Applicant's Overall Summary PID

• COV795 demonstrated a rapid and greater magnitude of increased PIDs after each dose of study drug. The separation in PIDs between the groups was seen within 30 minutes of the first dose and sustained throughout the 48-hour blinded dosing period, as illustrated graphically by PID over time, $SPID_{0-4}$, $SPID_{0-12}$, cumulative SPID, and SPID assessed Q12h.
• Maximum PID was considerably greater in the COV795 group compared to placebo (3.3 vs 1.6 after the first dose, $P < 0.0001$). The mean treatment difference in maximum observed PID was also significantly different for the 12 to 24, 24 to 36, and 36 to 48-hour dosing intervals ($P < 0.0001$, $P < 0.0001$, and $P = 0.0006$, respectively), suggesting COV795 provides a consistent magnitude of analgesia after each dose.

Total Pain Relief Over Time (TOTPAR)

The MI mean TOTPAR48 was 91.3 for COV795 and 70.9 for placebo. The mean TOTPAR48 treatment difference was 20.5, with a p<0.001. The TOTPAR over 0 to

4, 0-12, 0-24, and 0-36 hours using primary analysis imputation methods with censoring of 6-hour rescue medication use in the mITT population is shown below.

TOTPAR Interval	Statistic[a] (Number of Imputations = 50)	COV795 (N = 150)	Placebo (N = 153)	95% Confidence Interval	*P* value
0-4 hours	MI Mean (SE)	6.8 (0.36)	3.4 (0.36)		
	MI Mean Treatment Difference (SE)	3.4 (0.51)		2.4 to 4.4	< 0.001
0-12 hours	MI Mean (SE)	16.5 (0.87)	11.2 (0.84)		
	MI Mean Treatment Difference (SE)	5.3 (1.21)		2.9 to 7.7	< 0.001
0-24 hours	MI Mean (SE)	38.4 (1.67)	26.8 (1.62)		
	MI Mean Treatment Difference (SE)	11.6 (2.32)		7.1 to 16.2	< 0.001
0-36 hours	MI Mean (SE)	64.2 (2.54)	47.5 (2.50)		
	MI Mean Treatment Difference (SE)	16.8 (3.56)		9.8 to 23.8	< 0.001

Source: Table 14.2-7.1
SE = standard error.
[a] Multiple imputation mean, mean treatment differences, 95% confidence interval, and *P* values were generated from SAS MI Analyze Procedure using the analyst model with the indicated SPID ($SPID_{0-4}$, $SPID_{0-12}$,$SPID_{0-24}$, or $SPID_{0-36}$) as the dependent variable and baseline pain intensity score as covariate with factors for treatment, site and treatment-by-site interaction.

The cofactors for secondary analyses using primary analysis imputation methods with censoring of 6-hour rescue medication use in the mITT population is shown in the table below.

TOTPAR Over 12 to 24, 24 to 36 and 36 to 48 Hours Secondary Analyses Using Primary Analysis Imputation Methods, 6-hour Rescue Medication Use Censoring (mITT Population)

TOTPAR Interval	Statistic[a] (Number of Imputations = 50)	COV795 (N = 150)	Placebo (N = 153)	95% Confidence Interval	*P* Value
12 to 24 h	MI Mean (SE)	21.9 (1.06)	15.6 (1.04)		
	MI Mean Treatment Difference (SE)	6.3 (1.47)		3.4 to 9.2	< 0.0001
24 to 36 h	MI Mean (SE)	25.8 (1.12)	20.7 (1.12)		
	MI Mean Treatment Difference (SE)	5.2 (1.56)		2.1 to 8.2	0.0009
36 to 48 h	MI Mean (SE)	27.1 (1.20)	23.4 (1.18)		
	MI Mean Treatment Difference (SE)	3.7 (1.68)		0.4 to 7.0	0.0276

Source: Table 14.2-7.3
[a]Multiple imputation mean, mean treatment difference, 95% confidence interval, and *P* values were generated from SAS MI Analyze Procedure using the analyst model with the indicated TOTPAR ($TOTPAR_{12-24}$, $TOTPAR_{24-36}$, or $TOTPAR_{36-48}$) as the dependent variable and baseline pain intensity score as covariate with factors for treatment, site, and treatment-by-site interaction.

Applicant's Overall Summary TOTPAR

• The mean TOTPAR was greater in the COV795 group compared to the placebo group for each dosing interval, with the mean treatment difference of COV795 statistically significantly greater than placebo (12 to 24, 24 to 36, and 36 to 48 hours; $P < 0.03$).
• Mean TOTPAR48 was 91.3 for COV795 and 70.9 for placebo, with a treatment

difference of 20.5, which was statistically significant ($P < 0.001$). These findings indicate the pain relief in the COV795 analgesic group was greater than the placebo group over the 48-hour blinded dosing period.
• An early improvement in pain relief was observed with COV795 treatment compared with placebo as shown by the mean TOTPAR0-4 (6.8 for COV795 versus 3.4 for placebo; treatment difference of 3.4, $P < 0.001$).

Responder Analysis

• The Applicant states that a reduction of approximately 30% in the NPRS (PID) is a clinically important difference. From 30 minutes following the first dose through the end of the blinded evaluation period, more COV795 subjects than placebo subjects at every time point had a reduction in their pain intensity score of ≥30% with no prior use of rescue medication.
• A similar trend was seen when subjects were eligible to be included as responders regardless of rescue medication though the differences were not statistically significant at 24, 36 and 48 hour time points. The Applicant maintains that lack of statistically significant difference was due in part to a "significant" placebo response.
• Similar results to the 30% responder analysis were seen when responders were defined as those that had a 50% reduction in pain intensity score. From 30 minutes following the first dose through the end of the blinded evaluation period, significantly more COV795 subjects than placebo subjects at nearly every time point (with exceptions for the re-dosing time points of 12 hours, 24 hours, 36 hours, and 48 hours) had a reduction in their pain intensity score of ≥ 50%

Applicant's Overall Summary Responder Analysis

• From 30 minutes through the end of the blinded dosing period, statistically significantly more COV795 subjects than placebo subjects obtained a ≥ 30% reduction in pain intensity. Similar trends were observed when responder analyses were conducted with various pain intensity thresholds (i.e., 50% reduction in pain intensity) and with allowance for rescue medication usage.

Rescue Medication

Amount of Rescue Medication

• The mean number of rescue medication administrations was less in the COV795 group compared to the placebo group after the first dose, subsequent doses, and overall (2.91 vs 4.64, respectively, $P < 0.0001$).
• Rescue medication usage was greatest within the first dosing interval (0 to 12 hours) for both COV795 and placebo (79.7% and 96.7%; $P < 0.0001$). However, 61 of 118 COV795 subjects (51.7%) took 1 rescue medication while 94 of 146 placebo subjects (64.4%) took 2 or more rescue medications during first dosing period. These findings are summarized in the table below.

Percentage of Subjects Using Rescue Medication (mITT Population)

Subject Used Rescue Medication During Dosing Interval Category	COV795 (N = 150)[a] n (%)	Placebo (N = 153)[a] n (%)	*P* Value[b]
Subject Used at Least One Dose of Rescue Medication[c]			< 0.0001
Yes	127 (85.8)	150 (99.3)	
No	21 (14.2)	1 (0.7)	
Between Doses 1 to 2			< 0.0001
Yes	118 (79.7)	146 (96.7)	
No	30 (20.3)	5 (3.3)	
Between Doses 2 to 3			< 0.0001
Yes	69 (48.9)	119 (83.8)	
No	72 (51.1)	23 (16.2)	
Between Doses 3 to 4			< 0.0001
Yes	62 (45.9)	102 (75.6)	
No	73 (54.1)	33 (24.4)	
Between Dose 4 to End of Period			0.0006
Yes	53 (39.3)	79 (59.0)	
No	82 (60.7)	55 (41.0)	

Source: Table 14.2-13.1
[a] The number of subjects who entered the indicated time interval. Subjects who discontinued in a given interval and did not receive any rescue medication prior to their discontinuation were also not included in that interval.
[b] The *P* values for comparing active and placebo groups were obtained from the Cochran-Mantel-Haenszel general association test with the study site as the stratification variable.
[c] A subject who received at least 1 dose of rescue medication during the blinded dosing phase of the study was classified as having received rescue medication.

Time to 1st Rescue Medication Usage and Rescue Intervals

•The Kaplan-Meier estimate for the median time to first rescue medication use was significantly longer (5.80 hours) for subjects taking COV795 than for subjects taking placebo (2.16 hours, $P < 0.001$).

• The rescue interval was defined as the time from the dose of study drug to the first rescue medication use during the interval or the next dose, whichever came first. The mean rescue intervals for COV795 were significantly greater than placebo for each of the dosing intervals ($P < 0.0001$) over the 48-hour blinded dosing period. A lengthening of time of rescue was observed with each subsequent dose. The median rescue interval for the COV795 group was 5.8 hours between 0 and 12 hours, and increased to 12.0 hours for each subsequent COV795 dosing interval.

• Subjects achieving meaningful pain relief had longer rescue intervals than those not achieving meaningful pain relief; regardless of pain relief status, the mean rescue intervals for COV795 were significantly greater than placebo for each of the 4 dose intervals. Among subjects achieving meaningful pain relief, the median dose interval was 7.83 hours following the initial dose and 12.0 hours for each subsequent interval.

Applicant's Overall Summary Rescue Medication Use

• The mean interval between dosing and rescue medication lengthened from the first dose to subsequent doses over the 48-hour blinded dosing period, which the Applicant says is due to the natural diminishment of pain over time after surgery.

• After the first dosing interval, the median interval of rescue medication use lengthened to 12 hours in the COV795 group indicating that a 12-hour dosing interval is appropriate.

• A statistically significantly smaller proportion of subjects in the COV795 group compared with the placebo group used rescue medication after the first dose, subsequent doses, and overall during the 48-hour blinded dosing period.

•The mean number of rescue medication administrations was statistically

significantly less in the COV795 group compared with the placebo group after the first dose, subsequent doses, and overall (2.91 vs 4.64, *P* < 0.0001). • Median time to first rescue medication use was statistically significantly longer (5.80 hours) for subjects taking COV795 than for subjects taking placebo (2.16 hours, *P* < 0.001). • Both the mean and the median rescue intervals for COV795 were statistically significantly greater than placebo for each of the dosing intervals (*P* < 0.0001) over the 48-hour blinded dosing period.
Global Satisfaction
Applicant's Summary Global Assessment of Subject Satisfaction • Global satisfaction measured by the 'Level of Pain Relief by Pain Medicine' was better in the COV795 group compared to the placebo group. A statistically significantly greater number of subjects were either 'very satisfied' or 'satisfied' with their analgesic therapy ('Level of Pain Relief by Pain Medication'; 68.9% for COV795 versus 41.5% for placebo, *P* < 0.001). Greater percentages of subjects in the COV795 group compared to the placebo group were either 'very satisfied' or 'satisfied' with the 'Time Taken for Pain Medication to Work' (66.7% vs 26.7%, *P* < 0.001).

(Table, reviewer)

6.1.6 Other Endpoints

The efficacy endpoint for the OLE phase was global assessment of subject satisfaction with study drug.

According to the Applicant, during the open-label dosing period, the majority of subjects were 'very satisfied' or 'satisfied' at all visits with all of the global assessment questions. Subjects from both the COV795 and placebo groups reported achieving greater than an 80% very satisfied or satisfied response to the 'Level of Pain Relief by Pain Medication' at the last 2 visits of the study while receiving COV795 in the open-label extension.

6.1.7 Subpopulations

An efficacy subset was initially not included in the submission. However, in response to an Information Request from the Agency's statistical review team, the Applicant submitted subgroup analyses information for gender, age and race which Dr. Feng Li analyzed and found "that the findings from the subgroups' summaries were consistent with those observed in the overall population. COV795 was numerically better than placebo in all of the subpopulations." Refer to Dr. Li's statistical review for further discussion.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant states that there were three basic analyses used to support the proposed dosing:

1. Mean treatment difference in maximum observed PID
2. Responder analyses
3. Evaluation of response over time graphs

The Applicant's summary of these analyses are shown in Table 22.

Table 22. Summary of Results from Study 0182 Used to Verify Recommended Dosing Schedule

Endpoint Description	Results
Median time to rescue medication, 0-12 hours	5.8 hours
Median time to rescue medication, 12-24 hours	12.0 hours
Median time to rescue medication, 24-36 hours	12.0 hours
Median time to rescue medication, 36-48 hours	12.0 hours
Responder Analyses: COV795 > PBO (end of every dosing interval)	12 hours
Mean PID > 0, at each COV795 dose	> 12 hours

NDA Section 5.3.5.1, CSR Study 0182, Section 14, Table 14.2-13.3, Table 14.2-12.1, and Table 14.2-4.13.

(Source: Applicant's table, Summary Clinical Efficacy, p. 24)

The Applicant maintains that both the mean and the median rescue intervals for COV795 were significantly greater than placebo for each of the dosing intervals ($p<0.0001$) over the 48-hour blinded dosing period. After the first dosing interval, the median interval of rescue medication use lengthened to 12 hours for each subsequent interval in the COV795 group, indicating that a 12-hour dosing interval is appropriate. Among subjects achieving meaningful pain relief, the median dose interval was 7.83 hours following the initial dose and 12.0 hours for each subsequent interval. Rescue intervals are shown in Table 23, below.

Table 23. Rescue Intervals (mITT Population)

Dosing Interval (Hours)[a]	COV795 (N = 150)[b] n (%)	Placebo (N = 153)[b] n (%)	*P* value[c]
Between 0 and 12 hour Doses			
N	148	151	< 0.0001
Mean (SD)	6.19 (3.92)	3.35 (2.76)	
Median	5.75	2.15	
Q1, Q3	2.2, 9.8	1.4, 4.2	
Minimum, Maximum	1.1, 12.1	1.1, 12.0	
Between 12 and 24 hour Doses			
N	141	142	< 0.0001
Mean (SD)	8.61 (4.03)	4.81 (3.89)	
Median	12.0	2.99	
Q1, Q3	4.5, 12.0	1.8, 8.1	
Minimum, Maximum	0.8, 12.1	1.0, 12.1	
Between 24 and 36 hour Doses			
N	135	135	< 0.0001
Mean (SD)	9.43 (3.39)	6.29 (3.93)	
Median	12.0	5.12	
Q1, Q3	7.2, 12.0	2.7, 10.5	
Minimum, Maximum	0.5, 12.1	0.3, 12.1	
Between 36 and 48 hour Doses			
N	135	134	< 0.0001
Mean (SD)	9.61 (3.78)	7.27 (4.52)	
Median	12.0	7.85	
Q1, Q3	8.1, 12.0	2.3, 12.0	
Minimum, Maximum	0.7, 12.0	0.8, 12.0	
Average Dosing interval[d]			
N	148	151	< 0.0001
Mean (SD)	8.21 (3.10)	5.18 (2.68)	
Median	8.88	4.83	
Q1, Q3	5.6, 10.9	2.8, 7.2	
Minimum, Maximum	1.1, 12.0	1.1, 12.0	

Source: Table 14.2-13.3
Q = quartile.
[a] Rescue interval was defined as the time from the dose of study drug to the first rescue medication use during the interval or the next dose, whichever came first. For the last interval, the rescue interval was the time from the last dose in the blinded dosing period to first rescue medication or 12 hours post-dose. Subjects who discontinued early and did not receive any rescue medication within a given interval were not included in that interval.
[b] Summary was by randomized treatment during the blinded dosing period. Subjects 201-120 and 204-098 were randomized to placebo, but actually received COV795.
[c] *P* value was based on a ranked ANOVA with treatment as the main effect.
[d] For each subject, overall dosing interval was taken as the mean of the nonmissing dosing intervals.

(Applicant's table, Study 0182 CSR, p. 93)

The Applicant further states that COV795 is designed to reach therapeutic levels of both opioid and non-opioid APIs within one hour through the IR layer component, with sustained analgesia over the dosing interval (12 hours) due to the ER layer component.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and/or tolerance effects is not applicable, as the proposed indication is management of (b) (4) acute pain. The Applicant anticipates that the maximum intended duration of use would be 30 days. Relying upon 505(b)(2) previous findings regarding the safety and efficacy of the listed drugs, Roxicodone and

Ultracet for long-term efficacy and tolerance, long term safety and efficacy studies were not included in the COV795 development program.

6.1.10 Additional Efficacy Issues/Analyses

Refer to Dr. Feng Li's Agency statistical review.

7 Review of Safety

Safety Summary

Review of the Applicant's safety findings revealed that there were no deaths in the Phase 3 controlled study 0182. The two deaths which occurred in the Phase 3 open-label study 0181 appeared unlikely to be definitively related to study drug alone. There were six subjects who experienced SAEs in the Phase 3 studies (five study-drug treated and one placebo). These SAEs showed no patterns that were clinically meaningful. The common AEs in the drug-treated subjects were generally of mild to moderate severity and were consistent with expected opioid AEs related to GI (nausea and vomiting) and nervous system (dizziness and headache).

Specific hepatic safety analyses did not identify a definite hepatic safety signal. Although there were subjects with transient elevated serum transaminases, no Hy's Law cases were identified. One subject experienced elevated bilirubin (<2xULN) associated with elevated transaminases, however, the narrative for this case revealed that the subject had a medical history of cholelithiasis and prior cholecystectomy.

Overall, I am in agreement with the Applicant's review of the safety findings that the AEs seen in the safety population were generally consistent with those of the known safety profile of the listed drugs of Roxicodone and Ultracet.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant was advised by the Division that in the integrated safety analyses, the focus should be on the clinical studies that used the intended commercial dose regimen of 15mg OC/650mg APAP every 12 hours.

As noted in Section 5 of this review, the clinical development program consisted of 12 Phase 1 studies and two Phase 3 studies. Of these studies, the integrated safety database includes eight Phase 1 studies and two Phase 3 studies, with a total of 1,045 subjects. The safety database includes 834 subjects that received COV795 using the

intended commercial to-be-marketed dose regimen (15mg OC/650mg APAP every 12 hours) and includes all subjects that were treated with the LDs Roxicodone and Ultracet. The integrated safety database *did not* include subjects who received noncommercial dosage strengths (i.e., one COV795 tablet 7.5mg OC/325mg APAP every 12 hours).

According to the Applicant, within the 10 clinical studies that comprise the integrated safety database, there were eight subjects that did not receive the intended commercial dosage regimen (four subjects in Phase 1 studies and four subjects in Phase 3 studies who received only one COV795 tablet) and thus were excluded from the integrated database.

The primary sources for the safety review were the following:

- All relevant sections of the Applicant's NDA submission
- Integrated Summary of Safety (ISS)
- Relevant final study reports and study synopses
- Pertinent narratives and line listings from individual studies not included in the integrated safety database as well as those included in the integrated safety data
- Approved labels of listed drugs, Ultracet (NDA 21-123 approved August 15, 2001) and Roxicodone ((NDA 021-011, Oxycodone, approved August 31, 2000)
- Approved label of Ofirmev (IV acetaminophen; NDA 22450 approved November 2, 2010).
- Applicant's proposed label
- Literature

7.1.2 Categorization of Adverse Events

An AE was defined by the Applicant as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which did not necessarily have a causal relationship with this treatment.

