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*APPLICATION NUMBER:*  
**207621Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA  
Application Number(s) 207-621  
Priority or Standard Standard

Submit Date(s) December 19, 2014  
Received Date(s) December 19, 2014  
PDUFA Goal Date October 19, 2015  
Division / Office Anesthesia, Analgesia, and  
Addiction/ODE II

Reviewer Name(s) Elizabeth Kilgore, MD  
Review Completion Date September 14, 2015

Established Name Oxycodone/Naltrexone  
(Proposed) Trade Name Troxyca ER  
Therapeutic Class Combination Opioid Analgesic  
and Opioid Antagonist (Abuse  
Deterrent Formulation)  
Applicant Pfizer

Formulation(s) Oral  
Dosing Regimen Every 12 hours  
Indication(s) Chronic Pain  
Intended Population(s) Opioid-naïve and opioid-  
experienced patients with  
pain severe enough to require  
an around-the-clock opioid

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

Throughout this review, Troxyca ER may also be referred to as ALO-02, study drug, or oxycodone/naltrexone interchangeably.

This 505(b)(2) NDA references the listed drugs oxycodone HCL (Tradename Roxicodone; NDA 21-01; approved August 31, 2000) and naltrexone HCL (Tradename Revia; NDA 18-932; approved November 20, 1984).

The proposed Tradename for this product is Troxyca ER (extended-release) tablets. Approval is recommended for Troxyca ER for the indication of management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, based upon the efficacy and safety information included in the submission.

This product is similar to approved Embeda, which also contains sequestered naltrexone. However, unlike Embeda which contains morphine sulfate as the active opioid, Troxyca ER contains oxycodone. The intent of the addition of naltrexone in both products is to provide abuse deterrent properties.

Dr. Jim Tolliver, the Agency's CSS reviewer has determined that, "Based on the cumulative data from Category 1 and 3 studies submitted by the Applicant, Troxyca ER capsules when crushed provide a deterrent effect to abuse by oral, intranasal, and intravenous routes of abuse. However, results of Category 1 in vitro studies demonstrate that intact Troxyca ER pellets may be manipulated for purposes of abuse. These manipulations result in the preferential extraction of the oxycodone into an immediate release form without the presence of naltrexone or with lower amounts of naltrexone recovered."

The dosage units studied included oxycodone/naltrexone 10 mg/1.2 mg; 20 mg/2.4 mg; 30 mg/3.6 mg; 40 mg/4.8 mg; 60 mg/7.2 mg; and 80 mg/9.6 mg.

Efficacy was established based on findings of pain improvement in Troxyca ER-treated patients compared to placebo-treated patients in one adequate and well controlled clinical trial. There was adequate exposure during clinical trials to inform as to the safety of Troxyca ER and the adverse event profile appeared acceptable in the intended to-be-marketed formulation.

There were some study subjects who exhibited adverse events related to opioid

withdrawal, possibly due to systemic exposure to naltrexone, but most of these subjects also had other reasons to have experienced opioid withdrawal, such as dose adjustment due to tapering, conversion, or noncompliance. The exact relationship of systemic naltrexone or naltrexol in precipitating opioid withdrawal is unclear. The profile of adverse events was, otherwise, generally consistent with a mu-opioid agonist. The dosing recommendations are acceptable based on the data from the clinical development program.

## **1.2 Risk Benefit Assessment**

There were no deaths definitely or probably attributable to Troxyca ER and no unexpected or unusual adverse events of special interest were identified to suggest a safety signal or trend. It is not definitive, however, whether the increased incidence of withdrawal in Troxyca ER-treated subjects compared to placebo is due to the inclusion of naltrexone. Most cases identified as drug withdrawal syndrome were mild to moderate in severity, resolved spontaneously, and did not require intervention.

## **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).

## **1.4 Recommendations for Postmarket Requirements and Commitments**

In order to comply with the Pediatric Research Equity Act (PREA), the Applicant submitted an initial pediatric study plan.

The proposed pediatric plan was discussed at a PeRC (Pediatric Review Committee) meeting on August 19, 2015. The Committee was in agreement with the Applicant's proposal for a partial waiver for ages birth to 6 years as studies are impossible or highly impractical because of the small number of patients in this age group treated with longterm, around-the-clock opioid analgesics and a deferral for PK and safety studies in ages 7 < 17 years with extrapolation for efficacy. A deferral was requested for ages 7 to <17 years of age due to the fact that this product contains naltrexone, an opioid antagonist, and although sequestered does have the potential to result in systemic exposure and risk for inducing opioid withdrawal and/or limiting efficacy. Therefore, the efficacy and safety of this combination must be established in adults first. The Applicant's proposed timelines for the deferred pediatric studies are as follow:

Protocol Submission: April 2015  
Study Completion: January 2019  
Study Submission: July 2019

Refer to the CDTL (Cross-Discipline Team Leader) Memo for any additional postmarketing requirements.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

ALO-02 capsules are pellet-filled oxycodone ER (extended release) capsules developed using Abuse Deterrent Formulation (ADF) which is the same as that of Embeda (morphine sulfate/naltrexone HCl ER capsules).

The pellets consist of inert seed cores coated with multiple drug and polymer layers, The naltrexone HCl layer is separated and sequestered from the oxycodone HCl layer by additional excipients and coatings. (b) (4)

Clinical trial capsules used in the ALO-02 development program contained the following amounts of oxycodone HCl and naltrexone HCl: 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg.

(b) (4)

**Figure 1. Diagram of the Cross-Section of an AOL-02 Pellet**



(Applicant's figure, Clinical Overview, p. 13)

Naltrexone remains sequestered if taken as directed but is released if the dosage form is crushed or chewed, resulting in antagonist pharmacodynamic effects of oxycodone, including drug liking and high.

## **2.2 Tables of Currently Available Treatments for Proposed Indications**

Multiple products, shown in Table 1, are available for the treatment of moderate-to-severe pain, including immediate and extended-release opioids, prescription strength NSAIDs, tramadol, and tapentadol.

**Table 1. Currently Available Treatments for Proposed Indication**

<b>Product Class</b>	<b>Route of Administration</b>
NSAIDS	Oral
Acetaminophen	Oral
Opioids	Oral, Transdermal, Intramuscular, Subcutaneous, Intravenous, Sublingual, Patient Controlled Analgesia, Epidural, Intrathecal
Local Anesthetics (Regional and Local Analgesia)	Wound infiltration, nerve and plexus blocks, epidural, intrathecal

(Table, reviewer); NSAIDS=nonsteroidal anti-inflammatory drugs

### **2.3 Availability of Proposed Active Ingredient in the United States**

The active ingredient in this combination product is the opioid agonist, oxycodone. Naltrexone is sequestered and is not active when the product is taken as prescribed.

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.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

*Opioids:* The risks associated with the use of Troxyca ER appear similar to the risks of other extended-release opioids. These risks include death, respiratory depression, withdrawal, physical dependence, misuse, abuse, diversion and overdose (intended or accidental). The class of opioids, in general, include 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.

*Naltrexone:* The following warnings are included in the Revia label: 1) Vulnerability to Opioid Overdose: After opioid detoxification, patients may have reduced tolerance to opioids which could result in risk for overdose when opioids are resumed causing a potentially life-threatening opioid intoxication (overdose) characterized by respiratory and circulatory arrest; 2) Risk of Spontaneous Precipitated Opioid Withdrawal; 3) Hepatotoxicity; 4) Depression and Suicidality Opioid intoxication. In clinical trials with different populations, the most common adverse reactions have been nausea, headache, dizziness, nervousness, fatigue, insomnia, vomiting, anxiety, and somnolence. Liver function abnormalities have also been reported. In a patient population of alcoholics, adverse events of depression, suicidal ideation and suicidal attempts were reported in both the placebo and naltrexone groups.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

This product was developed under IND 107,037. There was ongoing correspondence between the Agency and the Applicant throughout the development process. Key communications for the End-of-Phase 2 meeting, other relevant correspondence, and pre-NDA meeting are summarize below:

- 11/19/10 – EOP2 Meeting
  - The dose range for the oxycodone component appeared acceptable. Whether the doses of naltrexone were appropriate would be a review issue.

- Measure naltrexone and 6-β-naltrexol levels in all studies. If the Sponsor had data showing that at the highest dose of ALO-02 there are no naltrexone levels, then a dose proportionality study would not be needed.
- 3/11/11 - FDA advised that the Sponsor evaluate the safety of the total daily dose of the excipients based on acceptance of levels up to (b) (4) gram/day (b) (4). FDA stated that further safety justification will be necessary for dibutyl sebacate, ethylcellulose, hydroxypropyl cellulose and talc.
- 7/21/11 - No agreement to Special Protocol Assessment submitted 6/10/11 but agreement that a single study, if positive, may be sufficient to establish efficacy.
- 12/2/11 – FDA agreed with the strategy for 505(b)(2) submission to reference Revia (NDA 18-932) to support safety of naltrexone and Roxicodone (NDA 21-011) to support safety and efficacy of oxycodone.
- 10/4/13 – Proprietary name Troxyca ER was conditionally acceptable by the Agency.
- 3/18/14 – PreNDA Meeting
  - FDA stated that based upon the excipients guidance, developmental and reproductive toxicology studies may be waived if it can be shown that systemic exposure of the compound does not occur.
  - Clinical: Agency recommended that an ISE be included in the NDA along with cited literature to support the efficacy of study drug.
  - Clinical Pharmacology: a) In lieu of conducting a dose proportionality study, the Sponsor may submit a biowaiver request as long as certain conditions are met b) Revia bioavailability study is required to establish the scientific bridge to naltrexone in ALO-02 and c) FDA requested that the in vitro alcohol studies be submitted to assess if an additional in vivo study is required.
  - There was general agreement on other questions posed to the FDA including narratives of special interest, abuse- related adverse event terms, data pooling strategy for B4531001 and B4531002, data presentation in summary documents and the proposed datasets for the NDA.

## 2.6 Other Relevant Background Information

Not applicable.

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

All data and documents in this NDA were electronically submitted. The datasets were submitted in SAS format. Overall, the submission was of good quality, well organized and generally easily navigated. The Applicant responded to clinical information requests in a timely manner and there are currently no outstanding clinical information requests.

#### 3.2 Compliance with Good Clinical Practices

All clinical studies were conducted in the accordance with applicable regulatory guidances according to the Applicant's statements in the clinical study reports.

Three sites were selected for Office of Scientific Investigations (OSI) clinical site inspections based upon the following criteria:

- Key efficacy Study 1002: Two domestic sites were selected. Site 1060 enrolled the largest number of subjects and Site 1028 demonstrated the largest treatment effect.
- Intranasal Human Abuse Potential Study B4531009: HAP studies site inspections were conducted since the data generated from these studies would be used to form the basis for the Agency's determination of any abuse-deterrence claims for the drug. Of the three abuse potential studies, two were conducted in Canada (oral abuse Study B4531008 and intranasal abuse study B4531009). The third abuse potential study was conducted in the US (IV B4981002). For US study B4981002, Dr. Lynn Webster was the primary investigator. [REDACTED] (b) (4)

[REDACTED] Site 1001 in Canada was selected to represent a Canadian site.

Although all site inspections have been completed, the final clinical inspection summaries are not available or finalized at the time of this review. Dr. John Lee, primary OSI reviewer, reported that preliminary findings revealed no significant problems. The final conclusion and results are pending. See the CDTL memo for any relevant information received after this review.

#### 3.3 Financial Disclosures

The Applicant identified six studies (ALO-02-07-201, B4531001; B4531002; B4531008; B453109, and B4981002) that met the 21 CFR Part 54 and Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators

criteria of a covered study. The Applicant's financial disclosure information covers the period from the start of the study through one year after completion. Of the 446 investigators listed in the covered studies, four had financial information to disclose.

For the investigators for whom no financial interests needed to be disclosed, the submission included the completed Form 3454 "Certification: Financial Interests and Arrangements of Clinical Investigators" in compliance with 21CFR part 54, which certified that the Applicant had not entered into any financial arrangements with the listed clinical investigators, that each clinical investigator had no financial interest to disclose and that no investigator was the recipient of any other sorts of payments from the Applicant for the covered studies as shown below:

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

A Financial Certification and Disclosure Bias Statement describing the Applicant's efforts to minimize the potential for bias of the six covered studies was also included in the submission. These included, for example, the Applicant's determination that the validity of the data collected during the study was confirmed by standard monitoring procedures, the study report was appropriately reviewed by members of the project team, and appropriate statistical methods were employed and pre-specified in the protocols with any changes to the planned analyses documented in the clinical study report. The steps described by the Applicant to minimize the potential for bias appear acceptable.

For the four investigators with financial information to disclose, the Applicant submitted Form 3455. Key information from the Form 3455 forms for the four investigators with financial interest are summarized as follow:

I) Study B4531002; Double-blind efficacy study; Principal Investigator Site (b) (6) received Honorariums for speaking and consulting. Site (b) (6) screened (b) (4) subjects (b) (6). These numbers of subjects are so small that they would not likely have affected the overall treatment efficacy results.

- any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

II) Study B4531001 (alias number ALO-02-10-3001); Supportive long-term open-label safety study; Principal Investigator Site (b) (6) received grants. This was a multicenter study and safety was not driven by this one investigator. In fact, the Guidance for industry Financial Disclosure by Clinical Investigators defines a covered

study as defined in 21 CFR 54.2 as a study that is used to establish effectiveness, is used to show equivalence to an effective product, or any study in which a single investigator makes a significant contribution to the demonstration of safety. Since Study B4531001 was a multi-center study and no one investigator drove the safety results, this is not a covered study. The financial disclosure information (b) (6) is noted, however, below.

- any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

III) (b) (6) Financial Disclosure statement included Study B4531001 (alias numbers ALO-02-10-3001 and B4981002) sit (b) (6) received payments for consulting, honoraria for expert panel involvement, and grants.

- any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

IV) Study B4531002; Key double-blind efficacy study: (b) (6) received payments for speaking engagements.

- any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

See Appendix D for the Clinical Investigator Financial Disclosure forms for the covered studies.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Dr. Yong Hu conducted the Agency's CMC review. See Dr. Hu's review for detailed discussion regarding CMC issues. At the time of this review, Dr. Hu has reported that there are no issues which would affect approvability of this product.

### 4.2 Clinical Microbiology

Not applicable.

### 4.3 Preclinical Pharmacology/Toxicology

Dr. Elizabeth Bolan performed the Agency's Pharmacology/Toxicology review. No preclinical pharmacology/toxicology studies were required for this NDA since the



- The results of Study B4531009 indicated that crushed ALO-02 (30 mg/3.6 mg crushed) showed significantly lower responses for both Drug-Liking and High for the Emax and AUE0-2h compared to crushed IR oxycodone when taken intranasally. Weight-matched placebo responses for Drug Liking and High Emax were significantly lower compared to both ALO-02 and IR oxycodone. Weight-matched placebo responses for Drug Liking and High AUE0-2h were significantly different than IR Oxycodone but not ALO-02.
- The results of Study B4981002 indicated that simulated IV ALO-02 20 mg/2.4 mg showed significantly lower responses for both Drug-Liking and High for the median and least square means Emax and AUE0-2h compared to IV oxycodone 20 mg. Placebo responses were significantly lower compared to both simulated IV ALO-02 and oxycodone except for median Drug-Liking AUE0-2h following simulated IV ALO-02.

#### 4.4.3 Pharmacokinetics

The following is from the proposed Troxyca ER label:

##### **Oxycodone Pharmacokinetics**

Oxycodone is a semi-synthetic narcotic with multiple actions qualitatively similar to those of morphine; the most prominent of these is mediated by the mu-opioid receptor and involves the central nervous system and organs composed of smooth muscle.

*Absorption:* Following oral administration of TROXYCA ER capsules, oxycodone T<sub>max</sub> is delayed to approximately 12 hours post dose AUC is equivalent and C<sub>max</sub> is reduced by approximately 67% when compared with IR oxycodone tablets. After administration of crushed TROXYCA ER, the peak plasma levels of oxycodone occurred at 0.6-1.0 hours orally and 1.6 hours intranasally. (b) (4)

When TROXYCA ER capsules are administered in fasted state or after a high-fat meal, or when the contents of TROXYCA ER capsules are sprinkled on applesauce and administered in fasted state, oxycodone pharmacokinetics are unaffected with similar AUC, C<sub>max</sub>, and T<sub>max</sub> values. (b) (4)

In humans, about 60% to 87% of an oral dose of oxycodone reaches the systemic circulation in comparison to a parenteral dose. This high oral bioavailability (compared

to other oral opioids) is due to lower presystemic metabolism of oxycodone. Dose proportionality of oxycodone has been established using IR oxycodone 5, 15 and 30 mg tablets based on extent of absorption (AUC).

The analgesic activity of TROXYCA ER is primarily due to the parent drug oxycodone. TROXYCA ER is designed to provide extended-release of oxycodone to support the use of TROXYCA ER twice daily, approximately 12 hours apart. Chewing, crushing or dissolving the pellets within the TROXYCA ER capsules impairs the extended-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone as well as complete release of sequestered (b) (4). Dose proportionality of oxycodone has been established using IR oxycodone 5, 15 and 30 mg tablets based on extent of absorption (AUC).

*Distribution:* Following intravenous administration, the volume of distribution ( $V_{ss}$ ) for oxycodone is 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 is about 45%. Oxycodone has been found to be excreted in breast milk.

*Metabolism:* In humans, oxycodone HCl is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. CYP3A-mediated N-demethylation to an inactive metabolite form noroxycodone is the principal metabolic pathway of oxycodone in humans. CYP2D6-mediated O-demethylation to an active metabolite oxymorphone is a minor metabolic pathway. Oxymorphone is present in the plasma only in low concentrations

*Excretion:* (b) (4)

(b) (4)  
Following oral administration of TROXYCA ER capsules, the apparent elimination half-life of oxycodone is approximately 7.2 hours and steady state is reached within 48 hours upon twice-daily dosing with TROXYCA ER capsules approximately 12 hours apart. (b) (4)

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

There were a total of 14 clinical trials included in the NDA submission. In this review, the terms clinical trial or clinical study may be used interchangeably. All trials were conducted in the U.S., except for four, which were conducted in Canada.

The sources of clinical data to support this NDA included five pharmacodynamic studies specifically conducted to assess the dose ratio for oxycodone to naltrexone, three studies to assess abuse potential, and Phase 3 efficacy and safety studies to assess whether sequestered naltrexone could potentially compromise analgesic effects of oxycodone or safety due to systemic exposure of naltrexone.

Details regarding the study designs and key features are listed below.

- Seven Phase 1 Clinical Pharmacology and PK studies in healthy volunteers as follow:
  - Four studies which included 70 subjects, used the to-be-marketed formulation (Studies B4531003; B4531004, B4531006; and B4531007)
  - Across all seven studies, 114 healthy subjects were dosed. All subjects received single oral doses except Study B4531006 where subjects received both single and multiple oral doses.
- Five Phase 1 Clinical PD (pharmacodynamic) studies in healthy volunteers as follow:
  - Two dose-ratio finding studies of naltrexone to oxycodone. In both studies subjects received a single oral dose of study drug over multiple treatment periods, discussed below:
    - Study ALO-02-07-201 was conducted in Canada in 30 subjects to assess the appropriate naltrexone to oxycodone ratio required to abate the euphoric effects of oxycodone in opiate-experienced non-dependent recreational drugs users.
    - Study ALO-02-09-2001 was conducted in Canada in 31 subjects to determine the naltrexone-to-oxycodone ratio required to adequately abate Drug-Liking and High effects of oxycodone as measured by the VAS (Visual Analog Scale) in recreational drug users.
  - Three HAP (human abuse potential) studies:
    - Study B4531008 [oral abuse potential in 41 non-dependent, recreational opioid users] conducted in Canada
    - Study B4531009 [intranasal abuse potential in 32 non-dependent, recreational opioid users] conducted in Canada
    - Study B4981002 [intravenous abuse potential in 33 non-dependent, recreational opioid users]
- Two Phase 3 Efficacy/Safety studies as follow:
  - Key efficacy and safety Study B4531002 was a multicenter, 12-week, double-blind, placebo-controlled, randomized withdrawal study in 410 patients with chronic low back pain (CLBP).
  - Supportive efficacy and safety Study B4531001 was a multicenter, 12-month, open-label, single-arm study in 395 patients with moderate-to-severe chronic noncancer pain (CNCP).

Further details regarding the study designs and key characteristics of all clinical trials included in the NDA submission are summarized below in Tables 2 and 3.

**Table 2. Key Studies Contributing to Efficacy and Safety**

Study	Design	Formulation	Study endpoints	Duration	N	Population
<b>Phase 3 Key Efficacy and Supportive Long-term Safety</b>						
B4531002	R, DB, PC	TBM q 12 h	Pain	4-6 wks OL 12 wk DB 2 wk taper	410	CLBP
B4531001	OL	TBM q 12 h or daily	Safety	12 months	395	CNCP
<b>Pharmacodynamic Dose-Ratio Finding Studies</b>						
ALO-02-07-201	R, DB, Cross-Over, PC	Intact OX/N	Dose ratio	5 treatment periods; single dose	30	Opioid-experienced
ALO-02-09-2001	R, DB, DD, PC	Intact OX/N	Dose ratio	6 treatment periods; crossover	31	Opioid-experienced
<b>Pharmacodynamic Human Abuse Potential Studies</b>						
B4531008		Intact or crushed	Oral abuse potential	4 way crossover	41	Nondependent recreational opioid users
B4531009	R, DB, PC	Crushed	Intranasal abuse potential	Single dose; 4 treatment periods	32	Nondependent recreational opioid users
B4981002	R, PC, DB	Simulated	IV abuse potential	3-way cross over	33	Opioid experienced, nondependent opioid users

(Reviewer); R=randomized; DB=double-blind; PC=placebo-controlled; DD=double-dummy; OL= open-label; CLBP=chronic low back pain; CNCP=chronic noncancer pain; TBM=to be marketed formulation; Wk=week; OX/N=oxycodone/naltrexone

**Table 3. Phase 1 Single and Multiple Dose Studies in Healthy Subjects**

Study	Formulation	N	Study Design
ALO-02-07-102-	Pilot	10	Non-randomized open-label, single-dose, 3-way <b>relative BA and PK</b> crossover study with two controlled-release oxycodone pilot formulations with

			sequestered naltrexone and an immediate-release oxycodone oral solution
ALO-02-08-103-	Pilot	10	Randomized, open-label, four-way crossover study to evaluate the <b>relative BA</b> of a pilot ALO-02 formulation to the same formulation taken concomitantly with 20% and 40% ethanol and with a high fat meal
ALO-02-09-1001-	Prototype	24	Randomized, open-label, single-dose, 2-way crossover study to determine the <b>relative BA</b> of a prototype controlled-release oxycodone formulation (ALO-02) compared with oxycodone immediate-release tablets
B4531003	TBM	24	Randomized, open-label, single-dose, 3-way crossover study to estimate the <b>effect of food</b> and sprinkling ALO-02 pellets on applesauce on the BA of oxycodone, naltrexone, and 6--naltrexol
B4531004	TBM	19	Randomized, open-label, single-dose, 3-way crossover study to estimate the effects of <b>ethanol</b> 20% and 40% on the BA of ALO-02
B4531007	TBM	14	Randomized, open-label, single-dose, 2-way crossover study to estimate the <b>relative BA</b> of ALO-02 compared with IR oxycodone tablets (Roxicodone)
B4531006	TBM	13	Randomized, open-label, <b>single-and multiple-dose</b> , crossover study to evaluate the <b>PK</b> , safety and tolerability of ALO-02 40 mg twice daily compared to ALO-02 80 mg once daily and to OxyContin 40 mg twice daily

(Reviewer); TBM=to be marketed

There were no ongoing studies or additional studies included in the 120-day safety update.

## 5.2 Review Strategy

The Phase 1 studies were reviewed primarily for pertinent safety sections. The full protocols and final reports for the key efficacy study B4531002 and key supportive long-term safety study B4531001 were reviewed and summarized in detail in this review. Synopses were read for all studies included in the submission.

Data from individual study reports, CRF's, ISS, ISE, proposed annotated label, relevant sections of consultant's reviews, pertinent literature, approved labels of the referenced

drugs oxycodone [Roxicodone ] and naltrexone [Revia], and other pertinent sections of the NDA submission were read and included in the review as appropriate.

### 5.3 Discussion of Individual Studies/Clinical Trials

The reader is referred to Section 5.1 for the study designs and key clinical features for the individual studies/clinical trials. Further discussion of individual studies and clinical trials is as follows:

- Seven PK/clinical pharmacology studies: The protocols or study designs for these Phase 1 studies are not discussed in further detail in this review. Only four of the studies used the to-be-marketed formulation. Safety findings from these studies are summarized in Safety Section 7 of this review as appropriate.
- Five PD and Human Abuse Potential Studies: Refer to Section 7.4.5 (Special Safety Studies/Clinical Trials) for specific discussion of and safety findings for the Human Abuse Potential studies.
- Two Phase 3 studies: The protocols and key clinical features of Phase 3 efficacy and safety Study B4531002 (hereafter referred to as Study 1002) and long-term study B4531001 (hereafter referred to as Study 1001) are discussed in detail in this section of the review. Efficacy findings from these studies are detailed in Section 6 (Efficacy) and safety findings from these studies are summarized in Section 7 (Safety).

#### **I) Key Efficacy Study B4531002 (Study 1002)**

**Title:** A Multicenter, 12-Week, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Determine the Efficacy and Safety of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride) Extended-Release Capsules in Subjects with Moderate to Severe Chronic Low Back Pain

**Date Issued:** The original protocol was dated January 12, 2012. There were three amendments (see discussion under Amendments to Protocol). The study was conducted under U.S. IND # 107,037 for the study drug ALO-02 [PF-06412527] oxycodone/naltrexone.

**Primary Objective:** The primary objective of this study was to determine the analgesic efficacy of ALO-02 extended-release capsules, when compared to placebo, in subjects with moderate to severe chronic low back pain (CLBP).

#### **Secondary Objectives:**

- To determine the safety of ALO-02 extended-release capsules, when compared to placebo, in subjects with moderate to severe CLBP;
- To determine the effect of ALO-02 extended-release capsules, when compared to placebo, on physical function in subjects with moderate to severe CLBP;

- To determine the effect of ALO-02 extended-release capsules, when compared to placebo, on participant ratings of global assessment and satisfaction with treatment in subjects with moderate to severe CLBP;
- To determine the effect of ALO-02 extended-release capsules, when compared to placebo, on health-related quality of life (HRQoL), work productivity, and healthcare resource use in subjects with moderate to severe CLBP;
- To describe the dosing patterns of ALO-02 extended-release capsules in subjects with moderate to severe CLBP.

**Population:** This study was to have enrolled approximately 500 subjects in the Open-Label Conversion and Titration Period in order to randomize approximately 250 subjects into the Double-Blind Treatment Period. The population for this study was to have been patients who were candidates for a continuous around-the-clock opioid analgesic for an extended period of time.

**Duration:** The duration of subject participation was to have been approximately 5 months.

**Study Design:** This was to have been a multicenter, 12-week, double-blind, placebo-controlled, randomized withdrawal study to demonstrate the efficacy and safety of ALO-02 extended-release capsules in subjects with moderate to severe CLBP who required a continuous around-the-clock opioid analgesic for an extended period of time.

**Study Drug:** The ALO-02 treatment dosing regimen was to have been 20 to 160 mg total daily dose (TDD) of oxycodone; divided into symmetric doses (same dose AM and PM) administered twice daily (approximately 12 hours apart).

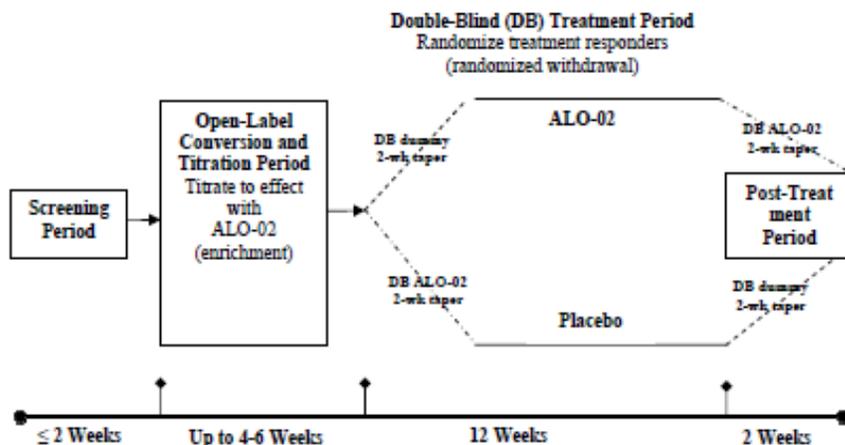
**Study Overview:** The study was to have been an enriched enrollment randomized withdrawal (EERW) design which included a 4-6 week Open-label titration enrichment phase where subjects were converted to ALO-02 and a 12-week double-blind randomized withdrawal phase where subjects remained on study drug or placebo. Only subjects who tolerated and achieved satisfactory efficacy with the study drug according to protocol-defined treatment response criteria were to have been randomly assigned to continue the study drug or switched to placebo to enter the Double-Blind Treatment Period. Entry into the study required an NRS (numeric rating scale) score  $\geq 5$  and  $\leq 9$  for at least 4 of the last 7 days of screening and requiring continuous opioids. Subjects could be opioid-experienced or opioid-naïve.

The study was to have consisted of the following four study periods:

- Up to a 2 week *Screening Period*;
- 4 to 6-week *Open-Label Conversion and Titration Period*;
- 12-week *Double-Blind Treatment Period*; and
- 2-week *Double-Blind Post-Treatment Period*

The study design schematic is shown in Figure 2.

**Figure 2. Study 1002 Design Schematic**



(Source: Protocol, p. 8)

#### Rescue Pain Medication:

- Subjects were to have been permitted to take acetaminophen up to 3 grams per day during the Screening Period, Open-Label Conversion and Titration Period, the Double-Blind Treatment Period and the Post-Treatment Period if needed as rescue medication for pain.
- Subjects were to have been permitted to take immediate-release oxycodone HCl (as a single ingredient product) in conjunction with ALO-02 extended-release capsules during the first 3 weeks of the Open-Label Conversion and Titration Period, to manage the initial conversion from their previous therapy.

#### Key Inclusion Criteria

1. Male and female subjects 18 years of age or older including:
  - a. Female subjects who are not of childbearing potential (i.e., meet at least one of the following criteria):
    - i. Have undergone hysterectomy or bilateral oophorectomy;
    - ii. Have medically confirmed ovarian failure or;
    - iii. Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and a serum FSH level within the laboratory's reference range for postmenopausal females).
  - b. Male and female subjects of childbearing potential must agree to use a highly effective method of contraception (defined in protocol) throughout the study and for at least 28 days after the last dose of assigned

treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

- c. Female subjects of childbearing potential are eligible for study participation if the female subject has a negative serum pregnancy test at Visit 1 of the Screening Period.
2. Subjects who have a documented diagnosis of nonspecific moderate to severe CLBP that has been present for at least 3 months. Nonspecific CLBP refers to the location of low back pain occurring primarily in the back between the 12th thoracic vertebra and the lower gluteal folds, with or without radiation into the posterior thigh, classified as Classification 1 or 2 according to the Quebec Task Force on Spinal Disorders.
3. Subjects who have daily average pain numerical rating scale (NRS-Pain) scores for low back pain of  $\geq 5$  and  $\leq 9$  for at least 4 of the last 7 days of the Screening Period.
4. Subjects who, in the opinion of the investigator, require a continuous around-the-clock opioid analgesic (at an oxycodone equivalent dose of  $\leq 160$  mg per day) for an extended period of time.
5. Subjects who are managing CLBP with a non-opioid analgesic, a PRN opioid, or daily opioid therapy and are appropriate candidates for around-the-clock long-acting opioid analgesic.
6. Subjects who agree to refrain from taking opioid and non-opioid analgesics (other than study drug and permitted medications) during the study.

### **Key Exclusion Criteria**

1. Subjects who have active or within the past 2 years a history of lumbosacral radiculopathy, spinal stenosis associated with neurologic impairment or neurogenic claudication, CLBP due to other underlying disorders such as cancer or tumor, infection, post-surgical intervention, cauda equine syndrome, vertebral compression fracture, ankylosing spondylitis, visceral disorder, Paget's disease of the spine, or recent major trauma within 6 months of Screening.
2. Subjects who have a documented diagnosis of ongoing pain due to other chronic pain conditions that, in the judgment of the Investigator, would interfere with assessment of CLBP. This may include, but not be limited to: cancer, osteoarthritis of the hip, knees or other major joints, rheumatoid arthritis, fibromyalgia, neuropathic pain syndromes, migraine, recent trauma, or infection.
3. Subjects who have ongoing or active alcohol or drug abuse or a documented significant history of alcohol or drug abuse prior to study entry that, in the judgment of the Investigator, would impact subject participation in this study.
4. Subjects who have positive urine drug test during the Screening Period for illicit drug substances or unexpected drug substances (other than those reported by the subject as therapeutic concomitant medications).

5. Subjects who have other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study. This may include, but not be limited to, a clinically significant medical condition (e.g., cardiovascular, neurological, renal, hepatic, pulmonary, gastrointestinal [including dysphagia], endocrine, hematological, immunological, rheumatological, metabolic, psychiatric) or physical examination, vital signs, ECG, clinical laboratory test abnormalities during Screening that, in the judgment of the Investigator, would impact the safety of the subject during study participation.
6. Subjects who have had a hospital admission for depression or suicide attempt within the last year of Screening or who have active, major depression at Screening (determined from medical history and the Patient Health Questionnaire-9 [PHQ-9], with a score of  $\geq 15$  on questions 1-9 of the PHQ-9).
7. Subjects who have had suicidal ideation and behavior associated with actual intent and/or method and/or plan and/or action (eg, self-harming behaviors) in the past year based on Sheehan-Suicidality Tracking Scale (S-STs) (Lifetime Assessment).
8. Subjects who are morbidly obese (body mass index  $>40 \text{ kg/m}^2$ ).
9. Subjects who have undergone back surgery within 6 months before study entry or plan to have back surgery during the time of study participation.
10. Subjects who have undergone a major surgical procedure within 2 months before study entry.
11. Subjects who have received a nerve or plexus block, including epidural corticosteroid injections within 3 months before the Screening Period.

#### Opioid Use Definition/Stratification

- Prior Non- Opioid Users: Subjects who prestudy were managing CLBP with a non-opioid analgesic alone
- Prior Opioid Users: 1) Subjects who prestudy were managing CLBP with a prn opioid with or without an adjunct non-opioid analgesic; 2) using a daily opioid analgesic (including tapentadol, tramadol, and transdermal buprenorphine)

#### Key Procedures:

##### Screening:

- Non-opioid management: Discontinue non-opioid analgesic,
- Prior opioid management: Determine average total daily opioid dose, including maintenance opioid and intermittent opioid usage, to guide the initial conversion
- NRS Pain Score entry criteria: At the conclusion of the Screening Period, if subjects had an NRS pain score for LBP of  $\geq 5$  and  $\leq 9$  for at least 4 of the last 7 days of the Screening Period, they were eligible to be converted to an initial dose of ALO-02 capsules and entered the OL Conversion and Titration Period

Open-Label Conversion and Titration (OL C/T) Period: The daily dose levels of ALO-02 available during the Open-Label Conversion and Titration Period was to have been 20 mg/day, 40 mg/day, 60 mg/day, 80 mg/day, 100 mg/day, 120 mg/day, 140 mg/day or 160 mg/day. Subjects were to have been stratified according to their prior analgesic use as either: 1) prior opioid users (which included subjects using prn opioids [with or without an adjunct non-opioid analgesic] and subjects using tapentadol, tramadol, or transdermal buprenorphine) or 2) prior non-opioid users.

The OL C/T Period could last from 4 to 6 weeks (i.e., subjects could enter the DB period at Week 4, 5, or 6) if they met the following responder criteria, shown in Table 4.

**Table 4. Treatment Response Criteria**

Criteria	Criteria Description
1	Subject had a reduction (to $\leq 4$ ) in the daily average NRS-pain scores for low back pain for at least 4 of the last 7 days of open-label treatment prior to randomization.  AND
2	The treatment with ALO-02 was considered tolerated by subject and corroborated as such by the investigator.  AND
3	Subject had remained on the same fixed dose of ALO-02 without a change in the dose for at least 7 consecutive days prior to randomization.

(CSR, p. 34)

During the conversion to study drug, subjects were converted using the Conversion Table as shown in Appendix A of this review.

- *Opioid-Naïve Subjects:* Per suggested outline from the protocol, opioid naïve subjects started treatment with ALO-02 10 mg/1.2 mg BID.
- *Opioid-Experienced Subjects:*
  - The protocol instructed investigators to calculate the starting dose of ALO-02 for opioid experienced subjects based on subject's prior total daily dose of opioids converted to an equivalent dose of oxycodone using established conversion factors where applicable (except for tramadol and fentanyl for which no established conversion exists) and then halved to obtain the BID dose and rounded down to an available dose strength of ALO-02. After the 50% reduction, if the calculated total daily dose of ALO-02 was  $\leq 20$  mg/day, the subject was initiated with ALO-02 at 10 mg/1.2 mg twice daily.
  - For subjects who were managing CLBP prestudy with oxycodone, no 50% reduction in the starting dose of ALO-02 was needed.