An SAE was defined as any untoward medical occurrence that at any dose resulted in any of the following outcomes: Death, life-threatening AE; inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that did not result in death, were not life-threatening, and that did not require hospitalization may have been considered serious when, based upon appropriate medical judgment, they jeopardized the patient or subject and required medical or surgical intervention to prevent 1 of the outcomes listed above.

Certain events, although not considered an SAE, must have been recorded, reported, and followed up as indicated for an SAE. This included pregnancy exposure to an investigational product.

Adverse events and SAEs were collected from the signing of informed consent through the end of study. The investigator evaluated all AEs for relationship to study medication using the following classifications: not related, unlikely related, possibly related, and related. Severity was classified as mild, moderate, or severe.

In the ISS, detailed TEAE analyses (such as most common TEAEs; TEAEs by total daily oxycodone dose, age, race; TEAs by severity; related TEAEs) were only presented for the two most similar integration sets (i.e., Phase 3 and Phase 1).

The Applicant's definitions and criteria of AEs appear acceptable.

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

Of the 14 studies conducted, the integrated safety database included a total of ten studies with 834 subjects who received COV795 at the intended commercial dose: eight Phase 1 studies (five single dose and three multiple dose) and two Phase 3 studies.

Safety analyses were performed on five integration sets: Phase 1 and 3; Phase 3; Phase 1; Phase 1 Single Dose and Phase 1 Multiple Dose.

The Applicant's rationale for the pooling categories was acceptable, with the most informative pool being the Phase 3 integrated safety database, to provide a complete overview of the data, the disposition, demographic and baseline characteristics, extent of exposure, and treatment-emergent adverse events (TEAEs).

The integrated safety database integration sets are summarized by study design, as shown in Table 24, below:

Table 24. Summary of Study Designs for Integrated Safety Data Set

Study	Study Design
Phase 3	
COV15000182	Randomized, double-blind, placebo-controlled, parallel-group, postbunionectomy
COV15000181	Open-label safety, OA (knee or hip) and CLBP
Phase 1 – Single Dose	
COV01300042	Randomized, open-label, single-dose, 2-period, 2-sequence crossover, food effect
COV01300107	Randomized, open-label, single-dose, 3-period, 6-sequence crossover, bioavailability, fed conditions
COV15000170	Randomized, open-label, single-dose, 3-period crossover, bioavailability, fasted conditions
COV15000171	Randomized, open-label, single-dose, 3-period, 6-sequence crossover, food effect
COV15000256	Randomized, open-label, single-dose, 4-period crossover, bioavailability, fasted conditions, Roxicodone, Ultracet, and Percocet comparators
Phase 1 – Multiple Dose	
COV01300045	Randomized, open-label, multiple-dose, 3-period crossover, bioavailability, fed conditions
COV15000172	Randomized, open-label, multiple-dose, 3-period crossover, bioavailability, fasted conditions
COV15000255	Randomized, open-label, multiple-dose, 4-period crossover, bioavailability, Roxicodone, Ultracet, and Percocet comparators

Source: NDA Section 2.7.4.1.1.2, Table 2.7.4.1.1.2-1.

(Source: Applicant's table, Clinical Overview, p. 12)

Description of Studies

The studies used in the Integrated Safety Database are described below. The safety findings from these studies are described in the appropriate sections of the Safety review.

Description of Phase 3 Studies Included in the Integrated Safety Data

These studies have been described in detail in Section 6 (Efficacy) of this review and, therefore, are only briefly summarized here.

1) **Study 0182**: This was a multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 3 study followed by an open-label extension (OLE) phase to evaluate the efficacy and safety of the administration of multiple doses of COV795 in subjects who were undergoing simple (uncomplicated) unilateral bunionectomy. The blinded dosing phase of the study was designed to evaluate the safety and efficacy of COV795 versus placebo. Study subjects with acute postoperative pain of moderate to severe intensity following unilateral bunionectomy surgery were randomized and stayed at the study site for the duration of the 48-hour blinded dosing phase.

2) **Study 0181:** This was a multicenter, open-label, Phase 3 study designed to collect safety data on the short-term use of COV795 in populations who frequently use low-dose opioids for short periods of time, similar to the treatment of acute pain, and to

obtain supportive efficacy data. It was planned to enroll approximately 400 subjects who were transitioning from Step 1 of the World Health Organization (WHO) pain scale (nonsteroidal anti-inflammatory drugs [NSAIDs] and other non-opioid medications to control pain) to Step 2 of the WHO pain scale (needing to escalate to opioid combinations, lower dose opioids, etc., plus NSAIDs to control pain). Subjects were treated with 2 tablets of COV795 every 12h for up to 35 days. Enrollment was stopped when at least 250 subjects had completed 10 or more days of exposure at the COV795 dose of 2 tablets Q12h (15 mg OC/650 mg APAP Q12h).

Description of the Phase 1 Studies Included in the Integrated Safety Database
The studies are described below with the major safety findings from the studies discussed in the Phase 1 integrated safety findings sections of this review.

Phase 1 Single-Dose Studies
1) Study COV01300042 (Study 0042) was an open-label, randomized, two-period crossover study to evaluate the PK, bioavailability, and safety of COV795 (15 mg OC/650 mg APAP) in normal, healthy subjects under fed and fasted conditions. In each period, subjects received 1 COV795 tablet (15 mg OC/650 mg APAP) under fed (high-fat) or fasted conditions with a minimum 7-day interval between the start of each period. The study included a screening visit up to 30 days prior to Period 1 check-in and two 3-day confinement periods. The total study duration, including a follow-up period of up to 28 days for SAEs was approximately 10 weeks.

2) Study COV01300107 (Study 0107) was an open-label, randomized, single-dose, 3-period crossover study to evaluate the PK, bioavailability, and safety of COV795 (15 mg OC/650 mg APAP) compared to IR Percocet (7.5 mg OC/325 mg APAP) in normal, healthy subjects under fed conditions. In each study period, subjects received either 1 COV795 tablet (15 mg OC/650 mg APAP) or 2 COV795 tablets (30 mg OC/1,300 mg APAP) or 1 Percocet tablet (7.5 mg OC/325 mg APAP) every 6 hours (Q6h) for 2 doses, with a minimum 7-day interval between the start of each period. The study included a screening visit up to 30 days prior to Period 1 check-in and three 3-day confinement periods. The total study duration, including follow-up of up to 28 days for SAEs, was approximately 12 weeks.

3) Study COV15000170 (Study 0170) was an open-label, randomized, single-dose, 3-period crossover study to evaluate the PK, bioavailability, and safety of COV795 (7.5 mg OC/325 mg APAP) compared to IR Percocet (7.5 mg OC/325 mg APAP) in normal, healthy subjects under fasted conditions. In each study period, subjects received either 1 COV795 tablet (7.5 mg OC/325 mg APAP) or 2 COV795 tablets (15 mg OC/650 mg APAP) or 1 Percocet tablet (7.5 mg OC/325 mg APAP) given Q6h for 2 doses (for a total of 15 mg OC/650 mg APAP Q12h). An additional evaluation of 2 Percocet tablets (7.5 mg OC/325 mg APAP) given Q6h for 2 doses (for a total of 30 mg OC/1,300 mg APAP Q12h) was conducted on all subjects who completed the 3 periods. Two subjects (Subjects 170-101 and 170-132) received only 1 COV795 tablet (7.5 mg OC/325 mg APAP) and were therefore not included in the integrated safety database (for inclusion

in the integrated safety database, subjects had to have received at least 1 COV795 treatment of 15 mg OC/650 mg APAP). Subject 170-101 was discontinued early from the study because he met withdrawal criteria (he took a prohibited medication [APAP] for the treatment of the TEAE of pyrexia in Period 1). Subject 170-132 discontinued due to a TEAE of vomiting. The study duration included a screening visit up to 30 days prior to Period 1 check-in, 4 confinement periods of approximately 60 hours each, and 3 minimum 7-day intervals between the start of each period. The total study duration, including a follow-up period of up to 7 days following the last dose for ongoing AEs and up to 28 days following the last dose for all SAEs, was approximately 12 weeks.

4) Study COV15000171 (Study 0171) was an open-label, randomized, 3-period crossover study to evaluate the PK, bioavailability, and safety of 2 COV795 tablets (7.5 mg OC/325 mg APAP per tablet), administered as a single dose in normal, healthy subjects under fed (high and low-fat) and fasted conditions. In each period, subjects received 2 COV795 tablets (7.5 mg OC/325 mg APAP per tablet) under fed with high-fat, fed with low-fat, or fasted conditions with a minimum 7-day interval between the start of each period. The study included a screening visit up to 45 days prior to Period 1 check-in, 3 confinement periods of approximately 60 hours each, and 2 minimum 7-day intervals between the start of each period. The total study duration, including a follow-up period of up to 7 days following the last dose for ongoing AEs and up to 28 days for SAEs, was approximately 13 weeks.

5) Study COV15000256 (Study 0256) was an open-label, randomized, single-dose, 4-period crossover study to evaluate the PK, bioavailability, and safety of COV795 compared to IR Roxicodone, Ultracet, and Percocet in normal, healthy subjects under fasted conditions. In each period, subjects received 2 COV795 tablets (7.5 mg OC/325 mg APAP per tablet) for 1 dose, 1 Roxicodone tablet (15 mg OC) Q6h for 2 doses, 1 Ultracet tablet (37.5 mg tramadol/325 mg APAP) Q6h for 2 doses, or 1 Percocet tablet (7.5 mg OC/325 mg APAP) Q6h for 2 doses. The study duration included a screening visit up to 30 days prior to 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.

Phase 1 Multiple Dose Studies:
1) Study COV01300045 (Study 0045) was an open-label, randomized, multiple-dose, 3-period, crossover study to evaluate the steady-state PK, bioavailability, and safety of COV795 (15 mg OC/650 mg APAP) compared to IR Percocet (7.5 mg OC/325 mg APAP per tablet) in normal, healthy subjects under fed conditions. In each study period, subjects received 1 COV795 tablet (15 mg OC/650 mg APAP) Q12h, 2 COV795 tablets (30 mg OC/1,300 mg APAP) Q12h, or 2 Percocet tablets (7.5 mg OC/325 mg APAP per tablet) Q6h for 4.5 days. The study included a screening visit within 30 days prior to Period 1 check-in and 3 confinement periods of approximately 7 days each with a minimum 14-day interval between the start of each period. The total study duration, from screening through discharge from Period 3, was up to approximately 14 weeks.

2) Study COV15000172 (Study 0172) was an open-label, randomized, multiple-dose, 3-period crossover study to evaluate the steady-state PK, bioavailability, and safety of 1 or 2 COV795 tablets (7.5 mg OC/325 mg APAP per tablet) administered Q12h compared to 1 IR Percocet tablet (7.5 mg OC/325 mg APAP) administered Q6h for 4.5 days in normal, healthy subjects under fasted conditions. Two subjects (Subjects 172-122 and 172-142) received only 1 COV795 tablet (7.5 mg OC/325 mg APAP) Q12h and were therefore not included in the integrated safety database (for inclusion in the integrated safety database, subjects had to have received at least 1 COV795 treatment 15 mg OC/650 mg APAP). The study included a screening visit up to 30 days prior to Period 1 check-in, 3 confinement periods of approximately 7 days each with a minimum 14-day interval between the start of each period, and a follow-up visit by telephone at least 7 days following the conclusion of the study for subjects with ongoing AEs and SAEs. The total study duration, including a follow-up period of up to 28 days after the last dose of study drug for all SAEs, was approximately 14 weeks.

3) Study COV15000255 (Study 0255) was an open-label, randomized, multiple-dose, 4-period crossover study to evaluate the PK, bioavailability, and safety of COV795 compared to IR Roxicodone, Ultracet, and Percocet in normal, healthy subjects. In each period, subjects received 1 COV795 tablet (7.5 mg OC/325 mg APAP per tablet) Q12h, 1 Roxicodone tablet (15 mg OC) Q6h, 1 Ultracet tablet (37.5 mg tramadol/325 mg APAP) Q6h, or 1 Percocet tablet (7.5 mg OC/325 mg APAP) Q6h. Each treatment was given for approximately 4.5 days. The study duration included a screening visit up to 30 days prior to 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.

Description of the Phase 1 Studies Not Included in Integrated Safety Database
Four Phase 1 studies (0041, 0043 and 0044) were not included in the integrated safety database because they were conducted with noncommercial formulations or dosage strengths or were conducted in nondependent, recreational opioid users (b) (4)). Although the safety findings for these subjects were not included in the integrated safety database, the safety findings were included in the submission in a separate section with electronic links to the individual Clinical Study Reports (CSRs). There were no deaths or SAEs in these studies and the common AEs were expected AEs of opioids (i.e., primarily GI). In studies 0041 and 0043, subjects were naltrexone-blocked. Human abuse liability study 0244 is described in Section 7.4.5, Special Safety Studies. The other three studies are described below:

1. **COV01300041 (Study 0041):** This Phase 1 study was titled, “An Open-Label, Single-Dose, Four-Period Crossover Study to Evaluate the Pharmacokinetics and Bioavailability of Three Controlled-Release, Gastroretentive Tablet Formulations of COV795 (15 mg Oxycodone Hydrochloride/**500 mg** Acetaminophen) and Immediate-Release Percocet Administered in Normal, Healthy Male Subjects Under Fed Conditions”. This crossover study was conducted in fed, normal healthy male subjects

21 to 45 years old, inclusive. Subjects underwent screening evaluations to determine eligibility within 30 days of Period 1, Hour 0. Subjects were randomly assigned to Treatments A, B, C, and D using a 4-period, 8-sequence (5 subjects per sequence), crossover design. All subjects received 50 mg **naltrexone** 12 hours before dosing, at Hour 0, and 12 hours after dosing to block the effects and potential risks of OC.

2. COV01300043 (Study 0043): This was a randomized, open-label, single-dose, 4-period crossover bioequivalence, PK and BA study of 3 formulations of COV795 vs Percocet. The test products included [COV795 (30 mg OC/**500 mg** APAP), 1 tablet, fast drug release, PO fed]; [COV795 (30 mg OC/500 mg APAP), 1 tablet, medium drug release, PO fed]; [COV795 (30 mg OC/500 mg APAP), 1 tablet, slow drug release, PO fed]; and [Percocet (7.5 mg OC/325 mg APAP), 1 tablet, 2 doses Q6h, PO fed] in 40; healthy subjects. Each treatment was administered once, separated by at least 7 days. All subjects received 50mg **naltrexone** 12 hours before dosing, at Hour 0, and 12 hours after dosing to block the effects and potential risks of oxycodone.

3. COV01300044 (Study 0044): This was a randomized, open-label, single dose, 2-period, 2-sequence crossover PK and BA study under fed and fasted conditions using [COV795 (15 mg OC/650 mg APAP), 2 tablets, PO fed] and [COV795 (15 mg OC/650 mg APAP) 2 tablets, PO fasted] in 30 healthy subjects. Each treatment was administered once, separated by at least 7 days.

7.2 Adequacy of Safety Assessments

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

The safety population included all subjects who received at least one dose of study treatment (i.e., COV795 [15 mg OC/650 mg APAP] Q12h, Percocet, Roxicodone, Ultracet, placebo). The Applicant reports that the safety of study drug COV795 was investigated in 12 Phase 1 studies and 2 Phase 3 studies, in which 1,028 subjects received any dose of COV795 (the commercial dose regimen of 15mg OC/650mg APAP every 12 hours was received by 834 subjects in the ISS database and 58 subjects in abuse liability study 0244); 77 subjects received any dose of Roxicodone; 64 subjects received any dose of Ultracet and 393 subjects received any dose of Percocet.

Subjects were analyzed according to the treatment actually received. For crossover studies or studies with multiple periods, the actual study treatment received during each period was used as the treatment group, where possible. As noted previously, a total of eight subjects (Study 0170: Subjects 170-101 and 170-132; Study 0172: Subjects 172-122 and 172-142; and Study 0181: Subjects 101-017, 145-003, 160-010, and 160-011) only received one COV795 tablet (7.5 mg OC/325 mg APAP) Q12h and those subjects are therefore not included in any of the integrated safety analyses.

Also as previously noted, the Applicant reported that four Phase 1 studies were not included in the integrated safety database because these studies were conducted with pilot formulations or noncommercial dosage strengths or were conducted in nondependent, recreational opioid users.

Therefore, as a result of the exclusion of the four Phase 1 studies listed above, there were 246 COV795 subject exposures excluded from the integrated safety database. These 246 subject exposures combined with the eight subjects, described previously, who were excluded for not receiving the intended commercial dosage regimen resulted in a total of 254 COV795 subject exposures excluded from the integrated safety database. As a result of the exclusion of Studies 0041 and 0043, 69 Percocet subject exposures were excluded from the integrated safety database.

These findings are summarized in Table 25, below:

Table 25. Exposures in COV795 Clinical Development Program and Integrated Safety Database

Program/Database Treatment	Total Number of Subjects[a]
Total Subjects in COV795 Clinical Development Program[b]	1,281
COV795 Subjects	1,028
Percocet Subjects	393
Roxicodone Subjects	77
Ultracet Subjects	64
Placebo Subjects	265
Total Subjects in Integrated Safety Database	1,045
COV795 Subjects	834
Percocet Subjects	219
Roxicodone Subjects	77
Ultracet Subjects	64
Placebo Subjects	163
Exposures Excluded From Integrated Safety Database[c]	
COV795 Exposures Excluded (noncommercial doses)	
COV795 (7.5 mg OC/325 mg APAP)[d]	83
COV795 (15 mg OC/500 mg APAP)	39
COV795 (30 mg OC/500 mg APAP)	39
COV795 (30 mg OC/1,300 mg APAP)	97
Percocet Exposures Excluded	
Percocet (15 mg OC/650 mg APAP)[e]	69
Roxicodone Exposures Excluded	0
Ultracet Exposures Excluded	0
Placebo Exposures Excluded	0

[a]The presence of crossover studies in this integration set resulted in the total number of subjects being less than the sum of the subtotals.
[b]Counts indicate all subjects from all studies regardless of study medication dosage.
[c]Counts indicate subject exposures during crossover studies that were excluded.
[d]Count includes 2 subjects from Study 0170 (Subjects 170-101 and 170-132), 2 subjects from Study 0172 (Subjects 172-122 and 172-142), and 4 subjects from Study 0181 (Subjects 101-017, 145-003, 160-010, and 160-011). Note that the pertinent safety findings of these subjects are discussed in Section 10.3 (the SAE of abdominal pain of Subject 160-010), Section 10.4.1 (the AEs of vomiting that led to the discontinuation of Subjects 101-017, 145-003, 160-010, and 160-011), and Section 10.4.2 (the AE of vomiting that led to the discontinuation of Subject 170-132).
[e]Studies 0041 and 0043 were not included in the integrated safety database because they were not conducted with the intended COV795 commercial dose regimen and, as a result, 69 Percocet subject exposures were excluded.

(Source: Applicant's table, ISS, p. 18)

As shown below in Table 26, the Applicant reported that during the blinded dosing period, 166 subjects were exposed to COV795 (164 were randomized to study drug and two subjects were randomized to placebo but actually received study drug). During the blinded dosing period, mean exposure to COV795 was 45.61 hours. Mean duration of exposure to study drug during the OL dosing period was 6.5 days. Mean duration of exposure to study drug during the entire study was 5.40 days.

Table 26. Extent of Exposure to COV795 during Study 0182 Blinded and OL Dosing Periods

	COV795-DB[a]	Placebo-DB[a]	Total
Total number of COV795 tablets during blinded dosing period			
n	166		
Mean (SD)	7.6 (1.40)		
Median	8.0		
Minimum, maximum	2, 8		
Duration of exposure to COV795 during blinded dosing period (hours)			
n	166		
Mean (SD)	45.61 (10.076)		
Median	48.00		
Minimum, maximum	1.3, 60.4		
Total number of COV795 tablets taken during open-label dosing period			
n	77	68	145
Mean (SD)	27.0 (17.95)	21.6 (17.03)	24.4 (17.67)
Median	23.0	18.0	20.0
Minimum, maximum	2, 62	2, 64	2, 64
Duration of exposure to COV795 during open-label dosing period (days)			
n	77	69	146
Mean (SD)	7.2 (4.48)	5.8 (4.38)	6.5 (4.48)
Median	6.0	5.0	5.0
Minimum, maximum	1, 15	1, 17	1, 17
Duration of exposure to COV795 during entire study (days)			
N	166	69	235
Mean (SD)	5.24 (4.809)	5.78 (4.382)	5.40 (4.685)
Median	2.15	5.00	3.00
Minimum, maximum	0.1, 17.1	1.0, 17.0	0.1, 17.1

DB=double blind; n=number of subjects with data available
[a]Treatment assignment based on actual treatment received during the blinded dosing period
(Source: Applicant's table, CSR, p. 100)

Integrated Exposure

Phase 3 Studies Integrated Exposure:

As seen in Table 27, in OL study 0181, the majority (i.e., 310/347 or ~90%) of subjects received study drug for ≥10 days, and ~77% of subjects in double-blind Study 0182 received study drug 5 to <10 days.

Table 27. Number of Subjects Exposed to Study Drug by Study and Treatment (Safety Population Phase 3 Integration Set)

	COV795-15/650					
Study[a]	< 5 days N = 172 n (%)	5 to < 10 days N = 88 n (%)	≥ 10 days N = 347 n (%)	Overall N = 607 n (%)	Placebo N = 163 n (%)	Total N = 701 n (%)
COV15000181	42 (24.4)	20 (22.7)	310 (89.3)	372 (61.3)	0	372 (53.1)
COV15000182	130 (75.6)	68 (77.3)	37 (10.7)	235 (38.7)	163 (100)	329 (46.9)

Source: Section 23, Table 1.2.
Note: Percentages were calculated based on the number of subjects in the safety population in each treatment group.
[a]Subjects presented are more accurately referred to as exposures.

(Source: Applicant's table, ISS, p. 40)

Reviewer comment: The extent of exposure in the Phase 3 studies appears to have been of a sufficient number and duration that adequate safety data could be obtained to support the proposed indication of treatment of acute pain.

Phase 1 Integrated Exposure

In the Phase 1 Integration Sets, there were 74 subjects who received two tablets of study drug in a multiple dose setting and 128 subjects who received two tablets of study drug in a single dose.

Phase 1 and Phase 3 Integrated Exposure

As shown in table 28 below, in the integrated exposure from Phase 1 and Phase 3 sets, a total of 809 subjects were exposed to two tablets of study drug with the majority (372/809=46%) exposed during OL study 0181, followed by 235/809=29% exposed during the blinded, placebo-controlled study 0182.

Table 28. Number of Subjects Exposed to Study Drug by Study and Treatment (Safety Population Phase 1 and 3 Integration Set)

	COV795-15/650			Percocet						
	2 Tablets N = 809	1 Tablet N = 94	Overall N = 903	15/650 N = 185	30/1,300 N = 67	Overall N = 219	Placebo N = 163	Roxi-30 N = 77	Ultra-650 N = 64	Total N = 1,045
Study[a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
COV01300042	0	30 (31.9)	30 (3.3)	0	0	0	0	0	0	30 (2.9)
COV01300045	0	29 (30.9)	29 (3.2)	0	34 (50.7)	34 (15.5)	0	0	0	39 (3.7)
COV01300107	0	35 (37.2)	35 (3.9)	34 (18.4)	0	34 (15.5)	0	0	0	39 (3.7)
COV15000170	41 (5.1)	0	41 (4.5)	39 (21.1)	33 (49.3)	39 (17.8)	0	0	0	46 (4.4)
COV15000171	48 (5.9)	0	48 (5.3)	0	0	0	0	0	0	48 (4.6)
COV15000172	41 (5.1)	0	41 (4.5)	41 (22.2)	0	41 (18.7)	0	0	0	46 (4.4)
COV15000181	372 (46.0)	0	372 (41.2)	0	0	0	0	0	0	372 (35.6)
COV15000182	235 (29.0)	0	235 (26.0)	0	0	0	163 (100)	0	0	329 (31.5)
COV15000255	33 (4.1)	0	33 (3.7)	31 (16.8)	0	31 (14.2)	0	34 (44.2)	28 (43.8)	48 (4.6)
COV15000256	39 (4.8)	0	39 (4.3)	40 (21.6)	0	40 (18.3)	0	43 (55.8)	36 (56.3)	48 (4.6)

Source: Section 23, Table 1.1.
Note: Roxi = Roxicodone, Ultra = Ultracet. Percentages were calculated based on the number of subjects in the safety population in each treatment group.
[a]Subjects presented are more accurately referred to as exposures.

(Source: Applicant's table, ISS, p. 39)

As shown in Table 29 below, the maximum duration of exposure was 42 days for the two tablet dosing regimen.

Table 29. Extent of Exposure (Safety Population) Phase 1 and 3 Integration Set

	COV795-15/650			Percocet					
	2 Tablets	1 Tablet	Overall	15/650	30/1300	Overall	Placebo	Roxi-30	Ultra-650
Statistic	N=809	N=94	N=903	N=185	N=67	N=219	N=163	N=77	N=64
n	809	94	903	185	67	219	163	77	64
Mean	15.9	2.5	14.5	2.4	2.3	2.7	2.8	2.4	2.7
Std Dev	15.49	1.71	15.23	1.89	1.89	1.85	0.62	1.90	1.99
Median	6.0	2.0	5.0	1.0	1.0	2.0	3.0	1.0	1.0
Min	1	1	1	1	1	1	1	1	1
Max	42	5	42	5	5	5	3	5	5

(Source: Applicant's table, ISS, p. 250)

Reviewer comment: The proposed dosage of COV795 is two tablets every 12 hours. There appears to have been a sufficient number of subjects exposed for a duration of up to 42 days to the two-tablet regimen to support safety of the proposed dosing for an acute indication.

Integrated Demographics

The Applicant presented demographic data for all of the integration sets (i.e., Phase 1 and 3, Phase 3, Phase 1, Phase 1 Single Dose and Phase 1 Multiple Dose).

In the Phase 1 and 3 Integration Set, the majority of subjects were female (62.8%), white (65.0%) and not Hispanic or Latino (73.9%). Mean subject age was 42.7 years. Most (93.4%) of subjects were 65 years or younger, with 0.9% of subjects being older than 75 years. The mean BMI was 27.77 kg/m^2.

The demographics of the key Phase 3 study 0182 have been previously discussed in Section 6 of this review (Efficacy).

In OL Study 0181, 41.5% of subjects were male and 58.5% of subjects were female. The mean subject age was 52.2 years. The majority of subjects were white (63.0%) and not Hispanic or Latino (84.6%). Mean BMI was 31.25 kg/m^2. Demographic characteristics were generally similar among exposure subgroups, although 78.8% of the subjects with < 10 days of exposure were female, compared to 54.2% of subjects with ≥ 10 days of exposure. Among subjects with < 10 days of exposure to COV795, 12.1% were black or African American, compared to 21.6% of subjects with ≥ 10 days of exposure.

In the Phase 3 Integration Set, demographics between study drug (overall) and placebo were generally similar.

In the Phase 1 Integration Set, the majority of subjects were male (52.8%), white (70.2%) and not Hispanic or Latino (61.5%). The mean subject age was 32.2 years and all subjects were 65 years or younger. The mean BMI was 25.69 kg/m^2.

Details of the drug-demographic interactions are presented in Section 7.5.3.

7.2.2 Explorations for Dose Response

There were no specific studies designed to explore dose response. In the clinical trials for the integrated safety database, all subjects received either one or two tablets of the to-be-marketed formulation of the product.

See Section 7.5.1 for discussion regarding dose dependency for AEs.

7.2.3 Special Animal and/or In Vitro Testing

Animal Studies: According to the Applicant, animal studies conducted for this NDA submission included a fluoroscopy study and PK study, both in dogs. No additional nonclinical testing or toxicity studies were conducted. See Dr. Beth Bolan's pharmacology toxicology review for further discussion of relevant animal studies. Below are the Applicant's summaries of the dog fluoroscopy and PK studies and their findings:

- Dog Fluoroscopy Tablet Erosion Study - Study IAC#983 Fluoroscopic Evaluation of Gastrointestinal Transit and Erosion of Oxycodone HCl/IAPAP Gastroretentive Dosage Form in Beagle Dogs evaluated 4 developmental formulations of COV795 OC/APAP. The test formulations included 2 strengths/ratios of OC/APAP (15 mg OC/500 mg APAP and 30 mg OC/500 mg APAP) and 2 different release characteristics for each strength. All animals tolerated the administered doses of OC/APAP and showed no major adverse effects. None of

the formulations showed any abrupt erosion that could result in dose dumping. The formulations were retained within the stomach from 3 to 9.25 hours

- Dog Pharmacokinetics Study 0130/09/131-E Pharmacokinetic Evaluation of Oxycodone HCl/Acetaminophen (ER Formulations) Following a Single Oral Dose in Beagle Dogs (non-GLP) was conducted as part of the formulation development of COV795. The objective of the study was to assess the PK profiles of 5 test formulations of COV795 containing OC/APAP (15 mg OC/500 mg APAP or 30 mg OC/500 mg APAP) after a single oral administration. Percocet (7.5 mg OC/325 mg APAP) was used as the reference formulation. According to the Applicant, all test formulations were safe and well tolerated by the study animals. Further, none of the test formulations showed any indication of dose dumping, and none of the animals showed any signs of toxicity that reflect dose dumping.

In Vitro Testing:
The Applicant maintains that, “the COV795 formulation was developed to be more tamper resistant than the IR comparator Percocet, due to the inherent hydroscopic properties of the polyethylene oxide (Polyox) that is a component of the COV795 tablet.”

(b) (4)

The Agency’s CSS review is ongoing at this time regarding final determination of the product’s abuse-deterrent properties.

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the development of COV795 appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to Section 4.4 and the Clinical Pharmacology Review of Dr Wei Qiu for information regarding the metabolic, clearance and interaction workup.

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

Study drug COV795 is a mu-opioid receptor agonist (oxycodone) combined with a non-opioid, non-salicylate analgesic and antipyretic (APAP).

Expected adverse events for the opioid component of the drug include those related to the central nervous system (i.e., sedation, dizziness, somnolence, headache, and respiratory depression), the gastrointestinal system (i.e. nausea, vomiting, and constipation) and other AEs such as pruritus and fatigue.

Serious possible adverse events for the APAP component of the drug include hepatotoxicity and severe cutaneous reactions.

The Applicant monitored for the expected AEs of opioid drug class and APAP by objective observation during examinations and subjective spontaneous reporting by the subjects. The Applicant obtained baseline and periodic liver function tests (LFTs) per protocols. In addition, the Applicant conducted a safety analysis of special AEs of interest based on the known safety profile of the listed drugs of Ultracet and Roxicodone.

Laboratory data, vital signs, and ECGs were collected throughout trials per protocol. The Applicant also conducted an analysis of withdrawal effects, abuse potential and overdose.

In general, the data collected allowed for adequate evaluation of the potential adverse events noted for similar drug classes.

7.3 Major Safety Results

7.3.1 Deaths

- Phase 1 studies: No deaths occurred
- Phase 3 studies: No deaths occurred in controlled study 0182. Two deaths occurred in Study 0181, an open-label study. Both deaths appear unlikely to be causally related to study drug. The narratives are described below in further detail.

Table 30. Narratives and Causality Assignment of Deaths

Patient ID	Narrative
147-012	71-year-old white male with OA of the knee. His pertinent medical history included hypercholesterolemia, hypertension, drug hypersensitivity (allergy to sulfa), and left knee arthroplasty. He consumed alcoholic beverages twice a week. Concomitant medications within 2 weeks of the SAE included lisinopril, fish oil, simvastatin, diltiazem, and multivitamins. The subject's last known dose of COV795 (2 tablets Q12h for a total daily dose of 30 mg OC and 1,300 mg APAP) was on Study Day (b) (6). On Study Day (b) (6), the subject experienced a severe (fatal) **cardio-respiratory arrest**, which was attributed to hypercholesterolemia and hypertension (per Death Certificate). The investigator considered this SAE to be not related to study treatment. *Reviewer's Comments: Although causality to study drug cannot be definitely ruled out, given the background rate of MIs in patients in this age group and the patient's risk factors of hypercholesterolemia and hypertension, causality to study drug alone is unlikely.*
168-013	76-year-old white male with OA of the knee. His medical history included acute myocardial infarction, coronary artery disease, hypercholesterolemia, and spinal OA. The only concomitant medication within 2 weeks of the SAE was simvastatin. The subject's last known dose of COV795 (2 tablets Q12h for a total daily dose of 30 mg OC and 1,300 mg APAP) was on Study Day (b) (6). On Study Day (b) (6), the subject was **killed** in a **road traffic accident** when his car was hit by a train. According to the safety report, the bottle of study drug dispensed at the Study Day 29 clinic visit was returned unopened after the subject's death. The investigator considered this SAE to be not related to study treatment. *Reviewer's Comments: Causality of road traffic accident resulting in death to study drug is unlikely. No information was provided regarding the patient's mental status (i.e., question if CNS effects from study drug such as somnolence may have been a factor). Given the information that was provided, causality to study drug alone is either unlikely or cannot be determined.*

(Table, reviewer)

7.3.2 Nonfatal Serious Adverse Events

There were a total of six non-fatal SAEs in the Phase 3 Integrated Set (five in study drug-treated and one in placebo-treated). These nonfatal SAEs showed no patterns or trends. The only SAE which, based on review of the narratives, was likely causally related to study drug was the SAE of abdominal pain in subject 160-010. Note that subject 160-010 was not included in the integrated safety database because she received only one tablet of study drug COV795. The other SAEs were unlikely related

to study drug given the patients' past medical histories. The Applicant also pointed out that in the clinical studies with COV795, pregnancy exposure to an investigational product, although not considered an SAE, was recorded, reported, and followed up as indicated for an SAE.

Nonfatal SAEs by integrated safety database are summarized as follows:

- Phase 1 studies: No nonfatal SAEs occurred in the integrated Phase 1 safety database

- Phase 3 studies: Six nonfatal SAEs occurred (Two in Study 0181 and Four in Study 0182).

The fatal and non-fatal SAEs which occurred in Phase 3 studies 0181 and 0182 are summarized below in Table 31. In Table 31, the fatal SAEs of road traffic accident and cardiorespiratory arrest have been discussed above under deaths. Narratives of the non-fatal SAEs are summarized in Table 32.

Table 31. Serious Adverse Events Phase 3 Integration Set

	COV795-15/650				Placebo	
System Organ Class Preferred Term	< 5 days N = 172 n (%)	5 to < 10 days N = 88 n (%)	≥ 10 days N = 347 n (%)	Overall N = 607 n (%)	N = 163 n (%)	Total N = 701 n (%)
Subjects with at least 1 SAE	2 (1.2)	1 (1.1)	3 (0.9)	6 (1.0)	1 (0.6)	7 (1.0)[a]
Cardiac Disorders	0	0	2 (0.6)	2 (0.3)	0	2 (0.3)
Atrial fibrillation	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Cardio-respiratory arrest	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Gastrointestinal Disorders	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Gastroesophageal reflux disease	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Immune System Disorders	0	0	0	0	1 (0.6)	1 (0.1)
Hypersensitivity	0	0	0	0	1 (0.6)	1 (0.1)
Injury, Poisoning and Procedural Complications	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Road traffic accident	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Investigations	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Pregnancy test urine positive	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Vascular Disorders	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Deep vein thrombosis	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)

Source: NDA Section 5.3.5.3, ISS, Section 23, Table 10.1.
Note: MedDRA = Medical Dictionary for Regulatory Activities, Adverse events were coded using MedDRA version 14.1. Percentages were calculated based on the number of subjects in the safety population in each treatment group. Subjects were counted only once within each system organ class and preferred term. Serious adverse events that occurred during blinded follow-up are assigned to the treatment received during the blinded dosing period. Events that occurred during the open-label follow-up period are assigned to the treatment received during the open-label extension phase (COV795).
[a]The number of SAEs does not match the sum of the SAEs presented in the clinical study reports of Study 0181 (NDA Section 5.3.5.2, CSR Study 0181, Section 12.3.3) and Study 0182 (NDA Section 5.3.5.1, CSR Study 0182, Section 12.3.1.2) because the integrated safety database did not include Subject 160-010 who received only 1 COV795 tablet with a dose of 7.5 mg OC/325 mg APAP.

(Source: Applicant's table, ISS, p. 118)

Table 32. Narratives of Non-fatal SAEs (Phase 3 Studies)

Study	Narrative
	Study Drug COV795
0181	Subject 175-012: 79 year old female with chronic low back pain experienced an SAE of **atrial fibrillation** after COV795 exposure ≥10 days (Day (b) (6)) requiring hospitalization. Her relevant past medical history was significant for prior atrial fibrillation. She was on multiple concomitant medications. She was treated with metoprolol for the atrial fibrillation and was reportedly discharged from the hospital the next day after converting to normal sinus rhythm. The patient remained in the study which she completed on Day 43, with the last dose of study drug on Day 36. The Investigator considered the event to be not related. *Reviewer's comment:* Causality to study drug alone is possible but unlikely, given this patient's pre-existing history of atrial fibrillation.
0181	Subject 160-010*: 73 year old woman with chronic low back pain experienced an SAE of **abdominal pain** requiring hospitalization after the first dosing with one tablet of study drug. The subject was withdrawn from the study due to the AE of moderate vomiting that began the same day. Her pertinent past medical history included diabetes mellitus, cervical carcinoma Stage II and hypertension. She also experienced moderate dizziness, nausea (not reported as an AE) and vomiting 3 times. She was on multiple concomitant medications. She subsequently was diagnosed with a large intestine ulcer and radiation colitis (considered unrelated to study drug). The Investigator considered the SAE of abdominal pain to be related to study drug. *Reviewer's comments*: It is likely that study drug was the causal reason for the patient's abdominal pain SAE. However, this patient did have risk factors of underlying cervical carcinoma and apparently had received prior radiation to the colon. This subject was not included in the integrated safety database because the subject received only one tablet of study drug.
0182	Subject 201-127: 57 year old male randomized to the COV795 treatment group experienced a **deep vein thrombosis** (DVT) during the OLE phase of the trial (Day (b) (6) PMH did not reveal risk for DVT with history of hypertension, dyspepsia, inguinal hernia and inguinal hernia repair. The subject was on multiple concomitant medications within 2 weeks prior to the SAE some of which included fentanyl, propofol, lidocaine, ropivacaine, ondanestron, ibuprofen, and HCTZ. The patient's initial dose of study drug was on 6/20/12 and last dose of study drug was on (b) (6). The patient required hospitalization for treatment of a moderate DVT. The SAE led to study

	discontinuation. The event was ongoing at the time of reporting. The subject discontinued due to the SAE. The Investigator considered the event to be not related. *Reviewer's comments:* While causality to study drug cannot be excluded, it appears unlikely given the known safety profile of both Oxycodone and APAP. It is concerning that the patient did not have risk factors for the development of DVT, however DVTs may arise without known risk factors.
0182	Subject 201-182: 52 year old female randomized to the COV795 treatment group who experienced vomiting after receiving dose (b) (6) in the blinded dosing phase, which led to discontinuation. On the next day, while in the double blind follow up phase, she developed chest pressure and burning, was admitted to a hospital and diagnosed with gastroesophageal reflux disease **(GERD)**. Pertinent past medical history was significant for chest pain. Concomitant medications within 2 weeks prior to the SAE included fentanyl, ketorolac tromethamine, acetylsalicylic acid, and cefazolin. This subject also experienced episodes of nausea and vomiting resulting in discontinuation from the study one day prior to the SAE of GERD, which was considered mild in intensity. The Investigator considered the event to be possibly related to study drug. No treatment was reported and the nausea/vomiting resolved the same day. *Reviewer's comments:* Causality of the SAE of GERD is possible but unlikely related to study drug. GERD suggests a chronic condition. It is likely that the nausea and vomiting were due to study drug, and the nausea/vomiting may have precipitated an exacerbation of preexisting GERD. GI adverse events of nausea and vomiting are expected in the opioid class of drugs.
0182	Subject 204-022: 29 year old female randomized to the placebo treatment group, experienced a positive urine **pregnancy** test after completing the OLE phase (i.e., after having received study drug during the OL phase). The subject's initial administration of study drug was on 3/20/12 and she received placebo on 3 days of the blinded dosing phase. She received a daily dose of 4 tablets of COV795 on 4 days during the OLE phase. The last dose of study drug was taken on 3/25/12 (OLE phase). On 3/14/12, the screening urine pregnancy test results were negative. On 3/26/12, the urine pregnancy test was positive as was an unscheduled visit urine pregnancy test on 3/28/12. The subject completed the study on 4/2/12. The positive pregnancy test was ongoing at the time the subject completed the study. The Investigator considered the SAE unrelated to study drug. Follow-up safety information revealed that the subject delivered a full-term healthy, female infant on (b) (6). *Reviewer's comment:* Causality of the SAE of pregnancy to study drug is unlikely.