- Subjects taking tramadol prior to entering the study were treated as opioid naïve and started on ALO- 02 10 mg/1.2 mg.
- For subjects taking fentanyl prior to starting the study, it was recommended that approximately 10 mg BID of ALO-02 should be initially substituted for each 25 mcg/hour fentanyl transdermal patch.
- *Titration:* Dose adjustments could be made in 20 mg total daily dose fixed increments (i.e., 10 mg twice daily increments) in response to inadequate analgesia or intolerable opioid effects at protocol-scheduled or unscheduled clinical visits. Dosage adjustments by telephone were not permitted. Before dose adjustments, it was recommended that a subject had been at his/her current dosage regimen for at least 3 days.

*Double-Blind Treatment Period:* The DB Treatment Period was the “Randomized Withdrawal Phase” of the study.

- This period was to have included scheduled center visits at the end of Weeks 1, 2, 4, 8, and 12 of the double-blind treatment. The exception to this was the additional study visits at the end of Weeks 6 and 10 for subjects randomized to receive either 100 mg/day or 140 mg/day as these doses required two additional visits to enhance study drug compliance for these particular subjects relative to the quantity of bottles of investigational product required over a monthly interval.
- Randomization: Subjects were randomized to one of two treatment arms in a 1:1 ratio to either ALO-02 or matching placebo.

*Double-Blind Taper and Double-Blind Treatment*

- *Taper:* To avoid opioid withdrawal during the first 2 weeks of this period, subjects randomized to placebo underwent a double-blind gradual taper from ALO-02 dose. After completion of the DB gradual taper, a subject randomized to placebo continued with placebo for the remaining 10 weeks. A subject randomized to ALO-02 treatment was to have a dummy taper to maintain the study blind but continued to receive ALO-02 during these 2 weeks.
- *Treatment:* After completion of the taper during the first 2 weeks of the Double-Blind Treatment Period, a subject was to have been administered a fixed dose of either ALO-02 or matching placebo. Dosage adjustments of the study drug were not permitted during the Double-Blind Treatment Period.

*Post-Treatment Period*

- Subjects who completed 12 weeks of DB treatment participated in a Post-Treatment Period occurring over 2 weeks in order to have had blinded study drug discontinued to avoid opioid withdrawal

**Schedule of Activities:** Refer to Table 5 below.

**Table 5. Study 1002 Schedule of Activities**

Study Procedures	Screening Period (Up to 2 weeks)		Open-Label (OL) Conversion and Titration Period (Up to 6 weeks) <sup>1</sup>		Double-Blind (DB) Treatment Period 12 Weeks								Post-Treatment Period		Un-Scheduled Visits
	1	2	3,4,5,6,7	8	9	10	11	12	13	14	15	16	17 <sup>a</sup>		
Visit	Visit 1 (Day-1 4 thru Day-7)	Visit 2 (Day 1) (±1 day)	End of OL Weeks 1, 2,3,4,5 (±2 days)	Randomization Visit (End of OL Week 4, 5 or 6) or Early Termination (±2 days)	End of DB Week 1 (±2 days)	End of DB Week 2 (±2 days)	End of DB Week 4 (±3 days)	End of DB Week 6 <sup>b</sup> (±3 days)	End of DB Week 8 (±3 days)	End of DB Week 10 <sup>c</sup> (±3 days)	End of DB Week 12 or Early Termination (±3days)	End of Post-Treatment Period Week 1 (±2 days)	End of Study (2 weeks post-End of DB Week 12) (±2 days)		
<b>STUDY ENTRY &amp; SAFETY PROCEDURES</b>															
Informed Consent	X														
Inclusion & Exclusion Criteria	X	X													
Assess Treatment Response			X	X											
Medical History	X														
Clinical Laboratory Tests (Chemistry and Hematology Labs)	X			X <sup>d</sup>							X				
Urinalysis (dip stick)	X			X <sup>d</sup>							X				
Physical Examination	X			X <sup>d</sup>							X				
Patient Health Questionnaire (PHQ-9) & Sheehan Suicidality Tracking Scale (S-STSS) <sup>7</sup>	X <sup>a</sup>														
Serum Pregnancy Test	X										X				
Urine Pregnancy Test			X <sup>e</sup>	X			X		X				X		
Urine Drug Test	X	X	X <sup>f</sup>	X <sup>a</sup>			X		X		X			X	
12 lead ECG	X			X <sup>g</sup>							X				

Clinical Review  
 Elizabeth Kilgore, MD  
 NDA 207-621  
 Troxyca ER (oxycodone/naltrexone)

Study Procedures	Screening Period (Up to 2 weeks)		Open-Label (OL) Conversion and Titration Period (Up to 6 weeks) <sup>1</sup>		Double-Blind (DB) Treatment Period 12 Weeks								Post-Treatment Period		Un-Scheduled Visits
	1	2	3,4,5,6,7	8	9	10	11	12	13	14	15	16	17		
Visit	Visit 1 (Day-1 4 thru Day-7)	Visit 2 (Day 1) (±1 day)	End of OL Weeks 1, 2,3,4,5 (±2 days)	Randomization Visit (End of OL Week 4, 5 or 6) or Early Termination (±2 days)	End of DB Week 1 (±2 days)	End of DB Week 2 (±2 days)	End of DB Week 4 (±3 days)	End of DB Week 6 <sup>2</sup> (±3 days)	End of DB Week 8 (±3 days)	End of DB Week 10 <sup>3</sup> (±3 days)	End of DB Week 12 or Early Termination (±3days)	End of Post-Treatment Period Week 1 (±2 days)	End of Study (2 weeks post-End of DB Week 12) (±2 days)		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE Assessment <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
COWS Assessment <sup>5</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	
SOWS Assessment <sup>10</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication and Rescue Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
<b>STUDY DRUG SUPPLIES</b>															
Obtain Package Assignment for OL Study Drug via IVRS/TWS		X													
Dispense Study Drug For OL Conversion		X	X											X <sup>11</sup>	
Randomization to Study Drug using the IVRS/TWS <sup>1</sup>				X											
Dispense DB Study Drug <sup>1</sup>				X <sup>12</sup>		X	X	X <sup>3</sup>	X	X <sup>2</sup>	X			X <sup>10</sup>	
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	
<b>ANALGESIC ASSESSMENTS</b>															
Train subject in use of ePRO device, log subject onto device, and dispense device <sup>13</sup>	X	X													

Clinical Review  
Elizabeth Kilgore, MD  
NDA 207-621  
Troxyca ER (oxycodone/naltrexone)

Study Procedures	Screening Period (Up to 2 weeks)		Open-Label (OL) Conversion and Titration Period (Up to 6 weeks) <sup>1</sup>		Double-Blind (DB) Treatment Period 12 Weeks								Post-Treatment Period		Un-Scheduled Visits
	1	2	3,4,5,6,7	8	9	10	11	12	13	14	15	16	17		
Visit	Visit 1 (Day-1 4 thru Day-7)	Visit 2 (Day 1) (±1 day)	End of OL Weeks 1, 2,3,4,5 (±2 days)	Randomization Visit (End of OL Week 4, 5 or 6) or Early Termination (±2 days)	End of DB Week 1 (±2 days)	End of DB Week 2 (±2 days)	End of DB Week 4 (±3 days)	End of DB Week 6 <sup>2</sup> (±3 days)	End of DB Week 8 (±3 days)	End of DB Week 10 <sup>2</sup> (±3 days)	End of DB Week 12 or Early Termination (±3days)	End of Post-Treatment Period Week 1 (±2 days)	End of Study (2 weeks post-End of DB Week 12) (±2 days)		
Patient use of ePRO device	X.....X														
Review ePRO vendor's web portal (Daily Pain NRS, and/or SOWS, and/or Rescue Medication Use) <sup>11</sup>		X	X	X	X	X	X		X		X	X	X		
Retrieve ePRO device and Log Subject Out of the device depending on patient status (Screen failure, non-responder, withdrawn or completed)		X		X									X		
Brief Pain Inventory-short form (BPI-sf) <sup>12</sup>		X	X	X		X	X		X		X			X	
<b>PHYSICAL FUNCTION ASSESSMENT</b>															
Roland Morris Disability Questionnaire (RMDQ) <sup>13</sup>		X		X		X	X		X		X				
<b>PARTICIPANT RATINGS ASSESSMENTS</b>															
Patient's Global Assessment of Low Back Pain <sup>14</sup>		X		X			X		X		X				
Treatment Satisfaction <sup>15</sup>				X							X				

Study Procedures	Screening Period (Up to 2 weeks)		Open-Label (OL) Conversion and Titration Period (Up to 6 weeks) <sup>1</sup>		Double-Blind (DB) Treatment Period 12 Weeks								Post-Treatment Period		Un-Scheduled Visits
	1	2	3,4,5,6,7	8	9	10	11	12	13	14	15	16	17		
Visit	Visit 1 (Day-1 thru Day-7)	Visit 2 (Day 1) (±1 day)	End of OL Weeks 1, 2,3,4,5 (±2 days)	Randomization Visit (End of OL Week: 4, 5 or 6) or Early Termination (±2 days)	End of DB Week 1 (±2 days)	End of DB Week 2 (±2 days)	End of DB Week 4 (±3 days)	End of DB Week 6 <sup>6</sup> (±3 days)	End of DB Week 8 (±3 days)	End of DB Week 10 <sup>6</sup> (±3 days)	End of DB Week 12 or Early Termination (±3days)	End of Post-Treatment Period Week 1 (±2 days)	End of Study (2 weeks post-End of DB Week 12) (±2 days)		
<b>HEALTH-RELATED QUALITY OF LIFE, WORK PRODUCTIVITY AND HEALTHCARE RESOURCE USE</b>															
SF-36v2 Health Survey <sup>7</sup>		X		X							X				
EQ-5D Health Questionnaire		X		X							X				
Work Productivity and Activity Impairment: Specific Health Problem <sup>8</sup>		X		X			X		X		X				
Healthcare Resource Use <sup>9</sup>		X		X			X		X		X				
<b>OTHER ASSESSMENTS</b>															
Plasma Sample for PK analysis <sup>13</sup>				X			X		X		X				

- Treatment responders identified from the Open-Label Conversion and Titration Period are randomized to double-blind treatment. A subject must complete at least 4 weeks of open-label treatment during this period before he/she is assessed to determine if he/she is considered a treatment responder. A subject meeting the protocol-defined treatment response criteria could potentially be randomized to double-blind treatment at the end of open-label Week 4, or 5, or 6. If a subject has met the protocol-defined treatment response criteria at end of open-label Week 4 or 5 visit, (before the end of open-label Week 6), the assessments outlined at the Randomization Visit are completed and the subject is randomized to double-blind treatment. If a subject has not met the protocol-defined treatment response criteria at the end of the open-label Week 4 or 5 visit (before the end of open-label Week 6), he/she will complete the assessments outlined at the designated open-label visit and will continue in the Open-Label Treatment and Conversion Period. For those subjects completing up to 6 weeks of open-label treatment, at the end of open-label Week 6, if a subject has met the protocol-defined treatment response criteria, the assessments outlined at the Randomization Visit are completed and the subject is randomized to double-blind treatment. If the subject has not met the protocol-defined treatment response criteria at the end of open-label Week 6, the subject is considered a Treatment Non-Responder, is not eligible for randomization and will complete the assessments required at the Early Termination Visit of the Open-label Conversion and Titration Period.
  - Study drug dispensed at Visit 8 in a blister card will be continued to be used until Visit 10.
  - The End of DB Week 6 and 10 study visits are ONLY required for subjects who are receiving either 100mg/day or 140mg/day of study drug. These additional study visits are to enhance study drug compliance for these particular subjects relative to the quantity of bottles of investigational product he/she are required to receive over a monthly interval.
  - Clinical laboratory tests are performed at the Early Termination Visit of the Open-Label Titration and Conversion Period for those subjects considered Treatment Non-Responders after 6 weeks of open-label treatment or who are withdrawn during the Open-Label Conversion and Titration Period. Clinical laboratory tests are not required for those subjects who are considered Treatment Responders and are eligible for randomization to the Double-Blind Treatment Period.
  - A brief physical examination is performed at the Early Termination Visit of the Open-Label Titration and Conversion Period for those subjects considered Treatment Non-Responders after 6 weeks of open-label treatment or who are withdrawn during the Open-Label Conversion and Titration Period. A brief physical examination is not required for those subjects who are considered Treatment Responders and are eligible for randomization to the Double-Blind Treatment Period.
  - An electronic tablet will be used to collect patient- and clinician-reported outcomes at the site during clinic visits.
  - When applicable, the screening window may be extended by an additional 2 weeks only for those subjects who need an assessment by a qualified mental health professional based on their responses on S-STS and PHQ-9.
  - A urine pregnancy test will be performed at End of OL Week 2 Visit.
  - A urine drug test with automatic confirmation will be performed at Visit 5 (End of OL Week 3). Aberrant UDT results may result in subject discontinuation, as outlined in Section 6.2.
  - A urine drug test with automatic confirmation will be performed at Visit 8 Randomization Visit (ie, End of OL Week 4, 5, or 6) or Early Termination Visit during the OL Conversion and Titration Period. Aberrant UDT results may result in subject discontinuation, as outlined in Section 6.2.
  - A 12-lead ECG is performed at the Early Termination Visit of the Open-Label Titration and Conversion Period for those subjects considered Treatment Non-Responders after 6 weeks of open-label treatment or who are withdrawn during the Open-Label Conversion and Titration Period. A 12-lead ECG is not required for those subjects who are considered Treatment Responders and are eligible for randomization to the Double-Blind Treatment Period.
  - Reports of SAEs are collected from the time of the signing of the informed consent form and adverse events are reported from the time of first dosing of study drug.
  - During any of the 2-week tapers from study drug as outlined in the Study Design, a subject will complete the SOWS daily via an ePRO device.
  - Study drug may be dispensed if a dose adjustment is made during the Open-Label Conversion and Titration Period or to begin the 2-week taper from study drug if a subject is withdrawn from the Double-Blind Treatment Period.
  - An ePRO device is physical hardware used by the subject to enter ePRO data (eg, smart phone, portable digital assistant). The ePRO device will be used to capture data completed by the subject throughout the study in the evening prior to bedtime. The subject will be trained on which assessments to complete depending on the Period of the study.
  - A blood sample for the purpose of quantifying oxycodone, noroxycodone, naltrexone, and 6-β-naltrexol is obtained (i) at the time of Randomization for Treatment Responders, (ii) at the End of OL Week 6 for Treatment Non-responders (iii) at the time of Early Termination from the Open-Label Titration and Conversion Period for subjects withdrawn from the Open-label Titration and Conversion Period, (iv) at the End of Double-Blind Weeks 4, 8 and 12 (or Early Termination) for randomized subjects and v) if a subject experiences a COWS score ≥13 at any of the scheduled or unscheduled clinic visits.

(Protocol, pages 10-14)

## Efficacy Endpoints

**Primary Efficacy Endpoint:** The primary analgesic efficacy endpoint of this study was to have been the difference between the mean changes from Baseline (time of randomization) to the final 2 weeks (Weeks 11 and 12) of the Double-Blind Treatment Period in the daily average pain numerical rating scale (NRS-Pain) scores for low back pain when comparing ALO-02 versus placebo.

*Protocol-Defined Key Secondary Efficacy Endpoints:*

- The mean changes from Baseline to the end of Double-Blind Week 12 (or Final Visit) in the Roland Morris Disability Questionnaire (RMDQ) Total Score;
- The changes from Baseline to the end of Double-Blind Week 12 (or Final Visit) in the Patient's Global Assessment (PGA) of Low Back Pain

*Analgesic Effect Secondary Endpoints*

- The percent reduction in the daily average pain numerical rating scale (NRS-Pain) scores for low back pain from the Screening Period to the final 2 weeks (Weeks 11 and 12) of the Double-Blind Treatment Period;
- The mean changes from the Screening Period to Baseline in the Brief Pain Inventory-Short Form (BPI-sf) (for all subjects and subjects who enter the Double-Blind Treatment Period);
- The mean changes from Baseline to the end of Double-Blind Weeks 2, 4, 8, and 12 (or Final Visit) in the BPI-sf;
- The mean changes from Screening Period to the end of Double-Blind Weeks 2, 4, 8, and 12 (or Final Visit) in the BPI-sf;
- The mean area under the curve of the daily average pain numerical rating scale (NRS-Pain) scores for low back pain from Baseline to the final 2 weeks (Weeks 11 and 12) of the Double-Blind Treatment Period;
- The amount of acetaminophen administered for each treatment during the Double-Blind Treatment Period;
- The time to 20%, 30%, 40% and 50% loss of analgesic response from Baseline during the Double-Blind Treatment Period;
- The time to treatment discontinuation as determined by investigator-reported lack of efficacy during the Double-Blind Treatment Period.

*Physical Function Secondary Endpoints*

- The mean changes from the Screening Period to Baseline in the RMDQ total score (for all subjects and subjects who enter the Double-Blind Treatment Period);
- The mean changes from Baseline to the end of Double-Blind Weeks 2, 4 and 8 in the RMDQ Total Score;
- The mean changes from Screening Period to the end of Double-Blind Weeks 2, 4, 8 and 12 (or Final Visit) in the RMDQ Total Score

*Participant Ratings of Global Assessment and Satisfaction with Treatment Secondary Endpoints*

- The changes from the Screening Period to Baseline in the Patient's Global Assessment (PGA) of Low Back Pain (for all subjects and subjects who enter the Double-Blind Treatment Period);

- The changes from Baseline to the end of Double-Blind Weeks 4 and 8 in the PGA of Low Back Pain;
- The percentage of subjects who report being “satisfied” or “very satisfied” on the Satisfaction with Treatment questionnaire during the Open-Label Conversion and Titration Period and the Double-Blind Treatment Period.

*Health Related Quality of Life, Work Productivity, and Healthcare Resource Use  
Secondary Endpoints*

- The mean changes from the Screening Period to Baseline in the Short Form-36v2 Health Survey (for all subjects and subjects who enter the Double-Blind Treatment Period);
- The mean changes from Baseline to the end of Double-Blind Week 12 (or Final Visit) in the Short Form-36v2 Health Survey;
- The mean changes from Screening Period to the end of Double-Blind Week 12 (or Final Visit) in the Short Form-36v2 Health Survey;
- The changes from the Screening Period to Baseline in the EQ-5D Health Questionnaire (for all subjects and subjects who enter the Double-Blind Treatment Period);
- The changes from Baseline to the end of Double-Blind Week 12 (or Final Visit) in the EQ-5D Health Questionnaire;
- The changes from Screening Period to the end of Double-Blind Week 12 (or Final Visit) in the EQ-5D Health Questionnaire;
- The mean changes from the Screening Period to Baseline in the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem(WPAI:SHP) in the percent work time missed due to low back pain, percent impairment while working due to low back pain, percent overall work impairment due to low back pain, and percent activity impairment due to low back pain (for all subjects and subjects who enter the Double-Blind Treatment Period);
- The mean changes from Baseline to the end of Double-Blind Weeks 4, 8 and 12 (or Final Visit) in the WPAI:SHP in the percent work time missed due to low back pain, percent impairment while working due to low back pain, percent overall work impairment due to low back pain, and percent activity impairment due to low back pain;
- The mean changes from Screening Period to the end of Double-Blind Weeks 4, 8 and 12 (or Final Visit) in the WPAI: SHP in the percent work time missed due to low back pain, percent impairment while working due to low back pain, percent overall work impairment due to low back pain, and percent activity impairment due to low back pain;
- The changes from the Screening Period to Baseline in the Healthcare Resource Use Questionnaire (for all subjects and subjects who enter the Double-Blind Treatment Period);
- The changes from Baseline to the end of Double-Blind Weeks 4, 8 and 12 (or Final Visit) in the Healthcare Resource Use Questionnaire(Appendix 16);

- The changes from Screening Period to the end of Double-Blind Weeks 4, 8 and 12 (or Final Visit) in the Healthcare Resource Use Questionnaire.

#### *Dosing Patterns Secondary Endpoints*

- The mean and median total daily dose of and duration of exposure to ALO-02 extended-release capsules during the Open-Label Conversion and Titration Period and during the Double-Blind Treatment Period.

#### *Other Secondary (Exploratory) Endpoints*

- The percentage of responders at Double-Blind Weeks 4, 8, and 12 (or Final Visit) in the Chronic Low Back Pain Responder Index (a composite end point of daily average low back pain intensity numerical rating scale scores, PGA of Low Back Pain and RMDQ total score).

#### **Safety Endpoints**

- The intensity, seriousness, and relationship to study drug of reported adverse events (AEs) during the Open-Label Conversion and Titration Period and during the Double-Blind Treatment Period
- The changes in vital signs (heart rate [HR], blood pressure [BP], respiratory rate [RR]), and clinical laboratory test values during the Open-Label Conversion and Titration Period and during the Double-Blind Treatment Period
- The changes in 12-lead electrocardiogram (ECG) from the Screening Period to the end of the Double-Blind Treatment Period
- The presence and intensity of clinical opiate withdrawal after treatment with ALO-02 extended-release capsules as determined by the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) during the Open-Label Conversion and Titration Period, the Double-Blind Treatment Period and during the Post-Treatment Period

#### **Statistical Methods**

- *Sample size determination:* Approximately 250 subjects were to have been randomized in the Double-Blind Treatment Period in a 1:1 ratio to receive ALO-02 extended-release capsules or placebo capsules (approximately 125 subjects per treatment arm). This sample size has 90% power for a 2-sided test, at  $\alpha = 0.05$ , to detect a 1 unit difference in mean change from Baseline (time of randomization) to the final 2 weeks (Weeks 11 and 12) of the Double-Blind Treatment Period in daily average pain numerical rating scale (NRS-Pain) scores for low back pain between the active and placebo treatment groups. A common standard deviation of 2.4 was assumed.
- *Populations analyzed:* 1) ITT (intent-to-treat) defined as all subjects who were randomized into the DB Treatment Period and received at least one dose of DB study medication after randomization and 2) Completer population defined as all

ITT subjects who complete 12 weeks of DB study medication in the DB Treatment Period and who record at least three pain scores during each of Weeks 11 and 12.

### **Primary Efficacy Analyses**

The primary analgesic efficacy endpoint was the difference between the mean changes from Randomization Baseline to the average of the scores from the final 2 weeks (Weeks 11 and 12) of the Double-Blind Treatment Period in the daily average NRS-pain scores for low back pain when comparing ALO-02 versus placebo.

The primary statistical analysis was an analysis of covariance (ANCOVA) with treatment and prior pain analgesic (opioid or non-opioid) as categorical factors and the Randomization Baseline score and final total daily dose of the Titration Period as covariates and performed on the ITT population.

The primary analysis was to employ a hybrid multiple and single imputation strategy to impute missing data for the calculation of the primary endpoint.

**Sensitivity Analyses:** Five sensitivity analyses, as summarized in Table 6 below with imputation strategies, were to have been performed as follows:

**Table 6. Imputations Applied for Primary Analysis and Sensitivity Analyses**

Analysis	Discontinuation due to:			
	Adverse Event	Lack of Efficacy	Opioid Withdrawal (if receiving placebo)	Any Other Reason
<b>Primary</b>				
Hybrid Multiple and Single Imputation	SOCF	SOCF	BOCF	multiple imputation
<b>Sensitivity</b>				
Complete-case	N/A	N/A	N/A	N/A
Modified Hybrid Multiple and Single Imputation (Pattern Mixture Model)	SOCF	multiple imputation—all subjects assumed to respond like placebo subjects after discontinuation	BOCF	multiple imputation—all subjects assumed to respond like placebo subjects after discontinuation
Single Imputation	SOCF	LOCF	BOCF	LOCF
Mixed Model Repeated Measures (MMRM)	MMRM	MMRM	MMRM	MMRM
SOCF Only	SOCF	SOCF	SOCF	SOCF

SOCF: screening observation carried forward; BOCF: randomization baseline observation carried forward;  
 N/A: not applicable; LOCF: last observation carried forward.

(Protocol, p. 85)

### Key Secondary Endpoints Efficacy Analyses

- RMDQ (Roland Morris Disability Questionnaire) Total Score mean change from BL to the end of DB Week 12 (or final visit) - ANCOVA analysis model with treatment, prior pain analgesic (opioid or non-opioid), and study center as categorical factors and the Randomization BL score and final total daily dose of the Titration Period as covariates.
- PGA (Patient's Global Assessment) of LBP change from baseline to the end of DB Week 12 (or final visit) – Cochran-Mantel-Haenszel (CMH) test (row mean scores) analysis stratified by study center.

**Other Clinically Important Analyses:** Clinical Opiate Withdrawal Scale (COWS) and Subject Opiate Withdrawal Scale (SOWS) scores were to have been summarized descriptively by study visit and treatment, as applicable. Additionally, for COWS, the proportion of subjects with mild (COWS Score 5-12), moderate (COWS Score 13-24), moderately severe (COWS Score 25-36), or severe withdrawal (COWS Score >36) was to have been presented.

**PK:** The observed steady-state plasma concentration ( $C_{obs}$ ) of oxycodone, noroxycodone, naltrexone, and 6- $\beta$ -naltrexol were to have been summarized at various time points through the study (including if a subject experienced a COWS score  $\geq 13$  at

any of the scheduled or unscheduled clinic visits). Where applicable, the dose-exposure relationship was to be evaluated for each analyte by plotting the observed steady-state concentration as a function of a daily dose of oxycodone.

**Interim or AdHoc Analyses:** No interim or AdHoc analyses were planned.

**PostHoc Analyses:** A post hoc analysis was not planned in the protocol.

**Protocol Amendments:** The original protocol was dated January 12, 2012. There were three protocol amendments. Most subjects enrolled under Protocol Amendment 2.

The Applicant's NDA submission initially did not include the specific amended revisions from version to version but only a summary of the clarifications. An IR was sent from the Agency to the Applicant in which they were advised to provide a table and revised protocols in track changes which delineated the actual changes between the protocol versions as well as provide the number of subjects enrolled/randomized for each protocol amendment. The Applicant provided the information regarding number of subjects enrolled by protocol amendment dates shown in Table 7 and the key revisions are shown in Table 8.

**Table 7. Number of Subjects Enrolled by Protocol Amendment Dates**

	Screened	Enrolled in the Open-Label Titration Period	Randomized to Treatment Period
Final Protocol, 12 Jan 2012	0	0	0
Protocol Amendment #1, 16 Mar 2012	0	0	0
Protocol Amendment #2, 11 Apr 2012 30 Apr 2012* to 09 Dec 2012	545	325	222
Protocol Amendment #3, 29 Oct 2012 10 Dec 2012* and after	118	85	59
<b>Total</b>	<b>663</b>	<b>410</b>	<b>281</b>

\* Dates when Amendments #2 and #3 were implemented at sites.

Source Data: Listings 16.2.7, 16.2.1.1

Source: /pub/studies/pfizer/9002\_0139/primary/tables/tablec.sas File Generation: 19JUL2015 21:56 Data

Extraction: 05May2014

(Applicant's table, Response to Agency IR, submitted 7/24/15)

Upon review of the Applicant's more detailed descriptions of the protocol amendments, I conclude that there were no major protocol revisions which would have affected efficacy. Most of the revisions provided additional monitoring or were for clarification purposes. The key protocol amendments are summarized below.

**Table 8. Key Protocol Amendments Study 1002**

Date	Key Revisions
March 16, 2012	<ul style="list-style-type: none"> <li>• Clarification of the rationale and implementation of the DB gradual or dummy taper during specific study periods</li> <li>• Revision of the Treatment Response Criteria and Subject Withdrawal Criteria for Positive Urine Drug Tests</li> </ul>
April 11, 2012	<ul style="list-style-type: none"> <li>• Clarification of the plan for transition of end of study care to post-study care</li> <li>• Revised criteria for reason for discontinuation based on urine drug testing during OL Titration and Double-Blind Periods</li> </ul>
October 29, 2012	<ul style="list-style-type: none"> <li>• Study endpoints: Clarification of the analgesic effect secondary endpoint that Baseline is the randomization baseline and not the Screening baseline.</li> <li>• Clarification of prohibited medications to include tapentadol and buprenorphine from the start of the OL Conversion until the end of the Post-Treatment Period</li> <li>• Added urine drug testing as a reason for discontinuation at various points of testing</li> </ul>

(Reviewer)

Changes to Planned Analyses: The SAP was amended once prior to unblinding (version 2, 11/18/13); key changes in the amendment included the removal of study center from the statistical models due to a small sample size in many of the centers, and the addition of a sensitivity analysis which excluded subjects with a major protocol deviation of errors in urine drug screens. Due to the small sample sizes in many study centers, there was no analysis of results by center. Overall, these changes as noted should not have affected efficacy results since they occurred prior to unblinding.

**II) Supportive Study B4531001 Long-Term Open-Label Study**

**Title:** A Multicenter, 12-Month, Open-Label, Single-Arm, Safety Study of Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules in Subjects with Moderate to Severe Chronic Noncancer Pain

There were two amendments to the protocol, with the final protocol being Amendment 2 version, dated February 22, 2012.

**Objectives:**

- The primary objective of this study was to evaluate the long-term safety of ALO-02 administered for up to 12 months.
- The secondary objectives were:
  - To evaluate the analgesic effect of ALO-02 administered for up to 12 months;

- To describe the dosing patterns of ALO-02 administered for up to 12 months
- To evaluate the observed steady-state plasma concentrations (Cobs) of oxycodone, noroxycodone, naltrexone, and 6β-naltrexol in subjects administered ALO-02 for up to 12 months; and
- To assess aberrant medication-related behaviors during a long-term opioid treatment study.

**Population:** The study was planned to enroll at least 350 male and female adult subjects with moderate-to-severe CNCP who required a continuous around-the-clock opioid analgesic for an extended period of time. Subjects eligible for participation in this study could have been receiving an opioid for the management of chronic pain at the time of study entry or could have been opioid-naïve. Subjects who were on continual opioid treatments were considered opioid-naïve if they stopped taking opioids for a significant amount of time (i.e., 3 months) prior to study entry. These subjects were started on a low dose of ALO-02 and titrated to effect per protocol.

**Study Drug/Dosing:** Oxycodone HCl and naltrexone HCl extended-release oral capsules in dosage strengths (oxycodone HCl/naltrexone HCl) of 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8mg, 60 mg/7.2 mg, and 80 mg/9.6 mg. The range of allowable daily doses of oxycodone HCl and naltrexone HCl for this study was to have been 20 mg to 160 mg of the oxycodone component in a 24 hour time interval, administered twice daily approximately 12 hours apart. At the discretion of the Investigator, oxycodone HCl and naltrexone HCl extended-release capsules could be administered once daily, at 24 hour intervals.

**Major Inclusion Criteria:**

1. Male and female subjects 18 years of age or older
2. Moderate to severe chronic noncancer pain (duration of at least 3 months) requiring a continuous, around-the-clock opioid analgesic for an extended period of time.

**Overall Study Design:** This was a multicenter, open-label, single-arm safety study with ALO-02 administered for up to 12 months . The study schematic is shown below in Table 9.

**Table 9. Design Overview for Study B4531001**

Pre-Treatment	Treatment	Post-Treatment
Screening & Baseline Visits	Open-label ALO-02 End of Weeks 1 & 4 & Monthly Visits	Tapering open-label ALO-02 End-of-Study Visit
1 week	12 months	2 weeks

Abbreviations: ALO-02=oxycodone HCl and naltrexone HCl ER capsules.  
 (Protocol, p. 123)

## Study Periods

- *Pre-Treatment Period:* The Pre-Treatment period was to occur over 1 week and included a Screening visit (Visit 1) and a Baseline visit (Visit 2). Initial eligibility for study participation was assessed at the Screening visit. For subjects who were currently receiving an opioid for the management of chronic pain, the average total daily opioid dose (including maintenance opioid and intermittent opioid usage) was ascertained over the 1-week Pre-Treatment Period. This average total daily opioid dose determined during the Pre-Treatment Period was used to guide the subject's conversion from the current opioid therapy to ALO-02.
- *Treatment Period:* This was a 12-month dosing of ALO-02 capsules, supplied in dosage strengths of 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, and 80 mg/9.6 mg. The range of allowable total daily dose of ALO-02 was 20 mg to 160 mg of the oxycodone component.
- *Post-Treatment Period:* Following the completion of the 12-month Treatment Period or upon discontinuation, subjects were to enter the Post-Treatment Period that occurred over 2 weeks. Subjects were gradually tapered from their current daily dose of ALO-02 and then transitioned to an investigator-determined standard of care. The tapering schedule was determined by the investigator and individualized according to the subject's current daily dose of ALO-02. Subjects were to return 2 weeks after the end of the 12-month Treatment Period (i.e., the end of the Post-Treatment Period) for an End of-Study visit to undergo safety assessments.

**Dosing:** The open-label design of this study allowed the investigator to make dose adjustments, in accordance with the investigator's clinical practice, for each subject upward in response to inadequate analgesia or downward in response to intolerable opioid effects.

The dosing and administration guidelines for initiating study drug treatment outlined in the protocol were essentially the same as those for Study 1002 (see Appendix C). However, investigators were permitted to use an alternative opioid conversion schedule at their discretion.

- *Opioid-Naïve Subjects:* Per suggested outline from the protocol, opioid naïve subjects started treatment with ALO-02 10 mg/1.2 mg BID.
- *Opioid-Experienced Subjects:* The protocol instructed investigators to calculate the starting dose of ALO-02 for opioid experienced subjects based on subject's prior total daily dose of opioids converted to an equivalent dose of oxycodone using established conversion factors where applicable (except for tramadol and fentanyl for which no established conversion exists) and then halved to obtain the BID dose and rounded down to an available dose strength of ALO-02. Subjects taking tramadol prior to entering the study were treated as opioid naïve and started on ALO- 02 10 mg/1.2 mg. For subjects taking fentanyl prior to starting

the study, it was recommended that approximately 10 mg BID of ALO-02 should be initially substituted for each 25 mcg/hour fentanyl transdermal patch.

- *End of treatment or Early Termination:* Subjects were tapered from their current total daily dose of ALO-02 and transitioned to the investigator-determined standard of care.
- *Rescue Therapy:* Acetaminophen was allowed as a rescue medication during the entire Treatment Period of the study. Subjects were allowed to take up to 2 grams per day, i.e., 500 mg every 6 hours as needed. IR oxycodone as a single ingredient product was allowed as a rescue medication only during the first 4 weeks of the Treatment Period to support the titration of ALO-02 treatment.

**Primary Endpoint:** The primary endpoint was a safety endpoint, i.e., the number (percentage) and type of AEs and adverse reactions (AEs assessed by the Investigator as treatment-related) reported after treatment with study drug ALO-02 for up to 12 months.

**Additional Safety Endpoints:** 1) Intensity, seriousness, and relationship to study drug of reported AEs, 2) changes in vital signs, 12-lead ECG, and clinical lab values after treatment with study drug for up to 12 months, 3) presence and intensity of clinical opiate withdrawal after treatment using COWS and SOWS, and 4) descriptions of the reasons for early discontinuation.

**Analgesic Effect Endpoints and Analyses:**

- Pain intensity scores were summarized descriptively by study visit and at the end of treatment. The four items of the Pain Severity Subscale of the Brief Pain Inventory-Short Form were summarized at each visit and the change and percent change from baseline was calculated. Paired t-test were used to analyze the change and percent change between each post-baseline time point and baseline.
- Treatment satisfaction scores and rescue medication use over time were summarized descriptively by study visit

**Other Endpoints:** Dosing patterns, PK, and Aberrant-Medication Behavior

## 6 Review of Efficacy

### Efficacy Summary

#### 6.1 Indication

The proposed indication for Troxyca ER is management of pain severe enough to require daily, around-the-clock (ATC), long-term opioid treatment and for which alternative treatment options are inadequate.

### 6.1.1 Methods

The Applicant reported that Studies B4531002 (DB efficacy and safety study), B45321001 (long-term open-label study), B4531007 (comparison of ALO-02 final formulation to Roxicodone) and literature (extended-release oxycodone or oxycodone/naloxone) served as the primary sources for efficacy.

Key efficacy study B4531002 was a phase 3, enriched-design, multicenter, randomized, 12-week, double-blind, placebo-controlled study conducted in the U.S. to assess the safety and efficacy of ALO-02 compared to placebo in opioid-experienced and opioid-naïve subjects with moderate to severe, nonneuropathic, nonmalignant, chronic low back pain who required around-the-clock opioid therapy.

Prior to randomization, each subject must have demonstrated analgesic benefit and acceptable tolerability study drug (responder) during the open-label, flexible-dose titration period. Qualified subjects were then randomized to receive either ALO-02 or placebo.

Efficacy results for study 1002 are discussed in detail in this section of the review. Note that percentages are rounded throughout this review.

### 6.1.2 Demographics

*Patient Characteristics:* The patient characteristics for the safety population and ITT population are shown below in Table 10. Overall, for the double-blind treatment period, the demographics were similar between placebo and ALO-02 groups. However, there were approximately 10% more females (56%) compared to males (44%) in each treatment group during both the double-blind period and open-label period. There was a median age of 51 years in both treatment groups, but few patients (11%) in either group were ≥65 years of age. In both treatment arms, 73% were Caucasian (white), but there were slightly more Caucasians in the placebo group (77%) compared to the ALO-02 group (70%). The mean duration since CLBP diagnosis was approximately 12 years for both treatment arms.