(Table, reviewer)*Subject 160-010 was not included in the Integrated safety data base because she received only one tablet of study drug.

Of note, subject 201-155, a 48-year-old female randomized to the placebo treatment group in Study 0182, experienced hypersensitivity on the first day of dosing in the double blind phase. She was discontinued from the study and transferred to a hospital, where she was diagnosed and treated for hypersensitivity. The investigator considered the SAE of hypersensitivity to be possibly related to study drug. Since the placebo contained all of the excipients in the study drug (minus the active ingredients of oxycodone and APAP), this case may inform labeling. Although the original submission provided a narrative for this case, more detailed information was needed and so, on 10/18/13, the following IR was sent via email to the Applicant:

> *In Study 0182, Subject 201-155 (randomized to placebo), experienced an SAE of hypersensitivity. The subject was hospitalized and treated with diphenhydramine for the SAE of hypersensitivity but the narrative does not describe symptoms. Provide a more detailed narrative including information on specific symptoms and any additional information from the hospital report if possible.*

The subsequent detailed narrative revealed that the subject had prior allergies to oral iron sucrose complex described as a skin rash and/or hives, nausea and/or vomiting, and an allergic reaction to an IV infusion of iron sucrose (Venofer) described as abdominal cramping with arm and leg edema. The subject's symptoms related to the SAE of hypersensitivity included complaints of numbness all over her body, chest pressure described as "someone/or a brick sitting" on her chest, shortness of breath, mild nausea and palpitations. An ECG showed normal sinus rhythm. The subject was treated with morphine IV and 81mg aspirin orally and transported to the emergency department (ED). In the ED, the subject reportedly developed an urticarial rash on the left arm that was mild but visible. She was diagnosed with an allergic reaction and treated with 25mg diphenhydramine IV. She was admitted to the hospital for observation. She recovered from the allergic reaction and was discharged the next day.

In my opinion, this SAE of hypersensitivity does not appear to be a case of anaphylaxis and may represent a mild allergic reaction (skin rash) with possible underlying anxiety.

7.3.3 Dropouts and/or Discontinuations

Phase 1 and 3 Integration Set

In the integrated safety database of Phase 1 and 3 Integration Sets, overall, approximately 74% of subjects completed the studies. The most common reasons for discontinuation were AEs (19.5%), other (4.2%) and withdrawal by subject (1.6%). The Applicant described that study discontinuation reason "other" included: met withdrawal criteria, lack of efficacy, physician decision, and recovery. In the subjects who

discontinued due to AEs, the most common reason was due to vomiting. The Phase 1 protocols required discontinuation following AEs of emesis/vomiting.

These subject disposition findings for the Phase 1 and 3 Integration Sets are summarized in the table, below:

Table 33. Subject Disposition (Safety Population Phase 1 and 3 Integration Set)

	Total n (%)
Safety population[a]	1,057
Completed study	779 (73.7)
Discontinued study	278 (26.3)
Reason for discontinuation	
Adverse event	206 (19.5)
Death	2 (0.2)
Withdrawal by subject	17 (1.6)
Protocol violation	3 (0.3)
Lost to follow-up	6 (0.6)
Other[b]	44 (4.2)

Source: Section 23, Table 2.1.
Note: Percentages were calculated based on the number of subjects in the safety population.
[a]The safety population included all subjects who received at least 1 dose of study treatment.
[b]Categories not available in all studies (met withdrawal criteria, lack of efficacy, physician decision, and recovery) are included in Other.

(Source: Applicant's table, ISS, p. 61)

Phase 3 Integration Set
A total of 80% of subjects (80.4% COV795 and 87.1% placebo) completed the studies in the Phase 3 Integration Set.

As seen in Table 34, below, the most common reasons for study discontinuation were AEs (12.6%), lack of efficacy (3.9%) and withdrawal by subject (1.9%). In the COV795 Overall group, the most common reasons for study discontinuation were AEs (14.2%), withdrawal by subject (1.8%) and lack of efficacy (1.6%). The most common reason for discontinuation due to AEs was vomiting.

Table 34. Subject Disposition (Safety Population Phase 3 Integration Set)

	COV795-15/650					
	< 5 days n (%)	5 to < 10 days n (%)	≥ 10 days n (%)	Overall n (%)	Placebo[b] n (%)	Total n (%)
Safety population[a]	172	88	347	607	163	701
Completed study	105 (61.0)	64 (72.7)	319 (91.9)	488 (80.4)	142 (87.1)	561 (80.0)
Discontinued study	67 (39.0)	24 (27.3)	28 (8.1)	119 (19.6)	21 (12.9)	140 (20.0)
Reason for discontinuation						
Adverse event	58 (33.7)	18 (20.5)	10 (2.9)	86 (14.2)	2 (1.2)[c]	88 (12.6)
Death	0	0	2 (0.6)	2 (0.3)	0	2 (0.3)
Lack of efficacy	7 (4.1)	1 (1.1)	2 (0.6)	10 (1.6)	17 (10.4)	27 (3.9)
Recovery	0	0	0	0	0	0
Withdrawal by subject	2 (1.2)	5 (5.7)	4 (1.2)	11 (1.8)	2 (1.2)	13 (1.9)
Physician decision	0	0	3 (0.9)	3 (0.5)	0	3 (0.4)
Protocol violation	0	0	3 (0.9)	3 (0.5)	0	3 (0.4)
Lost to follow-up	0	0	3 (0.9)	3 (0.5)	0	3 (0.4)
Other	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)

Source: Section 23, Table 2.2.
Note:. Percentages were calculated based on the number of subjects in the safety population.
[a]The safety population included all subjects who received at least 1 dose of study treatment.
[b]For study COV15000182, completed represents subjects who completed the blinded dosing phase.
[c]The AE that led to study discontinuation of Subject 201-155 occurred during the blinded follow-up period. The event was an SAE (Table 10.3-1). The AE occurred during the blinded follow-up period, while the subject was not receiving study treatment.

(Source: Applicant's table, ISS, p. 62)

Uncontrolled Phase 3 Study 0181 Discontinuation AEs
In OL Study 0181, a total of 235 subjects (~62%) had at least one TEAE. In terms of exposure, more subjects (~94%) with <10 days of exposure reported at least one TEAE compared to ~56% of those with exposure ≥10 days. The most common TEAEs were nausea (59%), vomiting (58%), dizziness (30%) and somnolence (17%) in the <10 days exposure. The types of TEAEs were similar in the ≥10 day and <10 days of exposure.

Controlled Phase 3 Study 0182 Discontinuation AEs
Detailed discussion regarding drop outs and discontinuations for controlled Study 0182 has been outlined in Section 6 (Efficacy) of this review. In Study 0182, approximately 89% of subjects completed the blinded dosing phase, approximately 98% completed blinded follow up, and approximately 88% of subjects in the open-label safety population completed the open-label extension phase with the most common reasons for early discontinuation being lack of efficacy, AEs and withdrawal of consent.

During the blinded dosing phase, 7.3% of subjects (4.7% COV795 and 9.8% placebo) in the mITT population discontinued due to lack of efficacy, 3% of subjects (4.7% COV795 and 1.3% placebo) discontinued due to a TEAE, and 1% (0.7% COV795 and 1.3% placebo) withdrew consent. In the open-label safety population, 8.2% of subjects discontinued due to a TEAE and 1.4% of subjects withdrew consent. No subject withdrew due to lack of efficacy during the open-label extension phase.

Phase 3 Integration Set Discontinuation AEs

The most common reasons for discontinuation due to AEs in the two Phase 3 studies (reported by ≥1% in any drug-treated dose group) were vomiting (4.8%) and nausea (4.1%) with no reports of these AEs in the placebo-treated group. All other AEs occurred with <1% frequency. This is summarized in Table 35, below:

Table 35. AEs Leading to Discontinuation (Safety Population Phase 3 Integration Set)

	COV795-15/650					
System Organ Class Preferred Term	< 5 days N = 172 n (%)	5 to < 10 days N = 88 n (%)	≥ 10 days N = 347 n (%)	Overall N = 607 n (%)	Placebo N = 163 n (%)	Total N = 701 n (%)
Subjects with at least 1 AE leading to discontinuation	56 (32.6)	18 (20.5)	12 (3.5)	86 (14.2)	1 (0.6)*	87 (12.4)
Cardiac Disorders	1 (0.6)	0	1 (0.3)	2 (0.3)	1 (0.6)	3 (0.4)
Cardio-respiratory arrest	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Palpitations	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Tachycardia	0	0	0	0	1 (0.6)	1 (0.1)
Ear and Labyrinth Disorders	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Vertigo	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Gastrointestinal Disorders	43 (25.0)	8 (9.1)	4 (1.2)	55 (9.1)	0	55 (7.8)
Dyspepsia	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Nausea	18 (10.5)	5 (5.7)	2 (0.6)	25 (4.1)	0	25 (3.6)
Vomiting	25 (14.5)	2 (2.3)	2 (0.6)	29 (4.8)	0	29 (4.1)
General Disorders and Administration Site Conditions	3 (1.7)	0	0	3 (0.5)	0	3 (0.4)
Chest discomfort	2 (1.2)	0	0	2 (0.3)	0	2 (0.3)
Fatigue	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Injury, Poisoning and Procedural Complications	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Road traffic accident	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Investigations	0	1 (1.1)	5 (1.4)	6 (1.0)	0	6 (0.9)
Alanine aminotransferase increased	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Hepatic enzyme increased	0	1 (1.1)	3 (0.9)	4 (0.7)	0	4 (0.6)
Liver function test abnormal	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Nervous System Disorders	5 (2.9)	5 (5.7)	1 (0.3)	11 (1.8)	0	11 (1.6)
Cognitive disorder	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Dizziness	2 (1.2)	2 (2.3)	1 (0.3)	5 (0.8)	0	5 (0.7)
Headache	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Sedation	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Somnolence	1 (0.6)	2 (2.3)	0	3 (0.5)	0	3 (0.4)
Psychiatric Disorders	0	2 (2.3)	0	2 (0.3)	0	2 (0.3)
Confusional state	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Dysphoria	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Hypopnoea	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Skin and Subcutaneous Tissue Disorders	2 (1.2)	1 (1.1)	0	3 (0.5)	0	3 (0.4)
Pruritus	1 (0.6)	1 (1.1)	0	2 (0.3)	0	2 (0.3)
Rash	1 (0.6)	0	0	1 (0.2)	0	1 (0.1)
Vascular Disorders	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)
Deep vein thrombosis	0	1 (1.1)	0	1 (0.2)	0	1 (0.1)

Source: Section 23, Table 8.1.
Note: Adverse events were coded using MedDRA version 14.1. Percentages were calculated based on the number of subjects in the safety population in each treatment group. Subjects were counted only once within each system organ class and preferred term.
*A second subject in the placebo group (Subject 201-155) discontinued the study due to an AE. The event was an SAE (Table 10.3-1). The AE occurred during the blinded follow-up period, while the subject was not receiving study treatment.

(Source: Applicant's table, ISS, p. 122)

7.3.4 Significant Adverse Events

The Applicant presented safety data for TEAEs of special interest as discussed below in Section 7.3.5.

7.3.5 Submission Specific Primary Safety Concerns

Adverse Events of Special Interest

Due to the known safety profile of opioids and APAP, the Applicant provided an analysis of TEAEs of special interest presented by system organ class and preferred term for the two most similar integration sets (i.e., the Phase 3 Integration Set and the Phase 1 Integration Set). These TEAEs were identified by the Applicant as AEs of interest either because of : 1) the formulation of the study drug or 2) the USPIs of the listed drugs, (Roxicodone and Ultracet) or the USPI of the IR comparator, Percocet.

The TEAEs that code to the following preferred terms were considered TEAEs of special interest: dizziness, somnolence, fatigue, sedation, hypotension, choking, obstructive airways disorder, or respiratory depression. In addition, TEAEs that code to the cardiac SOC or GI SOC were also considered TEAEs of special interest.

The Applicant's predefined AEs of special interest include the following: Nervous system disorders SOC (preferred terms dizziness, somnolence and sedation); General disorders and administration site conditions SOC (preferred term of fatigue); Respiratory, thoracic and mediastinal disorders (preferred terms choking, obstructive airways disorder and respiratory depression); Cardiac disorders SOC (preferred terms atrial fibrillation, cardio-respiratory arrest, extrasystoles, palpitations and tachycardia); Vascular disorders SOC (preferred term hypotension); GI disorders SOC (preferred terms constipation, diarrhea, nausea, and vomiting).

Skin and subcutaneous tissue disorders SOC (preferred terms skin swelling, urticarial, rash, and pruritus) and Immune system disorders SOC (preferred terms hypersensitivity, including events related to respiratory distress and anaphylaxis) were not predefined but were considered by the Applicant to be TEAEs of special interest.

Choking and obstructive airways disorder were predefined preferred terms due to the presence of Polyethylene Oxide in the formulation of COV795, a substance which has been associated with choking and swallowing difficulties.

Hepatic disorders SMQ and Severe cutaneous adverse reactions SMQ were also analyzed as AEs of special interest, based upon Agency advice, and are discussed in this review after the presentation of the predefined TEAEs of interest.

Phase 3 Integration Set

Of the predefined TEAEs of special interest in the Phase 3 Integration Set, none in the placebo group were considered severe while predefined TEAEs of special interest which were considered severe in COV795 group included nausea (six subjects), vomiting (four subjects), constipation (two subjects), atrial fibrillation (one subject) and cardiorespiratory arrest (one subject). SAEs of interest included atrial fibrillation, cardiorespiratory arrest and hypersensitivity. TEAES of special interest that led to study discontinuation in the COV795 group included vomiting (29 subjects), nausea (25 subjects), dizziness (five subjects), somnolence (three subjects), cardio-respiratory arrest, palpitations, fatigue and sedation occurred in one subject each.

The Applicant's predefined TEAEs with the frequency of occurrence are outlined and bulleted below:

I) TEAEs of Special Interest With No Cases Reported:

- Respiratory, thoracic and mediastinal disorders SOC: preferred terms of choking, obstructive airways disorder, and respiratory depression
- Vascular disorders SOC: preferred term of hypotension

I) TEAEs of Special Interest Most Frequently Occurring

- Nervous system disorders SOC: preferred terms of dizziness, somnolence, and sedation
    - Dizziness: Overall, dizziness occurred in 13% of drug treated compared to 1.2% placebo. The incidence of dizziness was greatest (16.3%) in the <5 days group, followed by the 5-< to <10 days in 15.9%. The incidence dropped to 10.7% in ≥10 days. In this reviewer's opinion, this may suggest a tolerance effect to dizziness.
    - Somnolence: The incidence in drug treated overall was 9.1% compared to 0.6% placebo with the highest incidence (10.2%) occurring in the 5-< to <10 days group of study drug. Although no event of somnolence was considered severe, somnolence led to study discontinuation in the COV795 Overall group in 3 subjects.
    - Sedation: The overall incidence was low in both drug treated and placebo being on 0.8% and 0%, respectively.
- Gastrointestinal disorders SOC: preferred terms of constipation, diarrhea, nausea, and vomiting:
    - Constipation: The incidence of constipation was higher by at least 5% in the COV795 Overall group (9.6%) than in the placebo group (3.1%) and increased with length of COV795 exposure. No subjects discontinued due to constipation.
    - Diarrhea: Diarrhea occurred in 6 (1.0%) COV795-treated subjects (all COV795 ≥ 10 days) and in none of the placebo-treated subjects. None of the events of diarrhea were considered severe or led to study discontinuation.
    - Nausea: The incidence of nausea was higher by at least 5% in the COV795 Overall group (25.7%) than in the placebo group (5.5%).

However, the incidence of nausea decreased with increasing length of COV795 exposure. A total of 25 (4.1%) subjects in the COV795 Overall group (18 [10.5%] COV795 < 5 days, 5 [5.7%] COV795 5 to < 10 days, and 2 [0.6%] COV795 ≥ 10 days) and none in the placebo group discontinued due to nausea.

- Vomiting: The incidence of vomiting was higher by at least 5% in the COV795 Overall group (12.9%) than in the placebo group (0%) and the incidence of vomiting decreased with increasing length of COV795 exposure. A total of 29 (4.8%) subjects in the COV795 Overall group (25 [14.5%] subjects COV795 < 5 days, 2 [2.3%] subjects COV795 5 to < 10 days, and 2 [0.6%] subjects COV795 ≥ 10 days) discontinued due to vomiting.

II) TEAEs of Special Interest Occurring Infrequently (at least one occurrence):

- Cardiac disorders SOC (preferred terms of atrial fibrillation, cardiorespiratory arrest, extrasystoles, palpitations, and tachycardia): The cases of atrial fibrillation (SAE) and cardio-respiratory arrest (death) were discussed previously under Deaths and Non-fatal SAEs section of this review. There were two case reports of palpitations, neither was considered severe although one subject in <5 days group discontinued due to palpitations. The event of tachycardia occurred in the placebo group.

- General disorders and administration site conditions SOC (preferred term of fatigue) There were nine cases of fatigue in the study-drug treated group and none in the placebo-treated group. None of the events was considered severe, although one subject in the drug-treated <5 days group discontinued due to fatigue.

- Skin and subcutaneous tissue disorders SOC (preferred terms of skin swelling, urticaria, rash, and pruritus): Of these listed preferred terms, only pruritus occurred with an incidence ≥2%. Pruritus was assessed as “pruritus” and “pruritus generalized”.

    - Pruritus occurred in 34 (5.6%) of drug-treated subjects and in 3 (1.8%) placebo-treated. The incidence was similar in the drug-treated exposure groups. Severe events of pruritus were experienced by 2 (0.3%) of subjects in the drug-treated Overall group and none in the placebo group. There were two subjects who discontinued due to pruritus.

- Pruritus generalized occurred in 6 (1.0%) subjects in the drug-treated Overall group and none in the placebo group.

- Immune system disorders SOC (preferred terms of hypersensitivity, including events related to respiratory distress and anaphylaxis): There were no reports of anaphylaxis. Dyspnea was the only event coded as related to respiratory distress and occurred in only one drug-treated subject.

Phase 1 Integration Set TEAES of Interest

Of the TEAEs of special interest, none were severe or serious. Vomiting was the only predefined TEAE of special interest that led to study discontinuation.

In general, the most common TEAEs of special interest were in the GI Disorders SOC with overall COV795 incidence being approximately 30% (due to nausea 28% and vomiting 13%) followed by the Nervous System Disorders SOC being 22% Overall due to dizziness (approximately 14% and somnolence 10%).

Dyspnea occurred in two study drug-treated subjects with no events leading to discontinuation.

A summary of the TEAEs of special interest for the Phase 3 and Phase 1 Integration Sets is shown below in Table 36.

Table 36. Predefined TEAEs Phase 3 and Phase 1 Integration Set

MedDRA SOC **Preferred Term**	**Phase 3** **COV795** N=607	**Phase 1** **COV795** N=296	**Placebo** N=163
	N (%) Experiencing TEAE		
SOC Preferred Term			
Gastrointestinal Disorders	215 (35)	88 (30)	14 (9)
Constipation	58 (10)	1 (<1)	5 (3)
Diarrhea	6 (1)	1 (<1)	0
Nausea	156 (26)	83 (28)	9 (5)
Vomiting	78 (13)	39 (13)	0
Nervous System Disorders	127 (21)	65 (22)	3 (2)
Dizziness	79 (13)	41 (14)	2 (1)
Sedation	5 (<1)	0	0
Somnolence	55 (9)	30 (10)	1 (<1)
General Disorders and Administration Site Conditions	9 (1)	5 (2)	0
Fatigue	9 (1)	5 (2)	0

Cardiac Disorders	4 (<1)	1 (<1)	1 (<1)
Atrial fibrillation	1 (<1)	0	0
Cardio-respiratory arrest	1 (<1)	0	0
Palpitations	2 (<1)	0	0
Tachycardia	0	1 (<1)	1
Skin and subcutaneous tissue disorders	49 (12)	44 (7)	3 (2)
Skin swelling	1 (<1)	0	0
Urticaria	1 (<1)	0	0
Rash	4 (<1)	2 (1)	2
Rash erythematous	2 (<1)	0	0
Rash pruritic	1 (<1)	0	0
Pruritus	34 (6)	42 (14)	3 (2)
Pruritus generalized	6 (1)	0	0
Immune system disorders	1	2	1
Hypersensitivity	0	0	1
Respiratory distress			
Dyspnea	1 (<1)	2 (<1)	0
Anaphylaxis	0	0	0

(Table, reviewer)

SMQ Terms of Special Interest

Severe Cutaneous Adverse Reaction SMQ

Phase 3 Integration Set: Blister was the only treatment-emergent severe cutaneous adverse reaction experienced by 3 (0.5%) COV795-treated subjects and 1 (0.6%) placebo-treated. None of the events of blister were considered severe or led to study discontinuation.

Phase 1 Integration Set: No subjects in the COV795-treated group experienced a severe cutaneous adverse reaction.

Hepatic Disorders SMQ

The Applicant reported that the USPIs of Ultracet and Percocet state that APAP has been associated with cases of acute liver failure, at times resulting in liver transplant and death. They further noted that most of the cases of liver injury were associated with the use of APAP at doses that exceed 4,000 milligrams per day, and often involve more than one APAP-containing product. The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking APAP.

The USPI of Ultracet states that hepatic function abnormal occurred in at least 1% of subjects treated with Ultracet. The USPI of Percocet lists the following events in the hepatic disorders SOC as adverse reactions obtained from postmarketing experiences with Percocet tablets: transient elevations of hepatic enzymes, increase in bilirubin, hepatitis, hepatic failure, jaundice, hepatotoxicity, and hepatic disorder.

The Applicant's submission initially included narratives for only those subjects whose abnormal LFTs resulted in discontinuation. Additionally, there was some discrepant information which needed further clarification.

Information requests were sent to the Applicant on two occasions to provide additional information and/or clarification for hepatic safety findings as follows:

I) On September 24, 2013, an Information Request was emailed to the Applicant from the Division and on September 27, 2013, the Applicant provided the information as requested in a correspondence titled, Efficacy Information Amendment (Section 1.11.3 of the electronic submission). Relevant sections of the Division's information request (bold font) and the Applicant's response (regular font) are provided below:

1. Identify the hepatic function laboratory criteria used to determine whether a subject with abnormal hepatic laboratory values continued or was discontinued from Studies 0182 and 0181.
Mallinckrodt Response: No specific hepatic function laboratory criteria was explicitly stated or used to determine whether a subject with abnormal hepatic laboratory values continued or was discontinued from the 0181 and 0182 studies. Each investigator decided whether a laboratory abnormality represented a clinically significant value or effect, and whether the finding was an adverse event. The determination as to whether the subject should continue or be discontinued from the studies was based on the onset, magnitude, specific LFT and/or combination of LFT abnormalities, and the subject's clinical presentation and/or course.

2. Provide a list of all subjects with elevated hepatic function tests >2x ULN in Studies 0182 and 0181, and provide narratives for all subjects with elevated hepatic function tests ≥3x ULN (whether the subject discontinued or continued in the study), since abnormal hepatic function tests and hepatic-related AEs have been identified as AEs of special interest.
Mallinckrodt Response: To support the Agency's review of all subjects with abnormal hepatic function tests or hepatic-related AEs, for each Phase 3 study Mallinckrodt has generated a table that lists the LFT results for all subjects with values > 2 times the upper limit of normal for any of the liver function tests (alanine aminotransferase (ALT)/ serum glutamic pyruvic transaminase (SGPT), aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), direct bilirubin, total bilirubin, and alkaline phosphatase). Narratives were provided for subjects with elevated hepatic function tests ≥3xULN.

II) On October 15, 2013, the following IR was sent via email to the Applicant from the Division:

For the Phase 3 studies 0182 and 0181 and Phase 1 studies which used the to-be-marketed formulation, provide a summary table(s) by treatment received (not treatment group assigned) for subjects with elevated LFTs to include:

- Total number of subjects with LFTs ≥2xULN
- Total number of subjects with LFTs ≥3xULN
- Total number of subjects with LFTs ≥5xULN
- Total number of subjects with LFTs ≥10xULN
- Total number of subjects with total bilirubin ≥ 2xULN
- Total number of discontinuations due to elevated LFTs

For the Phase 3 studies, provide the patient ID number for each case. The tables should clearly distinguish those subjects who received placebo only and those who received study drug.

The Applicant provided the response to the above Information Request on October 16, 2013.

This review incorporates information and data regarding liver function findings from both the Applicant's original submission and the Applicant's responses to the two clinical information requests.

The Applicant's hepatic safety information is summarized and discussed below:

Phase 3 Integration Set (Applicant's SMQ Analysis)
The Applicant stated that the treatment-emergent hepatic disorders consisted of liver function test abnormalities (hepatic enzyme increased, ALT increased, liver function test abnormal, AST increased, GGT increased, and transaminases increased).

In the Applicant's 10/16/13 response, they reiterated that the to-be-marketed formulation of study drug MNK795 (7.5mg OC/325mg APAP) was used in eight clinical trials (two Phase 3 studies and six Phase 1 studies).

The Applicant provided a summary table of the total number of subjects with elevated LFT values, and the number of subjects discontinued due to elevated LFTs in the Phase 3 and Phase 1 studies using the to-be-marketed formulation as shown below in Table 37.

Table 37. Summary of Liver Function Test (LFT) Elevations and Early Terminations due to Elevated LFTs

Total Number of Subjects	Phase 3			Phase 1	Total
	0182 (RCT)		0181 (OL)		
	MNK795	Placebo	MNK795	MNK795, Percocet, and Ultracet	
LFT 2.0 – 2.9 x ULN	4[a]	5[a]	13	1	23[a]
LFT 3.0 – 4.9 × ULN	2	4	6	-	12
LFT 5.0 – 9.9 × ULN	-	1[b]	4	1	6[b]
LFT ≥ 10 × ULN	2[b]	-	1	-	3[b]
Total bilirubin ≥ 2 × ULN	-	-	-	-	-
ET due to elevated LFTs	1	-	5	-	6

Note: Liver function test (LFT) values included: ALT, ALP, AST, direct bilirubin, GGT, LDH, total bilirubin; subjects are presented in the table with the greatest LFT value observed on study for any subject having an LFT ≥2 x ULN; - = '0' or no value
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ET = Early Termination (Discontinuation); GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; LFT = liver function test; OL = open label; RCT = randomized controlled trial; ULN = upper limit of normal.
[a]Subject 201-121 had LFT elevations in the Placebo treatment period (GGT), followed by elevations in the MNK795 treatment period- (GGT).
[b]Subject 202-047 had LFT elevations in the Placebo treatment period (ALT), followed by elevations in the MNK795 treatment periods (GGT).

(Source: Applicant's table, Efficacy Information Amendment #2, response to Clinical IR)

According to the Applicant's response to the first IR (Efficacy Information Amendment #1), a total of 20 subjects were identified with elevated liver function tests (LFTs) ≥3xULN and/or coded as experiencing hepatic-related AEs in the Phase 3 studies as summarized below:

- Study 0182: 10 narratives were provided for placebo-controlled Study 0182 for subjects with elevated hepatic function tests >3xULN or assessed as an AE (see narratives of this review). The narrative for Subject 201-178 was included because although the subject did not have elevated LFTs >3xULN, the subject did have a hepatic-related AE (i.e., "elevated LFTs"). Of these ten subjects, five were placebo-treated. Two subjects experienced elevations of GGT in the placebo treatment period and drug-treated period. Only four cases in the study drug-treated group were identified by this reviewer as likely causally related to study drug and are discussed in Table 38, narrative summaries.

- Study 0181: 10 narratives were provided for open-label Study 0181 for subjects with elevated hepatic function tests ≥3xULN (see narratives of this review). One additional narrative was not included in the Efficacy Information Amendment because the subject (152-005) did not have LFT's ≥3xULN. However, this subject was included in the original submission as a subject who discontinued due to coding of "moderate increased hepatic enzymes". Therefore, this subject's narrative was included in this review. These narratives are discussed in Table 40.

Reviewer's Hepatic Safety Conclusions

- None of the liver function test abnormalities met the criteria for Hy's Law (i.e., AST or ALT increase ≥ 3 times ULN, simultaneous total bilirubin increase ≥ 2 times ULN and elevated ALP).

- Only one subject had elevated total bilirubin associated with elevated transaminases and this subject had a history of cholilithiasis and cholecystectomy.

- None of the COV795-treated subjects presented with clinically apparent manifestations of liver abnormalities.

- The increase in levels of liver enzymes was transient for all subjects, with all values either returned to normal or normalizing over time

- Interpretation of results for open-label study 0181 are limited since this was not a controlled study, and subjects could have taken other drugs during the study which could have affected the LFTs.

- Detailed narratives regarding concomitant medications and co-morbid conditions were not provided for some subjects with elevated LFTs in controlled Study 0182 and open-label study 0181 limiting the ability to assign causality.

- Interpretation of results for blinded study 0182 are confounded since the subjects received pre-operative medication which could have affected LFTs.

- In general, the hepatic-related safety findings appear consistent with the known safety profile of APAP and do not represent a new safety signal.

Brief narratives provided by the Applicant for patients with abnormal liver function tests for Phase 3 studies 0182 with ≥3xULN are summarized below in Tables 38 and 39. The causality assignment designations were made by this reviewer. The Investigator assigned causality only in the narratives included in the original submission for subjects who discontinued due to hepatic-related AE coding.

Study 0182: Of the four cases (narratives below) of elevated LFTs which were likely causally due to study drug, none of these four subjects discontinued due to elevated LFTs and none appeared symptomatic. As previously noted, one case (201-178) did not have LFTs ≥3xULN but had mildly elevated LFTs (>2xULN) and was identified by the Applicant as a subject with an hepatic-related AE (i.e., the elevated LFTs). Therefore, this subject was included in the narratives below. In the narratives, the maximum elevated LFT (if ≥3xULN) and whether the subject discontinued is bolded. The maximum elevation for any subject in this group was ALT (12.2xULN) and AST (7.1xULN).

Table 38. Study 0182 Narratives LFTs Greater Than or Equal to 3xULN or Assessed Hepatic-Related AE Likely Causally Related

1. Subject 203-140: 37-year-old female randomized to study drug, had an elevated ALT (1.1 x ULN) at Baseline, while all other LFTs were within normal reference range. At the end of the Double Blind Period, 48 hours post-bunionectomy, elevated LFTs were ALT (2.9 x ULN), **AST** (**3xULN**), and GGT (1.5xULN). The subject did not enter the OLE; instead she entered the Double Blind follow-up period, in which continuing pain control was done per the investigator's standard of practice. At the final Double Blind follow-up visit, 10 days post-bunionectomy, the GGT (1.1 x ULN) was increased, while all other LFTs remained in the normal reference range. Reviewer comments: Transient elevation of LFTs are likely causally related to study drug with return to normal range within 10 days. This transient elevation is not considered clinically significant and is consistent with the known safety profile of APAP.
2. Subject 204-022: 29-year-old female randomized to Placebo, had normal LFTs at Baseline. At the end of the Double Blind Period, 48 hours post-bunionectomy, the subject had normal LFTs, and was started on study drug on entering the OLE. On day 6 of study (4 days on study drug), elevated LFTs included ALT (2.6 x ULN) and AST (1.8 x ULN), and subject had no further pain, so ended her OLE period. On day 8 of study (6 days on study drug), the subject had her Study Exit visit, at which time she had a positive serum pregnancy test. She also had elevated LFTs including **ALT (4.2 x ULN)** and AST (2.2 x ULN). Her ALP and total bilirubin remained normal throughout study period. Reviewer comments: Transient elevation of LFTs likely causally related to study drug. However, the extent of elevation is not clinically significant and is consistent with the known safety profile of APAP.
3. Subject 204-037: 22-year-old male randomized to study drug, had normal LFTs at Baseline. At the end of the Double Blind Period, 48 hours post-bunionectomy, elevated LFTs included ALT (4xULN), ALP (1.3xULN), AST (4xULN), GGT (2.4 x ULN), and LDH (1.2xULN). The subject did not enter the OLE, so continued pain control was done per investigator's standard of care. At the Double Blind follow-up 8 days postbunionectomy, the following values were noted: **ALT (12.2xULN**), **ALP (3.2 x ULN)**, **AST (7.1 x ULN), GGT (5.2 x ULN),** and LDH (1.5 x ULN). Two weeks after the Double Blind Period, ALT (3.4 x ULN), ALP (1.8x ULN), AST (1.2 x ULN),

GGT (3 x ULN), and LDH (1.1 x ULN) were declining toward the normal reference range. Follow-up labs 4 weeks after the end of the Double Blind Period showed normal ALT, AST, ALP, GGT, and LDH. Total bilirubin remained in the normal reference range. Reviewer comments: Transient elevation of LFTs is likely causally related to study drug since the elevation began within 48 hours after study drug was started. The values returned to normal range within 4 weeks.
4. Subject 201-178: 58-year-old female who was randomized to study drug, had normal LFTs at Baseline. At the end of the Double Blind period, 48 hours post-bunionectomy, all LFTs were within normal reference range. The subject entered into the OLE, and continued taking study drug for pain control. At Visit 7, which was 8 days post-op, the subject's pain was resolved and she no longer needed study drug for pain control. Last study drug dose was taken on Day 8 post-op, and all study meds were returned at that Visit. LFTs drawn at Visit 7 showed elevations of ALT (2.8xULN), ALP (1.1xUN), AST (2.2xULN), and GGT (2.3xULN**).** The investigator recorded these LFTs as an AE of "Elevated LFTs", assessed as mild, and unrelated to study medication. An unscheduled Visit lab assessment, 20 days post-op, showed that all LFTs had returned to within the normal reference range. Reviewer comments: This subject did not meet the elevated level of ≥3xULN but the narrative was included by the Applicant because elevated LFTs were recorded as an AE. Transient elevation of transaminases was likely related to study drug, but is not clinically significant.

The following table presents the narratives for subjects in Study 0182 who received study drug, and were determined by this reviewer to be unlikely to be causally related to study drug. The maximum elevation in any subject was an ALT (18xULN). However, this subject's ALT became elevated prior to receiving study drug. There was one subject in this group (202-047) who discontinued due to elevated LFTs.

Table 39. Study 0182 Narratives Greater Than or Equal to 3xULN LFTs or Assessed as Hepatic-related AE Unlikely Causally Related

1. Subject 202-047: 45-year- old female who was randomized to Placebo, had elevated LFTs at Baseline of ALT (1.7 x ULN), AST (1.4 x ULN), and GGT (1.3 x ULN). At the end of the Double Blind Period, 48 hours post-bunionectomy, elevated LFTs were ALT (5.4xULN), AST (3.3xULN), and GGT (2.5xULN**)**. The patient then started study drug, entered the OLE, and 5 days later had ALT (**6.5 x ULN**), ALP (1.2 x ULN), AST (**7.5 x ULN**), **GGT (10xULN**), and LDH (1.4 x ULN). The patient was **discontinued** early due to the AE of elevated LFTs on Day 7 of the OLE. Labs on day 13 of OLE included ALT (3.9 x ULN), ALP (1.1 x ULN), AST (2.1 x ULN), and GGT (7.2 x ULN). The last labs on day 18 of the OLE included GGT (4.2 x ULN), and normal ALT, AST, and ALP. The total bilirubin remained within normal reference range throughout the study period. *Reviewer comments:* This subject had mildly elevated baseline LFTs which increased after placebo and persisted after receiving study drug in the OLE phase.