**Table 10. Patient Characteristics: Open-Label Titration Period (Safety Population) and Double-Blind Treatment Period (ITT Population)**

	Open-Label	Double-Blind Treatment Period		
	Titration Period	Placebo	ALO-02	Overall
	ALO-02 N=410	N=134	N=146	N=280
<b>Gender, n (%)</b>				
Male	177 (43.2)	59 (44.0)	65 (44.5)	124 (44.3)
Female	233 (56.8)	75 (56.0)	81 (55.5)	156 (55.7)
<b>Age (years)<sup>a</sup></b>				
Mean (SD)	50.1 (12.48)	49.3 (12.24)	50.6 (12.98)	50.0 (12.63)
Median	51.0	51.0	51.0	51.0
Min, Max	19, 89	19, 76	23, 89	19, 89
<65 years	364 (88.8)	119 (88.8)	130 (89.0)	249 (88.9)
≥65 years	46 (11.2)	15 (11.2)	16 (11.0)	31 (11.1)
≥75 years	6 (1.5)	1 (0.7)	3 (2.1)	4 (1.4)
<b>Hispanic Ethnicity</b>				
<b>Race, n (%)</b>				
White	298 (72.7)	103 (76.9)	102 (69.9)	205 (73.2)
Black	104 (25.4)	29 (21.6)	41 (28.1)	70 (25.0)
Asian	3 (0.7)	1 (0.7)	1 (0.7)	2 (0.7)
Other	5 (1.2)	1 (0.7)	2 (1.4)	3 (1.1)
<b>BMI (kg/m<sup>2</sup>)<sup>a</sup></b>				
Mean (SD)	30.2 (5.46)	30.9 (5.77)	30.4 (5.57)	30.6 (5.66)
Median	30.1	31.4	29.6	30.7
Min, Max	17, 44	17, 44	18, 40	17, 44
<b>Duration Since Diagnosis of CLBP (years)<sup>b</sup></b>				
Mean (SD)	11.7 (10.27)	12.5 (11.19)	12.3 (10.17)	12.4 (10.65)
Median	8.3	9.1	8.7	8.8
Min, Max	0.3, 50.7	0.6, 50.7	0.3, 42.5	0.3, 50.7

Source: Table 14.1.2.2

Abbreviations: ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride extended-release capsule;

BMI = body mass index; CLBP = chronic low back pain; ITT = Intent-to-Treat; N = number of subjects;

SD = standard deviation

(CSR, p. 84)

**Medical history:** For subjects treated in the Double-Blind Treatment Period, the most common (≥10%) medical diagnoses overall (both placebo and ALO-02) included hypertension (37%), OA (24%), gastroesophageal reflux disease (23%), depression (19%), insomnia (19%), seasonal allergy (19%), anxiety (18%), hyperlipidemia (15%), hypercholesterolemia (14%), headache (14%), Type 2 diabetes mellitus (14%), constipation (11%), and obesity (10%).

The three most common medical history diagnoses by treatment arms for those randomized to the placebo group during the Double-Blind Period were: hypertension (37%), insomnia (25%), and depression (24%). For subjects in the ALO-02 group, the

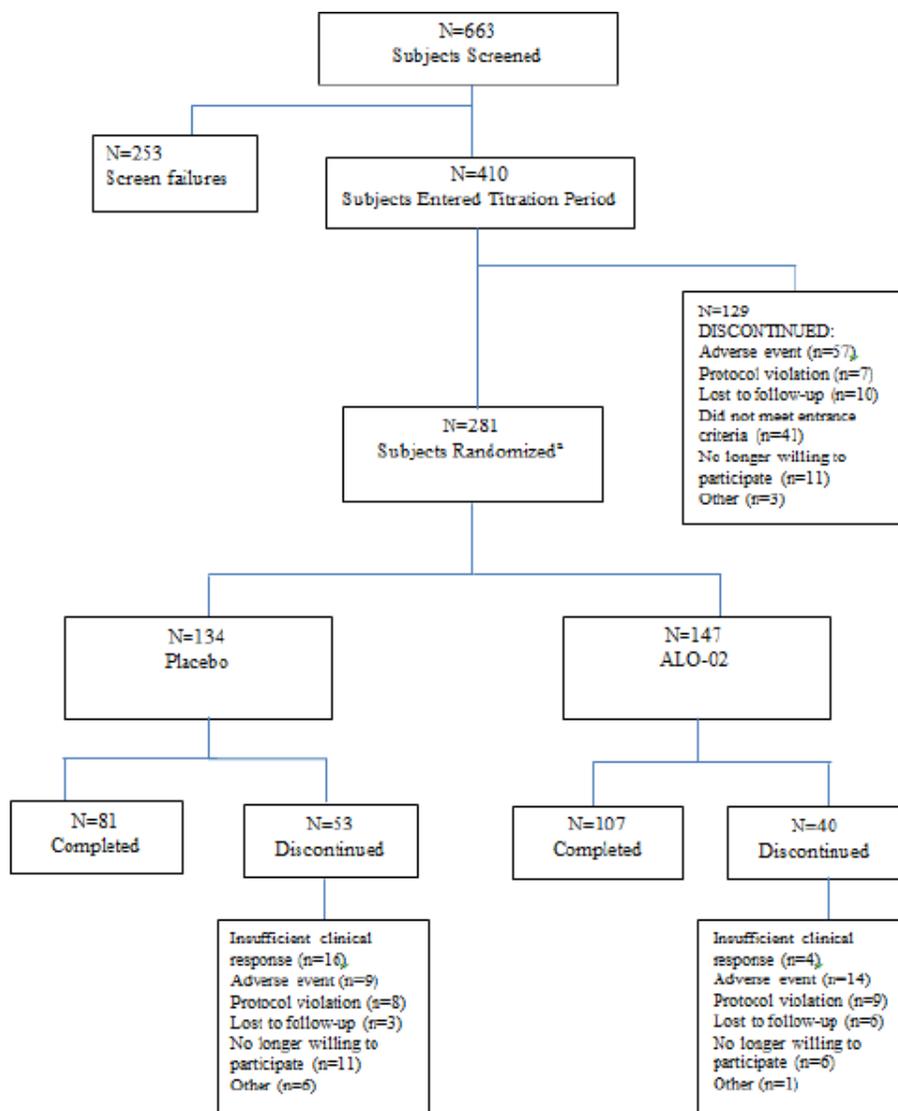
three most common diagnoses were: hypertension (38%), OA (24%), and gastroesophageal reflux disease (24%).

*Reviewer's comments:* Although generally balanced between the treatment arms, there were approximately 10% more females than males in both the Open-Label and Double-blind phases of the study and there were few patients (11%)  $\geq 65$  years of age. See Section 6.1.7 (Subpopulation) for further discussion of these demographics.

### **6.1.3 Subject Disposition**

Refer to Figure 3 below for details regarding the disposition of subjects. A total of 663 subjects were screened; 410 subjects were enrolled in the Open-Label Titration (OLT) Period and received at least one dose of study drug. A total of approximately 68% (281/410) completed the OLT Period and were randomized to the Double-Blind (DB) Treatment Period. The most common reasons subjects did not enter the DB Treatment Period were AEs (14%) and did not meet entrance criteria (10%).

**Figure 3. Disposition of Subjects**



Source: Tables 14.1.1.1.1 and 14.1.1.1.2

a. One subject (10171002) participated in the Open-Label Titration Period for 37 days, then was discontinued from the study after randomization into the Double-Blind Treatment Period but prior to receiving any double-blind treatment (Listing 16.2.1.1).

(CSR, p. 73)

As shown in Table 11 below, a total of 281 subjects (134 placebo and 147 ALO-02) were randomized into the DB Treatment Period. All subjects except one received at least one dose of study drug and were included in the ITT (Intent-to-treat) population. Of the 188 subjects that completed the DB Treatment Period, more subjects discontinued from

placebo (40%) than from study drug (27%). More subjects in placebo discontinued due to lack of efficacy (12%) compared to study drug (3%) and more subjects discontinued due to AEs in study drug (9%) compared to placebo (7%), as would be expected.

**Table 11. Subject Disposition: Double-Blind Treatment Period**

	Placebo N=134 n (%)	ALO-02 N=147 n (%)	Overall N=281 n (%)
Number of Subjects Randomized	134 (100.0)	147 (100.0)	281 (100.0)
Randomized but not treated <sup>a</sup>	0 (0.0)	1 (0.7)	1 (0.4)
Number of Subjects who Finished the Double-Blind Treatment Period	81 (60.4)	107 (72.8)	188 (66.9)
Number of Subjects Discontinued from the Double-Blind Treatment Period	53 (39.6)	40 (27.2)	93 (33.1)
Reasons for Discontinuation			
Insufficient clinical response	16 (11.9)	4 (2.7)	20 (7.1)
Adverse events	9 (6.7)	14 (9.5)	23 (8.2)
Subject died	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	8 (6.0)	9 (6.1)	17 (6.0)
Lost to follow-up	3 (2.2)	6 (4.1)	9 (3.2)
No longer willing to participate in study	11 (8.2)	6 (4.1)	17 (6.0)
Other	6 (4.5)	1 (0.7)	7 (2.5)

Source: Table 14.1.1.1.2

Abbreviations: ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride extended-release capsule;

N = number of subjects

a. Subject 10171002 participated in the Open-Label Titration Period for 37 days, then withdrew from the study after randomization into the Double-Blind Treatment Period but prior to receiving any double-blind treatment.

(CSR, p. 72)

*Protocol Deviations:* The protocol defined a major protocol deviation as “those deviations from the protocol likely to have an impact on the subject’s rights, safety, or well-being, and/or on the validity of the data for analysis”.

Discontinuations due to protocol deviations were reported for 6% placebo and 6% study drug. Of the overall 17 subjects discontinued from DB treatment due to protocol deviations, the majority (14/17 [82%]) were discontinued due to a positive urine drug screen due to illicit drug substances.

For purposes of this review, potentially significant protocol deviations were defined by this reviewer as those with 1) incidence >10% in any treatment group or 2) >5% difference between treatment arms. In general, the number and types of protocol deviations were similar between the two treatment arms and no differences >5% were noted between the groups. As shown in Table 12 below, protocol deviations >10% were seen with the following: 1) APAP used as rescue medication in excess of 4 g/day [DB placebo group], 2) urinalysis not done [OL titration period], 3) Urine Drug Screen (UDS) not done [OL titration period and in almost equal percentage of study drug and placebo in the double-blind period], 4) COWS not done [OL titration period and in almost equal percentage of study drug and placebo in the double-blind period], and 4) diary completion ≤70% [slightly higher in study drug at approximately 11% compared to placebo at approximately 10%]. Although the incidence for these deviations was high, the incidence was comparable between the two groups.

**Table 12. Protocol Deviations with Incidence ≥10% in any Treatment Group**

Protocol Deviation Category Key Protocol Deviation Sub-Category	Open-Label ALO-02 (Not Randomized to DB Treatment Period) N=129 n (%)	Randomized to ALO-02 N=147 n (%)	Randomized to Placebo N=134 n (%)
<b>Concomitant Medications</b>			
Acetaminophen used as rescue medication in excess of 4 grams/day	8 (6.2)	5 (3.4)	17 (12.7)
Urinalysis not done	13 (10.1)	8 (5.4)	11 (8.2)
UDS not done	16 (12.4)	30 (20.4)	30 (22.4)
<b>Procedures/Tests</b>			
COWS not done	15 (11.6)	44 (29.9)	38 (28.4)
Subject's diary completion was ≤70%	0 (0.0)	16 (10.9)	13 (9.7)

Source: Listing 16.2.2

Note: Subjects were counted only once for each protocol deviation sub-category.

Abbreviations: ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride extended-release capsule

a. Includes subjects under protocol deviation category "Laboratory" in Listing 16.2.2.

b. Includes subjects under protocol deviation category "Concomitant Medications" in Listing 16.2.2.

c. Prohibited use of concomitant medication for pain >1 day during the 7 days prior to Randomization Baseline, or during Week 11 and Week 12, or in the 2 weeks prior to discontinuation (efficacy) and use of opioids during the taper period or during the Post-Treatment Taper Period (safety).

d. Includes subjects under protocol deviation category "Study Drug" in Listing 16.2.2.

(Sponsor's table, p. 75 and 76, modified by reviewer)

The Applicant identified "key" protocol deviations in the following categories: 1) Inclusion/Exclusion, 2) Study Drug [administration or compliance], 3) Concomitant Medications, 4) Laboratory, 5) Visit Schedule, 6) Procedures/Tests, 7) Informed Consent Issues, and 8) Other.

Of the key protocol deviations, the following are discussed in further detail:

- *Key Inclusion/Exclusion Protocol Deviation* –An SAE narrative was provided for Subject 10151003, a 39 year-old female who missed a dose of medroxyprogesterone (DepoProvera) IM injection failing to consistently and correctly maintain the use of effective method of contraception. This resulted in a positive serum hCG at Visit 15. The subject was two to three weeks gestational age at that time. This unintended pregnancy resulted in a spontaneous abortion.
- *Errors in UDS Central Lab Requisition Forms*: During the study, nine study centers made an error when completing the UDS central lab requisition forms for 12 subjects. Specifically, the centers provided the visit number of an open-label treatment visit rather than a double-blind treatment visit. To assess the potential impact of this possible unblinding, the Applicant conducted a sensitivity analysis on the ITT Population, which excluded subjects with major protocol deviations as defined in the protocol. According to the Agency's statistical reviewer, Dr. Feng Li, this should not have impacted efficacy results.
- *Incorrect Starting Dose*: Nine subjects (10151006, 10171001, 10171002, 10221001, 10281006, 10391003, 10431002, 10481005, and 10481008) received an incorrect open-label starting dose of ALO-02. Incorrect starting doses were defined in these cases as protocol deviation subcategory "incorrect OL starting dose of ALO-02 used and dose is ≥2 times the total daily dose of the correct dose" based on subjects' pre-study opioid dose. All of these subjects except Subject 10221001 experienced AEs at some point during the study. Upon my review, I determined that the AEs experienced by these subjects were likely

unrelated to the protocol violation except Subject 10151006, randomized to ALO-02 treatment arm who experienced one event of opioid withdrawal during the OL Period and another during the Post-Treatment taper period. Specifically, for this subject, the protocol violation explanation was that the subject was not on a high enough dose of prior opioid to qualify for the trial under Amendment 2, however the subject was initiated on an ALO-02 dose of 60 mg total daily dose. The subject had been on hydrocodone/APAP 10 mg daily prior to entry into the study. Upon review of the narrative for this subject, she experienced an event of opioid withdrawal on treatment day three of the OL Period. This event of OW occurred during a period of transition (conversion) from one opioid to another so an AE of opioid withdrawal may be expected despite the fact that the prestudy opioid dose was lower than the starting ALO-02 dose. It is possible, however, that the error in starting dose may have contributed to the OW event.

- *Lack of 2-week Taper of Study Medication:* Three subjects, all randomized to placebo, did not complete a full 2-week taper of study medication at the end of Week 1 of the Double-Blind Treatment Period. No AEs of opiate withdrawal were reported. One subject was instructed by the study coordinator at Visit 6 (Open-Label Week 4) to take one capsule twice a day instead of two capsules twice a day. No AEs of opiate withdrawal were reported.

*Reviewer's comments:* Overall, the protocol deviations in the study were fairly equally distributed between the two treatment arms and should not have affected efficacy results. Further, the Applicant reported that there was formal acknowledgement by the study team that all deviations were reviewed and GCP (Good Clinical Practice) compliance was maintained.

#### **6.1.4 Analysis of Primary Endpoint(s)**

The Applicant found that the analysis of the primary efficacy endpoint, “the difference between the mean changes from Randomization Baseline to the average of the scores from the final 2 weeks (Weeks 11 and 12) of the Double-Blind Treatment Period in the daily average NRS-pain scores for low back pain when comparing ALO-02 versus placebo”, showed a statistically significant difference (LS mean treatment difference of -0.62; p value =0.0114).

##### *Applicant's Efficacy Results of Primary Endpoint:*

- At Randomization Baseline, weekly average mean (SD) eDiary NRS-pain score was 3.1 (1.04) for the placebo group compared to 3.0 (1.25) for the ALO-02 group. In the final 2 weeks (Weeks 11 and 12) of the Double-Blind Treatment Period, weekly average eDiary NRS-pain scores from the multiple imputations were 4.3 (2.24) and 3.6 (2.04) for each treatment group, respectively.
- The mean (SD) change from eDiary NRS-pain score Randomization Baseline to the final 2 weeks was statistically different (p=0.0114) between the ALO-02 group (0.6 [1.81]) and the placebo group (1.2 [1.93]), which indicated that subjects in

the placebo group experienced a significantly greater mean change (increase or worsening) in weekly average eDiary NRS-pain score from Randomization Baseline to the final 2 weeks than subjects treated with ALO-02 during the Double-Blind Treatment Period (LS mean treatment difference = -0.62, p=0.0114).

Table 13, below, summarizes the Applicant's primary efficacy endpoint analysis results.

**Table 13. Mean Change from Randomization Baseline in Weekly Average Diary NRS-Pain Score at Final 2 Weeks – Imputed Values (ITT Population)**

Visit	Placebo N=134	ALO-02 N=146
<b>Randomization Baseline</b>	N=134	N=145
Mean (SD)	3.1 (1.04)	3.0 (1.25)
Median	3.5	3.2
Min, Max	0.0, 5.1	0.0, 8.0
<b>Final 2 Weeks<sup>a</sup></b>	N=133	N=146
Mean (SD)	4.3 (2.24)	3.6 (2.04)
Median	4.3	3.5
Min, Max	0.0, 9.0	0.0, 8.9
<b>Change from Randomization Baseline to Final 2 Weeks<sup>a</sup></b>	N=133	N=145
Mean (SD)	1.2 (1.93)	0.6 (1.81)
Median	0.9	0.1
Min, Max	-4.1, 6.7	-4.4, 7.3
<b>Model-Adjusted Change from Randomization Baseline to Final 2 Weeks<sup>b</sup></b>		
LS Mean (SE)	1.23 (0.179)	0.60 (0.168)
95% CI	0.87, 1.58	0.27, 0.93
<b>Model-Adjusted Change from Randomization Baseline to Final 2 Weeks ALO-02 versus Placebo (multiple imputations)<sup>b,c</sup></b>		
Difference of LS Means (SE)		-0.62 (0.246)
95% CI		-1.11, -0.14
<b>p-value</b>		<b>0.0114</b>

Source: Table 14.2.1.1

Note: Weekly average eDiary NRS-pain scores were derived from the daily pain NRS and calculated as the mean of the last 7 days. Scores range from 0 = no pain to 10 = worst possible pain. Higher scores indicate greater pain.

Abbreviations: ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride extended-release capsule; CI = confidence interval; ITT = Intent-to-Treat; LS Mean = least squares mean; Max = maximum; Min = minimum; N = number of subjects; NRS-pain = Numerical Rating Scale for Pain; SD = standard deviation; SE = standard error

a. The averaged value for each subject from the 100 imputed datasets was used for this summary.

b. For each of the 100 imputed datasets, using proc MIANALYZE, the difference between treatment groups was evaluated by ANCOVA with treatment and prior pain analgesic (opioid or non-opioid) as categorical factors and the Randomization Baseline score and final total daily dose of the Open-Label Titration Period as covariates.

c. The overall assessment of difference between treatment groups was carried out by combining the results across 100 datasets using proc MIANALYZE.

(Applicant's table, CSR, p. 92)

***Applicant's Efficacy Results of Sensitivity Analyses:***

Results of the five sensitivity analyses, seen in Table 14 below, were generally supportive of the primary analysis, favoring ALO-02 over placebo and three of the five showed statistical significance (p<0.05).

**Table 14. Sensitivity Analysis Results: Least Squares Mean Change from Randomization Baseline to the Final 2 Weeks, ITT Population Study B4531002**

Analysis	Placebo LS Mean	ALO-02 LS Mean	Difference of LS Means	SE	95% CI	P-value
Completer Cases <sup>a</sup>	n=80 0.57	n=100 0.26	-0.30	0.242	-0.78, 0.17	0.2109
Pattern Mixture Model	n=133 1.06	n=145 0.61	-0.45	0.249	-0.94, 0.03	0.0686
Single Imputation	n=133 1.02	n=145 0.54	-0.48	0.217	-0.90, -0.05	0.0292
MMRM	n=134 1.02	n=146 0.22	-0.80	0.229	-1.25, -0.35	0.0005
SOCF Only	n=132 1.88	n=145 1.27	-0.61	0.270	-1.15, -0.08	0.0236

Abbreviations: ALO-02 = oxycodone HCl and naltrexone HCl ER capsules; ITT=Intent-to-Treat; CI = confidence interval; LS Mean = least squares mean; MMRM = mixed model repeated measures; n = number of subjects; N/A = not available; SE = standard error; SOCF = screening observation carried forward.

a. The Completers Population consisted of all ITT subjects who completed 12 weeks of double-blind study medication in the Double-Blind Treatment Period and who recorded at least 3 pain scores during each of Weeks 11 and 12.

Source: Tables 14.2.1.5.1, 14.2.1.5.2, 14.2.1.5.3, 14.2.1.5.5, and Supportive Table 3.2, Date of Table Generation 15AUG2014 (11:21).

(CSR, p. 93)

Overall, 51 subjects (28 placebo and 23 ALO-02) were excluded from the ITT Sensitivity Analysis Population due to one or more major protocol deviations. Subjects who did not record at least three NRS-pain scores during each of Weeks 11 and 12 were excluded from the Completer Population. The results of this analysis also favored ALO-02 with a p value of 0.0174, as shown in Table 15.

**Table 15. Sensitivity Analysis Results Excluding Subjects with at Least One Major Protocol Deviation: Least Squares Mean Change from Randomization BL to Weeks 11 and 12**

Analysis	Placebo LS Mean <sup>a</sup>	ALO-02 LS Mean	Difference of LS Means <sup>b</sup>	SE <sup>b</sup>	95% CI <sup>b</sup>	P-value <sup>b</sup>
Excluding Subjects with at Least 1 Major PD	n=106 1.33	n=123 0.69	-0.64	0.271	-1.18, -0.11	0.0174

Source: Table 14.2.1.5.6

Abbreviations: ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride extended-release capsule; CI = confidence interval; LS Means = least squares mean; n=number of subjects; PD = protocol deviation; SE = standard error

a. For each of the 100 imputed datasets, the difference between treatment groups was evaluated by ANCOVA with treatment and prior pain analgesic (opioid or non-opioid) as categorical factors and the Randomization Baseline score and final total daily dose of the Titration Period as covariates.

b. The overall assessment of difference between treatment groups was carried out by combining the results across 100 datasets using proc MIANALYZE.

(CSR, p. 94)

### 6.1.5 Analysis of Secondary Endpoints(s)

The Applicant did not control for multiplicity of the secondary endpoints and are not seeking labeling claims except for the “Percent Reduction in Weekly Average NRS Pain Scores from Screening to the final 2 weeks of DB”.

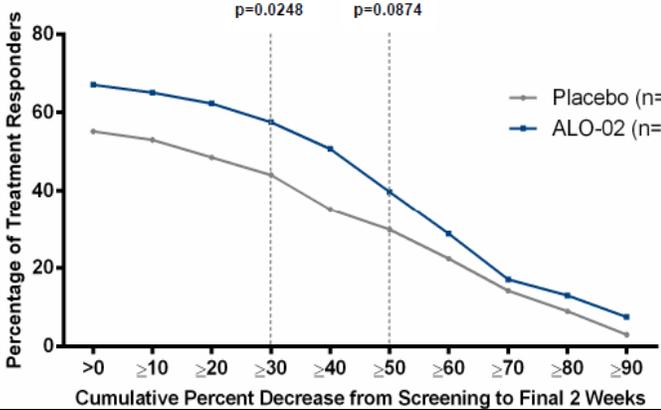
The efficacy results for the key secondary endpoints and secondary endpoints related to analgesic effect are summarized below in Tables 16 and 17.

**Table 16. Key Secondary Endpoints Physical Function Assessments**

<b>Endpoint</b>	<b>Results</b>
Roland-Morris Disability Questionnaire (RMDQ)	<ul style="list-style-type: none"><li>• No statistical significance was noted for the RMDQ change from Randomization BL to Week 12/Early Termination.</li><li>• The change in RMDQ score from Screening to Randomization BL (subjects entering the Double-Blind Treatment Period, ITT Population) was statistically significant (-4.8 [4.95], <math>p &lt; 0.0001</math>) indicating an overall improvement</li></ul>
Patient Global Assessment	<ul style="list-style-type: none"><li>• No statistical significance was noted for PGA shift from Randomization Baseline to Week 12/Early Termination.</li><li>• The overall shift in PGA of low back pain showed statistically significant (<math>p &lt; 0.0001</math>) improvement during the Open-Label Titration Period for the ITT Population.</li></ul>

(Reviewer)

**Table 17. Other Secondary Endpoints Related to Analgesic Efficacy**

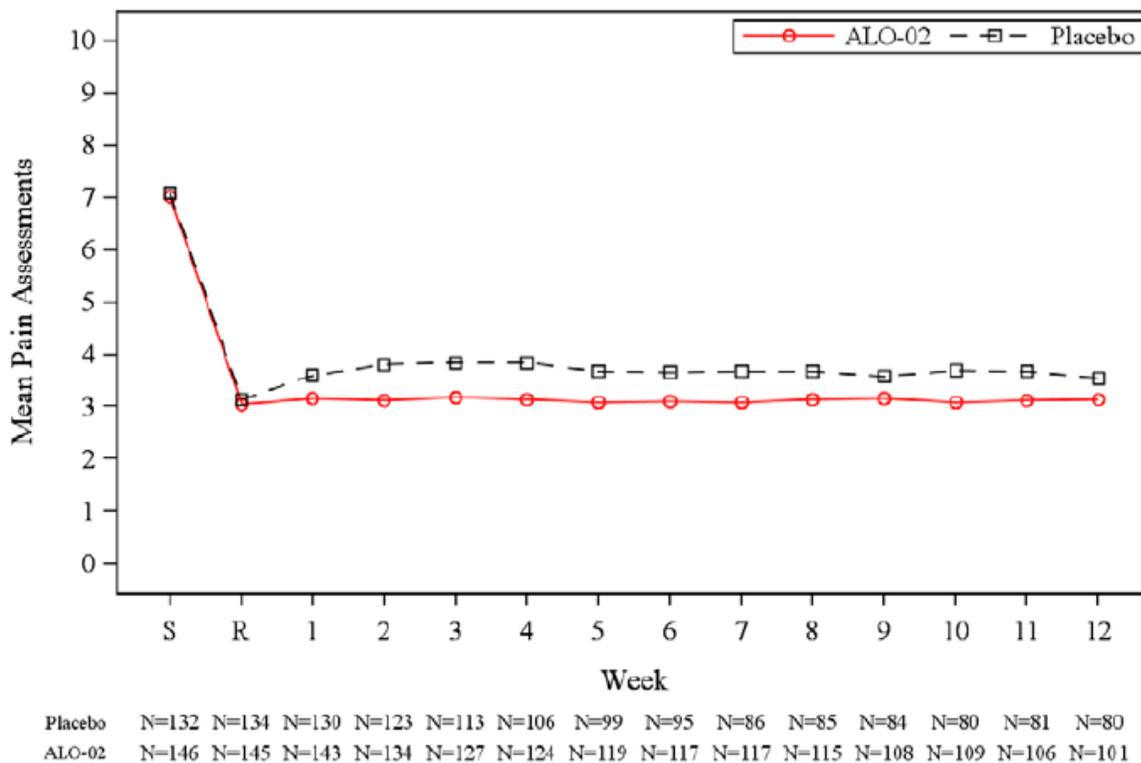
Endpoint	Results																																	
NRS Pain Scores	<ul style="list-style-type: none"> <li>• Placebo: Weekly average mean scores increased at each week from Randomization BL (3.1) to Week 4 (3.8) and Week 8 (3.7)</li> <li>• ALO-02: Weekly average mean scores showed less change from Randomization BL (3.0) to Week 4 (3.1) and Week 8 (3.1)</li> </ul>																																	
Percent reduction in Weekly Average NRS Pain Scores from Screening to the final 2 weeks of DB	<ul style="list-style-type: none"> <li>• Placebo: 59 (44%) had at least a 30% decrease (improvement) in NRS-pain score; 40 (30%) had at least a 50% decrease (improvement) in NRS</li> <li>• ALO-02: 84 (57%) had at least a 30% decrease (improvement) in NRS-pain score; 58 (40%) had at least a 50% decrease (improvement) in NRS</li> </ul>  <table border="1" data-bbox="516 835 1177 1245"> <caption>Data for Figure: Percentage of Treatment Responders by Cumulative Percent Decrease</caption> <thead> <tr> <th>Cumulative Percent Decrease</th> <th>Placebo (n=134)</th> <th>ALO-02 (n=146)</th> </tr> </thead> <tbody> <tr> <td>&gt;0</td> <td>~55%</td> <td>~68%</td> </tr> <tr> <td>≥10</td> <td>~52%</td> <td>~65%</td> </tr> <tr> <td>≥20</td> <td>~48%</td> <td>~62%</td> </tr> <tr> <td>≥30</td> <td>~44%</td> <td>~58%</td> </tr> <tr> <td>≥40</td> <td>~38%</td> <td>~52%</td> </tr> <tr> <td>≥50</td> <td>~32%</td> <td>~45%</td> </tr> <tr> <td>≥60</td> <td>~25%</td> <td>~38%</td> </tr> <tr> <td>≥70</td> <td>~18%</td> <td>~30%</td> </tr> <tr> <td>≥80</td> <td>~12%</td> <td>~22%</td> </tr> <tr> <td>≥90</td> <td>~8%</td> <td>~15%</td> </tr> </tbody> </table>	Cumulative Percent Decrease	Placebo (n=134)	ALO-02 (n=146)	>0	~55%	~68%	≥10	~52%	~65%	≥20	~48%	~62%	≥30	~44%	~58%	≥40	~38%	~52%	≥50	~32%	~45%	≥60	~25%	~38%	≥70	~18%	~30%	≥80	~12%	~22%	≥90	~8%	~15%
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Brief Pain Inventory –Short Form mean changes	<ul style="list-style-type: none"> <li>• Placebo scores were higher (statistically significant) compared to ALO-02 for all subscales of the BPI-sf at Week 2 and Week 4.</li> <li>• Significant differences between placebo and ALO-02 in favor of study drug were noted for the 4 pain subscales of the BPI-sf at Week 12.</li> <li>• Significant differences between placebo and ALO-02 in favor of study drug were noted for the Pain Severity Index (the mean of the 4 pain subscales) at Week 12.</li> <li>• ALO-02 had lower scores on the Pain Interference Index (mean of the 7 BPI-sf pain interference with function items)</li> </ul>																																	
Rescue Medication (APAP) Use	<ul style="list-style-type: none"> <li>• Placebo: Mean = 252.1 mg/day; 43% required rescue med</li> <li>• ALO-02: Mean = 167.7 mg/day; 35% required rescue med</li> </ul> <p>Values were not statistically significant.</p>																																	
Time to Analgesic Response from Screening to Randomization BL	<ul style="list-style-type: none"> <li>• Median time to 30% analgesic response = 20 days (95%CI: 17-22 days)</li> <li>• Median time to 50% analgesic response = 33 days (95% CI: 30-35 days)</li> </ul>																																	

(OLT Period)	
Time to Loss of Analgesic Response (DB Period from Randomization BL)	<p><i>30% Loss of Analgesic Response</i></p> <ul style="list-style-type: none"> <li>• <u>Placebo</u>: Median time to 30% loss of analgesic response = 21 days (95% CI range: 15-39 days)</li> <li>• <u>ALO-02</u>: Median time to 30% loss of analgesic response = too few had 30% loss to estimate the median.</li> </ul> <p>The cumulative probability of 30% loss of analgesic response from Randomization BL to the end of the DB Period was statistically significant favor ALO-02 over placebo (p=0.0024)</p> <p><i>50% Loss of Analgesic Response</i></p> <ul style="list-style-type: none"> <li>• <u>Placebo</u>: Median time = 62 days</li> <li>• <u>ALO-02</u>: Not calculable due to too few subjects who experienced a 50% loss of response</li> </ul> <p>Overall, treatment comparison using Kaplan-Meier analysis between the ALO-02 group and placebo was statistically significant (p=0.0021).</p>
Time to Treatment Discontinuation due to Lack of Efficacy (DB)	<p>Investigator-reported lack of efficacy discontinuations</p> <ul style="list-style-type: none"> <li>• <u>Placebo</u>: 16 (12%)</li> <li>• <u>ALO-02</u>: 4 (3%)</li> </ul> <p>p=0.006</p>
Satisfaction with Treatment	<p>59% of subjects in the placebo group compared to 80% of subjects in the ALO-02 group were “satisfied” or “very satisfied” with treatment; this difference was statistically significant (p=0.0004) for the ITT Population.</p>

(Table, reviewer)

Dr. Li summarized the average pain intensity score over time, shown below in Figure 4.

**Figure 4. Average Pain Intensity Score Over Time**



(Figure, Dr. Feng Li, Statistical Reviewer)

Approximately 43% of the subjects randomized to placebo and 35% of the subjects used acetaminophen as rescue medication during the double-blind period. According to Dr. Li, statistical reviewer, the adjusted average daily use is the model fitted mean, which is the ANXOCA model with terms including treatment, prior opioid use, average daily rescue use during the titration period, and the final total dose. As shown below taken from Dr. Li's review, the average daily use of rescue acetaminophen in the ALO-02 group was very similar to that of the placebo group after adjusting for average daily rescue use during the titration period and final total daily dose of study medication of the titration period, as shown below in Table 18.

**Table 18. Amount of Rescue Acetaminophen Administered During the Double-Blind Period**

	Statistics	Placebo (N=134)	ALO-02 (N=146)
Subjects used rescue	Non-rescued, n (%)	76 (57%)	95 (65%)
	Rescued, n (%)	58 (43%)	51 (35%)
Model adjusted daily use [a]	LS Mean (mg/day)	208	204
	SE	36	35
	Difference in LS Means	-4	
	SE	51	
	95% CI	(-103, 96)	
	p-value	0.9	

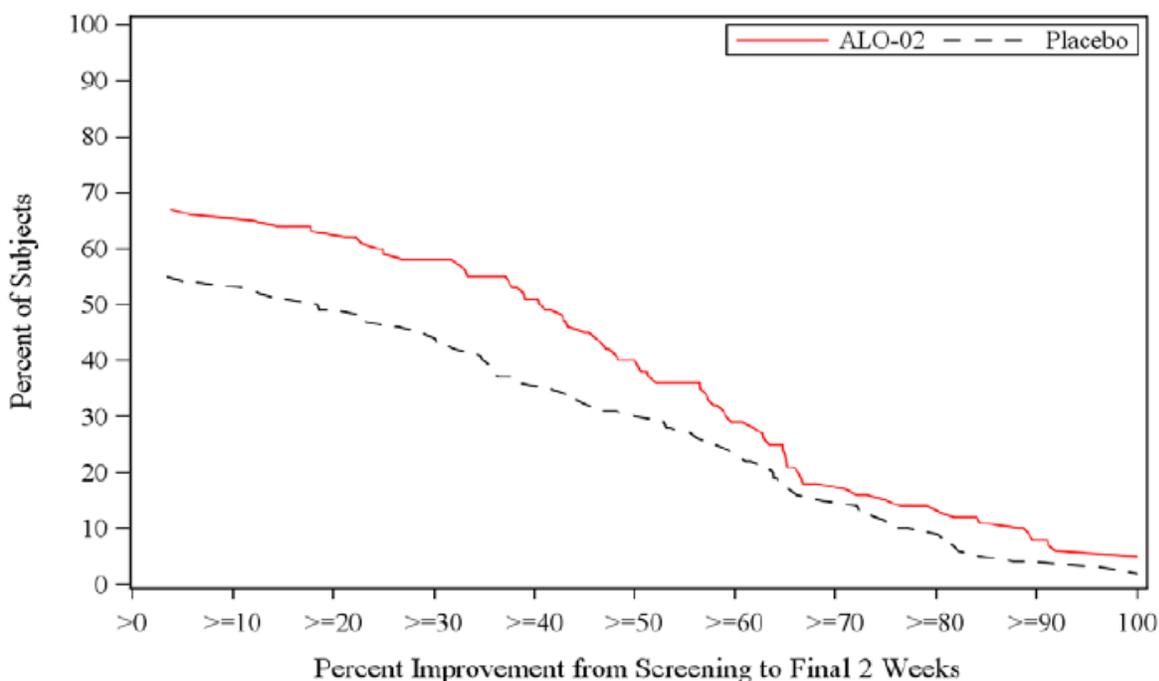
Source: Clinical Study Report, Table 14.2.3.4; SE: standard error; CI: confidence interval

[a] Analysis of covariance with treatment and prior pain analgesic as factors and the average daily rescue use during the titration period and final total daily dose of study medication of the titration period as covariates.

(Table, Dr. Feng Li, statistical reviewer)

There is apparent separation between the continuous responder curves of the two treatments (Figure 5). Approximately 58% of the subjects in the ALO-02 group had at least 30% improvement from screening. In contrast, approximately 44% of the placebo group had at least 30% improvement from screening. Subjects who discontinued study drug were considered as non-responders in the calculations.

**Figure 5. Continuous Responder Curve**



(Figure, Dr. Feng Li, statistical reviewer)

### 6.1.6 Other Endpoints

The Applicant reported that the non-analgesic and exploratory endpoints were generally supportive of the primary and secondary endpoints.