The maximum elevation of ALT and AST were reached on Day 5 after study drug with transaminases returning to normal by day 18 except for elevated GGT which was decreasing from peak elevation. Given that the LFTs initially increased while the subject was on placebo, causality of increased LFTs to study drug alone is unlikely, although study drug appeared to worsen the already rising LFTs
2. Subject 201-121: 60-year-old female with Baseline elevation of ALP (1.2 x ULN) and GGT (1.5x ULN), was randomized to Placebo for the Double Blind phase. At the end of the Double Blind phase, 48 hours post-bunionectomy, she had LFT elevations including ALP (1.3 x ULN), GGT (2.6 x ULN), and **ALT (18xULN**), and AST (1.6xULN). She then started on study drug, continued into, and completed, the OLE phase. Her last labs, collected on day 5 post-op, showed elevated LFTs of ALP (1.3 x ULN), GGT (2.8 x ULN), and ALT (1.2x ULN). All other LFTs remained within the normal reference range. *Reviewer comment*s: This subject's maximum elevation of ALT 18xULN occurred prior to receiving study drug. After starting study drug, her LFTs did not worsen and, in fact, within 5 days, the ALT had returned to baseline suggesting study drug was not the likely cause for elevated LFTs.
3. Subject 202-013: 46-year-old male with Baseline LFT elevations of ALT (1.3 x ULN) and AST (1.1 x ULN), was randomized to Placebo. At the end of the Double Blind Period, 48 hours post-bunionectomy, he had further LFT elevations of **ALT (3.3xULN),** AST (2.3 x ULN), and GGT (1.3 x ULN). The subject then started study drug on entering the OLE, and after 5 days (7 days post-op) the elevated LFTs included ALT (1. 6 x ULN), AST (1.2 x ULN), and GGT (1.3 x ULN). He continued on until the end of the OLE, 14 days post-bunionectomy. At that time the elevated LFTs were ALT (1.5 x ULN), AST (1.3 x ULN), and GGT (1.2 x ULN). All other LFTs remained within the normal reference range. *Reviewer comments:* This subject had baseline elevated transaminases which increased slightly while on placebo and decreased from maximum elevation while on study drug indicating study drug was not the probable cause for elevated LFTs.

Study 0181: Since this was an open-label study, determination of causality to study drug was confounded by variables such as the possible use of concomitant medications. There were five subjects who discontinued early due to elevated LFTs (103-006, 119-010, 152-005, 163-011 and 175-030). However, no subjects appeared to have symptoms definitely related to abnormal LFTs. In all of the cases below, the transient elevation of LFTs was likely causally related to study drug.

Table 40 summarizes the Applicant's narratives for subjects with LFTs ≥3xULN in OL Study 0181.

Table 40. Study 0181 Narratives LFTs Greater Than or Equal to 3xULN or Assessed as Hepatic-related AE

1. Subject 103-006: 44-year-old male, with normal Baseline LFTs, had an AE of increased ALT on Day 15 of study drug treatment. Medical history included pneumonia, hand fracture, fracture reduction and ligament rupture. No concomitant medications were recorded for the subject. Hepatic enzymes were increased on Day 8 and Day 15. The maximum values were on Day 15 with **ALT 3.2xULN; AST 2.3xULN;** and LDH 1.0 x ULN (LDH value was slightly outside the reference range). Study drug administration was stopped and the subject was **discontinued** from the study early due to the increased ALT (Day 17). Seven days after study drug discontinuation, all LFT values had returned to within the normal reference range (Day 24). Serum total bilirubin and alkaline phosphatase remained within the reference range. The investigator considered the AE of increased ALT to be related to study drug. Discontinuation narrative was included in the original submission.
2. Subject 119-010: 57-year-old white woman with OA of the knee, had hepatic enzyme increased (elevated liver enzymes) on the ninth day of dosing (Day 8 of treatment). The out of reference range labs were **ALT 6.4xULN**; AST 2.9xULN; and GGT 1.9xULN. Her medical history included gallbladder disorder, cholecystectomy, back pain, endometriosis, and hysterectomy. No concomitant medications within 2 weeks prior to the increased hepatic enzymes were recorded. Study drug administration was stopped and the subject was **discontinued** from the study due to the increased hepatic enzymes. Two days after study drug discontinuation, the ALT had decreased to 2.1xULN; GGT 1.3xULN and AST had returned to normal reference range. Serum total bilirubin and ALP remained within the reference range. The investigator considered the AE of increased hepatic enzymes to be possibly related to study drug. Discontinuation narrative was included in the original submission.
3. 163-011: 53-year-old male, with normal Baseline LFTs, except for elevated AST (1.1 x ULN) and GGT (1.1 x ULN), had an AE of abnormal liver function tests on Day 8 of study drug treatment. No hepatic risks were noted in the past medical history which included gout, OA (knees) and erectile dysfunction. No concomitant medications were reported prior to the event of abnormal liver function tests. The maximum values for AST, ALT and LDH were on Day 8 with **AST 7.5xULN**; **ALT 2.9xULN;** and LDH 1.0 x ULN. The maximum value for GGT (2.0 x ULN) was on Day 22 at an unscheduled repeat laboratories' visit. Study drug administration was stopped (Day 13) and the subject was **discontinued** from the study early due to the abnormal LFTs (Day 15). AST was 2.2 x ULN (Day 15) and remained increased 9 days after study drug discontinuation (4.8 x ULN). ALT was 1.3 x ULN (Day 15) and remained increased 9 days after study drug discontinuation (2.1 x ULN). GGT was increased on Day 8 (1.6 x ULN) and Day 15 (1.7 x ULN). LDH returned to within the normal reference range by Day 15. Serum total bilirubin and alkaline phosphatase remained within the reference range. The investigator considered the AE of abnormal liver function tests to be possibly related to study drug. Discontinuation narrative for this subject was included in the original submission.

4. Subject 175-030: 53-year-old female with chronic low back pain (CLBP), had increased hepatic enzymes that began on the eighth day of dosing. Her pertinent medical history included gastroesophageal reflux disease, **cholelithiasis,** GERD, and cholecystectomy. Concomitant medications within 2 weeks prior to the event included lisinopril, salbutamol (albuterol), clonidine, valproate semisodium, omeprazole, hydrochlorothiazide, and levothyroxine. The subject had normal Baseline LFTs. The out of reference range labs were **GGT (10.0xULN)**, **AST (9.0xULN**), **ALT (7.5x ULN),** Direct Bilirubin (2.7 x ULN), ALP (2.3 x ULN), LDH (1.9 x ULN) and **Total Bilirubin (1.8 x ULN)**. Study drug administration was stopped (Day 10) and the subject was **discontinued** from the study early due to the abnormal LFTs (Day 10). Repeat LFT labs on Day 10 revealed a GGT 8.5 x ULN, ALT 4.6 x ULN, AST 2.8 x ULN, ALP 2.2 x ULN, Direct Bilirubin 1.3 x ULN, and LDH 1.3 x ULN; Total Bilirubin was within the normal reference range. Repeat LFT labs on Day 13 revealed a GGT 5.8 x ULN, ALT 1.6 x ULN, ALP 1.4 x ULN, while all other LFTs were within the normal reference range. Ten days after study drug discontinuation, all LFT values had returned to within the normal reference range (Day 20), except for GGT (2.9 x ULN) and ALP (1.1 x ULN). The investigator considered the AE of hepatic enzyme increased to be possibly related to study drug. A discontinuation AE narrative summary was provided for this subject in the original submission. Reviewer comments: Transient elevated transaminases possibly related to study drug. This subject had a mildly elevated total bilirubin (<2xULN) but had a history of cholelithiasis.
5. 163-008: 51-year-old male, with normal Baseline LFTs, had AEs of increased ALT, increased AST, and increased LDH, with multiple LFTs elevated at multiple scheduled assessments. The maximum values for ALT and AST were on Day 29, with **ALT 3.3xULN**; and AST 2.0 x ULN. LDH was only increased on Day 22, at 1.1 x ULN. Study drug administration continued throughout the entire treatment phase (Day 37). ALT was increased on Day 15 (2.1 x ULN), Day 22 (2.4 x ULN), and Day 36 (2.2 x ULN), and returned to within the normal reference range by Day 44. AST was increased on Day 15 (1.6 x ULN), Day 22 (1.5 x ULN), Day 36 (1.3 x ULN), and returned to within the normal reference range by Day 44. Serum total bilirubin and alkaline phosphatase remained within the reference range.
6. Subject 174-003: 40-year-old male, with normal Baseline LFTs, had an AE of abnormal liver function tests on Day 22 of study drug treatment. Hepatic enzymes were increased on Day 22 and Day 29. The maximum value for both labs was on Day 22 with **AST 7.4xULN; and ALT 2.4xULN.** Study drug administration continued throughout the entire possible treatment phase (Day 36). AST declined to 1.4 x ULN on Day 29 and returned to within the normal reference range by Day 36. ALT declined to 1.6 x ULN on Day 29 and returned to within the normal reference range by Day 36. Serum total bilirubin and alkaline phosphatase remained within the reference range.
7. Subject 110-032: 59-year-old male, with normal Baseline LFTs, had multiple LFTs elevated at multiple scheduled assessments on study drug treatment. The maximum values were on Day 22 with **GGT 3.3xULN**; ALT 1.5 x ULN; and AST 1.2 x ULN. Study drug administration continued throughout the entire possible treatment phase (Day 36). GGT was increased on Day 8, Day 15, Day 22, Day 29 and Day 36 (declining to 1.5 x

ULN at the end of the study). ALT was increased on Day 15 and Day 22, and retuned to within the normal reference range by Day 29. AST was increased on Day 22, and returned to within the normal reference range by Day 29. Serum total bilirubin and alkaline phosphatase remained within the reference range.
8. Subject 112-002: 39-year-old female, with normal Baseline LFTs, except for an elevated GGT (1.9 x ULN), had multiple LFTs elevated at multiple scheduled assessments on study drug treatment. The maximum value for all LFTs was on Day 22 with GGT 6.9 x ULN; **ALT 6.8xULN; AST 4.0xULN**; ALP 1.2 x ULN; and LDH 1.1 x ULN. Study drug administration continued through the entire possible treatment phase (Day 37). ALP and LDH returned to within the normal reference range by Day 29. At Day 36, GGT had declined to 3.4 x ULN, ALT had declined to 1.2 x ULN, and AST had declined to 1.1 x ULN. Serum total bilirubin and alkaline phosphatase remained within the reference range.
9. Subject 147-014: 60-year-old female, with normal Baseline LFTs, had multiple LFTs elevated at multiple scheduled assessments on study drug treatment. The maximum values were on Day 8 with **GGT 3.9xULN;** ALT 2.1xULN; and AST 1.4 x ULN**.** Study drug administration continued throughout the entire possible treatment phase (Day 36). ALT and AST values had returned to within the normal reference range by Day 15. GGT values were increased but declined over Day 15 (2.2 x ULN), Day 22 (1.5 x ULN), Day 29 (1.6 x ULN), and Day 36 (1.1 x ULN). Serum total bilirubin and alkaline phosphatase remained within the reference range.
10. Subject 160-014: 82-year-old female, with normal Baseline LFTs, except for an elevated GGT (1.6 x ULN), had multiple LFTs elevated at multiple scheduled assessments on study drug treatment. The maximum values for all three labs were on Day 15 with **GGT 3.6xULN**; **ALT 1.8xULN**; and **AST 1.2xULN.** Study drug administration continued throughout the entire possible treatment phase (Day 36). ALT and AST values were increased on Day 22, and returned to within the normal reference range by Day 29. GGT values were increased on Day 8 (1.6 x ULN), Day 22 (3.1 x ULN), Day 29 (1.8 x ULN) and Day 36 (1.5 x ULN). Serum total bilirubin and alkaline phosphatase remained within the reference range.
11. Subject 152-005: 42-year-old female with OA of the knee, had increased hepatic enzymes that began on Day 22. Her medical history included drug hypersensitivity (allergy to penicillin), OA (left knee, hand), dysmenorrhea, and rhinitis seasonal. Concomitant medications within 2 weeks prior to the event of increased hepatic enzyme included cetirizine, ibuprofen, calcium, medroxyprogesterone acetate, bisacodyl, fish oil, and multivitamins. She first received study drug on 12/8/2011 (Day 1). On 12/29/2011 (Day 22), she experienced moderate increased hepatic enzymes. Maximum ALT 2.4xULN on Day 28 and AST 2xULN on Day 22. No other LFTs were elevated. She had previously experienced mild AEs of dyspepsia, nausea, and somnolence on Day 5, which had resolved, and constipation beginning on Day 11, which was ongoing at the time of this event. No treatment was recorded. On Day 26, she also experienced mild pruritus. No further study drug was taken after 1/4/2012 (Day 28). The AE of increased hepatic enzyme resolved on 1/12/2012 (Day 36). The investigator considered the AE of increased hepatic enzyme to be related to study medication. By Day 36, all LFTs had returned to normal. The subject discontinued

from the study. Discontinuation narrative was included in the original submission.
(Table, reviewer)

Phase 1 Integration Set (Hepatic SMQ)
The only subject with a treatment-emergent hepatic disorder (hepatic enzyme increased) was one subject in the Roxicodone group.

Reviewer's Summary (TEAEs and SMQ Terms of Special Interest)
In general, the safety findings of study drug COV795 are consistent with the known safety profile of the opioid class of drugs and APAP.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events for Phase 1 and Phase 3 studies were GI or Nervous System Disorders SOC and have been discussed in detail in Section 7.3.5 of this review.

The most common TEAEs with an incidence in the total treatment group of at least 2% by SOC and preferred terms in the safety population for the Phase 3 Integration Set is shown below in Table 41.

Table 41. Most Common Treatment-Emergent Adverse Events (Incidence in Total Treatment Group at Least 2%) by MedDRA System Organ Class and Preferred Term (Phase 3 Integration Set)

	COV795-15/650					
System Organ Class Preferred Term	< 5 days N = 172 n (%)	5 to < 10 days N = 88 n (%)	≥ 10 days N = 347 n (%)	Overall N = 607 n (%)	Placebo N = 163 n (%)	Total N = 701 n (%)
Subjects with at least 1 TEAE	115 (66.9)	59 (67.0)	195 (56.2)	369 (60.8)	35 (21.5)	392 (55.9)
Gastrointestinal Disorders	90 (52.3)	39 (44.3)	102 (29.4)	231 (38.1)	16 (9.8)	243 (34.7)
Nausea	76 (44.2)	24 (27.3)	56 (16.1)	156 (25.7)	9 (5.5)	162 (23.1)
Vomiting	45 (26.2)	11 (12.5)	22 (6.3)	78 (12.9)	0	78 (11.1)
Constipation	6 (3.5)	9 (10.2)	43 (12.4)	58 (9.6)	5 (3.1)	63 (9.0)
Nervous System Disorders	53 (30.8)	32 (36.4)	81 (23.3)	166 (27.3)	13 (8.0)	175 (25.0)
Dizziness	28 (16.3)	14 (15.9)	37 (10.7)	79 (13.0)	2 (1.2)	81 (11.6)
Somnolence	12 (7.0)	9 (10.2)	34 (9.8)	55 (9.1)	1 (0.6)	56 (8.0)
Headache	14 (8.1)	12 (13.6)	15 (4.3)	41 (6.8)	8 (4.9)	48 (6.8)
Skin and Subcutaneous Tissue Disorders	19 (11.0)	9 (10.2)	34 (9.8)	62 (10.2)	7 (4.3)	68 (9.7)
Pruritus	9 (5.2)	3 (3.4)	22 (6.3)	34 (5.6)	3 (1.8)	37 (5.3)

Source: Section 23, Table 5.5.1.
Note: Adverse events were coded using MedDRA version 14.1. Percentages were calculated based on the number of subjects in the safety population in each treatment group. Subjects were counted only once within each system organ class and preferred term. The TEAEs included from Study 0182 are those that occurred during the treatment periods.

(Source: Applicant's table, ISS, p. 83)

Details of the common AEs in the placebo-controlled, blinded Phase 3 study are discussed further below as follows:

Study 0182

Blinded Dosing Phase: During the blinding dosing phase, the proportion of subjects with at least one TEAE was approximately 54% in 89/166 subjects in the COV795 group compared to approximately 21% in 35/163 subjects in the placebo group. The most common TEAE for both COV795 group and placebo was nausea, being approximately 31% in COV795 compared to 5.5% in placebo. The next most frequently occurring TEAEs in the COV795 group were dizziness (13.3% COV795 vs 1.2% placebo) and headache (9.6% COV795 vs 4.9% placebo). At the System Organ Class level, the most frequently affected system was GI (38.6% study drug compared to 9.8% placebo) followed by Nervous System Disorders (25.9% study drug compared to 8% placebo). These findings are summarized in Table 42 below.

Table 42. Study 0182 All TEAEs Occurring in Greater Than 1% of Subjects by MedDRA System Organ Class and Preferred Term (Blinded Safety Population)

System Organ Class/ Preferred Term	n (%) COV795 (N = 166)	Placebo (N = 163)	Total (N = 329)
Subjects who reported any TEAE	89 (53.6)	35 (21.5)	124 (37.7)
Gastrointestinal disorders	64 (38.6)	16 (9.8)	80 (24.3)
Constipation	7 (4.2)	5 (3.1)	12 (3.6)
Dry mouth	1 (0.6)	2 (1.2)	3 (0.9)
Nausea	51 (30.7)	9 (5.5)	60 (18.2)
Vomiting	15 (9.0)	0	15 (4.6)
General disorders and administration site conditions	6 (3.6)	1 (0.6)	7 (2.1)
Oedema peripheral	2 (1.2)	0	2 (0.6)
Injury, poisoning and procedural complications	2 (1.2)	0	2 (0.6)
Excoriation	2 (1.2)	0	2 (0.6)
Nervous system disorders	43 (25.9)	13 (8.0)	56 (17.0)
Dizziness	22 (13.3)	2 (1.2)	24 (7.3)
Headache	16 (9.6)	8 (4.9)	24 (7.3)
Hypoaesthesia	1 (0.6)	2 (1.2)	3 (0.9)
Somnolence	6 (3.6)	1 (0.6)	7 (2.1)
Renal and urinary disorders	2 (1.2)	0	2 (0.6)
Dysuria	2 (1.2)	0	2 (0.6)
Skin and subcutaneous tissue disorders	15 (9.0)	7 (4.3)	22 (6.7)
Blister	2 (1.2)	1 (0.6)	3 (0.9)
Erythema	2 (1.2)	0	2 (0.6)
Pruritus generalized	2 (1.2)	0	2 (0.6)
Rash	3 (1.8)	2 (1.2)	5 (1.5)
Vascular disorders	2 (1.2)	1 (0.6)	3 (0.9)
Hot flush	2 (1.2)	1 (0.6)	3 (0.9)

Source: Table 14.3.1-6.
N = number of subjects in specified treatment arm; n = number of subjects with data available.
Medical Dictionary of Regulatory Activities, version 14.1 coding applied. Summary is by actual treatment received during the blinded dosing period.

(Source: Applicant's table, Study 0182 CSR, p. 104)

Blinded Follow-up Phase: During the blinded follow up phase, there were 15.7% (14 subjects) in the COV795 group who experienced at least one TEAE compared to 20.2% (19 subjects) in the placebo group with no TEAE reported in >3 subjects in either treatment group.

OL Extension Phase: During the OL extension phase, there were 43.8% (64 subjects) who experienced at least one TEAE with the most common TEAES being nausea (17.8%), vomiting (7.5%) and constipation (6.2%)

OL Follow-up Phase: During the OL follow up period, there were 9.6% (14 subjects) who experienced at least one TEAE with no TEAE reported in >2 subjects.

7.4.2 Laboratory Findings

In the ISS, laboratory test values were presented by the Applicant for the two most similar integration sets (i.e., Phase 3 and Phase 1) stating their rationale for this as follows: “due to differences in study designs and collection time points among the studies in the other three integration sets (Phase 1 and 3 Integration Set, Phase 1 Single Dose Integration Set and Phase 1 Multiple Dose Integration Set), laboratory test summaries for those integration sets would not be informative”. Since the Applicant has presented safety findings for all of the individual studies, this approach to presentation of laboratory findings for the two most similar integration sets appears acceptable to provide the most meaningful clinical information.