#### Quality of Life, Work Productivity, and Healthcare Resource Use

- SF-36v2: The difference between ALO-02 versus placebo for the model-adjusted change from Randomization Baseline to Week 12/Early Termination for the Short Form 36v2 Health Survey (SF-36v2) Health Survey was statistically significant for one subscale: bodily pain (LS Mean: placebo [-5.07] versus ALO-02 [-2.69],  $p=0.0100$ ).
- EQ-5D: The change from Screening to Randomization Baseline in EuroQol 5-Dimensions (EQ-5D) summary index and VAS showed statistically significant ( $p<0.0001$ ) improvement during the Open-Label Titration Period for the ITT Population.
- WPAI:SHI: No statistically significant differences were observed for changes from Randomization Baseline to Week 12/Early Termination for Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) categories.
- Healthcare Resource Use Questionnaire: Due to the exploratory nature of the Healthcare Resource Use Questionnaire, no inferential testing was performed and no conclusions were drawn.
- Chronic Low Back Pain Responder Index: This was an exploratory composite endpoint of daily average low back pain intensity NRS scores, PGA of low back pain, and RMDQ total score for this study and should be reviewed in that context. Few subjects in either treatment group met the responder criteria for this endpoint.

### 6.1.7 Subpopulations

Comparisons to evaluate the consistency of the treatment effect were conducted by the Applicant in the following selected subpopulations: age (<65 years versus  $\geq 65$  years), gender (female versus male), race (White versus Non-white), and by prior pre-study baseline opioid status (opioid-experienced versus opioid-naïve). These analyses are considered exploratory since the study was not prospectively powered for statistical analysis of subgroups. The applicant also investigated the subgroup effects on the primary endpoint for age, gender, and race by adding an indicator for a subgroup in the MMRM model and presented the results in the Integrated Summary of Efficacy. Dr. Li confirmed the Applicant's findings.

For each subpopulation, the analgesic effect of ALO-02 vs placebo was presented using the analysis of the NRS-pain scores over time from Randomization BL to the final 2 weeks of the 12-week DB treatment. The Applicant found that none of the subgroups

investigated was found to have significant factors affecting the primary efficacy endpoint.

Dr. Feng Li, the Agency's statistical reviewer, confirmed the Applicant's findings as shown in Table 19 below:

**Table 19. Subgroup Summaries Gender, Age, and Race**

Subgroups	Statistics	Placebo (N=134)	ALO-02 (N=146)
Sex			
Female	n (%)	75 (56%)	81 (55%)
	Mean (SD)	4.6 (2.6)	3.8 (2.2)
Male	n (%)	59 (44%)	65 (45%)
	Mean (SD)	5.5 (2.3)	4.6 (2.6)
Race			
White	n (%)	103 (77%)	102 (70%)
	Mean (SD)	5.3 (2.4)	4.3 (2.3)
Non-white	n (%)	31 (23%)	44 (30%)
	Mean (SD)	3.8 (2.5)	3.8 (2.6)
Age			
<65	n (%)	119 (89%)	130 (89%)
	Mean (SD)	5 (2.6)	4.3 (2.5)
≥65	n (%)	15 (11%)	16 (11%)
	Mean (SD)	4.8 (2.2)	3.1 (1.6)

SD: Standard deviation

(Table, Dr. Feng Li, Agency Statistical Reviewer)

*Pre-Study Opioid Status:* A similar pattern in the primary analgesic efficacy endpoint by treatment was noted for both groups of subjects treated with ALO-02 regardless of prior opioid status, with both groups reporting less pain at the final two weeks. These findings are confirmed by Dr. Li, as shown in Table 20 below:

**Table 20. Subgroup Summaries Opioid-Experienced vs Opioid-Naive**

Subgroups	Statistics	Placebo (N=134)	ALO-02 (N=146)
Opioid experienced subjects	n (%)	58 (43%)	61 (42%)
	Mean (SD)	5.3 (2.3)	4.3 (2.5)
Opioid naïve subjects	n (%)	76 (57%)	85 (58%)
	Mean (SD)	4.7 (2.7)	4.0 (2.4)

SD: Standard deviation

(Table, Dr. Feng Li, Agency Statistical Reviewer)

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Opioids are titrated to effect, limited by tolerance. There is no maximum dose recommended for this product.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The pivotal efficacy study was of a 12-week duration, which is standard for the evaluation of drugs intended for chronic use. Patients appeared to maintain efficacy throughout the 12 week period. There was no evidence that the addition of naltrexone impacted the efficacy. Dr. Li concurred that the drug effect was roughly maintained from Week 2 to Week 12. The study was not designed to analyze efficacy after treatment was stopped.

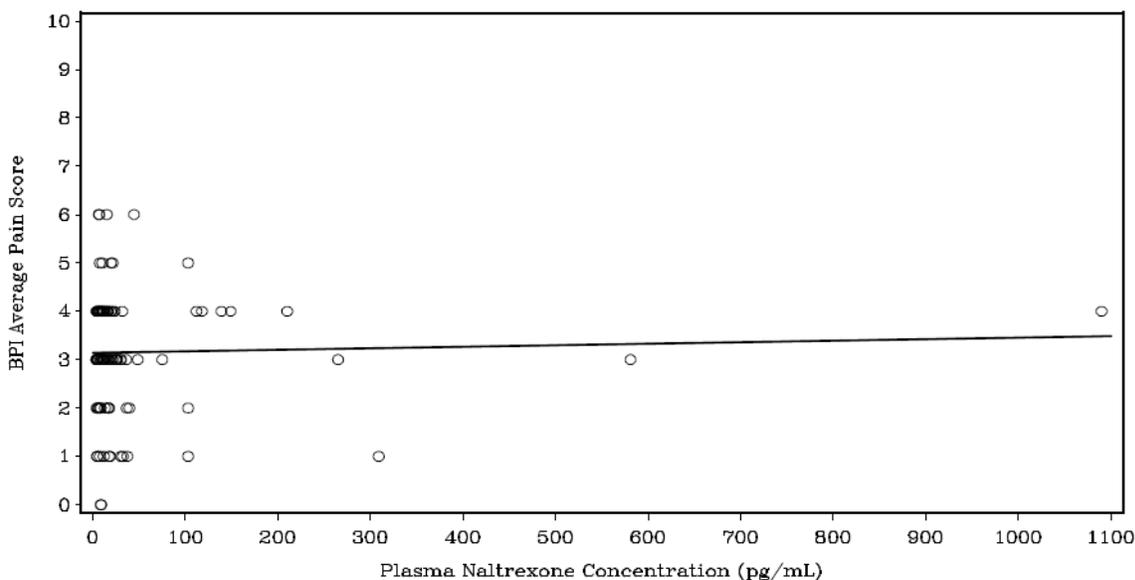
#### Pharmacokinetic Results:

Refer to Dr. Suresh Narahariseti's clinical pharmacology review for details regarding the PK and analyte results.

The  $C_{obs}$  (observed steady-state plasma concentration) of oxycodone, noroxycodone, naltrexone and 6- $\beta$ -naltrexol were summarized for the Open-Label and Double-Blind periods. For subjects treated with ALO-02, mean plasma concentrations of oxycodone were 25.9 ng/mL, 23.3 ng/mL, 23.1 ng/mL, and 22.6 ng/mL at Randomization Baseline, Week 4, Week 8, and Week 12/Early Termination, respectively.

There was no apparent relationship between naltrexone exposures and pain scores in Study 1002, as seen in Figure 6 below or change from baseline as shown in Figure 7.

**Figure 6. Time-matched Correlation of Plasma Naltrexone Concentration (pg/mL) and BPI Average Pain Score, ITT Population Study B4531002**



Abbreviations: ITT = Intent-to-treat; BPI = Brief Pain Inventory.

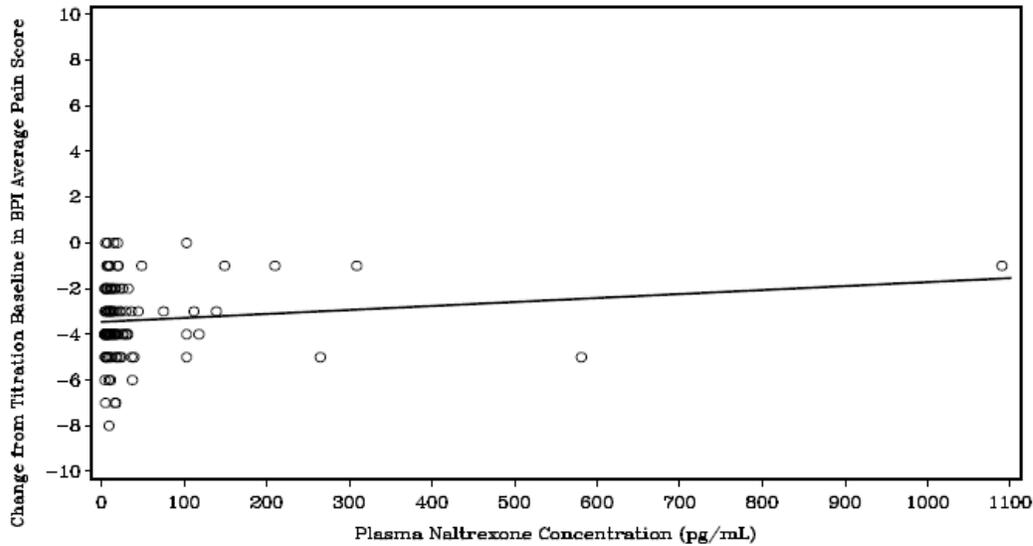
Regression Equation: BPI Average Pain Score=3.1330+0.0003 \*Plasma Naltrexone Concentration (pg/mL). R-square=0.0010.

Time-matched values include concentration and pain score values from the same visit.

Source: CSR Study B4531002, Tables 16.2.5.2.1 and 16.2.6.2.1. Figure 5.1.1.1 for ISE, date of table generation: 29AUG2014 (10:26).

(ISE p. 91)

**Figure 7. Time-Matched Correlation of Plasma Naltrexone Concentration (pg/mL) and Change from Titration Baseline in BPI Average Pain Score, ITT Population Study B4531002**

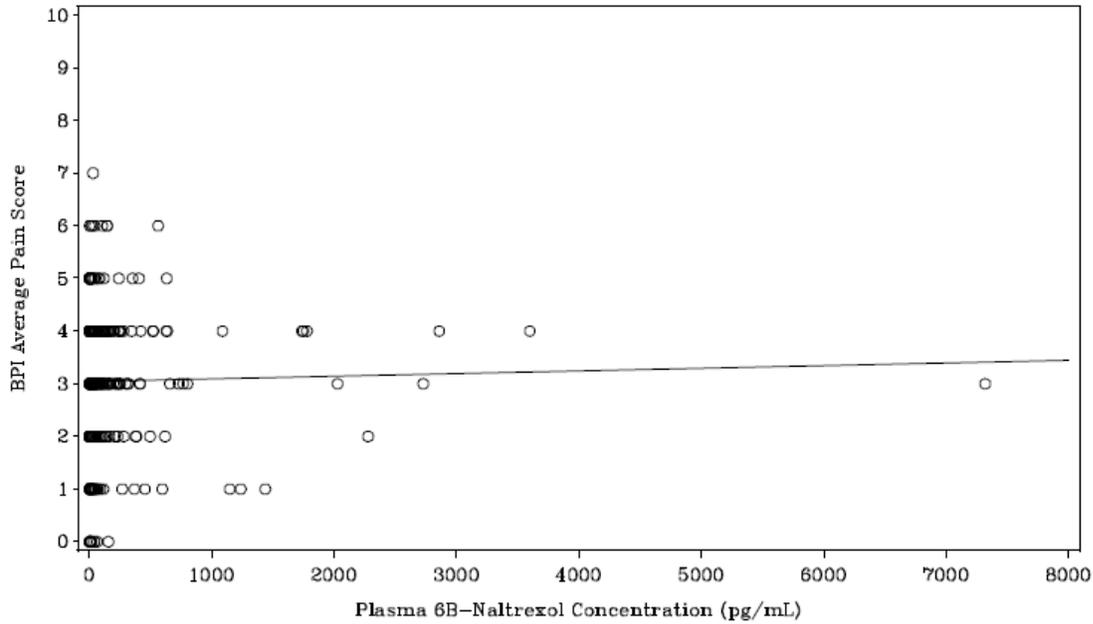


Abbreviations: ITT = Intent-to-Treat; BPI = Brief Pain Inventory.  
Regression Equation: Change from Titration Baseline in BPI Average Pain Score =  $-3.461 + 0.0017 * \text{Plasma Naltrexone Concentration (pg/mL)}$ .  
R-square = 0.0173.  
Time-matched values include concentration and pain score values from the same visit.  
Source: CSR Study B4531002, Tables 16.2.5.2.1 and 16.2.6.2.1. Figure 5.1.1.2 for ISE, date of table generation: 29AUG2014 (10:26).

(ISE, p. 92)

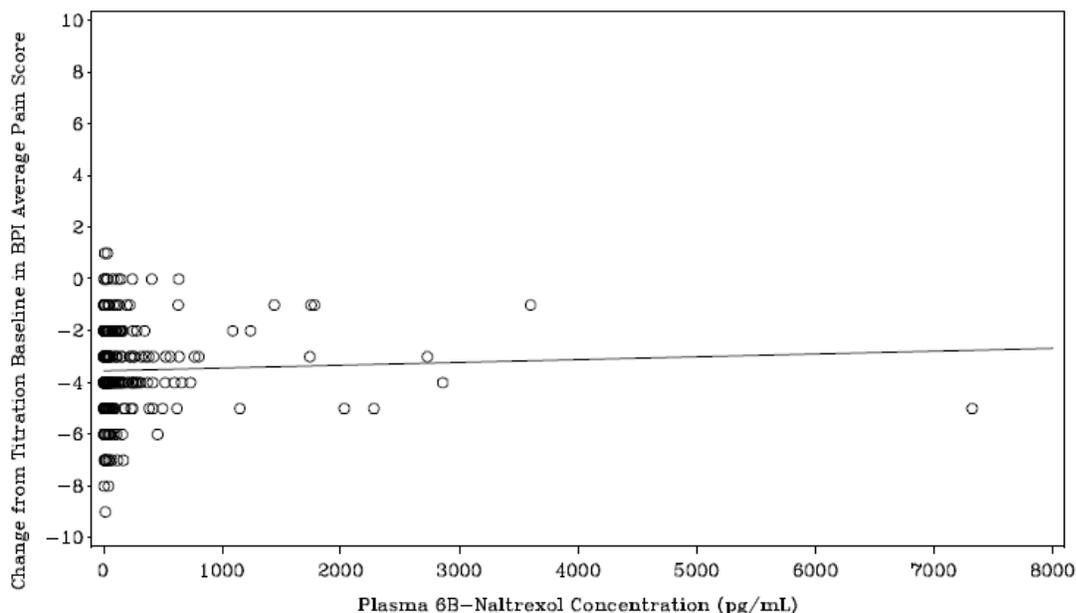
Similar patterns were seen for naltrexol as was seen for naltrexone, as shown below in Figures 8 and 9, which show no apparent relationship between naltrexol exposures and pain scores or change from titration baseline in pain scores in Study 1002.

**Figure 8. Time-Matched Correlation of Plasma 6-B-Naltrexol Concentration (pg/mL) and BPI Average Pain Score, ITT Population Study B4531002**



(SCE, ISE Supportive Tables/Figures, p. 56)

**Figure 9. Time-Matched Correlation of Plasma 6B-Naltrexol Concentration (pg/mL) and Change from Titration Baseline in BPI Average Pain Scores, ITT Population Study B4531002**



Regression Equation: Change from Titration Baseline in BPI Average Pain Score =  $-3.551 + 0.0001 * \text{Plasma 6B-Naltrexol Concentration (pg/mL)}$ .

R-square = 0.0015.

Time-matched values include concentration and pain score values from the same visit.

PFIZER CONFIDENTIAL Source Data: B4531002 CSR Tables 16.2.5.2.1 and 16.2.6.2.1 Date of Table Generation: 29AUG2014 (10:26)

(SCE, ISE Supportive Tables-Figures, p. 57)

Mean plasma oxycodone concentrations reached plateau levels relatively early in the study and fluctuated only minimally from approximately Week 4 out to Week 12/Early Termination for subjects treated with ALO-02. Plasma oxycodone concentrations increased in a dose-related manner with 25% of the variability accounted for by the daily dose of ALO-02 ( $R^2=0.2507$ ).

### Applicant's Key Efficacy Conclusions (Study 1002)

#### Analgesic Effect

- There was no apparent relationship between naltrexone or naltrexol exposures and pain scores in Study 1002.
- For the primary endpoint, the LS mean change in the weekly average NRS-pain score from Randomization Baseline to the final 2 weeks was statistically different between the ALO-02 group (0.60) and the placebo group (1.23), indicating that subjects in the placebo group experienced a greater mean change (increase or worsening) in pain than subjects treated with ALO-02 during the Double-Blind Treatment Period (LS mean treatment difference = -0.62,  $p=0.0114$ ).
- Results from the sensitivity analyses were supportive of the primary analysis. All treatment differences favored ALO-02, and 3 of the 5 analyses were statistically significant (i.e., MMRM, Single Imputation, and SOCF analyses).
- Of the subjects in the ALO-02 group, 84 (57.5%) subjects had at least a 30% decrease (improvement) in NRS-pain score compared to 59 (44.0%) subjects in the placebo group ( $p=0.0248$ ). Similarly, of the subjects in the ALO-02 group, 58

(39.7%) subjects had at least a 50% decrease in NRS-pain score compared to 40 (29.9%) subjects in the placebo group; while favoring ALO-02 treatment, comparison between the 2 treatments was not statistically significant ( $p=0.0874$ ).

- The mean AUC of NRS-pain scores during the Double-Blind Treatment Period was 37.8 for the placebo group compared to 11.6 for the ALO-02 group, which was statistically significantly different ( $p=0.0120$ ) in favor of ALO-02.
- Of the 134 subjects in the placebo group, 58 (43.3%) used rescue medication compared to 51/146 (34.9%) of subjects in the ALO-02 group. The mean average daily dose of rescue acetaminophen was 252.1 mg/day for the placebo group and 167.7 mg/day for subjects in the ALO-02 group, which was not statistically significant ( $p=0.9390$ ).
- Investigator-reported lack of efficacy during the Double-Blind Treatment Period led to 16 (11.9%) discontinuations for the placebo group, and 4 (2.7%) for the ALO-02 group.

**Reviewer's Efficacy Conclusions (Study 1002):** Protocol 1002 was adequately designed to assess the primary endpoint. The opioid conversion tables and opioid taper regimen were acceptable. The amendments to the protocol should not have affected the efficacy results. Overall, I agree with the Applicant's conclusions regarding efficacy of ALO-02.

#### **6.1.10 Additional Efficacy Issues/Analyses**

No additional efficacy analyses were conducted.

## **7 Review of Safety**

### **Safety Summary**

Overall, the integrated safety results from the two Phase 3 studies B4531001 (also referred to as Study 1001) and B4531002 (also referred to as Study 1002) demonstrate that ALO-02 administered in doses ranging from 10 mg/1.2 mg up to 80 mg/9.6 mg BID for up to 12 months has a safety and tolerability profile generally consistent with other extended-release opioids. There was no definite evidence that sequestered naltrexone reached a level of systemic exposure which affected overall safety or increased risk of opioid withdrawal.

Note that in this section of the review, percentages are rounded unless otherwise noted.

## **7.1 Methods**

### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

See Section 5.1 for the list of the 14 studies in the ALO-02 development program which contributed to the safety database.

### **7.1.2 Categorization of Adverse Events**

The Applicant's definitions of AEs, SAEs, and significant AEs were appropriate. Additionally, safety was evaluated by presenting an assessment of naltrexone systemic exposure and opioid withdrawal for the Phase 3 studies.

Different versions of MedDRA coding were applied to the AE data for each individual study report based on when the individual studies were conducted. The Sponsor's plan to use the original MedDRA version for each study report when results from individual study reports were referenced or presented in the SCS and ISS and MedDRA Version 16.1 for pooled clinical data presentations in the SCS, ISS, and the Clinical Overview was determined to be acceptable by the Agency at a preNDA meeting.

In addition to presenting the data using the MedDRA coding previously agreed to by the Agency, the Applicant also used MedDRA Version 17.0 for summaries of SAEs and deaths for pooled presentations of data derived from the Applicant's Corporate Safety database. Although this approach was previously not discussed with the Agency, this approach is acceptable since the Applicant used the same version for categories of AEs within any individual study and provided a coding dictionary (i.e., list of all investigator verbatim terms and the preferred terms to which they were mapped) between different dictionary versions. I evaluated the Applicant's translation of verbatim terms to preferred terms and determined that the translation of terms coded across the different versions of the MedDRA dictionaries used was acceptable and safety data for all subjects were captured.

The presented safety data was for the data lock point for each individual study report. For SAEs, information was presented from the Pfizer SAE database as of June 12, 2014.

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

The Applicant's pooling strategy for the safety data was agreed to by the FDA during the pre-NDA Type B meeting held April 11, 2014. I agree with the strategy as proposed.

Because of the variance in study designs, the only studies which were amenable to pooling were the Phase 3 studies. For these studies, the pooling strategy included safety presented by Titration Phase, Maintenance Phase, and Long-Term Maintenance Phase as shown below in Table 21. The safety results in the submission and discussed in this section of the review include: 1) individual and integrated (pooled) safety data from two Phase 3 studies 1001 and 1002; 2) individual safety data from five pharmacodynamic studies (i.e., two naltrexone dose ratio and three abuse potential) conducted in non-dependent, recreational opioid users; and 3) safety data from seven Phase 1 clinical pharmacology/pharmacokinetic (PK) studies in healthy volunteers. Safety data from the controlled studies compared to placebo and safety data from the OL study were presented separately as well as pooled.

**Table 21. Pooling for Phase 3 Data (Studies B4531001 and B4531002)**

Study Number	Pooled Analysis		
	Titration Phase	Maintenance Phase	Long-Term Maintenance
B4531001	Weeks 1 – 6	Weeks 7-18	Weeks 19 to 12 months
B4531002	Weeks 1 -4, 5, or 6	Double-Blind Weeks 1 -12 + Double-Blind Taper Period	N/A

Abbreviations: N/A=not applicable.

Source: B4531001 and B4531002 CSRs.

(Applicant's table, SCS, p. 25)

## 7.2 Adequacy of Safety Assessments

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

The safety population consisted of all subjects who received at least one dose of study drug in the ALO-02 clinical development program.

Overall, a total of 1,085 subjects were exposed to at least one dose of study drug in the 14 studies in the ALO-02 clinical program. Commercially available oxycodone HCl in combination with different ratios of naltrexone HCl (4% - 24%) was administered in 2 naltrexone dose ratio studies (ALO-02-07-201 and ALO-02-09-2001). Intravenous (IV) administration of the combination oxycodone HCl and 12% naltrexone HCl (simulated IV administration of crushed ALO-02) was administered in an abuse potential study (B4981002). A pilot or prototype formulation of extended-release (ER) oxycodone HCl and sequestered naltrexone HCl ( (b) (4) % ratio of naltrexone to oxycodone) was administered in 3 clinical pharmacology/PK studies (ALO-02-07-102, ALO-02-08-103, and ALO-02-09-1001). For all other studies the to-be-marketed formulation of ALO-02 capsules was used.

Table 22 below is the Applicant's study drug exposure table that presents the total number of unique subjects exposed to at least one dose of any oxycodone HCl/naltrexone HCl combination, or ALO-02, or simulated ALO-02 in the 14 studies. Of the 1,085 subjects, 1,080 received at least 1 dose of ALO-02 or any oxycodone/naltrexone combination. A total of 1,033 subjects received at least 1 dose of ALO-02 or simulated ALO-02 (oxycodone HCl/naltrexone HCl with naltrexone in a 12% ratio to oxycodone): 805 subjects in the Phase 3 studies, 160 subjects in the naltrexone dose ratio/abuse potential studies, and 68 subjects in the clinical pharmacology/PK studies.

**Table 22. Overall Extent of Exposure in the ALO-02 Clinical Development Program**

Study Design Study Number	Number of Subjects Exposed to at Least 1 Dose of Study Drug	Number of Subjects Exposed to at Least 1 Dose of ALO-02 or Any Oxycodone/Naltrexone Combination	Number of Subjects Exposed to at Least 1 Dose of ALO-02 or a 12% Oxycodone/Naltrexone Combination
<b>Phase 3 Studies</b>			
B4531001	395	395	395
B4531002	410	410	410
All Phase 3 Studies	805	805	805
<b>Naltrexone Dose Ratio/Abuse Potential Studies</b>			
ALO-02-07-201	30	30	29
ALO-02-09-2001	31	31	29
B4531008	41	40	40
B4531009	32	30	30
B4981002	33	32	32
All Naltrexone Dose Ratio/Abuse Potential Studies	167	163	160
<b>Clinical Pharmacology/PK Studies</b>			
ALO-02-07-102 <sup>a</sup>	10	10	0
ALO-02-08-103 <sup>a</sup>	10	10	0
ALO-02-09-1001	24	24	0
B4531003	24	24	24
B4531004	18	18	18
B4531006	13	13	13
B4531007	14	13	13
All Clinical Pharmacology/PK Studies	113	112	68
All Studies	1,085	1,080	1,033

Abbreviations: ALO-02=oxycodone HCl and naltrexone HCl ER capsules, PK=pharmacokinetic.

a. Exposure information obtained from study reports.

Source: ISS Table 1.4, Date of Table Generation: 12SEP2014 (16:07).

(SCS, p. 28)

The to-be-marketed pellet formulation of ALO-02 was administered in 8 studies: 2 Phase 3 studies (B4531001 [N=395] and B4531002 [N=410]), 2 abuse potential studies (B4531008 [N=41] and B4531009 [N=32]), and 4 clinical pharmacology/PK studies (B4531003, B4531004, B4531006, and B4531007 [N=69 total]) for a total exposure of 947 which includes 805 patients and 142 healthy subjects.

**Pooled Phase 3 Studies Overall Exposure:** The two Phase 3 studies evaluated a total of 805 subjects with moderate-to-severe chronic non-cancer pain (CNCP) who received at least one dose of the to-be-marketed formulation of ALO-02. The dosage strengths of ALO-02 administered were 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg. (b) (4)

In Study 1002, dosing was twice daily. In Study 1001, dosing could be once or twice daily. For those subjects treated for up to one year, most subjects received an average daily dose of >60-80 mg per day.

In the pooled Phase 3 studies, of the 805 subjects, at least 88 received dosing for at least 6 months and at least 105 for ≥361 days.

The overall exposure of subjects for the to-be-marketed formulation in the Phase 3 studies by dose and duration is shown below in Table 23 and exposure by average daily dose of oxycodone in Table 24.

**Table 23. Phase 3 Studies Exposure by Total Oxycodone Dose and Duration**

Dose Duration (Days)	Total Oxycodone HCl Received (g)								Total
	≤0.5	>0.5-1	>1-5	>5-10	>10-20	>20-50	>50-100	>100	
1	9	0	0	0	0	0	0	0	9
2-10	71	4	1	0	0	0	0	0	76
11-30	35	43	49	1	0	0	0	0	128
31-90	1	16	205	18	4	0	0	0	244
91-180	0	0	46	60	48	1	0	0	155
181-360	0	0	2	19	23	39	5	0	88
≥361	0	0	0	15	30	53	7	0	105
Total	116	63	303	113	105	93	12	0	805

Abbreviations: HCl=Hydrochloride; ALO-02=oxycodone HCl and naltrexone HCl ER capsules.

**Table 24. Phase 3 Studies Exposure by Average Daily Dose of Oxycodone**

Dose Duration (Days)	Average Daily Dose of Oxycodone HCl (mg)								Total	
	≤20	>20-40	>40-60	>60-80	>80-100	>100-120	>120-140	>140-160		>160
1	6	1	0	0	0	0	0	1	1	9
2-10	50	13	4	4	2	2	1	0	0	76
11-30	22	54	30	10	3	5	1	1	2	128
31-90	20	48	80	61	16	7	5	4	3	244
91-180	19	44	26	23	23	12	5	3	0	155
181-360	4	16	23	17	7	6	5	10	0	88
≥361	8	24	19	25	10	8	5	5	1	105
Total	129	200	182	140	61	40	22	24	7	805

Abbreviations: HCl=Hydrochloride; ALO-02=oxycodone HCl and naltrexone HCl ER capsules.

Of the 805 subjects exposed to ALO-02 during the Titration Phase in the Phase 3 program, the pooled duration of exposure to study drug ranged from 1 – 56 days (mean 33.4 days), the average daily dose ranged from 3 mg/day – 189 mg/day (mean 49.0 mg/day) and the total dose of oxycodone ranged from 0.0 g - 7.1 g (mean 1.73 g).

Of the 436 subjects exposed to ALO-02 during the Maintenance Phase in the Phase 3 program, the pooled duration of exposure to study drug ranged from 1 – 120 days (mean 74.1 days), the total dose of oxycodone ranged from 0.0 g – 14.3 g (mean 4.78 g), and the average daily dose ranged from 13 mg/day – 212 mg/day (mean 65.5

mg/day). For the Placebo subjects (N=134), the duration of exposure and total dose and average daily dose (dose the subject would have received if they had remained on ALO-02) during the Maintenance Phase was similar to the ALO-02 subjects; duration of exposure ranged from 7 – 119 days (mean 73.0 days), total dose ranged from 0.3 g – 14.1 g (mean 4.85 g), and average daily dose ranged from 20 mg/day – 152 mg/day (mean 70.3 mg/day).

In Study B4531001, the duration of exposure for the 213 subjects exposed to ALO-02 during the LT Maintenance Phase (weeks 19 to month 12) ranged from 2 – 280 days (mean 201.7 days), the total dose of oxycodone ranged from 0.0 g – 41.4 g (mean 14.91 g), and the average daily dose ranged from 13 mg/day – 227 mg/day (mean 73.9 mg/day). The average daily dose of ALO-02 were comparable in the LT Maintenance Phase of Study B4531001 and the pooled ALO-02 subjects in the Phase 3 Maintenance Phase (73.9 mg/day versus 65.5 mg/day, respectively).

*Key Study 1002 Exposure:* In key efficacy/safety study 1002, a total of 410 subjects were exposed to a mean (SD) duration of 31 (12.24) days during the OLT period. A total of 146 subjects in the ALO-02 group were exposed for a mean (SD) duration of 71 days (27.8) in the Double-Blind compared to 134 placebo subjects whose mean duration of exposure was 63 days (30.2).

*Pooled Demographics:* See Section 6.1.1 for demographics relating to key efficacy/safety study 1002. The pooled demographic and baseline characteristics of subjects in the Phase 3 studies were similar for subjects in the Titration Phase and Maintenance Phase. Most subjects were White and opioid experienced for the Titration and Maintenance Phases.

The key demographics for the pooled studies are shown below in Tables 25 and 26.

**Table 25. Key Demographics Pooled Phase 3 Studies Titration Phase**

Parameter	Study B4531001 ALO-02 (N=395)	Study B4531002 ALO-02 (N=410)	Pooled ALO-02 (N=805)
Age (years)			
N	395	410	805
Mean (SD)	53.8 (12.10)	50.1 (12.48)	51.9 (12.42)
Median	53.0	51.0	52.0
Min, Max	(25, 88)	(19, 89)	(19, 89)
Age Group, n%			
<65 years	320 (81.0)	364 (88.8)	684 (85.0)
≥65 years	75 (19.0)	46 (11.2)	121 (15.0)
≥75 years	22 (5.6)	6 (1.5)	28 (3.5)
Gender, n%			
Male	192 (48.6)	177 (43.2)	369 (45.8)
Female	203 (51.4)	233 (56.8)	436 (54.2)
Race, n%			
White	343 (86.8)	298 (72.7)	641 (79.6)
Black or African American	49 (12.4)	104 (25.4)	153 (19.0)
Asian	0	3 (<1.0)	3 (<1.0)
American Indian or Alaska Native	1 (<1.0)	0	1 (<1.0)
Other	2 (<1.0)	5 (1.2)	7 (<1.0)
Ethnicity, n%			
Hispanic or Latino	18 (4.6)	41 (10.0)	59 (7.3)
Not Hispanic or Latino	377 (95.4)	369 (90.0)	746 (92.7)
Weight (kg)			
N	395	410	805
Mean (SD)	87.2 (20.13)	87.4 (18.57)	87.3 (19.34)
Median	85.4	85.5	85.5
Min, Max	(44, 157)	(39, 142)	(39, 157)
BMI(kg/m <sup>2</sup> )			
N	395	410	805
Mean (SD)	29.6 (5.47)	30.2 (5.46)	29.9 (5.47)
Median	29.2	30.1	29.5
Min, Max	(18, 41)	(17, 44)	(17, 44)
Opioid Status, n%			
Opioid-Naive	93 (23.5)	230 (56.1)	323 (40.1)
Opioid-Experienced	302 (76.5)	180 (43.9)	482 (59.9)

Abbreviations: ALO-02=oxycodone HCl and naltrexone HCl ER capsules; N=total number of subjects; n%=number of subjects (%); Min=minimum; Max=maximum; SD=standard deviation; BMI=body mass index.

Studies Include: B4531001, B4531002.

Titration Phase is programmed as first 6 weeks for Study B4531001; and defined by Study B4531002 (planned as 4-6 weeks).

Source: ISS Table 3.1, Date of Table Generation: 09SEP2014 (10:07)

(SCS, p. 43-44)

**Table 26. Key Demographics Pooled Phase 3 Studies Maintenance Phase**

Parameter	Study B4531001 ALO-02 (N=290)	Study B4531002 ALO-02 (N=146)	Pooled ALO-02 (N=436)	Study B4531002 Placebo (N=134)	LT Maintenance ALO-02 (N=213)
Age (years)					
Mean (SD)	53.8 (11.76)	50.6 (12.98)	52.7 (12.27)	49.3 (12.24)	54.2 (11.85)
Median	53.5	51.0	53.0	51.0	54.0
Min, Max	(25, 86)	(23, 89)	(23, 89)	(19, 76)	(25, 86)
Age Group, n%					
<65 years	238 (82.1)	130 (89.0)	368 (84.4)	119 (88.8)	172 (80.8)
≥65 years	52 (17.9)	16 (11.0)	68 (15.6)	15 (11.2)	41 (19.2)
≥75 years	14 (4.8)	3 (2.1)	17 (3.9)	1 (<1.0)	12 (5.6)
Gender, n%					
Male	153 (52.8)	65 (44.5)	218 (50.0)	59 (44.0)	108 (50.7)
Female	137 (47.2)	81 (55.5)	218 (50.0)	75 (56.0)	105 (49.3)
Race, n%					
White	260 (89.7)	102 (69.9)	362 (83.0)	103 (76.9)	189 (88.7)
Black or African American	28 (9.7)	41 (28.1)	69 (15.8)	29 (21.6)	22 (10.3)
Asian	0	1 (<1.0)	1 (<1.0)	1 (<1.0)	0
American Indian or Alaska Native	1 (<1.0)	0	1 (<1.0)	0	1 (<1.0)
Other	1 (<1.0)	2 (1.4)	3 (<1.0)	1 (<1.0)	1 (<1.0)
Ethnicity, n%					
Hispanic or Latino	12 (4.1)	13 (8.9)	25 (5.7)	15 (11.2)	9 (4.2)
Not Hispanic or Latino	278 (95.9)	133 (91.1)	411 (94.3)	119 (88.8)	204 (95.8)
Weight (kg)					
Mean (SD)	88.4 (20.54)	88.9 (19.02)	88.6 (20.02)	89.5 (19.81)	88.7 (20.00)
Median	86.4	86.0	86.3	88.6	89.0
Min, Max	(44, 157)	(52, 132)	(44, 157)	(47, 142)	(44, 154)
BMI (kg/m <sup>2</sup> )					
Mean (SD)	29.7 (5.57)	30.4 (5.57)	29.9 (5.57)	30.9 (5.77)	29.9 (5.56)
Median	29.2	29.6	29.3	31.4	29.5
Min, Max	(18, 41)	(18, 40)	(18, 41)	(17, 44)	(18, 41)
Opioid Status, n%					
Opioid-Naïve	70 (24.1)	84 (57.5)	154 (35.3)	74 (55.2)	48 (22.5)
Opioid-Experienced	220 (75.9)	62 (42.5)	282 (64.7)	60 (44.8)	165 (77.5)

Abbreviations: ALO-02=oxycodone HCl and naltrexone HCl ER capsules; N=total number of subjects; n%=number of subjects (%); LT=Long-Term; Min=minimum; Max=maximum; SD=standard deviation; BMI=body mass index.

Studies Include: B4531001, B4531002.

Maintenance Phase is programmed as weeks 7-18 for Study B4531001 and defined in Study B4531002 as Double Blind + Taper Phase.

Source: ISS Table 3.2 and ISS Table 3.3, Date of Table Generation: 09SEP2014(10:07) and 08SEP2014(19:17)

(SCS, p. 45-46)

Opioid-Naïve vs Opioid Experienced Exposure:

Although in both Phase 3 studies subjects who required a continuous around-the-clock opioid analgesic for an extended period of time were enrolled, whether or not they were receiving opioids before the study, there were differences between the studies in the determination of prior opioid status. For example, subjects on tramadol who entered the Study B4531001 were considered as opioid-naïve but were classified as opioid-experienced in Study B4531002.

The Phase 3 protocols did not provide a defined period for determining the prior opioid status but required an evaluation by the Investigator based on the subject's medical history and prior medication. As a result of these differences, for purposes of subgroup analysis in the ISS, the Applicant applied a post hoc analysis to subjects in both studies to determine opioid status and standardize the results for pooling. Subjects were considered opioid-experienced if the prior and concomitant medications Case Report Form (CRF) pages indicated that the subject received opioids (including tramadol) at any time within 30 days prior to beginning ALO-02 treatment i.e., if the prior and concomitant medications CRF pages indicated that the subject received opioids at any time within 30 days prior to beginning ALO-02 treatment; otherwise, they were considered opioid-naïve.

In the Summary Clinical Safety (SCS) and ISS (Integrated Summary of Safety), the Applicant analyzed the average daily oxycodone dose and duration of exposure for opioid-naïve and opioid-experienced subjects using the standardization approach described above. As a result of this standardization approach, results for this categorization of subjects as to opioid-experienced or opioid-naïve differ in the SCS and ISS compared to the respective CSRs. Average daily dose of oxycodone and exposure using the standardized approach is shown in Table 27.

**Table 27. Average Daily Oxycodone HCL Dose and Exposure from ALO-02 (Opioid-Naïve and Opioid-Experienced) Phase 3 Studies Safety Population**

Dose Duration (Days)	Average Daily Dose of Oxycodone HCl (mg)								Total	
	≤20	>20-40	>40-60	>60-80	>80-100	>100-120	>120-140	>140-160		>160
<b>Opioid-Naïve</b>										
1	2	1	0	0	0	0	0	1	0	4
2-10	29	2	1	1	1	0	0	0	0	34
11-30	12	35	14	1	0	0	0	0	0	62
31-90	15	27	29	26	3	0	0	0	0	100
91-180	10	33	16	10	8	4	0	0	0	81
181-360	3	8	4	6	1	0	0	0	0	22
≥361	3	7	4	3	3	0	0	0	0	20
<b>Total</b>	<b>74</b>	<b>113</b>	<b>68</b>	<b>47</b>	<b>16</b>	<b>4</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>323</b>
<b>Opioid-Experienced</b>										
1	4	0	0	0	0	0	0	0	1	5
2-10	21	11	3	3	1	2	1	0	0	42
11-30	10	19	16	9	3	5	1	1	2	66
31-90	5	21	51	35	13	7	5	4	3	144
91-180	9	11	10	13	15	8	5	3	0	74
181-360	1	8	19	11	6	6	5	10	0	66
≥361	5	17	15	22	7	8	5	5	1	85
<b>Total</b>	<b>55</b>	<b>87</b>	<b>114</b>	<b>93</b>	<b>45</b>	<b>36</b>	<b>22</b>	<b>23</b>	<b>7</b>	<b>482</b>

Abbreviations: HCl=hydrochloride; ALO-02=oxycodone HCl and naltrexone HCl ER capsules.  
 Studies Include: B4531001, B4531002.

(SCS, p. 37)

*Reviewer's comment: The overall exposure (dose and duration) is adequate to assess the safety of the formulation. The Applicant's process of standardization of opioid-naïve and opioid-experienced subjects to analyze pooled data is acceptable. For individual Study 1002 treating Tramadol as an opioid was acceptable. Study 1001 should also have treated those on Tramadol as opioid experienced. However, the standardization*

*approach adequately addressed this issue to ensure that integrated safety results appropriately captured prior opioid use.*

## **7.2.2 Explorations for Dose Response**

Phase 2 dose-response studies with ALO-02 were not conducted. The extent of oxycodone BA from ALO-02 was shown to be equivalent to IR oxycodone and the efficacy and safety of oxycodone has been established as an approved IR formulation of oxycodone.

Oxycodone is titrated to effect for management of pain with limitations due to AEs of respiratory or central nervous effects. See Section 7.3.5 (Submission Specific Primary Safety Concerns) for further discussion of the effect of naltrexone on safety.

A maximum daily dose is not recommended.

## **7.2.3 Special Animal and/or In Vitro Testing**

Animal Studies: No special animal studies were conducted.

In Vitro Testing: As part of the Applicant's Evaluation of Drug Abuse Liability, laboratory-based studies were conducted to evaluate the ease with which the abuse-deterrent properties of ALO-02 could be defeated or compromised. Based upon the in vitro studies, the Applicant concluded that, "When ALO-02 is crushed, oxycodone and naltrexone are simultaneously extracted in a variety of solvents and confirm that ALO-02 has properties are expected to reduce abuse by the oral and intranasal routes." See the CMC review of Dr. Ben Stevens for full discussion of the in vitro studies. See Dr. Tolliver's CSS review for the Agency's further discussion and interpretation of the in-vitro testing as it relates the abuse deterrence.

## **7.2.4 Routine Clinical Testing**

The routine clinical testing conducted during the clinical trials in both healthy subjects and chronic pain patients appears adequate in terms of safety monitoring types and frequency. Routine clinical testing in the Phase 3 studies included laboratory tests, urinalysis, physical examination (including weight and height), serum pregnancy test, urine drug tests for illicit drugs, 12-lead ECG, vital signs (including HR, BP, and RR), SAE assessment, and concomitant medication review.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4 and the Clinical Pharmacology review of Dr. Suresh Narahariseti for information regarding the metabolic, clearance, and interaction workup.

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

See Section 2.4 regarding important safety issues with consideration to related drugs. The Applicant monitored for the expected AEs of the opioid drug class and naltrexone by objective observation during examinations and subjective spontaneous reporting by the subjects. In addition, the Applicant conducted a safety analysis of AEs of special interest based on the known safety profile of the listed drugs naltrexone (Revia) and oxycodone (Roxicodone). Monitoring and analyses of opioid withdrawal, abuse potential, and overdose were adequately evaluated in the studies. Specifically, the Applicant included assessment of opiate withdrawal symptoms using the Clinical Opiate Withdrawal Scale (COWS) and Subject Opiate Withdrawal Scale in the Phase 3 studies with the assessments conducted frequently enough to monitor for signs or symptoms of withdrawal. In addition, COWS scores  $\geq 13$  were prespecified as potential opioid withdrawal cases and included specific investigator procedures if identified. Plasma naltrexone and naltrexol levels were obtained per protocols to assess systemic exposure of these analytes. If urine drug tests were positive for illicit or unexpected substances, subjects could be discontinued.

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were a total of two deaths across all clinical trials, both of which occurred in long-term study B4531001 (one during the study and one approximately one year after study completion). There were no deaths in key efficacy study B4531002, the Naltrexone Dose Ratio/Abuse Potential Studies, or the Phase 1 clinical pharmacology/PK studies.

Based upon my review of the narratives for these deaths, causality of study drug to the deaths is unlikely in both cases. The death narratives are provided below, with Subject ID, MedDRA preferred term, and reviewer's determination of causality in bold font.

#### **Case 1: Subject 0029-0002; Acute MI; Unlikely Causality**

This was a 66 year old white male who experienced an acute myocardial infarction approximately 2 months after starting ALO-02. The subject was started on ALO2 capsules 30 mg/3.6 mg BID from 2/17/11 (Study day 1) to (b) (6) (study day (b) (4)) with an average daily dose of 83 mg of study drug. On (b) (6), the subject experienced (b) (4) an acute MI and died with the cause of death reported as acute MI. No autopsy was done. The subject's past medical history included prior MI in 1993, coronary artery disease,

hypertension, dyslipidemia, and peripheral vascular disease. Concomitant medications included isosorbide, metoprolol, simvastatin, furosemide, and doxazosin. The investigator considered the MI that led to death as not related to study drug. *Reviewer's comments: Given this subject's history of prior MI and other cardiovascular risk factors, as well as the incidence of MI in the general population, causality of study drug to the MI and subsequent death is either unlikely or cannot be determined.*

**Case 2: Subject 0016-0004; Disease Progression (cancer); Unlikely causality**

This was a 48 year old white male who was enrolled in the study for severe chronic noncancer pain. ALO-02, 70 mg twice daily, was administered from 3/14/11 (Day 1), increased to 80 mg twice daily from 3/18/11 (Day 5) to 2/29/12 (Day 353) for a total of 353 days. On 12/8/11 (Day 270), the subject was diagnosed with metastatic squamous cell anal cancer. The subject was treated with radiation and chemotherapy and completed the study on 3/7/12 (Day 360). On [REDACTED] (b) (6) [REDACTED] the subject died due to underlying cancer. The cause of death was reported as disease progression. An autopsy was not performed. PMH and concomitant medications were likely not contributory. The investigator considered this event not related to study medication. *Reviewer's comments: The most likely causality for the subject's death was due to the underlying cancer and disease progression. Causality of study drug to the subject's subsequent death is unlikely, given that the death occurred greater than one year after study completion. Note, this narrative reflects the Applicant's updated narrative as of 6/12/14.*

**7.3.2 Serious Adverse Events (SAEs)**

SAEs Study 1002: A total of 10 subjects of 410 (2%) experienced 18 SAEs during the entire study (i.e., Open-Label Titration period and Double-Blind Period). Of the 10 subjects, eight were ALO-02-treated and two were placebo at the time of the SAE.

The SAEs that occurred in subjects who received ALO-02 during the Double-Blind Phase included preferred terms atrial flutter, MI (myocardial infarction), cholecystitis, cholelithiasis, cholesterosis, arthritis, costochondritis, drug administration error (maladministration of birth control), spontaneous abortion, and unintended pregnancy. No term occurred in more than one subject. Some subjects experienced more than one term (event).

Table 28 below displays the key information regarding subjects who experienced SAEs including causality assignment as determined by this reviewer.

**Table 28. Subjects with SAEs During Study 1002**

Subject ID	Age/ Sex	Preferred Term	Onset	TDD mg	Intensity; Outcome; Action Taken	Causality
<b>Subjects with SAEs during Titration Phase Study 1002</b>						
10071011	70/F	COPD/ Bronchitis	T24	0	Severe; Resolved; Drug withdrawn and withdrawn from study/ Severe; Resolved; Drug withdrawn and withdrawn from study	Unlikely (risk factors)
10321011	72/M	UTI	T15	40	Severe; Resolved; Drug Withdrawn and Withdrawn from study	Unlikely
10661001	58/M	Depression/ Suicide attempt	T17	40	Both Severe; Severe; Resolved; Drug withdrawn and Withdrawn from study	Unlikely
<b>Subjects with SAEs during the Double-Blind Phase ALO-02 Treatment Arm</b>						
10101009	28/F	Cholesterosis/ Cholecystitis/ Cholelithiasis	F94	40	Moderate/ Moderate/ Severe; All resolved; All dose unchanged	Unlikely/ Possible/ Possible
10151003	39/F	Drug Administration Error/ Unintended pregnancy/ Spontaneous abortion	DB 85	80	Mild/Mild/Severe; All resolved; Dose unchanged; D&C performed	Unlikely / Unrelated/ Possible
10331014	62/M	Myocardial Infarction	DB 77	100	Severe; Resolved; Drug withdrawn/ Withdrawn from study	Unlikely (risk factors)
10511004	73/F	Costochondritis/ Arthritis	DB 75/ DB 79	20	Mild; Resolved; Dose unchanged/ Mild; Resolved; Drug Interrupted	Unlikely
10661006	69/M	Atrial flutter	DB 87	60	Mild; Ongoing; Dose unchanged	Possible

Subjects with SAEs during the Double-Blind Phase Placebo Treatment Arm						
10321010	48/M	Road traffic accident	DB 7		Severe; Resolved; Dose unchanged with no action taken	Possible
10601038	53/M	Intermittent claudication/ Peripheral arterial disease	DB 50		Moderate/Resolved; Moderate/Resolved; Both dose unchanged	Unlikely (risk factors)

(Table, reviewer); T=Titration Phase; DB=double-blind (Maintenance Phase); F= Follow-up (Maintenance Phase); TDD=total daily dose; mg=milligram; M=male; F=female

All SAE MedDRA SOC and preferred terms are shown in Table 29 below, which summarize the SAEs experienced during OL titration and Double-blind periods by treatment arm. Preferred terms which I determined to be possibly causally related to ALO-02 are in bold font.

**Table 29. SAEs OL Titration and Double-Blind Treatment Periods, Study 1002**

	Open-Label	Double-Blind	
	ALO-02 N=410	ALO-02 N=146	Placebo N=134
Subjects experiencing SAEs (%)	3 (<1) 3 subjects with 5 preferred terms	5 (3) 5 subjects with 10 preferred terms	2 (1) 2 subjects with 3 preferred terms
<b>MedDRA SOC</b>	<b>Preferred Terms</b>	<b>Preferred Terms</b>	<b>Preferred Terms</b>
Infections and infestations	1 bronchitis 1 UTI		
Respiratory, thoracic and mediastinal disorders	1 COPD		
Cardiac disorders		<b>1 atrial flutter</b> 1 MI	
Hepatobiliary disorders		<b>1 cholecystitis</b> <b>1 cholelithiasis</b>	
Injury, poisoning and procedural complications		1 drug administration error	<b>1 road traffic accident</b>
Musculoskeletal and connective tissue disorders		1 arthritis 1 costochondritis	
Psychiatric disorders	1 depression 1 suicide attempt		
Metabolism and nutrition disorders		1 cholesterosis	
Pregnancy, puerperium and perinatal conditions		1 spontaneous abortion	

		1 unintended pregnancy	
Vascular disease			1 intermittent claudication 1 peripheral arterial occlusive disease

(Reviewer): Each term is counted separately but more than one term (event) may have occurred in the same subject.

**Causality:** Of the 10 subjects who experienced SAEs, the Applicant found all cases to be causally unrelated to ALO-02. My determination of causality was based on the review of SAE narratives and case report forms as needed. For subjects treated with ALO-02, I found no cases to be definitely or probably related to study drug; two subjects who experienced three SAEs to be possibly causally related to study drug (Subject 10661006; preferred term new onset atrial flutter and Subject 10101009; preferred terms cholecystitis and cholelithiasis); all other cases to be unlikely related. One subject assigned to placebo experienced an SAE of road traffic accident possibly causally related to ALO-02 received during the Open-Label Titration period.

**Indeterminate Causality:** I found one event (Subject 10151003; preferred term Drug Administration Error) to be indeterminate causality because it is not clear how a missed dose of Depo-provera was a Drug Administration Error for the study.

**Possible causality:** Narratives for the subjects during the Open-Label and Double-Blind periods that I determined were possibly related to ALO-02 treatment or that the role of ALO-02 treatment could not be excluded are summarized below. One subject in the placebo group was included because although the subject was randomized to placebo, he received study drug for over a month during the OL titration period, so the role of study drug to the onset of the SAE of road traffic accident could not be ruled out.

In the narrative summaries below, the Subject ID, SAE MedDRA preferred terms, and reviewer's determination of causality are in bold font. Abbreviated terms in the narratives are as follow: OL=open label; DB=double-blind; TDD=total daily dose; PMH=past medical history; ED=emergency department.

**Subject 10101009: Cholecystitis/Cholelithiasis; Possible Causality**

28 year old female admitted to the hospital on Study Day (b) (6) of the DB period while on 40 mg TDD of study drug and was diagnosed with cholecystitis, cholesterosis, and severe cholelithiasis. She underwent a cholecystectomy (b) (6) and was discharged from the hospital (b) (6). PMH included hypercholesterolemia. She completed the study and the last dose of study drug was taken on 2/13/13 (Day 98). *Reviewer's comment: Although no prior history of cholecystitis was reported, hypercholesterolemia may have contributed to cholesterosis (abnormal deposition of cholesterol in tissues)*

*and resultant cholelithiasis (gallstones). Causality of the SAEs of cholecystitis and cholelithiasis to study drug is possible and cannot be excluded. However, given the relatively high incidence of cholecystitis and cholelithiasis in the general population, causality to study drug alone, though possible, is less likely.*

**Subject 10661006: Atrial flutter; Possible Causality**

69 year old male began the OL period with ALO-02 at 20 mg TDD on 8/28/12, up-titrated to 60 mg TDD on 9/13/12 (Study Day 17 OL) then began ALO-02 in the DB on 9/25/12 (Day 1 DB). The subject had an abnormal screening ECG (b) (6) which showed 1<sup>st</sup> degree AV block, anteroseptal MI, and sinus rhythm. The subject had no discomfort and the investigator determined the ECG to not be clinically significant. On 10/25/12 (Study Day 31 DB), the subject experienced mild withdrawal syndrome required no treatment and no action with study drug. On (b) (6) (Study Day (b) (6) DB), the end of treatment visit showed an ECG with atrial flutter, considered by the investigator as a serious AE of mild severity. Again, the subject was asymptomatic but was advised by the investigator to go to the ED where he presented on (b) (6) (Study Day (b) (6) DB) and was admitted overnight with a diagnosis of new-onset atrial flutter. The subject completed the study and the last dose of blinded therapy was 1/2/13 (Study Day 100). The event of atrial flutter did not resolve and was ongoing at the last study visit. No relevant significant PMH or concomitant medications were identified. *Reviewer's comment: The SAE of new-onset atrial flutter is possibly causally related to study drug. Although the screening ECG was abnormal, there was no documented evidence of atrial flutter prior to the use of ALO-02.*

**Subject 10321010; Road Traffic Accident; Possible Causality**

This subject began the OL period on 9/11/12 and received study drug titrated to 40 mg TDD. On 10/8/12 (Day 1 of DB) he was randomized to placebo. The road traffic accident occurred on (b) (6) (Study Day (b) (6) DB). The last dose of placebo was the day of the accident and the subject withdrew from the study. *Reviewer's comment: Although the SAE occurred while on placebo, the subject had received approximately (b) (6) study drug prior to the accident and had only been on placebo for (b) (6) days when the accident occurred so the role of study drug to the accident must be considered. COWS/SOWS scores or other details regarding mental status were not reported in the narrative.*

**Subject 10151003; Drug Administration Error/Unintended pregnancy/Spontaneous abortion/miscarriage; Indeterminate Causality**

39 year female enrolled in the study on 8/16/12 and was titrated to 80 mg TDD of ALO-02 which she received until 1/2/13. This subject's relevant concomitant medication included Depo-Provera every three months for birth control. She also reported use of condoms as birth control method. On 12/1/12 (Study Day 68) of the Double-Blind Treatment Period, the subject's Depo Provera injection was not administered; therefore, her last contraceptive injection was 9/1/12 (Study Day 5 of the OL Period). The narrative did not provide information about why the drug was not administered but it was

recorded as a “drug administration error”. On 12/18/12, she was seen for her Week 12 visit. At that time, a serum pregnancy test was performed and on 12/19/12 the test was reported as positive. The Investigator reported the SAE as maladministration and unintended pregnancy. The action taken with study drug was dose reduced and medroxyprogesterone acetate was permanently withdrawn. The investigator considered this to be an unintentional pregnancy which resulted from her maladministration of the Depo Provera. Two more serum pregnancy tests were performed on 12/20/12 (Study Day 87) and 12/26/12 (Study Day 93) both of which were negative. HCG (human chorionic gonadotropin) was within normal range on 12/26/12 and 1/2/13 in her OB Gyn’s office. On (b) (6) (Study Day (b) (6)), an ultrasound showed a sac with no heartbeat, probable pregnancy and the fetus was found to have no heartbeat. On (b) (6) (Study Day (b) (6)), the subject underwent a D&C (dilation and curettage) and, as a result, reportedly experienced a spontaneous abortion/miscarriage with no complications to remove the products of conception. The subject completed the study and the last dose of study treatment was taken on 1/2/13 (Study Day 100). No further details were provided in the narrative. *Reviewer’s comment: The final diagnosis for this subject as to whether she experienced a fetal death in utero, a spontaneous abortion, or other events requiring a D&C is not clear in the narrative. It is also not clear why the missed dose of Depo Provera was considered a drug administration error. The causality of ALO-02 to any of these events is unclear, given the relatively high incidence of spontaneous abortions in the population.*

*Reviewer’s Conclusions SAEs Controlled Study 1002: Cholecystitis, cholelithiasis, atrial flutter and road traffic accident were four events which were possibly related to study drug ALO-02. However, there is no strong evidence for causality in these cases to the extent that specific labeling would be required. There were no patterns or trends regarding dose or duration and onset of SAE.*

OL Study 1001:

A total of 27 subjects experienced 40 SAEs. However, one subject (0003-0021) experienced three SAEs before study drug was received. Therefore, of the 395 treated subjects, 26 experienced 36 SAEs, two of which were fatal. Although deaths have been previously discussed, both fatal and nonfatal SAEs are included in the analysis counts and discussion below.

The Applicant considered only two SAEs to be treatment-related which included one subject with cholelithiasis and one subject with abdominal pain. I agree with the Applicant’s determination of possible causality for these two subjects. In addition, based upon review of the narratives and selected Case Report Forms, I determined that the term intestinal obstruction was probably related to study drug and the terms cholecystitis and convulsion were possibly causally related. Two subjects experienced four events of convulsion (seizure), with Subject 0001-0017 experiencing three events and Subject 0032-0006 experiencing one event. I found the seizure event for Subject 0001-0017 to be possibly causally related to study drug due to a possible lowered

seizure threshold. Subject 0032-0006 did not have a witnessed seizure and the EEG showed no epileptiform or seizure activity. This subject also had a history of alcohol abuse. I did not determine that ALO-02 was probably or possibly causally related in this instance. Subject 0003-0002 (cerebrovascular accident) was considered unlikely causality due to multiple risk factors.

Table 30 below lists the SAEs by preferred term and other important identifiers.

**Table 30. Serious Adverse Events Study 1001**

Subject Number	Sex/ Age (years)	Average Daily Dose	SAE Preferred Term	SAE Start Day	Investigator Causality	Clinical Outcome
0001-0017	M/41	54.10 mg	Convulsion	146	Not related	Resolved
			Convulsion	161	Not related	Resolved
			Convulsion	172	Not related	Resolved
0002-0008	F/45	27.55 mg	Hypochromic anemia	180	Not related	Resolved
0003-0002	F/59	11.21 mg	Cerebrovascular accident	27	Not related	Res with seq
0003-0012	F/65	N/A	Hypoglycemia	5	Not related	Resolved
0003-0021	F/53	18.67 mg	Asthma	-13	Not related	Resolved
			Bronchospasm	-13	Not related	Resolved
			Hypoxia	-13	Not related	Resolved
			Intervertebral disc degeneration	45	Not related	Res with seq
0005-0005	F/46	49.58 mg	Pneumonia	7	Not related	Resolved
0007-0001	F/70	38.81 mg	Hiatus hernia	14	Not related	Res with seq
0007-0002	F/51	103.35 mg	Infected skin ulcer	107	Not related	Resolved
			Osteomyelitis	107	Not related	Res with seq
0007-0004	F/64	18.75 mg	Acute myocardial infarction	8	Not related	Res with seq
0007-0010	F/76	87.76 mg	Cardiac failure congestive	264	Not related	Unresolved
			Lung infiltration	264	Not related	Resolved
			Pleural effusion	264	Not related	Unresolved
			Small intestinal obstruction	252	Not related	Unresolved
			Cholecystitis	48	Not related	Resolved
0014-0005	F/50	77.20 mg	Cholecystitis	48	Not related	Resolved
0014-0006	F/71	108.62 mg	Non-cardiac chest pain	34	Not related	Resolved
0016-0004	M/48	159.01 mg	Anal cancer	270	Not related	Unresolved
0017-0016	F/55	77.50 mg	Chest pain	333	Not related	Resolved
0020-0010	M/51	53.41 mg	Nephrolithiasis	98	Not related	Resolved
0021-0001	F/31	49.05 mg	Nephrolithiasis	33	Not related	Res with seq
0021-0013	M/66	71.00 mg	Muscular weakness	228	Not related	Resolved
0024-0003	M/65	80.19 mg	Pneumonia	130	Not related	Resolved
0024-0021	M/77	33.54 mg	Blood pressure increased	358	Not related	Resolved
			Chest discomfort	358	Not related	Resolved
			Cholelithiasis	95	Related	Unresolved
0025-0003	F/37	50.28 mg	Cholelithiasis	95	Related	Unresolved
0025-0023	F/41	53.48 mg	Abdominal pain	181	Related	Lost to FU
0027-0001	F/51	46.22 mg	Chronic obstructive pulmonary disease	41	Not related	Resolved
			Non-cardiac chest pain	41	Not related	Resolved
			Acute myocardial infarction	66	Not related	Fatal
0031-0013	M/67	57.24 mg	Urinary tract infection	256	Not related	Resolved
0032-0006	M/62	57.94 mg	Convulsion	153	Not related	Resolved
			Mental status changes	153	Not related	Resolved
0037-0017	F/46	148.47 mg	Pancreatitis acute	166	Not related	Resolved

Day is the day relative to the first dose of study drug.

F = female; FU = follow-up; M = male; N/A = not available; Res with seq = resolved with sequelae; SAE = serious adverse event.

Source: Table 14.3.2.3

(CSR 1001, p. 86)

Preferred terms occurring in more than one subject included noncardiac chest pain, acute MI, pneumonia, hiatus hernia, nephrolithiasis, and convulsions.

The MedDRA SOC and preferred terms are shown in Table 31 below with preferred terms possibly related to ALO-02 bolded.

**Table 31. Serious Adverse Events Safety Population Study B4531001**

	<b>Titration Weeks 1-6</b>	<b>Maintenance Weeks 7-18</b>	<b>Long-term Maintenance</b>
Total Number	N=395	N=290	N=213
<b>Subjects experiencing SAEs (%)</b>	8 (2)	6 (2)	12(6)
<b>MedDRA SOC</b>	<b>Preferred Terms</b>	<b>Preferred Terms</b>	<b>Preferred Terms</b>
Gastrointestinal disorders	1 hiatus hernia		1 hiatus hernia <b>1 abdominal pain</b> 1 acute pancreatitis <b>1 small intestinal obstruction</b>
Infections and infestations	1 pneumonia	1 diabetic foot infection 1 osteomyelitis	1 pneumonia 1 UTI 1 osteomyelitis
General disorders and administration site conditions	2 noncardiac chest pain		1 asthenia 1 chest discomfort 1 chest pain
Respiratory, thoracic and mediastinal disorders	1 COPD		1 lung infiltration 1 pleural effusion
Cardiac disorders	1 acute MI	1 acute MI [fatal]	1 congestive heart failure 1 pericardial effusion
Metabolism and nutrition disorders	1 hypoglycemia		
Nervous system disorders	1 cerebrovascular accident		2 <b>convulsions*</b>
Renal and urinary disorders	1 nephrolithiasis	1 nephrolithiasis	
Hepatobiliary disorders		<b>1 cholecystitis</b> <b>1 cholelithiasis</b>	
Musculoskeletal and connective tissue disorders		1 intervertebral disc degeneration	
Blood and lymphatic disorders			1 hypochromic anemia
Investigations			1 BP increased
Psychiatric disorders			1 mental status changes

Neoplasms benign, malignant and unspecified (including cysts and polyps)			1 anal cancer metastatic [fatal]
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(Reviewer); \*One subject experienced three events of convulsion; preferred terms are counted only once if the same term occurred more than once in the same subject.

Non-fatal SAE Narratives (Study 1001): All SAE narratives were reviewed. One case of intestinal obstruction was probably related to ALO-02. Four cases (cholecystitis, cholelithiasis, abdominal pain, and convulsion) determined by my review of the narratives with possible causality to ALO-02 are discussed below.

**Subject 00070010: Hiatus hernia/Small intestinal obstruction/Lung infiltration/Pleural effusion/Cardiac Congestive failure/Pericardial effusion; Probable Causality for Intestinal obstruction**

Information was obtained from the narrative and CRF. This was a 76 year old female with a history of chronic low back pain, GERD, previous hysterectomy and a recent five-month history of intermittent nausea and vomiting. She began treatment with ALO-02 on 4/13/11 (Study Day 1) at 40 mg TDD and was uptitrated to 100 mg TDD by 9/28/11 (Study Day 141) which was maintained through (b) (6) (Study Day (b) (6)). Pertinent past surgical history included hysterectomy and PMH included GERD. On (b) (6) (Study Day (b) (6)), she experienced abdominal pain, vomiting and dehydration requiring hospitalization. On (b) (6) she was diagnosed with a hiatal hernia. A gastroesophageal junction-balloon dilation was performed. Upon endoscopy, gastric retention and bezoar formation in the fundus of the stomach within the hiatal hernia was removed on (b) (6) (Study Day (b) (6)). On (b) (6) (Study Day (b) (6)) a paraesophageal hernia with closed loop bowel obstruction was patch-repaired with lysis of the closed loop small bowel obstruction. The subject was later diagnosed with congestive heart failure and lung infiltration on (b) (6) (Study Day (b) (6)) and bilateral pleural effusion, pericardial effusion, hypomagnesemia, and hypokalemia on (b) (6) (Study Day (b) (6)). Prior opioid therapy was hydrocodone, tramadol, and methadone.

*Reviewer's comments: A bezoar is a mass or concretion of partly or wholly undigested material. Risk factors are any factors that impede peristalsis. Case reports of bezoars have included risk factors separated into four categories: those associated with alterations in GI anatomy, dysmotility, other medical conditions, and medications. Various medications have been implicated, including opioids due to impaired GI mobility. Prior abdominal surgeries also are risk factors. This subject had a history of hysterectomy. The role of study drug to the development of intestinal obstruction is probable but the role of ALO-02 in the bezoar is indeterminate since the contents of the*

*bezoar were not reported. Class wide opioids are labeled for contraindication in patients with paralytic ileus and to avoid use in patients with GI obstruction.*

**Subject 0014-0005; Cholecystitis; Possible Causality**

50 year female who began ALO-02 on 5/4/11 (Study Day 1), titrated up to 60 mg TDD by 6/3/11 (Study Day 31). On (b) (6) (Study Day (b) (6)) she developed severe cholecystitis and was hospitalized overnight to undergo a cholecystectomy. The PMH included chronic cholelithiasis, a subtotal colon resection with sigmoid anastomosis and chronic constipation and diarrhea. Concomitant medications were not reported. She withdrew from the study (b) (6). *Reviewer's comments: Although this subject did have a history of chronic cholelithiasis and other risk factors, the role of ALO-02 in precipitating the acute event of cholecystitis cannot be ruled out.*

**Subject 0025-0003; Cholelithiasis; Possible Causality**

37 year old female began ALO-02 on 2/7/11 (Study Day 1) increased to 80 mg TDD on 4/8/11 (Study Day 61). On (b) (6) (Study Day (b) (6)), the subject experienced severe vomiting and diarrhea and went to the emergency department (ED) with details of the visit not provided. On (b) (6), she returned to the ED with dizziness, nausea and diarrhea. She had yet another ED visit on (b) (6) (Day (b) (6)) where her LFTs were found to be elevated with ALT=144; AST=91; Tbili=2.1. The narrative states that these labs were noted as "increased", but units and reference ranges for the ED were not provided. Upon hospitalization, the subject was found to have an abdominal ultrasound which showed gallbladder sludge. PMH was positive for cardiomyopathy and drug abuse. Treatment with study drug was permanently withdrawn due to the events. On (b) (6), her LFTs were decreasing (ALT=122; AST=59; Tbili=1.4) although the outcome of the event was unresolved at the time of the last report. The subject was permanently withdrawn from the study. *Reviewer's comment: The positive abdominal ultrasound showing gallbladder sludge suggests that the elevated LFTs were likely related to hepatobiliary disorder (i.e., gallbladder disease) and/or possibly related to a medical history of "drug abuse". Screening LFTs were normal. It is unlikely that study drug was a causal factor in the subject's gallbladder sludge which suggests more of a chronic event, but it is possible that study drug ALO-02 exacerbated the underlying condition.*

**Subject 0025-0023; Abdominal Pain; Possible Causality**

41 year old female began ALO-02 on 5/4/11 (Study Day 1) at 40 mg TDD; increased to 50 mg TDD on 5/11/11 (Study Day 8). On (b) (6) (Study Day (b) (6)), the subject presented to the emergency department (ED) with complaints of abdominal pain, diarrhea, severe nausea, and vomiting. A CT scan showed a possible bacterial infection in the small/large intestine with subsequent hospitalization that same day. Study drug was permanently discontinued on that date. The abdominal pain resolved on (b) (6) when she was discharged from the hospital. Details regarding the hospital stay were not provided except that she was placed on multiple medications including ciprofloxacin (Cipro), metronidazole (Flagyl), prednisone, pantoprazole (Protonix) as

well as other medications. She was advised to have a colonoscopy, the results of which were unknown at the time of the narrative. Pertinent PMH included type 2 diabetes, diabetic peripheral neuropathy, and irritable bowel syndrome. Outcome was reported as lost to follow-up. The investigator considered this event related to ALO-02.

*Reviewer's comments: The role of study drug to the SAE of abdominal pain is possible, although the subject had risk factors to include diabetes and diabetic peripheral neuropathy with diabetic gastroparesis risk, as well as a history of irritable bowel syndrome. Class-wide opioids are currently labeled for GI AEs, including abdominal pain.*

**Subject 0001-0017I; Convulsion; Possible Causality (Lowered Threshold)**

41 year old male received ALO-02 administered 10 mg twice daily from 4/19/11 (Study Day 1) and increased to 30 mg twice daily from 5/17/12 to (b) (6) for a total of (b) (6) days. On (b) (6) (Study Day (b) (6)), the subject experienced an "acute grade 3 seizure". The subject, however, had a past medical history of three prior seizures in 2001 after back surgery and another in 2004. He also reportedly had an episode on 9/6/11 similar to the one he experienced on (b) (6) but was discharged from the ED without treatment. The subject was treated with levetiracetam (Keppra) and gabapentin (Neurontin), as anticonvulsants and reportedly recovered from the event (b) (6). On (b) (6) (Day (b) (6)), he experienced another seizure requiring hospitalization and on (b) (6) (Study Day (b) (6)) experienced yet another seizure and apparently was subsequently started on lacosamide (Vimpat). The study drug was permanently discontinued and the subject was withdrawn from the study (b) (6). Diagnostic work up were all negative or nondiagnostic. The subject's other medical history, concomitant medications or prestudy seizure medications were not provided.

*Reviewer's comments: Although the subject's past history of seizures does put him at increased risk for recurrent seizures, the role of study drug cannot be ruled out as it is possible that the seizure threshold was lowered due to study drug. Current class-wide opioid labels: The oxycodone in [Tradename] may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during [Tradename] therapy.*

*Reviewer's Conclusions Uncontrolled Study 1001: Most SAEs occurred during the Long-Term Maintenance Phase, otherwise, no patterns or trends regarding dose or duration and onset of SAE were noted. Of the five cases identified by this reviewer as probably or possibly causally related to ALO-02, seizure and abdominal pain are already labeled. Risk of delayed GI motility and contraindication in patients with GI obstruction is labeled. In the cases of cholecystitis and cholelithiasis, the subjects had other risk factors and causality to ALO-02 alone is not definite. Therefore, I do not believe these events rise to the level where labeling is required. The presence of these events in an uncontrolled study also make interpretation and causality assignment more challenging.*

**Pooled Phase 3 Studies:** A total of 36 subjects experienced 54 SAEs in the pooled Phase 3 studies. By treatment phase 11 of 805 (1%) subjects experienced SAEs during the Titration Phase, 11 of 436 (2%) subjects treated with ALO-02 experienced SAEs during the Maintenance Phase, 2 of 134 (1%) placebo subjects experienced SAEs during the Maintenance Phase, and 12 of 213 (6%) of subjects experienced SAEs during the Long-Term Maintenance Phase.

SAEs by SOC and preferred term are shown in Table 32 below for the Titration Phase.

**Table 32. Pooled Phase 3 Studies Incidence of SAEs Titration Phase**

	Study B4531001 ALO-02 (N=395)	Study B4531002 ALO-02 (N=410)	Pooled ALO-02 (N=805)
System Organ Class			
Preferred Term	n (%)	n (%)	n (%)
Any adverse event	8 (2.0)	3 (0.7)	11 (1.4)
Infections and infestations	1 (0.3)	2 (0.5)	3 (0.4)
Bronchitis	0	1 (0.2)	1 (0.1)
Pneumonia	1 (0.3)	0	1 (0.1)
Urinary tract infection	0	1 (0.2)	1 (0.1)
General disorders and administration site conditions	2 (0.5)	0	2 (0.2)
Non-cardiac chest pain	2 (0.5)	0	2 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	1 (0.2)	2 (0.2)
Chronic obstructive pulmonary disease	1 (0.3)	1 (0.2)	2 (0.2)
Cardiac disorders	1 (0.3)	0	1 (0.1)
Acute myocardial infarction	1 (0.3)	0	1 (0.1)
Gastrointestinal disorders	1 (0.3)	0	1 (0.1)
Hiatus hernia	1 (0.3)	0	1 (0.1)
Metabolism and nutrition disorders	1 (0.3)	0	1 (0.1)
Hypoglycaemia	1 (0.3)	0	1 (0.1)
Nervous system disorders	1 (0.3)	0	1 (0.1)
Cerebrovascular accident	1 (0.3)	0	1 (0.1)
Psychiatric disorders	0	1 (0.2)	1 (0.1)
Depression	0	1 (0.2)	1 (0.1)
Suicide attempt	0	1 (0.2)	1 (0.1)

Renal and urinary disorders	1 (0.3)	0	1 (0.1)
Nephrolithiasis	1 (0.3)	0	1 (0.1)

Studies Include: B4531001, B4531002.

Titration Phase is programmed as first 6 weeks for Study B4531001; and defined by Study B4531002 (planned as 4-6 weeks).

Note: Adverse Events are presented in descending order of frequency for the Pooled ALO-02 column.

Note: At each level of summation (overall, system organ class, preferred term), patients reporting more than one adverse event are counted only once.

Serious adverse event tables use the Pfizer corporate safety database as source and not the clinical study database.

MedDRA (v17.0) coding dictionary applied in the safety database (ARGUS).