Hepatic Function Laboratory Findings
In response to two clinical Information Requests, the Applicant provided a list of all subjects in the Phase 3 Studies with hepatic function tests ≥2xULN. Based upon that information, the following conclusions were drawn:

- Phase 3 Studies:
  Study 0182: The Applicant identified eight subjects who received study drug and ten subjects who received placebo who experienced hepatic function tests ≥2xULN.

  Study 0181: The Applicant identified 24 subjects who experienced hepatic function tests ≥2xULN.

- Phase 1 Integration Set
  According to the Applicant, in general, few COV795 subjects experienced shifts from normal baseline to high end-of-study values for liver function tests (e.g., shifts from normal to high in AST: 1.6% and 0% in COV795 2 Tablets and 1 Tablet groups, respectively; 5.6% to 14.7% in active treatment groups).

Aside from the LFTs, there were no other abnormal laboratory values in the Phase 3 or Phase 1 Integration Sets which were identified by this reviewer as being clinically meaningful or showed any patterns or trends regarding safety.

In general, the hepatic laboratory values in the Integrated Phase 1 and 3 studies appear consistent with the known safety profile of APAP with overall, mild transient elevations of LFTs.

7.4.3 Vital Signs

Vital signs and pulse oximetry summaries were presented only for the most similar integration set of the Phase 1 studies, the Phase 1 Integration Set. According to the Applicant, study designs of the Phase 3 studies did not allow integration of the vital

signs and pulse oximetry results. Results from individual studies, however, were included in the individual Clinical Study Reports.

The vital signs' AEs of special interest were those associated with vital sign abnormalities with preferred terms of tachycardia, hypotension and respiratory depression and which have been previously discussed in Section 7.3.5 of this review.

The major vital signs findings from the Phase 3 and Integrated Phase 1 safety data base are summarized below:

Phase 3 Studies

Study 0182: Vital signs were collected on an hourly basis during the blinded dosing phase. The Applicant summarized vital signs by cohort. Cohort 1 (enrolled before Amendment 2 and given a single dose and then initiated Q12 hour dosing at the time a second dose was requested) or Cohort 2 (enrolled under Amendment 2 or later and administered two COV795 tablets Q12 hours throughout the blinded dosing phase for a total of four doses over 48 hours).

- In Cohort 1, in general, shifts were similar between treatment groups in the blinded dosing periods and similar between blinded and open-label phases. The small number of subjects limited interpretation of clinically meaningful data.
- In Cohort 2, shifts from normal to abnormal in oxygen saturation occurred in the largest proportions of COV795-treated subjects at 40 hours (12 [8.8%] subjects) and of placebo-treated subjects at 20 hours (7 [5.3%] subjects. No changes required treatment intervention.

Study 0181: Vital signs were collected on a weekly basis. Changes from baseline in vital signs were generally small and not clinically significant. The only vital sign-related TEAE leading to discontinuation was hypopnea (1 [0.6%] subject) in Subject 101-040 (COV795 < 5 days) who experienced moderate hypopnea that resolved the same day, was considered related to COV795, and led to study discontinuation. Changes in oxygen saturation were not clinically significant.

Phase 1 Integration Set

The Phase 1 studies included in the Phase 1 Integration Set did not include subjects who were naltrexone blocked.

Baseline (predose), postbaseline, and change from baseline were summarized for each vital sign and pulse oximetry value for the Phase 1 Integration Set at the following time points common across the Phase 1 studies: 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 36 hours, and 48 hours. For crossover studies where COV795 was taken in more than one period, the period where the subject received COV795 while fasting was

used. If a subject did not have vital signs measured during the fasting period, the first period on study was used. Overall, there were no clinically meaningful or significant changes reported. In the Phase 1 Integration Set, there were no reports of TEAEs related to vital signs or oxygen saturation the led to study discontinuation and none of the subjects experienced events of respiratory depression or hypotension.

In general, there were no unexpected or clinically significant safety findings in the vital signs or pulse oximetry results from Integrated Phase 1 studies or individual Phase 3 studies. None of the subjects who received COV795 experienced respiratory depression or hypotension.

7.4.4 Electrocardiograms (ECGs)

The ECG results of the studies in the Phase 3 Integration Set could not be integrated because the Phase 3 studies had no assessment time points in common. Results from the individual studies were presented.

Shifts from baseline to postbaseline in overall ECG results (normal, abnormal) were reported for the Phase 1 integration set. Studies 0107, 0170, and 0256 were not used in the ECG evaluations for the Phase 1 Integration Set, because different treatments were received in each treatment period and laboratory assessments were only made at the beginning and end of the study.

None of the COV795-treated subjects had shifts to clinically significant findings in the Phase 3 studies and none of the COV795-treated subjects had ECG changes that were considered clinically significant in the Phase 1 studies.

7.4.5 Special Safety Studies/Clinical Trials

Relative Abuse Liability Study
The relative abuse potential of COV795 tablets was investigated in Study 0244, a human abuse liability study in nondependent, recreational opioid users.

See Dr. Jim Tolliver's CSS review for full details regarding the analysis of the findings from the Agency's Controlled Substances Staff perspective. The description of the study and the major safety findings are presented below.

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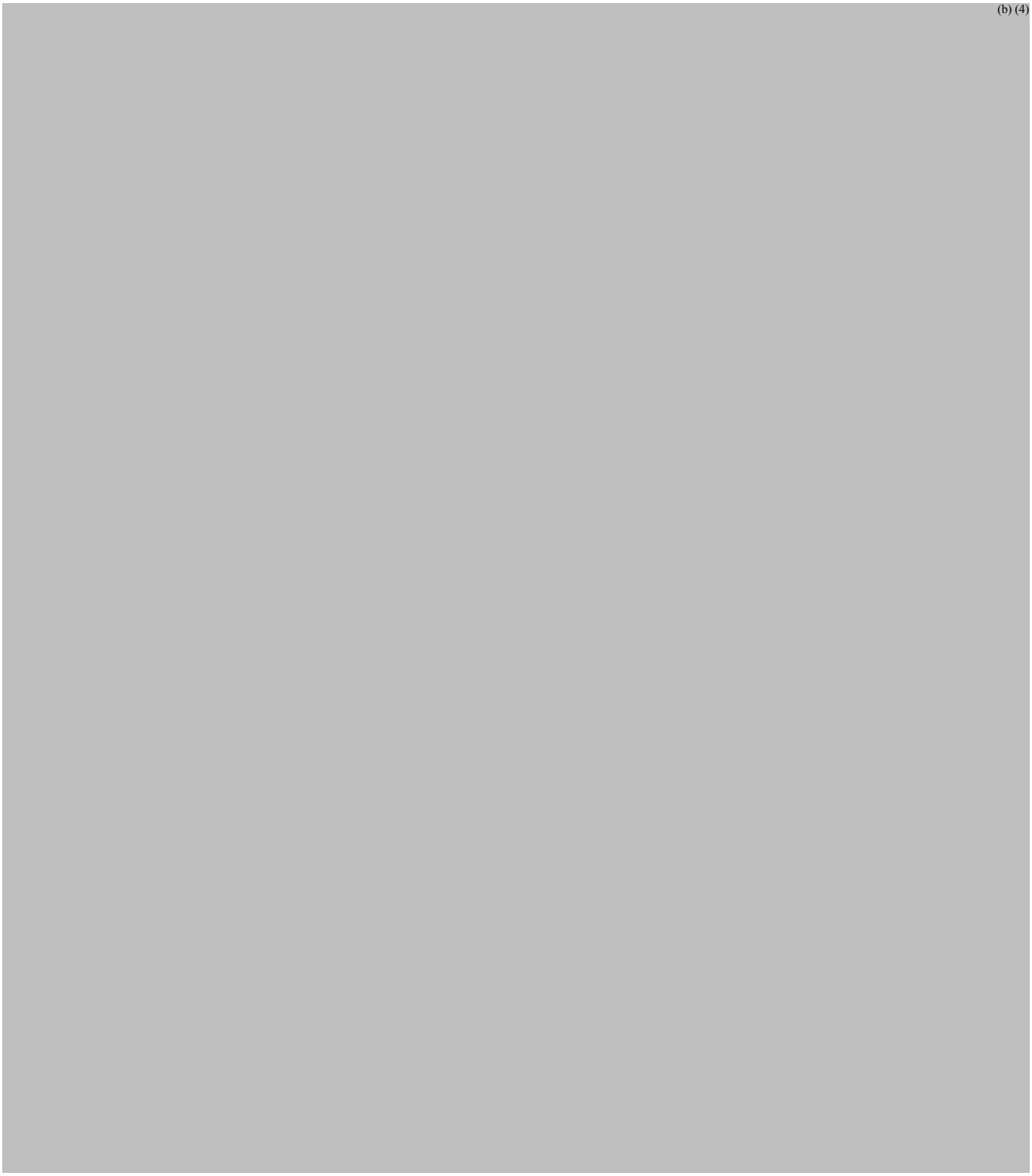

Major Safety Results:

- During the Drug Discrimination Test, the most common AEs (≥ 5% of subjects) among subjects who received IR-OC/APAP (15 mg OC/650 mg APAP) were nausea, pruritus, generalized pruritus, and vomiting.

- Except for five subjects who met protocol-mandated study withdrawal criteria, no subject experienced an AE that resulted in early discontinuation from the study during the Drug Discrimination Test. Five subjects met the study exclusion criterion of being intolerant to study treatments (e.g., emesis within the first 2 h after dosing, n = four and inability to swallow all tablets and capsules, n = one), which precluded them from entering the Treatment Phase.

- During the Treatment Phase, 82% of subjects experienced at least one AE at some time during the study. The incidence of AEs was higher for the IR-OC/APAP treatments than the corresponding doses of COV795, although the types of events experienced were similar. Overall, for the high dose, 41.1% of subjects experienced at least one AE with COV795 compared with 59.3% of subjects with IR-OC/APAP. For the low dose, 19% of subjects experienced at least one AE with COV795 compared with 29.3% of subjects with IR-OC/APAP. For the tampered doses, 31.0% of subjects had at least one AE with COV795 compared with 50.0% of subjects with IR-OC/APAP.

- The only treatment-related AE (i.e., AEs that the investigator considered to be either possibly related or related to study drug) that occurred in ≥ 10% of subjects receiving COV795 was nausea, which occurred in 10.7% of subjects with the intact high dose COV795. Treatment-related AEs that occurred in ≥ 10% of subjects receiving IR-OC/APAP included pruritus (13.8%, 13.6%, and 17.2% for the intact 15 mg OC/650 mg APAP dose, intact 30 mg OC/1,300 mg APAP dose, and tampered 30 mg OC/1,300 mg APAP dose, respectively), generalized pruritus (15.3%, and 13.8% for the high dose intact and tampered treatments, respectively), nausea (15.3% and 12.1% for the high dose intact and tampered treatments, respectively), vomiting (10.2% for the high dose intact IR-OC/APAP), and headache (10.3% for the high dose tampered treatment).

- All but two of the AEs that occurred in this study were rated as mild in severity by the investigator. Two subjects (3.3%) experienced AEs that were considered moderate in severity (probably not related to study drug).

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7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the COV795 integrated safety database, all subjects who were treated with COV795 received the same total dose of 15mg oxycodone/650mg APAP, as either one or two tablets q12 hours. The findings related to total daily dose of oxycodone and TEAEs are discussed below. As expected, in general, there were more AEs at the higher doses of opioid.

Phase 3 Studies:
The total incidence of TEAEs was greater in Study 0181 (62.5%), in which subjects received open-label treatment with two COV795 tablets Q12h for up to 42 days, than in Study 0182 (blinded dosing phase, 53.6%; open-label extension phase, 43.8%), in which subjects received blinded treatment with two COV795 tablets Q12h or placebo for 2 days and open-label treatment with two COV795 tablets Q12h for up to 17 days. The incidence of individual TEAEs decreased with length of COV795 exposure for nausea, vomiting, and dizziness, and increased with length of COV795 exposure for constipation.

Phase 1 Studies:
Observations regarding the relation between TEAE incidence and dose regimen were based on the TEAE analysis by daily OC dose (15mg vs 30mg) for the Phase 1 Integration Set.

Subjects in the COV795 (OC 15 mg/day) received a single dose of COV795 at the intended commercial dose regimen (15 mg OC/650 mg APAP Q12h), resulting in a total dose of 15 mg OC both per 12-hour period and per day, while subjects in the COV795 (OC 30 mg/day) received multiple doses of COV795 (15 mg OC/650 mg APAP Q12h), resulting in a total dose of 15 mg OC per 12-hour period and of 30 mg OC per day. Overall, no clinically meaningful effect of dose regimen on the total TEAE incidence among COV795-treated subjects was observed; the total TEAE incidence was similar between subjects who received a single dose of COV795 (15 mg OC/650 mg APAP Q12h) (52.9%) and those in the COV795 (OC 30 mg/day) group who received multiple doses of COV795 (15 mg OC/650 mg APAP Q12h) (55.0%)

In general, it appears that the TEAEs in the Phase 1 Integration Set were consistent with the known safety profile of opioids and include AEs of nausea, vomiting, constipation, dizziness, pruritus and euphoric mood. The Applicant found that the proportion of subjects with at least one TEAE for those who received Roxicdone (OC

30mg/day) was similar between the COV795 30mg/day group at 55% compared to Roxidone 3mg/day group at 58.1%.

A comparison of the most common AEs of the Phase 1 Integration Set is shown below in table 43.

Table 43. Summary of Most Common COV795-Treated TEAEs by Total Oxycodone Daily Doses Phase 1 Integration Set

Treatment	COV795		Percocet			Roxicodone		Ultracet
	Oxycodone /day							
	15mg (%) N=187	30mg (%) N=109	15mg (%) N=113	30mg (%) N=105	60mg (%) N=34	30mg (%) N=43	60mg (%) N=34	0mg (%) N=64
Subjects with at least 1 TEAE - N(%)	99 (53)	60 (55)	56 (50)	75 (71)	28 (82)	25 (58)	28 (82)	20 (31)
SOC Preferred term								
GI Disorders	65 (35)	37 (34)	35 (31)	48 (46)	21 (62)	20 (46)	17 (50)	7 (11)
Nausea	56 (30)	27 (25)	34 (30)	39 (37)	16 (47)	15 (35)	13 (38)	5 (8)
Vomiting	27 (14)	12 (11)	12 (11)	15 (14)	13 (38)	10 (23)	8 (23)	3 (5)
Nervous System Disorders	57 (30)	32 (29)	29 (26)	37 (35)	15 (44)	14 (33)	17 (50)	10 (16)
Dizziness	27 (14)	14 (13)	11(10)	18 (17)	8 (23)	10 (23)	13 (38)	(<10)
Headache	17 (9)	17 (16)	11 (10)	14 (13)	5 (15)	5 (12)	5 (15)	(<10)
Somnolence	23 (12)	7 (6)	10 (9)	11 (10)	4 (12)	2 (5)	1 (3)	2 (3)
Skin and SubQ Tissue Disorders	18 (10)	30 (27)	8 (7)	26 (25)	17 (50)	6 (14)	13 (38)	5 (8)
Pruritus	15 (8)	27 (25)	7 (6)	24 (23)	17 (50)	5 (12)	13 (38)	5 (8)

(Table, reviewer; Modified Applicant's table, p. 97 ISS)

7.5.2 Time Dependency for Adverse Events

The Applicant reported that in the Phase 3 Integration Set, with increasing length of COV795 exposure (< 5 days, 5 to < 10 days, and ≥ 10 days, respectively), a decrease was observed in the proportion of subjects who discontinued the studies due to an AE (33.7%, 20.5%, and 2.9%) or due to lack of efficacy (4.1%, 1.1%, and 0.6%).

The proportion of COV795-treated subjects who discontinued due to withdrawal by subject was the same (1.2%) in the COV795 < 5 days and COV795 ≥ 10 days groups and was highest (5.7%) in the COV795 5 to < 10 days group. The clinical significance of this finding is not clear. In the placebo group, most subjects discontinued the studies due to lack of efficacy (10.4%), with equal proportions (1.2%) discontinuing due to AE and withdrawal by subject.

In general, it appears that fewer subjects discontinued due to AEs in the ≥10 days compared to<10 days. This may suggest a tolerance to the common AEs which led to study discontinuation (i.e., nausea and vomiting).

The reasons for discontinuation by exposure duration are depicted in Table 44, below:

Table 44. Subject Disposition (Safety Population) Phase 3 Integration Set

	COV795-15/650					
	< 5 days n (%)	5 to < 10 days n (%)	≥ 10 days n (%)	Overall n (%)	Placebo[b] n (%)	Total n (%)
Safety population[a]	172	88	347	607	163	701
Completed study	105 (61.0)	64 (72.7)	319 (91.9)	488 (80.4)	142 (87.1)	561 (80.0)
Discontinued study	67 (39.0)	24 (27.3)	28 (8.1)	119 (19.6)	21 (12.9)	140 (20.0)
Reason for discontinuation						
Adverse event	58 (33.7)	18 (20.5)	10 (2.9)	86 (14.2)	2 (1.2)[c]	88 (12.6)
Death	0	0	2 (0.6)	2 (0.3)	0	2 (0.3)
Lack of efficacy	7 (4.1)	1 (1.1)	2 (0.6)	10 (1.6)	17 (10.4)	27 (3.9)
Recovery	0	0	0	0	0	0
Withdrawal by subject	2 (1.2)	5 (5.7)	4 (1.2)	11 (1.8)	2 (1.2)	13 (1.9)
Physician decision	0	0	3 (0.9)	3 (0.5)	0	3 (0.4)
Protocol violation	0	0	3 (0.9)	3 (0.5)	0	3 (0.4)
Lost to follow-up	0	0	3 (0.9)	3 (0.5)	0	3 (0.4)
Other	0	0	1 (0.3)	1 (0.2)	0	1 (0.1)

Source: Section 23, Table 2.2.
Note:. Percentages were calculated based on the number of subjects in the safety population.
[a]The safety population included all subjects who received at least 1 dose of study treatment.
[b]For study COV15000182, completed represents subjects who completed the blinded dosing phase.
[c]The AE that led to study discontinuation of Subject 201-155 occurred during the blinded follow-up period. The event was an SAE (Table 10.3-1). The AE occurred during the blinded follow-up period, while the subject was not receiving study treatment.

(Source: Applicant's table, ISS, p. 62)

7.5.3 Drug-Demographic Interactions

The following demographic subgroups were used to further characterize TEAEs in the Phase 3 Integration Set and the Phase 1 Integration Set.

- Age: ≤ 65 years, > 65 years to ≤ 75 years, > 75 years
- Sex: Male/Female
- Race: White or Caucasian, Black or African American, Asian, Other (For race subgroups only, categories of American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander were combined with Other). For demographics tables, all race categories were reported.

TEAEs by Age - Phase 3 Integration Set

Mean subject age was 48.2 years (range among exposure categories, 41.9 to 50.3 years). Most COV795-treated subjects were 65 years or younger (89.6%; range among exposure categories, 87.9% to 94.3%), with 1.6% of subjects being older than 75 years (range 0% to 2.6%). A higher proportion of COV795 experienced at least 1 TEAE in the 65-75 year compared to <65 years.

The proportion of COV795-treated subjects with at least 1 TEAE (< 5 days, 5 to < 10 days, and ≥ 10 days, respectively) was higher by at least 5% among subjects between 65 and 75 years than among subjects 65 years or younger (86.7% vs 64.7%, 80.0% vs 66.3%, and 72.7% vs 53.8%).