Source: ISS Table 4.3.1, Date of Table Generation: 07NOV2014(17:33)

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Findings for the Pooled Maintenance and Long-Term Maintenance are shown below in Table 33. For the pooled analysis, Titration Phase=First 6 Weeks in Study 1001 and First 4-6 Weeks Study 1002. Maintenance Phase=Weeks 7-18 for Study 1001 and Double Blind+Taper Phase in Study 1002. At each level of summation, patients reporting more than one AE are counted once.

**Table 33. Pooled Phase 3 Studies Incidence of SAEs Maintenance and Long-Term Maintenance Phases**

	Study B4531001 ALO-02 (N=290)	Study B4531002 ALO-02 (N=146)	Pooled ALO-02 (N=436)	Study B4531002 Placebo (N=134)	Study B4531001 ALO-02 (LT Maintenance) (N=213)
<b>System Organ Class</b>					
<b>Preferred Term</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Any adverse event	6 (2.1)	5 (3.4)	11 (2.5)	2 (1.5)	12 (5.6)
Gastrointestinal disorders	0	0	0	0	3 (1.4)
Hiatus hernia	0	0	0	0	1 (0.5)
Abdominal pain	0	0	0	0	1 (0.5)
Pancreatitis acute	0	0	0	0	1 (0.5)
Small intestinal obstruction	0	0	0	0	1 (0.5)
General disorders and administration site conditions	0	0	0	0	3 (1.4)
Asthenia	0	0	0	0	1 (0.5)
Chest discomfort	0	0	0	0	1 (0.5)
Chest pain	0	0	0	0	1 (0.5)
Cardiac disorders	1 (0.3)	2 (1.4)	3 (0.7)	0	1 (0.5)
Acute myocardial infarction	1 (0.3)	0	1 (0.2)	0	0
Atrial flutter	0	1 (0.7)	1 (0.2)	0	0
Myocardial infarction	0	1 (0.7)	1 (0.2)	0	0
Cardiac failure congestive	0	0	0	0	1 (0.5)
Pericardial effusion	0	0	0	0	1 (0.5)
Nervous system disorders	0	0	0	0	2 (0.9)
Convulsion	0	0	0	0	2 (0.9)
Hepatobiliary disorders	2 (0.7)	1 (0.7)	3 (0.7)	0	0
Cholecystitis	1 (0.3)	1 (0.7)	2 (0.5)	0	0
Cholelithiasis	1 (0.3)	1 (0.7)	2 (0.5)	0	0
Musculoskeletal and connective tissue disorders	1 (0.3)	1 (0.7)	2 (0.5)	0	0
Arthritis	0	1 (0.7)	1 (0.2)	0	0

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Costochondritis	0	1 (0.7)	1 (0.2)	0	0
Intervertebral disc degeneration	1 (0.3)	0	1 (0.2)	0	0
Infections and infestations	1 (0.3)	0	1 (0.2)	0	3 (1.4)
Osteomyelitis	1 (0.3)	0	1 (0.2)	0	1 (0.5)
Pneumonia	0	0	0	0	1 (0.5)
Diabetic foot infection	1 (0.3)	0	1 (0.2)	0	0
Urinary tract infection	0	0	0	0	1 (0.5)
Injury, poisoning and procedural complications	0	1 (0.7)	1 (0.2)	1 (0.7)	0
Drug administration error	0	1 (0.7)	1 (0.2)	0	0
Road traffic accident	0	0	0	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (0.5)
Lung infiltration	0	0	0	0	1 (0.5)
Pleural effusion	0	0	0	0	1 (0.5)
Blood and lymphatic system disorders	0	0	0	0	1 (0.5)
Hypochromic anaemia	0	0	0	0	1 (0.5)
Investigations	0	0	0	0	1 (0.5)
Blood pressure increased	0	0	0	0	1 (0.5)
Metabolism and nutrition disorders	0	1 (0.7)	1 (0.2)	0	0
Cholesterosis	0	1 (0.7)	1 (0.2)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (0.5)
Anal cancer metastatic	0	0	0	0	1 (0.5)
Pregnancy, puerperium and perinatal conditions	0	1 (0.7)	1 (0.2)	0	0
Abortion spontaneous	0	1 (0.7)	1 (0.2)	0	0
Unintended pregnancy	0	1 (0.7)	1 (0.2)	0	0
Psychiatric disorders	0	0	0	0	1 (0.5)
Mental status changes	0	0	0	0	1 (0.5)
Renal and urinary disorders	1 (0.3)	0	1 (0.2)	0	0
Nephrolithiasis	1 (0.3)	0	1 (0.2)	0	0
Vascular disorders	0	0	0	1 (0.7)	0
Intermittent claudication	0	0	0	1 (0.7)	0
Peripheral arterial occlusive disease	0	0	0	1 (0.7)	0

Studies Include: [B4531001](#), [B4531002](#).

Maintenance Phase is programmed as weeks 7-18 for Study B4531001 and defined in Study B4531002 as Double Blind + Taper Phase.

Note: Adverse Events are presented in descending order of frequency for the Pooled ALO-02 column.

Note: At each level of summation (overall, system organ class, preferred term), patients reporting more than one adverse event are counted once.

Serious adverse event tables use the Pfizer corporate safety database as source and not the clinical study database.

MedDRA (v17.0) coding dictionary applied in the safety database (ARGUS).

Source Data: [Table 4.3.2](#), [ISS Table 10.2](#) Date of Table Generation: 07NOV2014(17:33)

For the Long-Term Maintenance Phase, [Table 4.3.3](#), [ISS Table 10.2](#) Date of Table Generation: 07NOV2014(15:51).

(ISS, p. 98-100).

*Reviewer's Conclusion: Overall, the SAEs in placebo-controlled study 1002, long-term OL study 1001, and pooled Phase 3 studies revealed no trends or patterns which would result in labeling or change the risk-benefit profile of ALO-02.*

### 7.3.3 Dropouts and/or Discontinuations

The Applicant analyzed discontinuations due to AEs as those resulting in 1) permanent discontinuation and/or 2) Dose reduction or temporary discontinuation.

The common AEs that led to permanent discontinuation and or dose reduction/temporary discontinuation were mostly due to severe common GI-related AEs or those less likely related to treatment of the study drug as summarized and discussed below.

#### Study 1002 Discontinuations

*OLT Period:* Of the 410 subjects enrolled in the Open-Label Titration Period, 62 (15%) subjects permanently discontinued study drug due to TEAEs. The most common TEAEs leading to discontinuation by MedDRA SOC were Gastrointestinal Disorders and Nervous System Disorders. There were 19/410 (5%) subjects who required a dose reduction or temporarily discontinued.

*DB Period:* During the Double-Blind Treatment Period, more subjects in the ALO-02 group discontinued due to TEAEs than in the placebo group, as would be expected. In the DB Period with ALO-02 treated subjects, the greatest number of discontinuations due to AEs was due to nausea which occurred in 2% of ALO-02 treated subjects compared to zero placebo. In the ALO-02 treatment arm, 5/146 (3%) required dose reduction or temporarily discontinued due to TEAE compared to 2/134 (1%) in the placebo arm.

The most common AEs Leading to Discontinuation of the study drug and/or study in the OL titration and DB Periods are summarized in Table 34 below.

**Table 34. TEAEs ≥2% Leading to Study Drug and/or Study Discontinuation, Titration Period and Double-Blind Safety Populations Study 1002**

MedDRA SOC Preferred Term	Open-Label Titration Period <sup>a</sup> (Titration Period Safety Population)	Double-Blind Treatment Period <sup>b</sup> (Double-Blind Safety Population)	
	ALO-02 N=410 n (%)	Placebo N=134 n (%)	ALO-02 N=146 n (%)
Subjects with at least 1 TEAE leading to study drug and/or study discontinuation	62 (15.1)	8 (6.0)	12 (8.2)

<b>Gastrointestinal disorders</b>	<b>32 (7.8)</b>	<b>0 (0.0)</b>	<b>5 (3.4)</b>
Abdominal pain	1 (0.2)	0 (0.0)	0 (0.0)
Abdominal pain upper	1 (0.2)	0 (0.0)	0 (0.0)
Constipation	6 (1.5)	0 (0.0)	0 (0.0)
Diarrhea	2 (0.5)	0 (0.0)	1 (0.7)
Nausea	19 (4.6)	0 (0.0)	3 (2.1)
Retching	1 (0.2)	0 (0.0)	0 (0.0)
Vomiting	8 (2.0)	0 (0.0)	2 (1.4)

AEs were classified by SOC and PT as defined by the MedDRA v16.1. If a subject had more than 1 AE that coded to the same PT, the subject was counted only once for that PT. Similarly, if a subject had more than 1 AE within a SOC the subject was counted only once in that SOC.

Abbreviations: AE = adverse event; ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride extended-release capsule; n/N = number of subjects; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

a TEAEs were defined as AEs that commenced on or after the start of ALO-02 administration for the Open-Label Titration Period but prior to the start of randomized double-blind study medication for the Double-Blind Treatment Period.

b. TEAEs were defined as AEs that commence on or after the start of randomized double-blind study medication for the Double-Blind Treatment Period, including the Post-Treatment Period follow-up.

(Applicant's table, modified by reviewer, CSR 1002, p. 142)

**Study 1001 Discontinuations:** Across all treatment phases, there were 19% of subjects who had study treatment permanently discontinued due to a TEAE and 11% who had dose reduction or temporary discontinuation due to an AE. The most common TEAEs that led to treatment discontinuation were opioid-related events of nausea and constipation. By dose group, discontinuations due to AEs were more common in the 10-40 mg/day dose group (33%) and least common in the >120 mg/day dose group (9%).

#### Pooled Phase 3 Studies Discontinuation Due to AEs

- Titration Phase: TEAEs leading to discontinuation of study drug in  $\geq 1\%$  of pooled subjects (included nausea, constipation, vomiting, somnolence, headache, fatigue and dizziness. Most discontinuation TEAEs were of moderate severity.
- Maintenance Phase: TEAE leading to discontinuation of study drug in  $\geq 1\%$  of pooled subjects was nausea. The majority of the nausea TEAEs leading to discontinuation of study drug were considered of moderate severity.
- Long-Term Maintenance Phase: No TEAE led to discontinuation of study drug in  $\geq 1\%$  of ALO-02 subjects in Study B4531001.

Table 35 displays the incidence of permanent discontinuation or dose reduction by treatment phase.

**Table 35. Incidence of Permanent Discontinuation or Dose Reduction by Treatment Phase**

	Titration Phase			Maintenance			PLAC	LTM
	Study	Study	Pooled	Study	Study	Pooled		
<b>Subjects D/C due to AE, n (%)</b>	1001 N=395	1002 N=410	N=805	1001 N=290	1002 N=146	N=436	N=134	N=213
	61 (15)	62 (15)	123 (15)	12 (4)	12 (8)	24 (5)	8 (6)	4 (2)
<b>Dose reduced or temporary D/C due to AE</b>	19 (5)	19 (5)	38 (5)	13 (4)	5 (3)	18 (4)	2 (1)	11 (5)

(Reviewer); D/C=discontinuation; LTM=Long-Term Maintenance; Plac=placebo

Preferred terms leading to discontinuation with incidence  $\geq 1\%$  are shown below in Table 36.

**Table 36. Discontinuation AEs Occurring with Incidence  $\geq 1\%$  in ALO-02 Treated Subjects Pooled Phase 3 Studies**

	Titration N=805 (%)	Maintenance N=436 (%)	Long-term Maintenance N=213 (%)
<b>MedDRA Preferred Term</b>	123 (15)		
Nausea	34 (4)	6 (1)	0
Constipation	16 (2)	--	--
Vomiting	15 (2)	--	0
Somnolence	11 (1)	--	--
Headache	9 (1)	--	--
Dizziness	8 (1)	--	--
Fatigue	9 (1)	--	--

(Reviewer); -- denotes incidence  $< 1\%$

*Reviewer's Conclusions: Most discontinuations related to AEs occurred during the Titration Phase of both Phase 3 studies and the most frequent reason for discontinuation of study drug or study was due to GI-related events of nausea, constipation, or vomiting. This is generally consistent with what is known about opioids.*

**Safety from the Clinical Pharmacology/Pharmacokinetic Studies:** Four of the seven Clinical Pharmacology/PK studies used the to-be-marketed formulation of ALO-02. See Section 5.1 for a description of the studies. Study B4531003 was a food effect study, B451004 an alcohol interaction study, B4531007 a relative BA study of ALO-02 compared with IR oxycodone (Roxicodone) in healthy subjects, and B4531006 an OL, single- and multiple-dose, naltrexone-blocked study where 13 healthy subjects received

ALO-02 40 mg twice daily compared to ALO-02 80 mg once daily and to OxyContin 40 mg twice daily. Overall, there were no major safety findings in these studies which would change the benefit to risk of ALO-02. No subjects discontinued from the Phase 1 Studies ALO-02-08-103, B4531003, B4531004, or B4531006, because of TEAEs. Three subjects discontinued study medication because of AE with one subject each due to emesis (Study ALO-02-07-102, Subject 104; oxycodone HCl with sequestered naltrexone, 20 mg capsule), vomiting (Study ALO-02-09-1001, Subject 21; oxycodone HCl dose 20 mg), and gastroenteritis, dizziness and headache (Study B4531007, Subject 10011012; IR oxycodone 20 mg).

### 7.3.4 Significant Adverse Events

Other significant AEs included subjects with Exposure in Utero. The Applicant identified four cases of Exposure in Utero in four different clinical trials. Only the two subjects in the Phase 3 studies actually received study drug ALO-02. The other two subjects in the Human Abuse Potential studies did not receive ALO-02. No subjects experienced Exposure in Utero in the clinical pharmacology/PK studies. Narratives for the subjects are summarized below in Table 37.

**Table 37. Narratives Exposure in Utero Clinical Trials ALO-02 Drug Development**

Phase 3 Studies
<p><b>Study 1002, Subject 10151003; Drug Administration Error/Unintended pregnancy/Spontaneous abortion/miscarriage.</b> See SAE narrative previously discussed in Section 7.3.2.</p>
<p><b>Study B4531001, Subject 00030014; Pregnancy:</b> This was a 41-year-old white female who received ALO-02 start date 3/8/11 (Study Day 1), titrated up to 40 mg which she received from 5/5/11-6/15/11 (total of 100 days). Subject's last menstrual period was 5/16/11. A pregnancy test due on 6/20/11 was positive. Study drug was permanently discontinued on 6/15/11 (reason for discontinuation was not provided). Follow-up information indicated that the subject delivered a full-term baby with no health problems (b) (6). <i>Reviewer's comments: Subject received study drug for 100 days without other AEs reported. The subject's concomitant medications included APAP, hydrocodone/APAP (Lortab) and prenatal vitamins.</i></p>
Abuse Potential Studies
<p><b>Study B4531008, Subject 10011084; Exposure in utero:</b> This 24-year-old female subject was enrolled in the oral abuse potential study on 4/1/13. The subject was discontinued from the study on 4/2/13 during the Naloxone Challenge due to second degree atrioventricular block, which was considered not related to the study drug by the Investigator. In August 2013, the site learned the subject was 2 months pregnant. The subject refused to provide additional information. The outcome of the pregnancy was unknown.. <i>Reviewer's comments: The subject was discontinued from the study during the Drug Discrimination Phase and did not enter the Treatment Phase. No study drug was administered in the Drug Discrimination Phase. Further, any pregnancy-related issues would be confounded by the subject's self-reported use of alcohol and other</i></p>

*recreational drugs. This does not represent a case of exposure in utero to study drug ALO-02.*

**Study B4981002, Subject 10011002; Exposure in Utero:** This 19-year-old female subject was enrolled in the IV abuse potential study on 7/18/13 for the Naloxone Challenge and received one dose of IV oxycodone 20mg on 7/19/13 during the Drug Discrimination Phase. On 7/20/13, the subject was discontinued from the study on Day 1 of the Drug Discrimination Phase for not meeting protocol-specified randomization criteria (could not tolerate study treatments safely: SpO<sub>2</sub>=90% at 30 minutes post-dose). Serum hCG was negative on 7/9/13 (screening) and negative urine hCG on 7/18/13. Serum hCG was positive on 7/21/13. Follow-up revealed that the subject reported the pregnancy was terminated (induced abortion) in August 2013 (approximately 4 weeks gestation). *Reviewer's comments: This does not represent a case of exposure in utero to study drug ALO-02.*

(Reviewer)

### 7.3.5 Submission Specific Primary Safety Concerns

This section of the review describes the results of the naltrexone and 6- $\beta$ -naltrexol (naltrexol) plasma concentrations measured during the studies and whether these concentrations demonstrated any effect on the safety of ALO-02. This portion of the review is arranged in three sections: I) Effect of Naltrexone and 6- $\beta$ -Naltrexol Systemic Exposure on Safety of ALO-02, II) COWS (Clinical Opioid Withdrawal Scale Scores), and III) Opioid Withdrawal Cases

See Dr. Suresh Naraharisetti's Clinical Pharmacology review for details regarding the naltrexone and naltrexol systemic exposure findings and full discussion. Dr. Naraharisetti's overall findings: Following single dose administration of intact TROXYCA ER in Phase 1 studies, naltrexone was undetected (limit of quantitation, 4 pg/mL). The 6- $\beta$ -naltrexol (limit of quantitation, 4 pg/mL) was observed in 19 out of 37 subjects with a median of 7.78 pg/mL and a range of 4.08 – 45.4 pg/mL. In the patients treated with intact TROXYCA ER 10 mg/1.2 mg - 80 mg/9.6 mg twice daily, naltrexone concentrations was detectable in 249 subjects (34%) out of 725 subjects with median of 11.65 pg/mL and range of 4.05 -1090 pg/mL. The 6- $\beta$ -naltrexol concentrations was observed in 536 subjects (73%) out of 735 subjects with median of 42.75 pg/mL and range of 4.05 -7320 pg/mL.

#### **I) Effect of Naltrexone and 6- $\beta$ -Naltrexol Systemic Exposure on Safety of ALO-02**

The information discussed in this section of the review is based upon data included in the original submission as well as the Applicant's responses to information requests sent by the Agency's review team.

According to the Revia label, naltrexone is extensively metabolized after oral administration, with the activity of naltrexone believed to be due to both the parent and the 6- $\beta$ -naltrexol metabolite. The mean elimination half-life for naltrexone is four hours

and about 13 hours for 6- $\beta$ -naltrexol. The Applicant reported that in a published study with Revia 50 mg tablets, the mean naltrexone C<sub>max</sub> and AUC values were 8,550 pg/mL and 24,820 pg\*hr/mL, respectively.

According to the protocol for Study 1002, a blood sample for the purpose of quantifying oxycodone, noroxycodone, naltrexone, and 6- $\beta$ -naltrexol was to be obtained (i) at the time of Randomization for Treatment Responders, (ii) at the End of OL Week 6 for Treatment Non-responders (iii) at the time of Early Termination from the Open-Label Titration and Conversion Period for subjects withdrawn from the Open-label Titration and Conversion Period, (iv) at the End of Double-Blind Weeks 4, 8 and 12 (or Early Termination) for randomized subjects and v) if a subject experienced a COWS score  $\geq 13$  at any of the scheduled or unscheduled clinic visits.

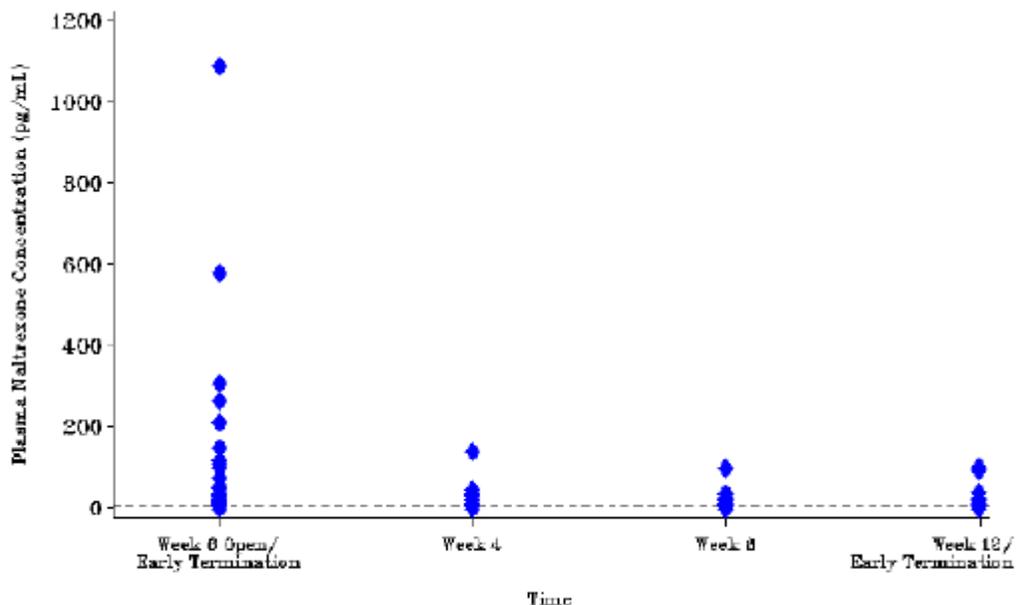
Study 1002 (Naltrexone/Naltrexol) Results: There were 687 naltrexone samples obtained from 350 subjects. Of all naltrexone samples, 82% (563/687) were BLQ (below the limit of quantification) of 4 pg/mL. Of the 124 samples that showed measurable naltrexone exposures, 103 were below 40 pg/mL and five were above 200 pg/mL. The Applicant found that most plasma concentrations of naltrexol were in the lower end of the spectrum and not related to ALO-02 dose. There were 100% of subjects who at least one sample of naltrexone, 38% had at least two samples, and 31% had at least three samples.

For the naltrexone and 6- $\beta$ -naltrexol analytes, the dose exposure relationship was evaluated by plotting the C<sub>obs</sub> as a function of the total daily dose of naltrexone in ALO-02.

*Naltrexone Exposure:* For subjects treated with ALO-02 during the Double-Blind Treatment Period, mean plasma concentrations of naltrexone were 5.3 pg/mL, 3.4 pg/mL, 2.9 pg/mL, and 3.0 pg/mL at Randomization Baseline, Week 4, Week 8, and Week 12/Early Termination, respectively. Three study samples, collected during the Open-Label Titration Period, were outside of the naltrexone established frozen matrix stability at the time of analysis for Subjects 10011002, 10041006, and 10601010 who were early terminated and were not randomized to the Double-Blind Treatment Period. The Applicant reported that additional naltrexone stability for these subjects was ongoing and was to be evaluated and reported under (b) (4) Study 8253977. See Dr. Naraharisetti's review.

The detectable plasma naltrexone concentration-time profile for all subjects is displayed below in Figures 10 and 11. Most outliers were found During Titration/Early Termination. There does not appear to be evidence of increased detectable plasma naltrexone or naltrexol concentrations over time or by dose.

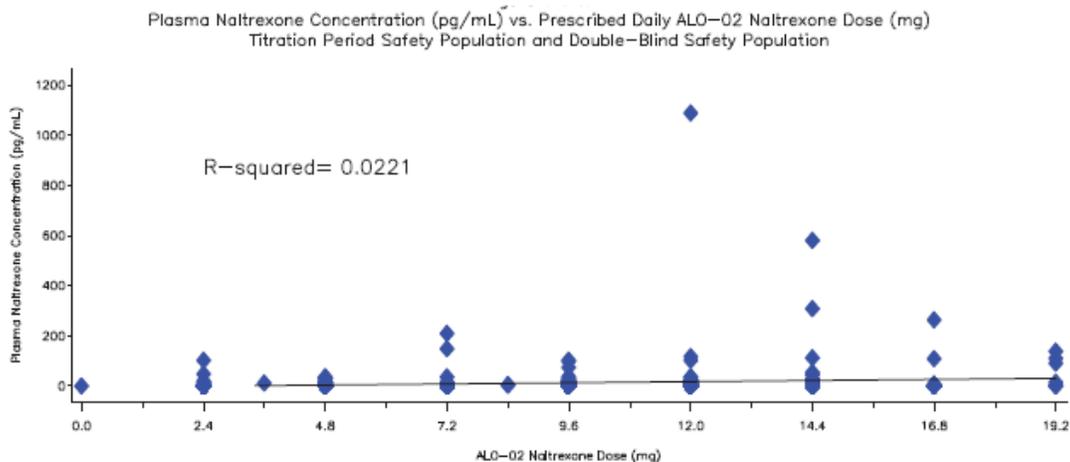
**Figure 10. Detectable Plasma Naltrexone Concentration (pg/mL) Over Time, Titration Period Safety Population and Double-Blind Safety Population Study 1002**



(CSR, Study 1002, p. 129); Note: The dashed line represents the lower limit of quantification (4 pg/mL); x axis= time; Y axis =Plasma Naltrexone Concentration (pg/mL)

The Applicant found no apparent correlation between plasma naltrexone concentrations and the daily dose of naltrexone present in ALO-02 ( $R^2=0.0221$ ) which suggests that observed naltrexone exposures were not dose-related.

**Figure 11. Plasma Naltrexone Concentration (pg/mL) vs Prescribed Daily ALO-02 Naltrexone Dose (mg) Titration Period Safety Population and Double-Blind Safety Population Study 1002**



R-squared is based on a regression analysis of plasma naltrexone concentration as a function of prescribed daily ALO-02 naltrexone dose. Includes all concentration values for all subjects receiving ALO-02 at the time of the pharmacokinetic sample.

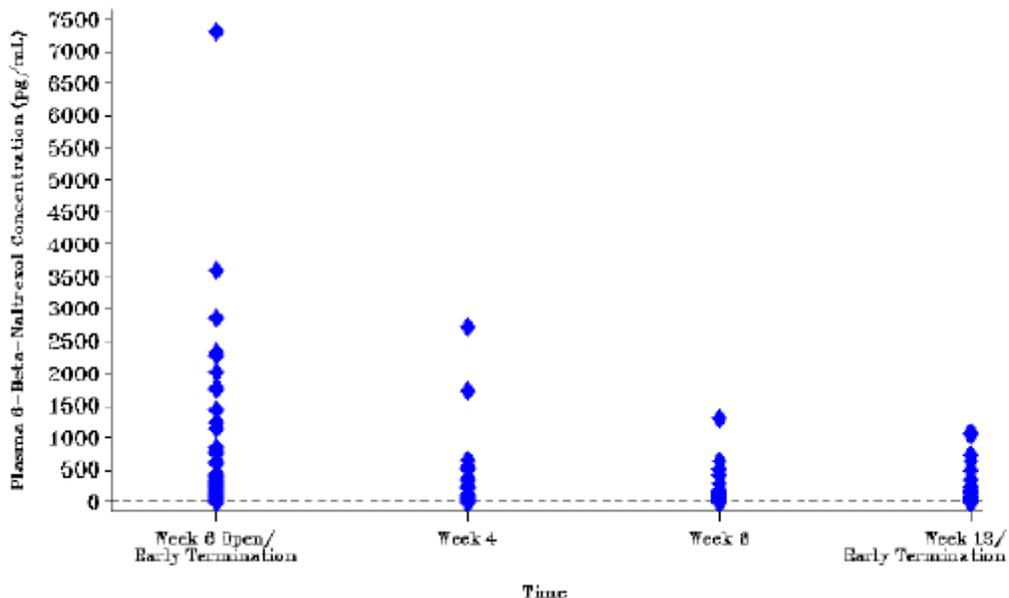
1.2 mg ALO-02 naltrexone dose is 10/1.2 mg ALO-02 dose, 2.4 mg ALO-02 naltrexone dose is 20/2.4 mg ALO-02 dose, etc.

(CSR, p. 1283); x axis=ALO-02 Naltrexone Dose (mg); Y axis = Plasma Naltrexone Concentration (pg/mL)

*6-β -Naltrexol Exposure:* For subjects treated with ALO-02 during the Double-Blind Treatment Period, mean plasma concentrations of 6-B-naltrexol were 97.5 pg/mL, 86.1 pg/mL, 48.3 pg/mL, and 55.6 pg/mL at Randomization Baseline, Week 4, Week 8, and Week 12/Early Termination, respectively.

The detectable plasma naltrexol concentration-time profile for all subjects is displayed below in Figure 12.

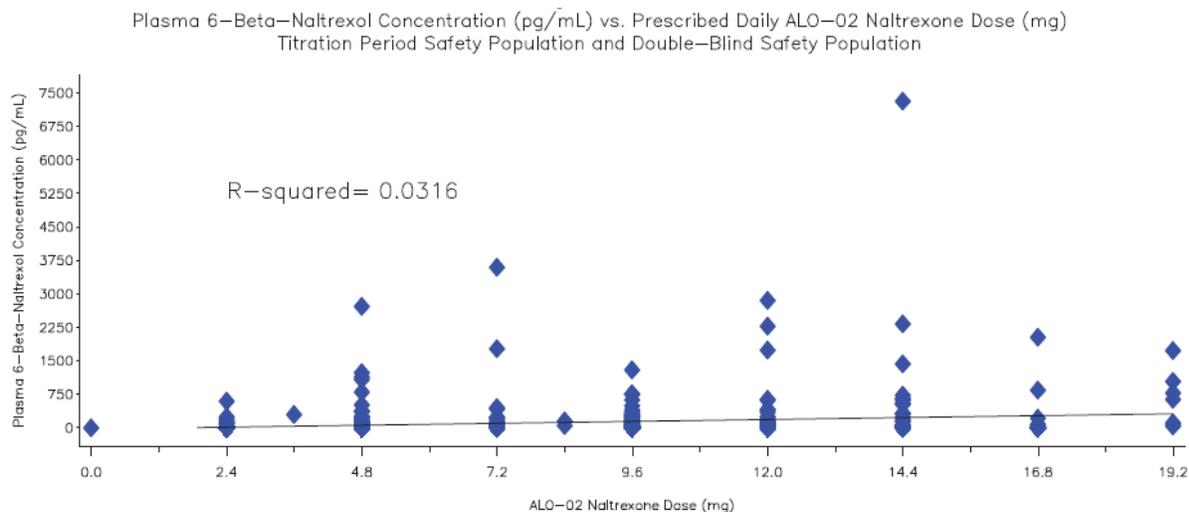
**Figure 12. Detectable Plasma 6-β-Naltrexol Concentration (pg/mL) Over Time, Titration Period Safety Population and Double-Blind Safety Population Study 1002**



Note: The dashed line represents the lower limit of quantification (4 pg/mL)

The detectable plasma 6-β-naltrexol concentration versus the prescribed daily dose of naltrexone in ALO-02 showed no apparent correlation between plasma 6-B-naltrexol concentrations and the daily dose of naltrexone present in ALO-02 ( $R^2=0.0316$ ) seen in Figure 13.

**Figure 13. Plasma 6-β-Naltrexol Concentration (pg/mL) vs Prescribed Daily ALO-02 Naltrexone Dose (mg) Titration Period Safety Population and Double-Blind Safety Population Study 1002**



(CSR, Study 1002, p. 1284); R-squared is based on regression analysis of plasma-6-B-Naltrexol concentration as a function of prescribed daily ALO-02 naltrexone dose. Includes all concentration values for all subjects receiving ALO-02 at the time of the PK

sample. 1.2 mg ALP-02 naltrexone dose is 10/1.2 mg; 2.4 mg ALO-02 naltrexone dose is 20/2.4 mg, ALO-02 dose, etc.

*Naltrexone/Naltrexol Levels and AEs:* The Applicant arbitrarily determined that naltrexone values >200 pg/mL was considered clinically important. Narratives were provided for subjects with “high” naltrexone concentrations (i.e., >200 pg/ml). The Applicant did not identify an upper range for naltrexol that they considered to be clinically important.

For subjects treated with ALO-02 during the Double-Blind Treatment Period, mean plasma concentrations of naltrexone were 5.3 pg/mL, 3.4 pg/mL, 2.9 pg/mL, and 3.0 pg/mL at Randomization Baseline, Week 4, Week 8, and Week 12/Early Termination, respectively; the corresponding values for 6-β-naltrexol were 97.5 pg/mL, 86.1 pg/mL, 48.3 pg/mL, and 55.6 pg/mL, respectively.

Five subjects were identified with naltrexone concentrations >200 pg/mL at some time point during Study 1002. The maximum naltrexone/naltrexol concentrations, maximum COWS scores, TDD (total daily dose), and total exposure days on ALO-02 at the time the samples were drawn are summarized for those five subjects in Table 39 below.

**Table 38. Naltrexone Levels ≥200 pg/mL Study 1002**

ID	TDD mg	Naltrexone pg/mL	Naltrexol pg/mL	COWS Scores
10321004	60	210	3600	0
10221001	140	265	2030	0
10051001	120	309	1440	1
10221015	120	581	7320	1
10271011	100	1090	1750	2

(Reviewer); TDD=total daily dose; COWS=Clinical Opioid Withdrawal Scale ; mg=milligram

All of the above subjects received ALO-02 only during the OL period and were randomized to placebo. No other trends were identified. The Investigators did not identify any of these subjects as experiencing opioid withdrawal (OW), although the Applicant retrospectively considered Subject 10271011, who experienced nasopharyngitis, as an AE term possibly related to OW. In addition, I found that Subject 10051001 experienced AEs of anxiety, depression, and hot flashes which could be symptoms of OW. COWS scores for all of these subjects, however, were ≤2 at each time point. The other three subjects with naltrexone ≥200 pg/mL did not experience AEs.

Two of those subjects with elevated naltrexone levels (>200 pg/mL) had one or more symptoms (AE terms) possibly related to opioid withdrawal as summarized below:

- Subject 10051001: The subject reported moderate AEs of mild insomnia (DB Study Day 1), exacerbation of anxiety and depression, dyspepsia, and hot flashes (DB Study Day 3), exacerbation of low back pain (DB Study Day 5), hot flashes (DB Study Day 22), fatigue (DB Study Day 32). The subject discontinued from the study due to AE of intolerable fatigue (DB Study Day 32). There was no time relationship of the reported AEs to ALO-02 or the naltrexone concentration of 309 pg/mL as the subject was on placebo at the time of the AEs. *Reviewer's comment: This subject (while tapering from ALO-02 to placebo) was on placebo when the AEs of insomnia (Day 1 DB); anxiety, depression, and hot flashes (Day 3 DB) occurred and may represent symptoms of Opioid Withdrawal due to taper of ALO-02. The role of the elevated naltrexone is not clear, although given the ½ life of naltrexone (four hours), it is not likely that elevated naltrexone was contributing to possible OW symptoms on Day 3 or later.*
- Subject 10271011: This subject was on ALO-02 up to 100 mg TDD for 29 days (start date 9/18/12) prior to beginning the DB period on placebo. On 10/23/12 (DB Study Day 1) the subject had a naltrexone plasma concentration of 1090 pg/mL and 6-β-naltrexol concentration of 1,750 at the same visit. His prescribed total daily dose of oxycodone in ALO-02 at that time was 100 mg. The subject experienced AEs of ear infection (9/18/12-12/30/12), influenza (11/15/12-11/20/12), and nasopharyngitis (10/20/12-10/23/12) none of which was considered related to study drug. The subject completed the study. The Applicant retrospectively determined that they considered the AE of nasopharyngitis may have been related to naltrexone exposure (i.e., symptom of OW). *Reviewer's comments: It is possible that elevated naltrexone may have contributed to the AE of nasopharyngitis since there is temporal association but this isolated AE is not likely due to OW, especially given that the maximum COWS score was 2 and SOWS was 9 during the time of the elevated naltrexone and nasopharyngitis.*

#### Study 1001 (Naltrexone/Naltrexol) Results:

Pharmacokinetic samples were to have been taken at the End of Weeks 1 and 4, at the End of Months 2, 3, 6, 9, and 12 or early termination, and was optional, at the discretion of the investigator during any unscheduled visits for the purpose of quantifying oxycodone, noroxycodone, naltrexone and 6-β- naltrexol in plasma.

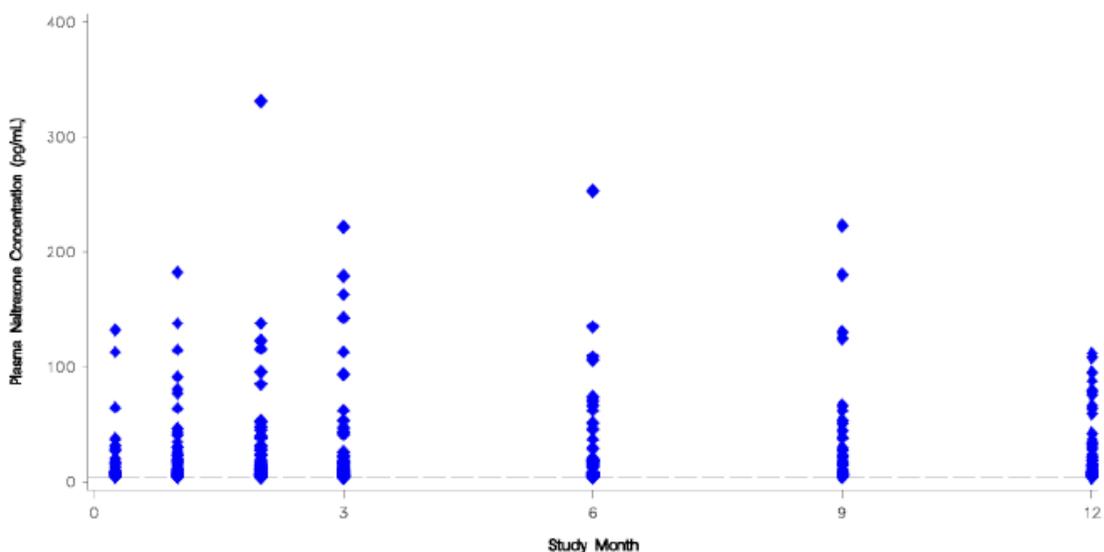
This study provides information regarding naltrexone/naltrexol levels over long-term exposure to ALO-02. There were 1,720 samples obtained from 375 subjects, and 1,324 (77%) were BLQ (<4 pg/mL). Of the 396 samples that showed measurable naltrexone exposures, 329 were below 40 pg/mL and 4 were above 200 pg/mL. The

plasma concentrations of naltrexone were BLQ (<4 pg/mL) in a majority of samples (77%), and the highest observed naltrexone concentrations was 331 pg/mL.