The most common TEAEs by subject age and days of exposure are shown in Table 45, below:

Table 45. Most Common TEAEs (Phase 3 Integration Set) by Age and Exposure

Treatment Arm	**COV795-15/650**								
Age	≤65 years			>65 - ≤75 years			>75 years		
Days Exposure	<5	5 - <10	≥10	<5	5- <10	≥10	<5	5- <10	≥10
Total # Treated	N=156	N=83	N=305	N=15	N=5	N=33	N=1	N=0	N=9
% experiencing at least 1 TEAE	65	66	54	87	80	73	100	0	78
Preferred Term									
Nausea	42	28	16	67	20	21	0	0	11
Vomiting	21	12	5	73	20	12	100	0	22
Dizziness	16	14	9	20	40	18	0	0	44
Headache	8	14	4	7	0	6	0	0	0
Somnolence	6	10	8	13	20	15	0	0	33
Sedation	<1	0	1	0	20	0	0	0	0
	Placebo								
	≤65 years			65-75 years			>75 years		
Total # Treated	N=155			N=8			N=0		
% experiencing at least 1 TEAE	21			25			0		

(Table, reviewer, reference Applicant's table 5.2.1, ISS p. 411-443); percentages rounded

TEAEs by Age – Phase 1 Integration Set
In the Phase 1 Integration Set, there were no subjects ≥65 years of age, therefore TEAEs could not be analyzed by age.

In general, more subjects in the Phase 3 Integrated Set >65 to ≤75 years age group experienced at least one TEAE. Dizziness, nausea and vomiting were the most frequently occurring AE preferred terms in this age group. Given the much smaller number of subjects in this age group compared to the ≤65 year age group, the clinical significance of this is not clear. At the present time, these findings do not rise to the level that would require inclusion in the label as some differences may be expected and the small number of subjects in the >65 year age group makes it problematic to generalize the findings in this age group.

TEAEs by Gender– Phase 3 Integration Set
Demographic and baseline characteristics of the Phase 3 Integration Set reveal that the demographic characteristics were generally similar among COV795 (15 mg OC/650 mg APAP) exposure categories with the exception of the percentage of women. One of the studies in the Phase 3 Integration Set, the bunionectomy Study 0182, enrolled mostly women (85.1%). The Applicant pointed out that because subjects of Study 0182 made up the majority in the COV795 <5 days and COV795 5 to < 10 days exposure groups, the sex ratio in those groups was skewed towards women (87.2% and 80.7%, respectively) and the majority of subjects in the COV795 Overall group for COV795-treated subjects were female (68.5%); with the female:male ratio more balanced in the group of subjects with ≥ 10 days of exposure (56.2% female, 43.8% male).

The difference in AEs by gender is shown below in the Table.

Table 46. TEAEs by Gender (Phase 3 Integration Set)

Treatment Group	**COV795-15/650**						**Placebo**	
Exposure Days	<5 days		5 to <10 days		≥10 days			
Sex	[M] N=22	[F] N=150	[M] N=17	[F] N=71	[M] N=152	[F] N=195	[M] N=28	[F] N=135
% experiencing at least 1 TEAE	54	69	59	69	49	62	21	21
Preferred Term								
Nausea	9	49	12	31	7	23	0	7
Vomiting	14	28	0	15	2	10	0	0
Dizziness	0	19	18	15	8	13	0	1
Somnolence	9	7	18	8	8	11	0	<1

(Table, reviewer); [M]=male; [F]=female; percentages rounded

Gender differences were seen with nausea, dizziness and vomiting where the incidence for each of these occurred more frequently in females than males. Gender differences were also seen with the preferred term somnolence which occurred in 18% males compared to 8% females.

The Applicant opines that the observed difference in TEAE incidence between COV795-treated women and men was as expected for a low-dose opioid/APAP combination product and was consistent with the differences in TEAE incidence between women and men observed in Phase 1 studies after treatment with the listed drugs, Roxicodone and Ultracet and the IR comparator, Percocet. The Applicant further points out that the USPIs of Roxicodone, Ultracet and Percocet do not address sex-related differences in TEAE incidence and they conclude that the safety data for the Phase 3 Integration Set do not indicate a clinically significant effect of sex on the safety profile of study drug COV795. Overall, I am in agreement with the Applicant's interpretation of the data.

TEAEs by Race – Phase 3 Integration Set

The majority of COV795-treated subjects were white (62.9%; range among exposure categories, 59.9% to 67.4%) and not Hispanic or Latino (81.9%; range 76.1% to 86.2%).

In the COV795 Overall group in the Phase 3 Integration Set, 62.9% of subjects were white, 23.7% of subjects were black, 12.2% of subjects were Asian, and approximately 1% of subjects were from Native or Other racial groups. Because of small Ns for Asian subjects (COV795 < 5 days and COV7955 to < 10 days) and Native and Other subjects (all COV795 exposure groups), the Applicant determined that meaningful race-based comparisons could be made only in white subjects, black subjects, and Asian subjects (COV795 ≥ 10 days only).

The proportion of COV795-treated subjects with at least 1 TEAE was generally similar (less than a 5% difference) for white subjects compared to black subjects in the COV795 < 5 days group (66.4% vs 64.9%) and for white subjects compared to both black subjects and Asian subjects in the COV795 ≥ 10 days group (57.2% vs 54.2% vs 55.6%). However, a difference between racial groups of at least 5% was noted for white subjects compared to black subjects in the 5 to < 10 days group (63.8% vs 70.8%). No particular TEAEs appeared to account for this difference; however, the number of black subjects in that group was relatively small (N = 24).

Among subjects in the COV795 ≥ 10 days group, for white subjects compared to black and Asian subjects, the incidence of dizziness differed by at least 5% across each racial group (white, black, and Asian subjects, being highest for Asian subjects: 4.3% vs 9.6% vs 37.0%, respectively. For the other 2 COV795 exposure groups, a comparison of white vs black subjects, respectively, revealed a difference of at least 5% in the indicated COV795 groups as follows: vomiting (COV795 < 5 days: 28.4% vs 16.2%), dizziness (COV795 5 to < 10 days: 20.7% vs 8.3%), and headache (COV795 5 to < 10 days: 13.8% vs 4.2%).

These findings do not represent safety findings which would require labeling.

7.5.4 Drug-Disease Interactions

The two specific drug-disease categories that were addressed by the Applicant in the submission were renal impairment and hepatic impairment.

Renal Impairment: COV795 was not studied in renally-impaired subjects. The Applicant summarized the key applicable statements regarding renal impairment from the USPI of Roxicodone as follows:

> "*Published data reported that elimination of OC was impaired in end-stage renal failure. Mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation. The USPI of Percocet includes a similar statement."*

Because the Ultracet USPI does not include DDI language regarding renal impairment and APAP, the clinical pharmacology team is in the process of determining appropriate language regarding renal impairment to be included in the Xartemis label.

At the present time, the Applicant's proposed label is still under review.

Hepatic Impairment: COV795 was not studied in patients with hepatic impairment.

The Applicant notes the following:

> *"The USPI of Roxicodone states that since oxycodone is extensively metabolized, its clearance may decrease in hepatic failure patients. Dose initiation in patients with hepatic impairment should follow a conservative approach. Dosages should be adjusted according to the clinical situation. The USPI of Percocet includes a similar statement.*
>
> *The USPI of Ultracet states that the PK and tolerability of Ultracet in patients with impaired hepatic function have not been studied. Since tramadol and APAP are both extensively metabolized by the liver, the use of Ultracet in patients with hepatic impairment is not recommended*."

At the present time, the Applicant's proposed label is still under review.

7.5.5 Drug-Drug Interactions

There were no specific drug-drug interaction studies conducted for this submission. The Applicant plans to rely on what is known and labeled for the listed drugs and class of drugs (opioids) as applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See the Agency's pharmacology toxicology review by Dr. Beth Bolan.

7.6.2 Human Reproduction and Pregnancy Data

No specific studies were conducted to assess this safety category. The Applicant plans to rely on what is known regarding opioids and acetaminophen as class products. Dr. Leyla Sahin from the Agency's Office of Pediatric and Maternal Health consulted with the Division's pharmacology toxicology reviewers.

At the present time, the Applicant's proposed labeling is still under review.

7.6.3 Pediatrics and Assessment of Effects on Growth

No event of pediatric exposure was reported in the submission. COV795 was not studied in subjects younger than 18 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Withdrawal:
The Applicant reported than an investigation of potential withdrawal signs and symptoms observed during the COV795 clinical development program was performed using the terms and recommendations of the drug abuse, dependence and withdrawal SMQ (version 15.1). Standardized MedDRA queries were intended to aid in the identification and retrieval of potentially relevant individual case safety reports. The included terms relate to signs, symptoms, diagnoses, syndromes, physical findings, and laboratory and other physiologic test data. A list of withdrawal signs and symptoms and expert advice was applied to the safety database to identify potential subjects exhibiting withdrawal from the Phase 3 Integration Set and the Phase 1 Integration Set.

According to the Applicant, withdrawal was highly suspected if the signs and symptoms began after discontinuation of therapy in subjects on COV795 for at least 1 week (suggesting some degree of physical dependency), within 24 hours after discontinuation of therapy with a duration no longer than 14 days after discontinuation of therapy, lasted at least 1 day with a CNS AE component (and possibly accompanied by GI symptom[s]), or were symptoms described as a "withdrawal syndrome" that occurred during the course of the study.

Phase 3 Integration Set
The Applicant found multiple COV795-treated subjects who exhibited symptoms that could potentially be related to opioid withdrawal syndrome, but these were typically GI in origin, occurred immediately after therapy was initiated, and were limited to less than 1 day in duration. Subjects were also identified as having these events before treatment was started (ie, the events were not treatment-emergent). Therefore, the Applicant determined that it was unlikely that these events were actual withdrawal effects.

The Applicant identified a total of 5 subjects (2 subjects in Study 0182, 3 subjects in Study 0181) who they considered experienced potential withdrawal symptoms while receiving COV795 during the course of the clinical development program. These events were mild (except for 1 subject whose symptoms were considered moderate). The AEs were coded as anxiety or insomnia and lasted up to 4 days.

In the initial submission, it was not clear from the narratives for the 5 subjects that withdrawal occurred after cessation of study drug. An Information Request was sent via email to the Applicant on 10/18/13 to clarify whether the withdrawal symptoms in these subjects occurred after cessation of study drug. The Applicant's response, received on 10/24/13, clarified that the potential withdrawal symptoms for four of the subjects (204-004 and 110; 131-009 and 145-012) occurred after the cessation of study drug. An adverse event of "withdrawal syndrome" which began eight days into 36 days of treatment and was less than one day in duration was reported for Subject 110-023. The narratives are summarized below:

Table 47. Narratives for Subjects with Possible Withdrawal (Phase 3 Integration Set)

Study/ID	Narrative
0182/204-004	37-year-old white female; Anxiety (mild), restlessness (mild), nausea (mild), beginning 1 day after cessation of 17 days of treatment, 4 days in duration
0182/204-110	20-year-old white female; Anxiety (moderate), insomnia (moderate), beginning 1 day after cessation of 10 days of treatment, 4 days in duration
0181/220-023	45-year-old white female; Withdrawal syndrome (mild), insomnia (mild), beginning 8 days into 36 days of treatment, less than 1 day duration (single episode)
0181/131-009	45-year-old white male; Anxiety (mild), beginning 1 day after cessation of study drug with 36 days of treatment, 2 days in duration
0181/145-012	62-year-old white female; Anxiety (mild), beginning 1 day after cessation of 36 days of treatment lasting 3 days in duration

(Table, reviewer)

Abuse:
The Applicant reported that the AE database from the Phase 3 and Phase 1 Integration Sets was screened to identify subjects exhibiting potential signs and symptoms of abuse using the terms and recommendations of the drug abuse, dependence and withdrawal SMQ.

Among COV795-treated subjects in the Phase 3 Integration Set, 9 subjects (three in COV795-treated subjects in Study 0182 and six in OL Study 0181) exhibited symptoms that could be related to a potential of abuse (euphoric mood, cognitive disorder, feeling jittery, and mood altered).

Table 48, below provides the brief narratives with key preferred terms as summarized by the Applicant for the controlled study 0182.

Table 48. Narratives for Subjects with Possible Abuse (Phase 3 Controlled Study 0182)

0182/201-130	50-year-old female; Euphoric mood (mild), onset Day 1, continued through Day 3 of treatment; lightheadedness (mild), onset Day 1, less than 1 day duration; total treatment 3 days
0182/204-004	37-year-old female; Cognitive disorder (mild), onset Day 3, continued through Day 10 of treatment; total treatment 17 days
0182/204-066	57-year-old male; Cognitive disorder (mild), onset Day 3, duration less than 1 day; total treatment 3 days

(Table, reviewer)

In the OL Study 0181, there were six subjects who were identified as having possible abuse-related terms. Those narratives were presented in the submission and were read by this reviewer. Of those six subjects, four had terms of “euphoric mood”, one had preferred term of “feeling jittery” and one had the preferred term of “mood altered”. All of the cases were mild and duration of symptoms ranged from four days to total treatment of 36 days.

Drug Accountability (Diversion):
Although the Applicant stated that they searched the AE database for potential “diversion”, I believe it is more accurate to use the term “drug accountability”.

Study 0182: In the OL extension phase of blinded Study 0182, the Applicant found 13 subjects who were identified who returned fewer (2 to 6 less) COV795 tablets than expected according to their dosing records. One of these subjects experienced a TEAE that met the criteria for potential abuse (Subject 204-004 reported in Table 48, above).

Study 0181:

- Three subjects were lost to follow up and did not return their remaining study drug for accountability determination. No TEAEs of potential abuse were reported for these 3 subjects.

- Three incidents occurred in which more than ten COV795 tablets were not returned:

    - 798 tablets were stolen from Site 105 after the study was completed (86 kits were stolen with most kits containing ≤8 tablets per kit)
    - 216 tablets were damaged or lost during a study drug shipment to Site 131
    - One subject did not return 22 tablets (discrepancy could not be explained)

- Three subjects returned six to eight fewer COV795 tablets than expected

    - Eight tablets were reportedly stolen from one of these subjects, which the Applicant considered to be a case of diversion.
    - In the other two cases, no explanation for the discrepancies could be found.

- Forty-nine subjects returned four or fewer COV795 tablets

    - 23 cases were unexplained
    - 26 cases were secondary to extra dose administration or lost, dropped, or destroyed tablets over the course of the study). The Applicant did not consider these cases to represent significant misuse or abuse.

The Office of Scientific Investigation was notified regarding Study site 105. At this time, information from OSI regarding this site is pending. However, since the stolen kits occurred after the study was completed, it should not have affected the overall results of the study.

Phase I Integration Set
Withdrawal: The Applicant reported that their review identified many TEAEs associated with COV795, Roxicodone, Ultracet, and Percocet that occurred as single events immediately after the start of study treatment and were confined to the GI tract with no CNS involvement.

Abuse:

- Euphoric mood: 24 subjects reported 30 TEAES of mild euphoric mood, with 22 events lasting longer than one day and eight events lasting up to one day. No

COV795-related events of euphoric mood occurred the multiple dose study 0255, with one event each reported for Percocet and Roxicodone.

- Feeling drunk: 27 subjects reported 33 TEAEs of mild feeling drunk, with 19 events lasting longer than one day and 14 events lasting up to one day. Five COV-795-related events were reported in Study 0171 (fed-fasted food assessment). The Applicant reported that the remaining TEAEs of feeling drunk occurred with the earlier formulations or in the non-LD studies.
- Jittery feelings: Two reports both in Percocet. No reports of jittery feelings in study drug.

Because Xartemis contains oxycodone, a Schedule II opioid analgesic with a known abuse potential, it is expected that there would be reports of euphoric mood and other CNS-related adverse events consistent with the opioid class of medications. CSS is also reviewing this information.

Overdose: In the integrated safety database among COV795-treated subjects, no subjects were reported as having experienced signs or symptoms of overdose.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

This drug is not currently marketed.

9 Appendices

9.1 Literature Review/References

The Applicant acknowledged that numerous reviews have been published since the introduction of oxycodone, APAP and OC/APAP products since they were first introduced into the marketplace many decades ago. The Applicant also noted that more recent articles since the 2001 approval of Ultracet and 2010 approval of the reformulated abuse-deterrent Oxycontin provided additional safety and tolerability information for marketed OC and APAP containing products.

Understandably, it would be impossible to cite or reference all of those publications. Therefore, the Applicant focused on key literature “to augment the clinical observations and safety of the combination of OC and APAP used in the AcuForm GR technology investigated in the COV795 clinical development program.” The safety information was

summarized briefly for each key citation with the most relevant findings and/or conclusions. The Applicant stated that, in general, key literature articles were defined as those that described meta-analyses, randomized, and uncontrolled studies of oral OC/APAP formulations for pain management. Additional articles describing special populations (e.g., pediatric, geriatric), drug-drug interactions, and the GR technology platform were added as appropriate and available. The Applicant's overall approach to the literature search was conducted for articles appearing before February 2013 in the databases of MEDLINE, BIOSIS, Current Contents, Embase, Scopus, PubMed, and International Pharmaceutical Abstracts for identified key terms.

The Applicant's articles cited in the submission were categorized as follows:

- Meta-Analysis (1) - Cochrane literature review which included a review 20 randomized, double-blind, placebo-controlled studies
- Randomized Controlled Studies (18)
- Non-Randomized Studies (8)
- Literature Review (11)

Overall, a review of the literature revealed no new safety data which would affect labeling or approvability.

9.2 Labeling Recommendations

The labeling review is ongoing. The proprietary name of Xartemis XR was granted (i.e., conditionally acceptable) by the Division of Medication Error Prevention and Analysis [DMEPA], Office of Surveillance and Epidemiology in a letter dated October 3, 2013. The label will be consistent with the ERLA (extended-release, long-acting) opioid class label.

9.3 Advisory Committee Meeting

No Advisory Committee meeting was held for this product.

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

/s/

ELIZABETH M KILGORE
10/27/2013

ELLEN W FIELDS
10/27/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204031 Applicant: Mallinckrodt Stamp Date: May 24, 2013

Drug Name: Xartemis (proposed) NDA/BLA Type: NDA
Oxycodone/APAP

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Only 1 efficacy study; ISE N/A
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug? 1) Roxicodone [15mg oxycodoneHCL]; NDA 21011 and 2) Ultracet [325mg APAP/37.5mg tramadol HCL]; NDA 21123	(b)(2)			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 COV15000182 (Study 0182)	X			Reference IND 104702

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: Management of (b) (4) acute pain Pivotal Study #2 Indication:				Randomized, double blind, placebo-controlled, parallel-group
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	(Acute indication)
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			Sponsor's safety database is consistent with preNDA Agency advice
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			No special studies were requested. The ISS analysis was to include liver function lab assessments and SMQ assessments for Severe Cutaneous Adverse Reactions and Hepatic Disorders/Drug-Related Investigations
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			A pediatric study plan and a request for deferral of pediatric studies were provided. A protocol for the initial pediatric study was submitted to IND 104,702
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	There are no derived or composite endpoints
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	drop-outs) as previously requested by the Division?				
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical 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.

Elizabeth Kilgore July 3, 2013

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

ELIZABETH M KILGORE
07/03/2013

ELLEN W FIELDS
07/03/2013