*Naltrexone:* The mean steady-state concentrations of naltrexone were 1.7 pg/mL for the 10-40 mg/day dose group, 10.0 pg/mL for the >40-80 mg/day dose group, 9.0 pg/mL for the >80-120 mg/day dose group, and 11.6 pg/mL for the >120 mg/day dose group. Plasma naltrexone concentrations did not accumulate during the study. Throughout the study, the naltrexone concentrations averaged 1.7-11.6 pg/mL across the average daily dose groups.

The detectable plasma naltrexone concentration over time is shown in Figure 14.

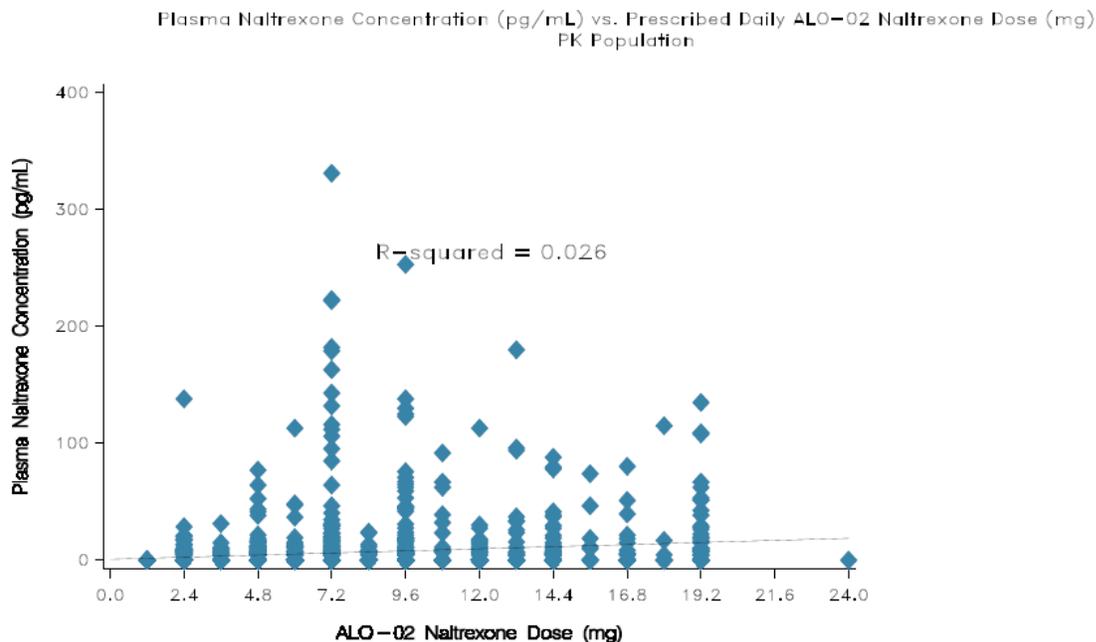
**Figure 14. Detectable Plasma Naltrexone Concentration (pg/mL) Over Time (PK Population)**



(Study 1001, CSR, p. 66); x axis=Study Month; Y axis=Plasma Naltrexone Concentration (pg/mL); Dashed line=lower limit of quantitation (4 pg/mL).

There was no apparent relationship between plasma naltrexone concentrations and the naltrexone HCL daily dose ( $R^2=0.026$ ) as shown in Figure 15.

**Figure 15. Plasma Naltrexone Concentration (pg/mL) vs Prescribed Daily ALO-02 Naltrexone Dose (mg) PK Population**

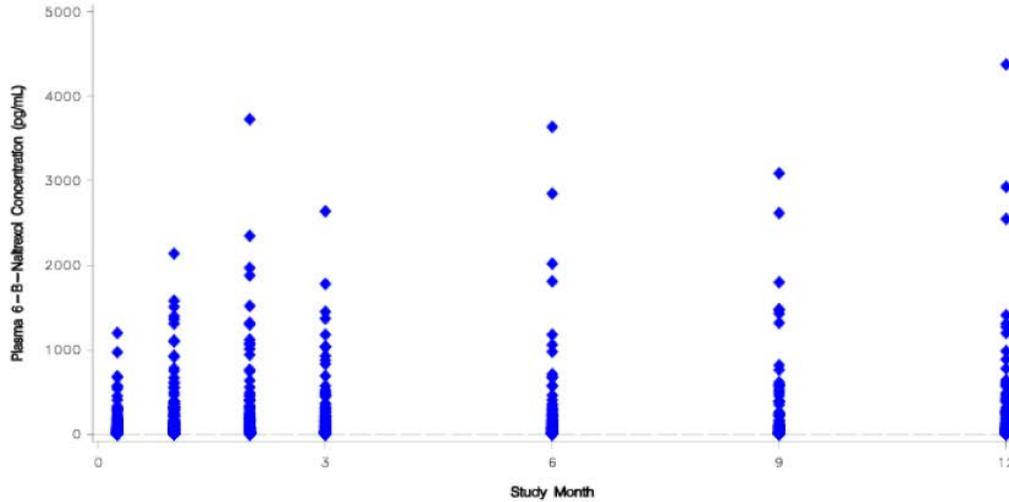


(Study 1001 CSR, p. 1065); x axis=ALO-02 naltrexone dose (mg); Y axis=Plasma Naltrexone concentration (pg/mL);  $R^2$  is based on a regression analysis of plasma naltrexone concentration as a function of prescribed daily ALO-02 naltrexone dose. 1.2 mg=ALO-02 naltrexone dose of 10/1.2 mg; 2.4mg ALO-02 naltrexone dose is 20/2.4 mg ALO-02 dose, etc. N=386.

*6-B-Naltrexol*: The mean steady state concentrations of 6- $\beta$  -naltrexol were 43.8 pg/mL for the 10-40 mg/day dose group, 155.6 pg/mL for the >40-80 mg/day dose group, 162.0 pg/mL for the >80-120 mg/day dose group, and 227.4 pg/mL for the >120 mg/day dose group. Plasma 6- $\beta$  -naltrexol concentrations were higher for female than male subjects.

The detectable plasma 6- $\beta$  -naltrexol concentration-time profile for all subjects, seen in Figure 16, shows that plasma naltrexol concentrations did not accumulate during the study, although there were outliers throughout the study.

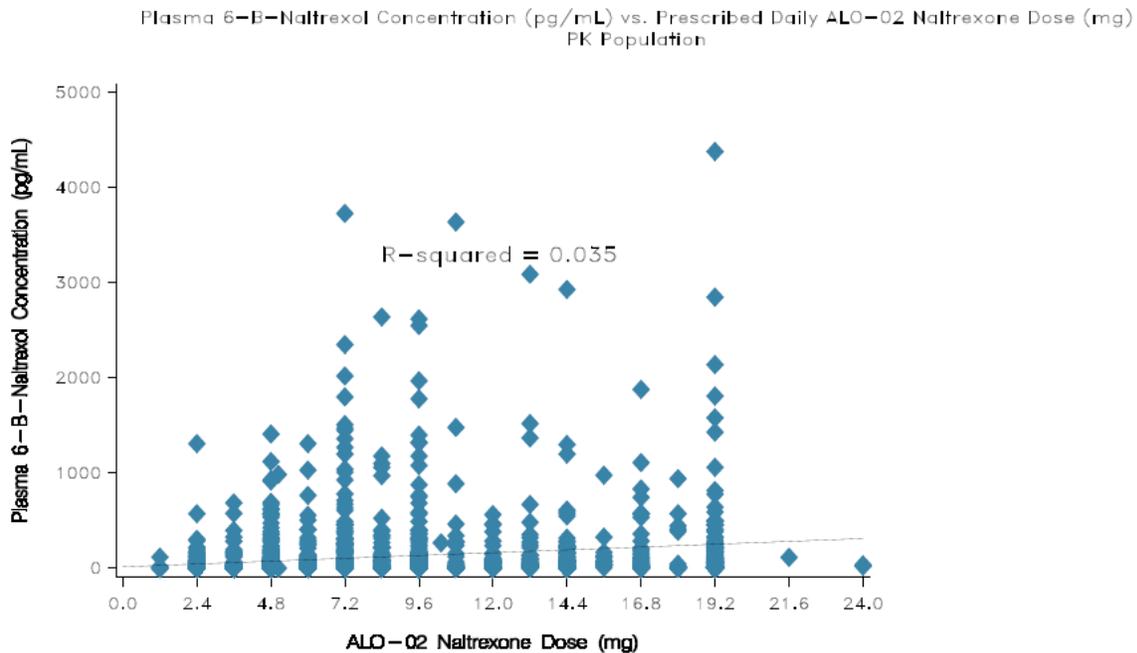
**Figure 16. Detectable Plasma 6-B-Naltrexol Concentration (pg/mL) Over Time (PK Population)**



(Study 1001, CSR p. 67); x axis=Study Month; Y axis=Plasma 6-B-Naltrexol Concentration (pg/mL); dashed line represents the lower limit of quantitation (4 pg/mL)

There was no apparent relationship between plasma 6-B-naltrexol concentrations and the naltrexone HCL daily dose with  $R^2=0.035$ , as shown in Figure 17.

**Figure 17. Plasma 6-B-Naltrexol Concentration (pg/mL) vs Prescribed Daily ALO-02 Naltrexone Dose (mg) PK Population**



(Study 1001, CSR p. 1068); x axis= ALO-02 Naltrexone Dose (mg); y axis= Plasma-6-B Naltrexol Concentration (pg/mL); R<sup>2</sup> is based on a regression analysis of plasma naltrexone concentration as a function of prescribed daily ALO-02 naltrexone dose. 1.2 mg=ALO-02 naltrexone dose of 10/1.2 mg; 2.4mg ALO-02 naltrexone dose is 20/2.4 mg ALO-02 dose, etc. N=386.

*Naltrexone/Naltrexol Levels and AEs:* Three subjects (0007-0016, 0016-0002, and 0035-0021) had four naltrexone level values >200 pg/mL. Subject 0007-0016 had naltrexone level >200 pg/mL twice. The highest individual naltrexone level was 331 pg/mL exposure in Subject 0007-0016. The highest 6-β-naltrexol concentrations was 4380 pg/mL in Subject 00140004.

The naltrexone concentrations, maximum COWS scores, TDD (total daily dose), and total exposure days on ALO-02 at the time of the samples were drawn are summarized in Table 39 below.

**Table 39. Naltrexone Levels ≥200 pg/mL Study 1001**

ID	TDD	Naltrexone pg/mL	COWS Scores	Exposure Days
0007-0016	60	331	0	58
0007-0016	60	223	0	271
0035-0021	90	253	0	167
0016-0002	60	222	0	89

(Reviewer) TDD=total daily dose; COWS=Clinical Opiate Withdrawal Scale

*Narratives:* Although the three subjects with naltrexone levels ≥200 pg/mL experienced mild or moderate AEs, none of the AEs was severe or serious and none was associated with a probable case of OW. Narratives for the three subjects with elevated naltrexone ≥200 pg/mL are summarized below.

- Subject 0007-0016 had the highest naltrexone concentration of 331 pg/mL (naltrexol level 1430 pg/mL). This was an 80 year old female who began ALO-02 at a starting dose of 50 mg daily divided into 2 equal doses (start date 4/21/11 [Study Day 1]). The dose was increased to 60 mg on Study Day 9 and that dose was continued through Study Day 359 (4/13/15). No rescue medication was taken throughout the study. On 7/17/11 (Study Day 58), the subject had a naltrexone plasma concentration of 331 pg/mL with COWS score=0 and SOWS=1 on that day. An AE of dry mouth (mild) was experienced beginning on Study Day 1. On 1/16/12 (Study Day 271) the naltrexone level was 223 pg/mL with COWS=0 and SOWS=6. The subject completed the study with no other

AEs. *Reviewer's comment: The single AE of dry mouth is not likely related to OW.*

- 00350021 – 58 year old female was on 120 mg TDD of ALO-02 by 2/13/12 (Study Day 284) which was continued through 3/15/12 (Study Day 315). On 10/19/11 (Study Day 167), naltrexone level was 253 pg/mL with COWS=1 and SOWS=12. AEs experienced by the subject included moderate fatigue, mouth ulceration, pruritus, and back pain and mild dry mouth, excoriation, fall, posttraumatic pain, dizziness, blister, procedural pain, and musculoskeletal chest pain. *Reviewer's comment: These AEs do not appear related to OW.*
- Subject 00160002 – 68 year old female was on 60 mg ALO-02. On Study Day 89, naltrexone level was 222 pg/mL, COWS=0, SOWS=0. *Reviewer's comments: The subject experienced nasopharyngitis and vomiting at some points during the study but not during the time when the naltrexone level was obtained.*

The submission did not include a full narrative for the subject with the highest naltrexol level (Subject 00140004) as the submission included narratives for elevated naltrexone but not naltrexol. Based upon the Applicant's summarized information for this subject, the subject had reported AEs of increasing headache and yeast infection, both occurring before the elevated 6- $\beta$ -naltrexol sample and had a total COWS score of 5 at some time but the temporal relationship between the COWS score and elevated 6- $\beta$ -naltrexol is unknown.

Naltrexone Dose Ratio/Abuse Potential Studies and Clinical Pharmacology/PK Studies Results: In the naltrexone dose ratio/abuse potential or clinical pharmacology/PK studies, where naltrexone plasma concentrations were measured, the concentrations were BLQ (<4 pg/mL) in all samples following single oral doses of the ALO-02 (intact) to healthy volunteers (40 mg/4.8 mg) or non-dependent recreational drug users (60 mg/7.2 mg).

***Applicant's Conclusions (Naltrexone/Naltrexol Exposure)***

- The mean C<sub>max</sub> of naltrexone following single oral doses of Revia 50 mg tablets is over 300-fold higher compared with the highest mean concentration (24.9 pg/mL) and over 7-fold higher than the highest individual concentration (1,090 pg/mL) observed following administration of intact ALO-02 capsules. Mean exposures of naltrexone with Revia tables are orders of magnitude above the naltrexone exposures seen with ALO-02 when administered as intact in the highest strengths of ALO-02 80 mg/9.6 mg capsules.

- The overall frequency of quantifiable naltrexone concentrations (>4 pg/mL) was low (18-23% of samples) and similar between the two Phase 3 studies.
- There was no naltrexone accumulation at any timepoint throughout the studies.
- Based on the individual subject data, there was no apparent relationship between plasma naltrexone or 6- $\beta$ -naltrexol concentrations and the naltrexone HCl daily dose.

### ***Reviewer's Conclusions (Naltrexone/Naltrexol Concentrations)***

- Overall, I agree with the Applicant's conclusions. There was no definite evidence that in cases where naltrexone/naltrexol was highest that there were serious AEs or definite evidence of opioid withdrawal with use of intact ALO-02.

### **II) Clinical Opiate Withdrawal Scale (COWS) Scores**

The COWS contains 11 common opiate withdrawal signs or symptoms rated by the clinician. The summed score of the 11 items was used to assess a subject's level of opiate withdrawal. The possible COWS scores to assess symptoms of withdrawal were as follows: no symptoms (COWS score 0-4), mild (COWS score 5-12), moderate (COWS score 13-24), moderately severe (COWS score 25-36), or severe withdrawal (COWS score >36).

Across both Phase 3 studies, only two subjects had maximum COWS scores consistent with moderate or moderately severe OW: 1) Subject 10591008 in Study 1002 had a COWS score maximum of 14 that occurred four days after the DB taper and 2) Subject 0027-0004 in Study 1001 had a COWS score maximum of 33 that occurred five days after the subject had stopped taking ALO-02. Both of these subjects are discussed in the Opioid Withdrawal section of this review.

Study B4531002: COWS and SOWS scores were assessed at baseline, at every scheduled clinic visit with the exception of Visits 12 and 14, at any of the unscheduled visits, and at both of the post-treatments visits.

#### ***Results:***

- OLT: Mean (SD) COWS score at Screening was 0.6 (1.09) and remained relatively constant ( $\pm 0.1$ ) throughout the OL Titration Period. The mean (SD) maximum value during the Titration Period was 1.2 (1.42). The majority (363/410 [97%]) of ALO-02 subjects had a maximum COWS score <5 (no withdrawal); 12 (3%) had a maximum COWS score 5-12 (mild withdrawal), and no subject had a maximum COWS score  $\geq 13$  (moderate withdrawal).

- Double-blind Period: Mean (SD) COWS scores were similar for the placebo and study drug groups at BL (0.6 [0.85] and 0.4 [0.73], respectively) and remained relatively constant ( $\pm 0.1$ ) throughout the DB Treatment Period, with a maximum mean change from baseline of 0.9 for the placebo group and 0.9 for the drug-treated group. The mean (SD) change from BL to post-treatment week 2 was -0.1 (1.12) for placebo and 0.7 (1.83) for drug-treated group. No notable differences were reported compared to placebo. The maximum COWS score for nearly all subjects in both treatment groups remained  $<5$  (ALO-02 group, 133 [95%] subjects; placebo group, 123 [98%] subjects). In the ALO-02 group, 7 (5.0%) subjects had a maximum COWS score of mild. In the placebo group, 2 (1.6%) subjects had a maximum COWS score of mild and 1 (0.8%) subject in the placebo group (10591008) had a maximum score of 14 (moderate) previously discussed in the Opioid Withdrawal section of this review. During the first two weeks of the Double-Blind Treatment Period, the proportion of subjects in the placebo group with a COWS score  $<5$  remained 99%.
- Post-Treatment Period: All placebo subjects (94 [100.0%]) and nearly all ALO-02 subjects (104 [96.3%]) had a maximum score of  $<5$ .

It should be noted that for Study 1002, missing COWS scores were a protocol violation and was observed with a frequency during the OLT Period for ALO-02 not randomized to DB in 15/129 (12%), for those randomized to ALO-02 (44/147 (30%)), and those randomized to placebo 38/134 (28%).

Study B4531001: Clinical opioid withdrawal was assessed by the COWS and SOWS at baseline, end of every clinic visit or at the unscheduled visits, and at the end of study visit.

*Results*: The majority of ALO-02 subjects (342) [87%] had a maximum COWS score mild (COWS score  $<5$ ), 52 (13.2%) had a COWS score consistent with mild withdrawal (COWS score 5-12), and 1 (0.3%) subject had a COWS score consistent with moderately severe (COWS score 25-36). Subject 0027-0004 had a COWS score of 33 at the end of treatment visit after not taking ALO-02 for 5 days (subject discussed under Opioid Withdrawal section of this review).

The change from baseline in mean total scores was minimal throughout the study with a magnitude of change from -0.2 to 0.4. The median change was 0 at all visits. There were no notable differences among average daily dose groups in change from baseline in mean total score COWS. Findings are summarized in Table 40, below.

**Table 40. Clinical Opiate Withdrawal Scale Total Score (Safety Population) Study 1001**

Category	Average Daily Dose				Total
	10-40 mg	>40-80 mg	>80-120 mg	>120 mg	
Maximum Score	(N=129)	(N=155)	(N=58)	(N=43)	(N=395)
<Mild withdrawal (score 0-4)	120 (93.0)	127 (81.9)	47 (81.0)	38 (88.4)	342 (86.6)
Mild withdrawal (score 5-12)	9 (7.0)	27 (17.4)	11 (19.0)	5 (11.6)	52 (13.2)
Moderate withdrawal (score 13-24)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderately severe withdrawal (score 25-36)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)
Severe withdrawal (score >36)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = the number of subjects with non-missing values at the specified visit.

(CSR, 1001, p 93)

**SOWS scores:** The SOWS contains 16 symptoms of opiate withdrawal rated by the subject. Subjects were instructed to rate each symptom on a scale of 0 to 4 (0= not at all, 1 = a little, 2= moderately, 3= quite a bit, 4 = extremely) based on how they were feeling at the time of testing. The sum of the scores on each item was the total SOWS score. The minimum possible SOWS score was 0, the maximum 64. SOWS was completed daily by subjects during the taper periods.

**Study 1002:** For the Open-Label Titration Period, the mean (SD) SOWS score at Screening was 4.1 (4.92). Throughout the Open-Label Titration Period, SOWS scores were reduced compared to Screening. The mean (SD) maximum change from Screening at any time point during the Open-Label Titration Period was 0.7 (5.51). For the Double-Blind Treatment Period, mean (SD) Randomization Baseline SOWS scores were 2.4 (3.88) for the placebo group, and 1.5 (2.20) for the ALO-02 group. The mean (SD) maximum change from Randomization Baseline during the first 2 weeks was 3.9 (5.86) for the placebo group and 2.9 (4.27) for the ALO-02 group; the mean (SD) maximum change from Randomization Baseline at any time point during the Double-Blind Treatment Period was 4.3 (5.82) for the placebo group and 3.7 (5.14) for the ALO-02 group. At Post-Treatment Week 2, SOWS scores remained increased from Randomization Baseline: mean (SD) changes at Post-Treatment Week 2 for the placebo and ALO-02 groups 0.2 (4.49) and 1.0 (3.35), respectively.

**Study 1001:** At baseline, the mean SOWS total score was 5.4. Mean scores decreased after baseline and the magnitude of the change ranged from -0.8 to -3.0. There were no consistent trends in mean values by dose group or study visit.

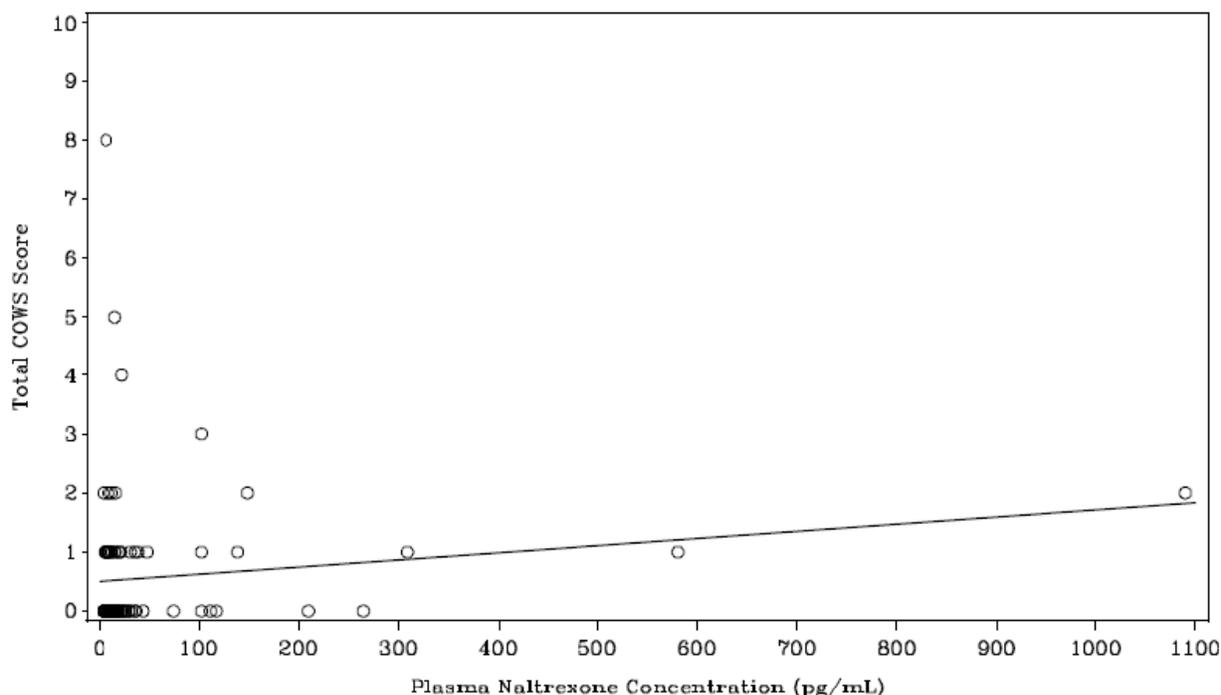
**COWS and Naltrexone/Naltrexol Exposures**

To evaluate the clinical effects of naltrexone and 6-β-naltrexol exposures on withdrawal symptoms, the Applicant conducted a correlation analysis between the observed naltrexone and 6-β-naltrexol concentrations and the time-matched COWS scores in Studies B4531001 and B4531002.

The Applicant found no apparent relationship between naltrexone exposure and total COWS scores in either of these studies.

For Study 1002, as shown in Figure 18 below, the regression analysis revealed  $R^2=0.0184$  which suggests no apparent relationship between naltrexone exposure and total COWS scores.

**Figure 18. Time-matched Correlation of Plasma Naltrexone Concentration (pg/mL) and Total COWS Score Study 1002**



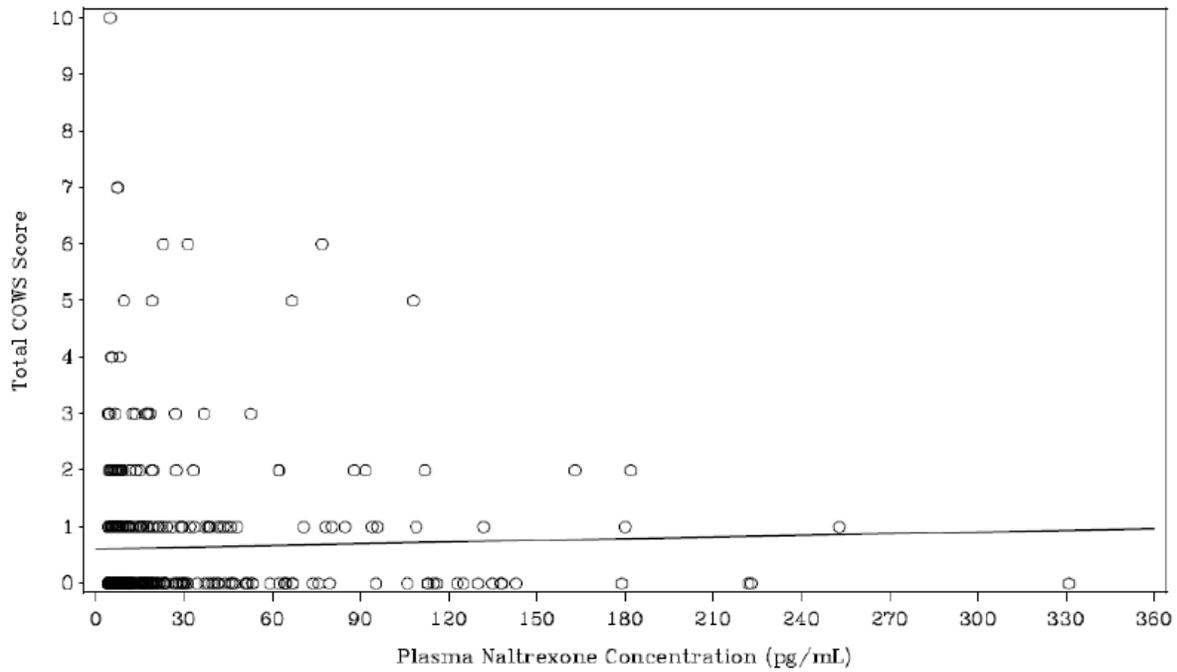
Regression Equation: Total COWS Score = 0.5034 + 0.0012 \* Plasma Naltrexone Concentration (pg/mL).  
R-square = 0.0184.

Time-matched values include concentration and COWS score values from the same visit.

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Figure 19, below, shows  $R^2=0.0010$  for Study 1001 which suggests no apparent relationship between naltrexone exposure and Total COWS score.

**Figure 19. Time-Matched Correlation of Plasma Naltrexone Concentration (pg/mL) and Total COWS Score Study 1001**



Regression Equation: Total COWS Score = 0.6038 + 0.0010 \* Plasma Naltrexone Concentration (pg/mL).

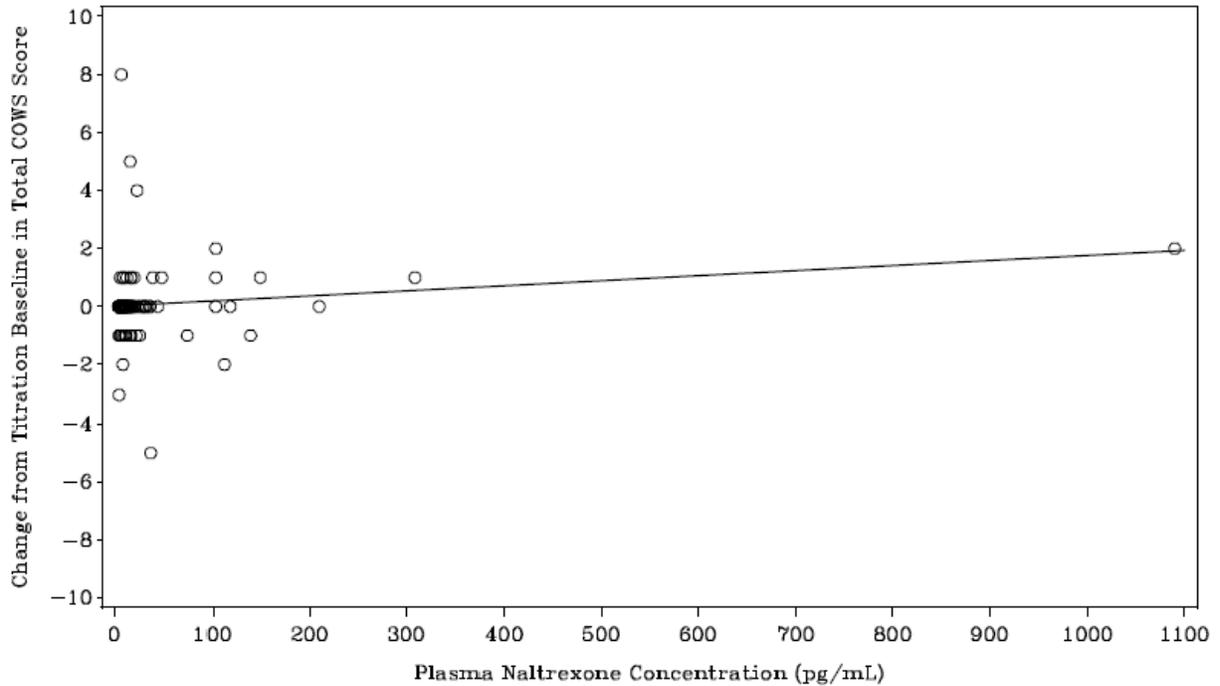
R-square = 0.0010.

Time-matched values include concentration and COWS score values from the same visit.

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Likewise, there was no apparent relationship between naltrexone exposure and change from baseline COWS scores in either of these studies, as shown in Figure 20 for Study 1002 with an  $R^2=0.0224$  and Figure 21 for Study 1001 which shows an  $R^2=0.0000$ .

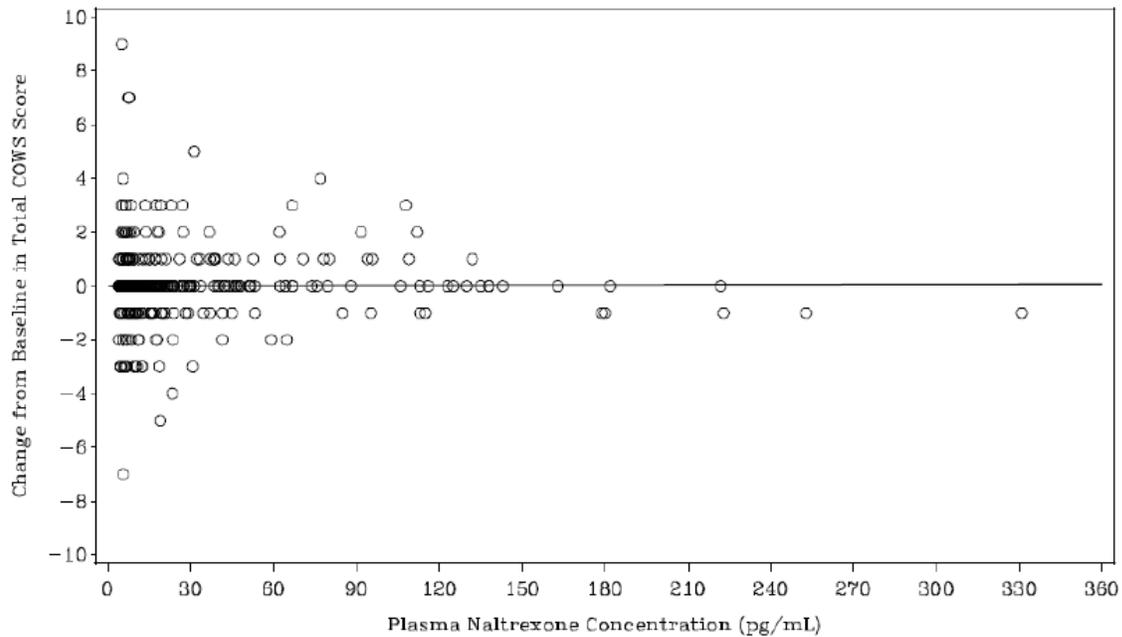
**Figure 20. Time-Matched Correlation of Plasma Naltrexone Concentration (pg/mL) and Change from Titration Baseline in Total COWS Score Study 1002**



Regression Equation: Change from Titration Baseline in Total COWS Score =  $-0.0047 + 0.0018 * \text{Plasma Naltrexone Concentration (pg/mL)}$ .  
R-square = 0.0224.  
Time-matched values include concentration and COWS score values from the same visit.

(ISS, p. 196)

**Figure 21. Time-Matched Correlation of Plasma Naltrexone Concentration (pg/mL) and Change from Baseline in Total COWS Score Study 1001**



Regression Equation: Change from Baseline in Total COWS Score = 0.0229 + 0.0001 \* Plasma Naltrexone Concentration (pg/mL).  
R-square = 0.0000.  
Time-matched values include concentration and COWS score values from the same visit.

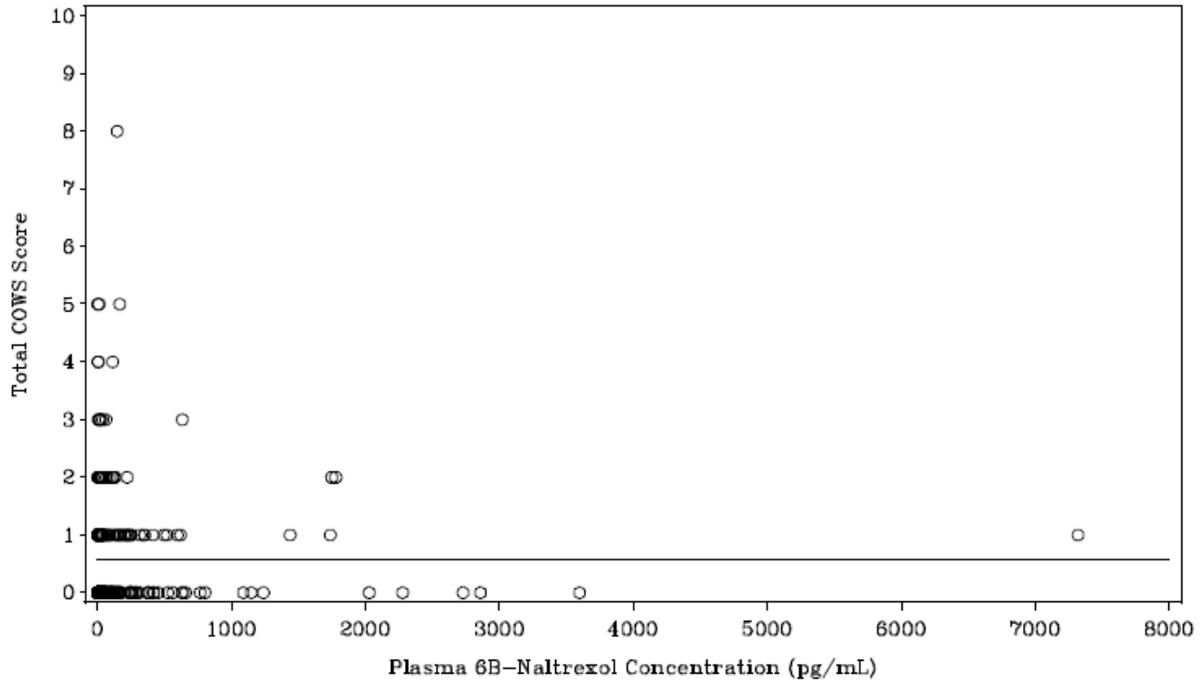
(ISS, p. 195)

### COWS and Naltrexol Exposure

There was apparent lack of relationship between 6-β-naltrexol concentrations and Total COWS scores or change from baseline COWS scores in either of the Phase 3 studies.

Total COWS scores showed no relationship to 6-B-naltrexol concentration with a  $R^2=0.0000$  for Study B4531002 shown in Figure 22 below and for Study 1001,  $R^2=0.0020$  showing lack of relationship between these two variables as seen in Figure 23.

**Figure 22. Time-matched Correlation of Plasma Naltrexol Concentration (pg/mL) and Total COWS Score Study (Study 1002)**

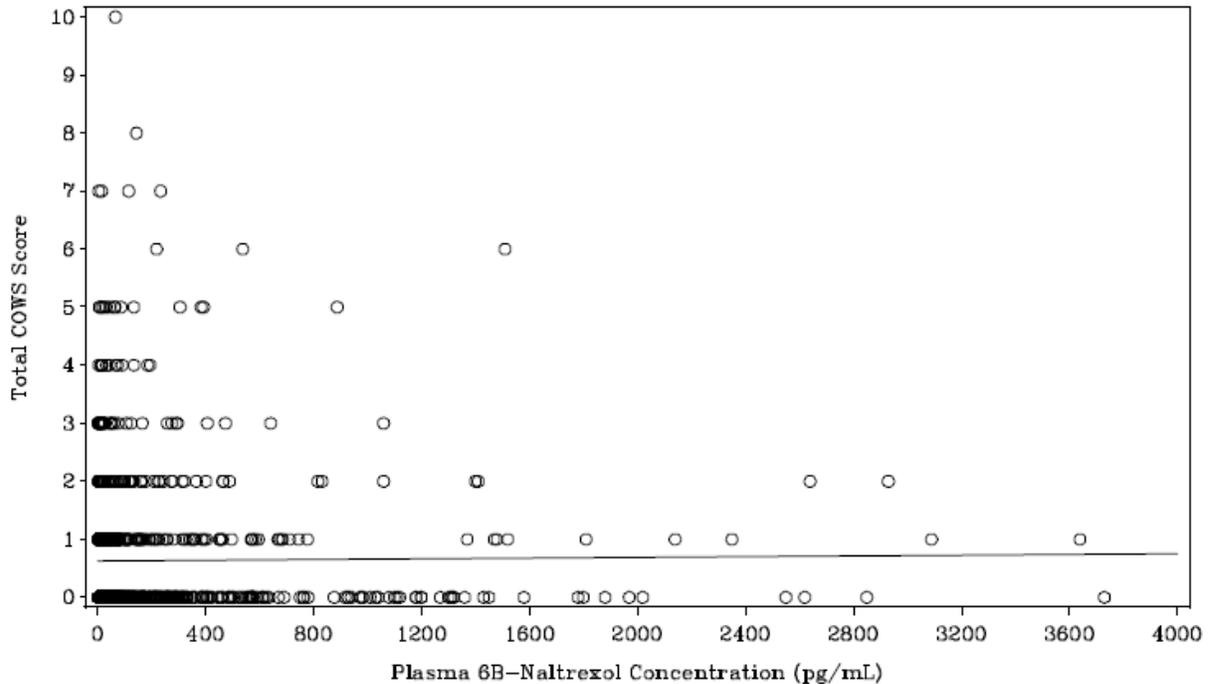


Regression Equation: Total COWS Score = 0.5578 + 0.0000 \* Plasma 6B-Naltrexol Concentration (pg/mL).  
R-square = 0.0000.

Time-matched values include concentration and COWS score values from the same visit.

(ISS, p. 710)

**Figure 23. Time-matched Correlation of Plasma Naltrexol Concentration (pg/mL) and Total COWS Score Study (Study 1001)**



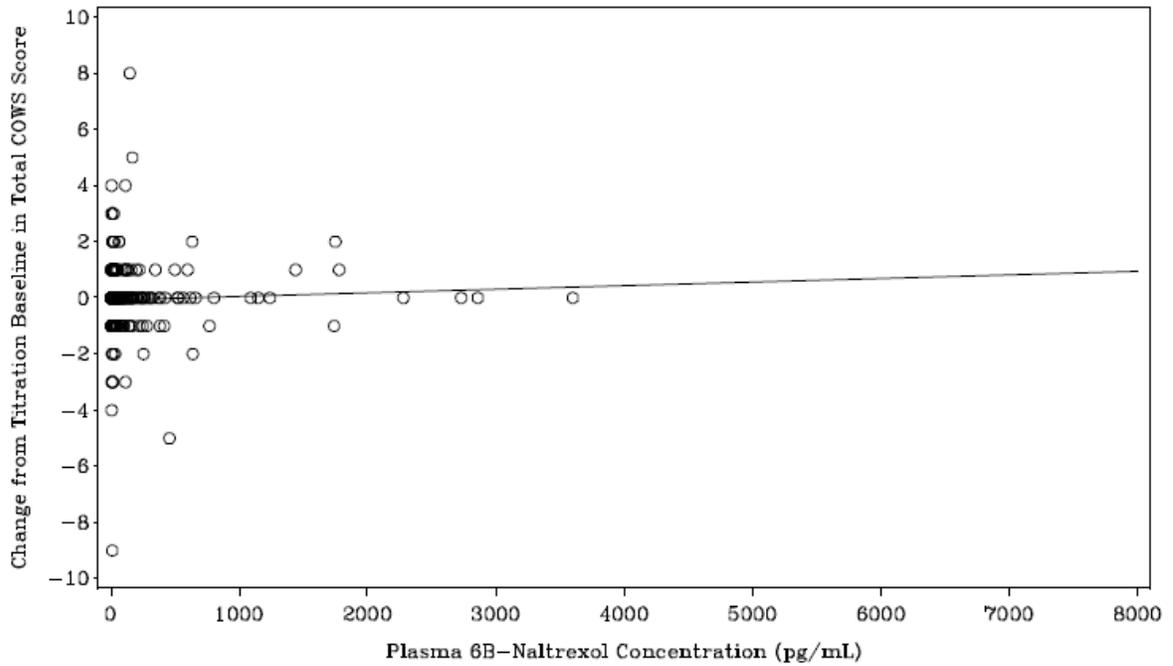
Regression Equation: Total COWS Score = 0.6105 + 0.0001 \* Plasma 6B-Naltrexol Concentration (pg/mL).  
R-square = 0.0020.

Time-matched values include concentration and COWS score values from the same visit.

(ISS, p. 714)

A similar apparent lack of relationship between 6-β-naltrexol concentrations and change from baseline COWS scores in either of these studies was also noted with  $R^2=0.0018$  for Study B4531002 and  $R^2=0.0005$  for Study B4531001 shown in Figures 24 and 25, below.

**Figure 24. Time-Matched Correlation of Plasma Naltrexol Concentration (pg/mL) and Change from Titration Baseline in Total COWS Score Study 1002**



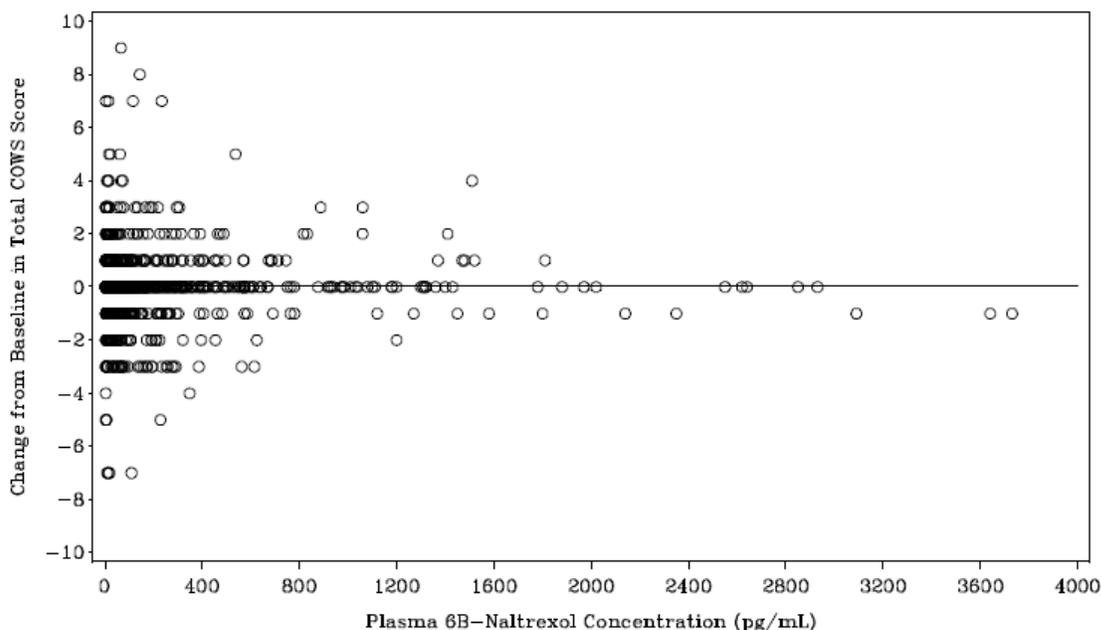
Regression Equation: Change from Titration Baseline in Total COWS Score =  $-.0898 + 0.0001 \times \text{Plasma 6B-Naltrexol Concentration (pg/mL)}$ .

R-square = 0.0018.

Time-matched values include concentration and COWS score values from the same visit.

(ISS, p. 711)

**Figure 25. Time-Matched Correlation of Plasma Naltrexol Concentration (pg/mL) and Change from Titration Baseline in Total COWS Score Study 1001**



Regression Equation: Change from Baseline in Total COWS Score =  $-.0016 + 0.0001 * \text{Plasma 6B-Naltrexol Concentration (pg/mL)}$ .  
R-square = 0.0005.  
Time-matched values include concentration and COWS score values from the same visit.

(ISS, p715)

### Applicant's Conclusions (COWS Scores)

- There was no apparent relationship between naltrexone or 6-β-naltrexol exposure and total COWS scores or change in COWS score

### Reviewer's Conclusions:

- I agree with the Applicant that there appeared to be no clinically important relationship between COWS scores and naltrexone/naltrexol levels. Most COWS scores were mild in both Phase 3 studies.

### III) Cases of Opioid Withdrawal (OW)

The terms, *opioid withdrawal*, *drug withdrawal*, and *drug withdrawal syndrome* may be used interchangeably in this section of the review. Because Troxyca ER contains 12% sequestered naltrexone, the potential exists for systemic exposure and resultant opioid antagonist AEs, such as opioid withdrawal. Therefore, considerable attention was focused on the safety findings related to opioid withdrawal.

In the Phase 3 studies, the Applicant's criteria for opioid withdrawal were 1) those cases identified by Investigator based upon withdrawal SMQ which includes the preferred

terms of Drug withdrawal convulsions; Drug withdrawal headache; Rebound effect; Drug withdrawal maintenance therapy; Drug withdrawal syndrome; Drug withdrawal syndrome neonatal; Drug rehabilitation; Steroid withdrawal syndrome; Withdrawal arrhythmia; and Withdrawal syndrome and/or 2) COWS score  $\geq 13$ . This section of the review summarizes the key findings regarding OW from the Phase 3 studies. I agree with the Applicant's criteria for determination of opioid withdrawal.

This review is based upon the findings in the original submission as well information supplied by the Applicant in response to an IR from the Agency to provide additional information regarding the opioid withdrawal events. As a result, this review differs somewhat from the Applicant's findings as reported in the individual study reports, CSR, and ISS. These differences are noted in the review when appropriate.

Study 1002 OW Cases: A total of 10 of 410 (2%) subjects met at least one of the criteria for opioid withdrawal TEAE (i.e., eight subjects were identified by the Investigator, one subject had a COWS score  $\geq 13$ , and one subject was initially miscoded as Tramadol withdrawal but it was subsequently determined that the subject had not been on Tramadol so the case was included in this review as an OW due to ALO-02). Therefore, although the Applicant identified nine subjects who met at least one criteria for OW as experiencing 10 events of OW (one subject [10151006] experienced two OW events), I have identified 10 subjects who experienced 11 OW events. Nine events occurred in the ALO-02 treatment arm and two in the placebo treatment arm. For those placebo subjects, the OW occurred during the two-week DB taper period from ALO-02 to placebo.

During the first 2 weeks of the Double-Blind Treatment Period, to avoid opioid withdrawal signs and symptoms a subject randomized to receive placebo underwent a double-blind gradual taper from the last ALO-02 dose identified from the Open-Label Conversion and Titration Period to placebo treatment. After completion of the double-blind gradual taper, a subject randomized to the placebo treatment arm continued with placebo treatment for the remaining 10 weeks of this period. A subject randomized to the ALO-02 treatment arm underwent a dummy taper to maintain the study blind, though continued to receive ALO-02 during these 2 weeks.

Of the 11 events, five occurred during OL titration period when all subjects were receiving ALO-02 and six events occurred during Maintenance Phase (two in placebo; four in ALO-02).

*Opioid Withdrawal and Demographics:* Of the 10 subjects who experienced OW, five were males and five were females with five were  $\geq 50$  years. Prestudy opioids included single or a combination of the following: Oxycontin (three subjects), Hydrocodone/APAP (Procet) two subjects; oxycodone two subjects; oxycocet (Percocet) two subjects; hydromorphone (Dilaudid) one subject, and no prior opioids two subjects.

*Opioid Withdrawal and Naltrexone/Naltrexol Levels:* Four subjects had BLQ (denoted as 0) naltrexone levels with the remainder having relatively low levels of naltrexone. Only one subject (10151006) who experienced OW had a naltrexone level >100 (139) and 6-β-naltrexol level >1000 (1,740). This subject experienced two OW events. This subject was discontinued due to a protocol violation (positive cannabinoids) so there may have been other unknown factors which affected the naltrexone/naltrexol levels in this subject. Further, the OW occurred during times in which it may be expected (i.e., during conversion and during taper) so it is unlikely (or at least indeterminate) that the OW occurred solely as a result of elevated naltrexone/naltrexol.

Nine of the ten subjects who experienced OW discontinued the study, but only three (10171003, 10171004, 10591008) of the subject discontinuations were due to AEs possibly related to OW. Most subjects only had one naltrexone/naltrexol level available (reported) but in some cases, two results at more than one time point were available. Table 42 below summarizes the key information related to subjects who experienced OW during Study 1002.

**Table 41. OW Events Study 1002**

Subject ID	Age/ Sex	Onset Phase	TDD mg	NTX (pg/mL)	6-β	COWS SOWS	Causality of OW
10041014	53/F	M	140	9.1	223	11 6	Day 7 DB Taper Post treatment Period
10151006 Event 1	50/F	OL	60	NR	NR	9 34	Day 2 OL Conversion
10151006 Event 2	--	M	160	139	1740	5 19	Day 4 DB Taper Post treatment Period
10561011	56/ F	OL	60	5	162	NR	Day 54 DB (Investigator error; drug not administered for 2 days)
10171003	47/M	M	120	0	45.4		Day 3 DB noncompliance
10661006	69/M	M	60	0	47.1	0 0	Day 30 DB noncompliance
10051005	51/F	OL	160	4.31	50	1 7	Day 25 OL stable dose
10151010	60/M	OL	0	NR	NR	0 17	Day 7 OL dose interruption
10491003 [Tramadol]	44/M	OL	60	NR	NR	7 24	Day 6 OL conversion
10171004 [Placebo]	39/F	M	160	0	122	4 27	Day 8 DB Taper
10591008 [Placebo]	57/M	M	120	0	6.68	14 NR	Day 5 DB Taper

(Reviewer); NR=not reported; NTX=naltrexone; 6-β=6β naltrexol; TDD=Total Daily Dose; mg=milligram; COWS=Clinical Opiate Withdrawal Scale Score; SOWS=Subject Opiate Withdrawal Scale Score

*Narratives OW Cases:* All narratives for OW cases were reviewed. Only one subject (Subject 10051005) met the criteria of experiencing OW while on a stable dose of ALO-02. Although the Applicant initially reported that Subject 10151010 also met this criteria, updated information in response to an IR revealed that this subject had a dosing interruption. The detailed narrative for Subject 10051005 is presented below:

- Subject 10051005: 51 year old female was on pre-study opioid analgesics of oxycodone hydrochloride (OxyContin) 160 mg total daily dose and hydromorphone hydrochloride (Dilaudid) 8 mg as needed. On 10/30/12 (OL Study Day 1) the subject began a starting dose of ALO-02 of 160 mg total daily dose (TDD). On 11/23/12 (Study Day 25) of the Open-Label Titration Period, while receiving ALO-02 160 mg total daily dose, the subject experienced withdrawal syndrome of moderate severity with symptoms of abdominal pain, hot flush, and rhinorrhea, all of moderate severity and related to study drug in the opinion of the investigator. There was no use of rescue. Concomitant medications included zolpidem tartrate, lubiprostone, fexofenadine HCL, oxymetazoline HCL, and dextromethorphan HBr/doxylamine succinate/paracetamol (Nyquil). Past and current medical history was significant for multiple musculoskeletal diagnoses. The subject had been randomized to placebo and began blinded placebo therapy on 11/27/12 (DB Study Day 1) with ALO-02 taper. The subject was discontinued from the study on 12/7/12 (DB Study Day 11) of the Double-Blind Treatment Period due to insufficient clinical response. On that day, COWS total score was 1 and the SOWS total score was 7. The subject recovered from the event withdrawal syndrome on 12/11/12 (Study Day 43). *Reviewer's comment: The AE of OW occurred while on a stable dose of ALO-02 from 10/30/12-11/27/12. The onset of OW is within a two-three week period when, clinically, OW symptoms are most likely to occur if subjects are receiving "inadequate" doses of opioid. The most likely explanation for this is that the subject was started on too low a conversion or the dosing should have been increased during the OL conversion period. Naltrexone exposure may, however, have been a contributor and cannot be ruled out.*

*Study 1001 OW Cases:* Five (1.0%) subjects overall had TEAEs of drug withdrawal syndrome (four coded by the Investigator as Drug Withdrawal or Drug Withdrawal Syndrome and one with COWS≥13). All subjects had a reason for opioid withdrawal due to conversion (one subject), tapering (one subject), or dose interruption (three subjects).

One subject required treatment with hydrocodone/APAP prn to manage the OW symptoms but otherwise, no intervention or treatment for the OW symptoms was required in the other cases. Most cases were mild (based on COWS scores). Naltrexone was Below Level of Quantification (<4 pg/mL) in three of the five cases and low (28.2 and 22.3 pg/mL) in the other two cases, suggesting that there was no correlation between naltrexone level and onset of OW.

Of the five subjects who experienced OW, all were males, ages 49-63 years. All were on prestudy opioids except one. There were otherwise no trends. There were no deaths or SAEs due to OW. A total of four of the five subjects who experienced OW discontinued for the following reasons: one due to the AE of OW, two subjects “withdrew consent”, and one subject discontinued due to AE of constipation. One subject who experienced OW completed the study. See Table 43 for further discussion of the OW events.

**Table 42. OW Events Study 1001**

Subject ID	Age/ Sex	Onset Phase	TDD mg	NTX pg/ml	6-β pg/ml	COWS SOWS	Causality
0003-0015	49/M	LTM	86	28.2	266	6 30	Day 379 Taper at end of Post Treatment Period
0017-0013	62/M	M	60	BLQ	16.6	5 1	Dosing interrupted
0027-0004	51/M	M	100	BLQ	BLQ	33 39	Noncompliance
0031-0010	63/M	OL	80	BLQ	20.2	0 37	Day 2 OL conversion
0021-0009	59/M	LTM	160	22.3	62.4	0 5	Day 311 dosing interrupted

(Reviewer); BLQ=Below Limit Quantification (<4.00 pg/mL); NTX=naltrexone; 6-B=naltrexol; M=Maintenance Phase; LTM=Long-Term Maintenance Phase

Note that the naltrexone and 6-β-naltrexol concentrations were taken around the time of each withdrawal event (not on the day of event) as listed below in the table. In most of events, the naltrexone concentrations are BLQ or lower. The highest naltrexone concentration was 139 pg/mL and the highest 6-β-naltrexol concentration was 1,740 pg/mL. Two subjects (10221015 and 10271011) in the study B4531002 who had concentrations >500 pg/mL did not experience opioid withdrawal and COWS scores for these subjects were ≤2 at each time point.

Pooled OW Cases

In the pooled studies, a total of 6/805 (2%) subjects experienced OW during the Titration Phase, 6/436 (1%) during the Maintenance Phase ALO-02 treated compared to 2/134 (1%) placebo, and 2/213 (1%) during the Long-Term Maintenance Phase. One subject who experienced two OW events was counted separately in each phase in which an OW event occurred. These findings are summarized in Table 44.

**Table 43. OW Events by Treatment Phase Pooled Phase 3 Studies**

Study	Titration Phase Pooled ALO-02 N=805	Maintenance Phase Pooled ALO-02 N=436	Maintenance Phase Placebo N=134	Long-term Maintenance N=213
1001 OW Subjects	1	2	N/A	2
1002 OW Subjects	5	4	2	N/A
Total Subjects OW	6 (<1%)	6 (1%)	2 (1%)	2 (1%)

(Reviewer); N/A=not applicable since Study 1002 did not include a long-term maintenance phase. Total percentages represent subjects. One subject experienced two events so was counted in each phase where the event occurred.

As shown below in Table 45, the naltrexone and naltrexol levels were drawn as close as possible to the onset of the OW but usually not on the same day.

**Table 44. Naltrexone and Naltrexol Levels in Relation to OW Onset**

Study	Subject ID	Date of Withdrawal or COWS Score $\geq 13$	Date the Naltrexone or 6- $\beta$ samples obtained	Naltrexone 6- $\beta$ -naltrexol (pg/mL)
B4531001	0003-0015	17 Apr 2012	02 Apr 2012	28.2 266
	0017-0013	22 Jul 2011	21 Jul 2011	BLQ 16.6
	0021-0009	03 Mar 2012	08 Mar 2012	22.3 62.4
	0027-0004	05 Jul 2011	5 Jul 2011	BLQ BLQ
	0031-0010	13 Apr 2011	19 Apr 2011	BLQ 20.2
	10481003	22 Dec 2012	27 Dec 2012	0 36.3

B4531002	10041014	19 Feb 2013	12 Feb 2013	BLQ 33.7	
	10051005	23 Nov 2012	27 Nov 2012	4.3 50	
	10151006	26 Oct 2012		Not available	
		13 Jan 2013	04 Jan 2013	139 1740	
	10151010	16 Jan 2013		Not available	
	10171003	19 Sep 2012	12 Sep 2012		BLQ 45
			19 Sep 2012		6.9 149
	10171004	21 Sep 2012	14 Sep 2012		BLQ 122
	10561011	01 Mar 2013	19 Feb 2013		5 162
	10591008	08 Oct 2012	04 Oct 2012		BLQ 6.7
10661006	25 Oct 2012	25 Oct 2012)		BLQ 47.1	

(Dr. Suresh Narihariseti, Clinical Pharmacolgy Reviewer)

**Other OW Assessments:** In addition to the data submitted in the NDA review, I conducted a JMP analysis for  $\geq$  three DSM (Diagnostic and Statistical Manual) V terms occurring in the same subject on the same date. The DSM V terms used in the search are listed below:

- Depression
- Nausea
- Vomiting
- Muscle aches [Myalgia]
- Lacrimation increased
- Rhinorrhea [can also be spelled rhinorrhoea]
- Pupillary dilation
- Piloerection
- Sweating
- Diarrhea [can also be spelled diarrhoea]
- Yawning
- Fever [Pyrexia]
- Insomnia

This analysis revealed no new definite or probable cases of OW since most of the terms occurring on the same date were GI-related nausea, vomiting, or diarrhea. Given the

high incidence of occurrence of these isolated terms, it is problematic to conclude that these terms, even when they occur on the same date, are due to OW.

**Applicant's Conclusions Opioid Withdrawal:**

- The majority of withdrawal events occurred during study medication dosage adjustment
- Plasma concentrations of naltrexone and naltrexol taken around the time of each withdrawal event demonstrated that the highest naltrexone concentration was 139 pg/mL and 6- $\beta$ -naltrexol concentration was 1,740 pg/mL. Events of withdrawal were not associated with naltrexone exposure at these highest doses.

**Reviewer's OW Conclusions:** In general I agree with the Applicant's conclusions.

- The total number of subjects and events with OW in this review differ from the Applicant's due to my inclusion of one subject who was originally coded as experiencing Tramadol withdrawal when it was later determined that the subject had erroneously stated in the diary that he was on Tramadol but was not.
- Most cases of opioid withdrawal in ALO-02-treated patients occurred during times of transition (i.e., when there was a change in ALO-02 dosing as subjects were being converted, tapered, or dosing was interrupted).
- In the pooled studies, a total of 6/805 (2%) subjects experienced OW during the Titration Phase, 6/436 (1%) during the Maintenance Phase ALO-02 treated compared to 2/134 (1%) placebo, and 2/213 (1%) during the Long-Term Maintenance Phase. One subject who experienced two OW events was counted separately in each phase in which an OW event occurred.
- I found no evidence that any particular concentration of naltrexone or naltrexol resulted in OW.

In addition to the above submission specific analyses of AEs, the Applicant also conducted an additional analysis for Study 1002 for the Double-Blind safety population where they specifically reviewed Clusters of the following SMQ terms: Drug abuse and dependence, Drug Withdrawal, and Respiratory Failure. Overall, they identified no unexpected findings and the findings were consistent with the events already captured by other safety analyses previously discussed.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Controlled Study 1002: In the controlled study, of the 410 subjects enrolled in the Open-Label Titration Period, the most common preferred term TEAEs were nausea, constipation, and vomiting all of which are expected AEs with opioid use. More subjects experienced AEs during the Open-Label period than Double-Blind period, possibly due to the conversion and titration as subjects were being switched from incoming opioids.

During the Double-Blind Treatment Period, slightly more subjects in the ALO-02 group experienced TEAEs compared with subjects in the placebo group, as would be expected, but the incidence was similar between both groups. As with the open-label period, the most common TEAEs in the Double-Blind for both placebo and ALO-02 were GI-related nausea, vomiting, diarrhea, and constipation. Nausea occurred in the ALO-02 group almost four times as frequently as in placebo and vomiting occurring almost twice as frequently in study drug compared to placebo. Aside from GI-related AEs, other AEs of interest which occurred more frequently in study drug than placebo included hyperhidrosis, withdrawal syndrome, and oropharyngeal pain. Hyperhidrosis may be seen with opioid withdrawal. The clinical significance of the higher incidence of oropharyngeal pain in ALO-02 compared to placebo is unclear. The Applicant's results in Table x, below, were confirmed internally using JMP analysis.

All causality TEAEs occurring in  $\geq 2\%$  of subjects during any Treatment Period are shown below in Table 46.

**Table 45. SOC and Preferred Term TEAEs Occurring in ≥2% of Subjects During any Treatment Period (Study 1002)**

MedDRA SOC Preferred Term	Open-Label Titration Period	Double-Blind Treatment Period (Double-Blind Safety Population)	
	(Titration Period Safety Population)		
	ALO-02 N=410 n (%)	Placebo N=134 n (%)	ALO-02 N=146 n (%)
<b>Subjects with at least one TEAE</b>	<b>258 (62.9)</b>	<b>75 (56.0)</b>	<b>83 (56.8)</b>
<b>Gastrointestinal disorders</b>	<b>156 (38.0)</b>	<b>23 (17.2)</b>	<b>34 (23.3)</b>
Abdominal pain upper	5 (1.2)	4 (3.0)	0 (0.0)
Constipation	61 (14.9)	3 (2.2)	5 (3.4)
Diarrhea	9 (2.2)	6 (4.5)	8 (5.5)
Dry mouth	13 (3.2)	0 (0.0)	0 (0.0)
Nausea	84 (20.5)	5 (3.7)	21 (14.4)
Vomiting	37 (9.0)	4 (3.0)	9 (6.2)
<b>General disorders and administration site conditions</b>	<b>36 (8.8)</b>	<b>6 (4.5)</b>	<b>17 (11.6)</b>
Edema peripheral	3 (0.7)	1 (0.7)	3 (2.1)
Fatigue	13 (3.2)	1 (0.7)	5 (3.4)
<b>Infections and infestations</b>	<b>54 (13.2)</b>	<b>27 (20.1)</b>	<b>26 (17.8)</b>
Gastroenteritis viral	2 (0.5)	2 (1.5)	3 (2.1)
Influenza	6 (1.5)	3 (2.2)	5 (3.4)
Nasopharyngitis	13 (3.2)	6 (4.5)	7 (4.8)
Upper respiratory tract infection	11 (2.7)	6 (4.5)	3 (2.1)
Urinary tract infection	3 (0.7)	3 (2.2)	2 (1.4)
<b>Injury, poisoning, and procedural complications</b>	<b>11 (2.7)</b>	<b>12 (9.0)</b>	<b>6 (4.1)</b>
<b>Investigations</b>	<b>4 (1.0)</b>	<b>7 (5.2)</b>	<b>6 (4.1)</b>
<b>Metabolism and nutrition disorders</b>	<b>10 (2.4)</b>	<b>1 (0.7)</b>	<b>4 (2.7)</b>
<b>Musculoskeletal and connective tissue disorders</b>	<b>24 (5.9)</b>	<b>13 (9.7)</b>	<b>14 (9.6)</b>
Arthralgia	3 (0.7)	1 (0.7)	3 (2.1)
Back pain	5 (1.2)	8 (6.0)	3 (2.1)
Muscle spasms	1 (0.2)	1 (0.7)	4 (2.7)
<b>Nervous system disorders</b>	<b>90 (22.0)</b>	<b>10 (7.5)</b>	<b>15 (10.3)</b>
Dizziness	24 (5.9)	1 (0.7)	6 (4.1)
Headache	30 (7.3)	7 (5.2)	2 (1.4)
Hypoaesthesia	0 (0.0)	0 (0.0)	3 (2.1)
Somnolence	36 (8.8)	1 (0.7)	1 (0.7)
<b>Psychiatric disorders</b>	<b>25 (6.1)</b>	<b>11 (8.2)</b>	<b>8 (5.5)</b>
Anxiety	9 (2.2)	6 (4.5)	1 (0.7)
Depression	3 (0.7)	4 (3.0)	2 (1.4)
Insomnia	8 (2.0)	1 (0.7)	1 (0.7)
Withdrawal syndrome	3 (0.7)	1 (0.7)	4 (2.7)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>18 (4.4)</b>	<b>3 (2.2)</b>	<b>11 (7.5)</b>
Oropharyngeal pain	1 (0.2)	1 (0.7)	4 (2.7)
<b>Skin and subcutaneous tissue disorders</b>	<b>41 (10.0)</b>	<b>2 (1.5)</b>	<b>12 (8.2)</b>
Hyperhidrosis	8 (2.0)	1 (0.7)	4 (2.7)
Pruritus	26 (6.3)	0 (0.0)	2 (1.4)

Vascular disorders	13 (3.2)	4 (3.0)	4 (2.7)
Hot flush	10 (2.4)	3 (2.2)	2 (1.4)

Source: Tables 14.3.1.3.1 and 14.3.1.4.1.

TEAEs were defined as AEs that commenced on or after the start of ALO-02 administration for the Open-Label Titration Period but prior to the start of randomized double-blind study medication for the Double-Blind Treatment Period, including the Post-Treatment Period follow-up.

Adverse events were classified by SOC and PT as defined by the MedDRA, v16.1. If a subject had more than one AE that coded to the same PT, the subject was counted only once for that PT. Similarly, if a subject had more than one AE within a SOC, the subject was counted only once in that SOC.

Abbreviations: AE = adverse event; ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride extended-release capsule; n/N = number of subjects; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

(CSR, Study 1002, p. 137-138)

*Pooled:* The most frequent ( $\geq 5\%$ ) TEAEs in the Phase 3 studies for the Titration Phase were nausea, constipation, vomiting, somnolence, headache, and dizziness. The most frequent TEAE for the Maintenance Phase for the pooled ALO-02 treated subjects was nausea. In the long-term maintenance, nausea was again the most frequently occurring TEAE. Long-term maintenance for Weeks 19-Month 12 had a higher incidence of abdominal pain, constipation, diarrhea, and vomiting compared to the 18-week pooled Maintenance Phase. The significance of this observation is not clear as it relates to ALO-02, since the Long-term Maintenance Phase consisted of the open-label, uncontrolled Study 1001 and there is no placebo for comparison. There were no severe TEAEs reported with a frequency of  $\geq 5\%$  in the Titration or Maintenance Phases of the Phase 3 studies when evaluated as pooled, by either study, or by placebo.

Adverse drug reactions  $\geq 2\%$  which occurred during any treatment phase in ALO-02 treated subjects are shown in Table 47 below.

**Table 46. Adverse Reactions Reported in ≥2% of Subjects in any Phase of the ALO-02 Phase 3 Studies**

System Organ Class Adverse Drug Reaction (ADR)	Titration Phase Pooled TROXYCA ER (N=805) n (%)	Maintenance Phase Pooled TROXYCA ER (N=436) n (%)	Weeks 19-Month 12 (N=213) n (%)
<b>Gastrointestinal disorders</b>			
Abdominal pain <sup>a</sup>	30 (3.7)	11 (2.5)	9 (4.2)
Constipation	120 (14.9)	18 (4.1)	15 (7.0)
Diarrhoea	24 (3.0)	15 (3.4)	16 (7.5)
Dry mouth	21 (2.6)	0	1 (0.5)
Nausea	153 (19.0)	43 (9.9)	19 (8.9)
Vomiting	69 (8.6)	19 (4.4)	15 (7.0)
<b>General disorders and administration site conditions</b>			
Fatigue	37 (4.6)	11 (2.5)	8 (3.8)
Oedema peripheral	9 (1.1)	10 (2.3)	2 (0.9)
<b>Musculoskeletal and connective tissue disorders</b>			
Arthralgia	6 (0.7)	6 (1.4)	9 (4.2)
Back pain	14 (1.7)	6 (1.4)	13 (6.1)
Muscle spasms	5 (0.6)	5 (1.1)	5 (2.3)
<b>Nervous system disorders</b>			
Dizziness	47 (5.8)	14 (3.2)	7 (3.3)
Headache	67 (8.3)	5 (1.1)	6 (2.8)
Somnolence <sup>b</sup>	70 (8.7)	9 (2.1)	1 (0.5)
<b>Psychiatric disorders</b>			
Depression	6 (0.7)	5 (1.1)	7 (3.3)
Insomnia	17 (2.1)	3 (0.7)	9 (4.2)
Restlessness	5 (0.6)	1 (0.2)	6 (2.8)
<b>Respiratory, thoracic and mediastinal disorders</b>			
Cough	5 (0.6)	3 (0.7)	6 (2.8)
Oropharyngeal pain	3 (0.4)	6 (1.4)	5 (2.3)
<b>Skin and subcutaneous tissue disorders</b>			
Hyperhidrosis <sup>c</sup>	28 (3.5)	11 (2.5)	6 (2.8)
Pruritus <sup>d</sup>	47 (5.8)	4 (0.9)	1 (0.5)
<b>Vascular disorders</b>			
Hot flush <sup>e</sup>	21 (2.6)	5 (1.1)	5 (2.3)
a. Abdominal pain also includes Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, and Gastrointestinal pain. b. Somnolence also includes Sedation. c. Hyperhidrosis also includes Cold sweat. d. Pruritus also includes Pruritus generalised. e. Hot flush also includes Flushing.			

(Summary of Clinical Safety, p. 75)

Adverse reactions specific to this submission which are terms potentially related to opioid withdrawal include all of the above terms excluding fatigue, peripheral edema, headache, somnolence, dizziness, cough, and oropharyngeal pain. However, although these terms are associated with opioid withdrawal, they are also terms frequently seen with any opioid. Further, most of these terms occurred during the Titration Phase when dosing was being adjusted and some withdrawal symptoms may be expected to occur.

Based upon the safety data presented and reviewed, I conclude that the common TEAEs seen with ALO-02 are consistent with those typically associated with opioid use.

#### 7.4.2 Laboratory Findings

Common Laboratory Findings: For the Phase 3 studies, the laboratory test results were not pooled due to the difference in the laboratory data collection schemes between the studies. Laboratory data were summarized for each study and the changes from Screening Period were summarized descriptively by study visit and treatment, as applicable.

There were no clinically relevant changes in mean values during treatment, overall, or by treatment group to suggest a trend or signal in chemistry or hematology results in Studies 1002 or 1001.

Laboratory Abnormalities of Interest –Elevated Liver Function Tests (LFTS): The Revia label contains a Hepatotoxicity warning that “Cases of hepatitis and clinically significant liver dysfunction were observed in association with Revia exposure during the clinical development program and in the postmarketing period.” Given this information, I paid particular attention to identifying cases of elevated LFT’s since some patients did experience systemic exposure of naltrexone during the Phase 3 studies.

In the Phase 3 studies, there were five subjects who received ALO-02 and two who received placebo that experienced an AE of a possible drug-related hepatic disorder due to elevated transaminases. The seven cases are summarized below.

*Study 1002:* Four subjects experienced elevated LFTs, one during OL and three during DB. Of the three subjects who experienced elevated LFTs during the DB, two were in the placebo arm and one ALO-02. Narratives or brief summaries for these subjects were reviewed. In all of these cases, the LFTs (ALT and/or AST) were <3 times ULN (upper limit of normal). I could not determine whether the LFTs were transient in all cases as follow-up labs after the elevations were not provided for every subject. The highest ALT level was 2.6 xULN and the highest AST level was 2.9xULN. No subjects had associated elevated Total bilirubin and there were no Hy’s Law cases. One subject in the ALO-02 treatment arm (Subject 10391003) discontinued due to an AE of elevated LFT with ALT 101 (2.5xULN) and AST 49 (1.3xULN) on Study Day 86. There were no concomitant medications except multivitamins reported, although the subject did take rescue acetaminophen and IR oxycodone during the study. *Reviewer’s comment: Causality of elevated LFTs to study drug alone cannot be determined since rescue APAP and oxycodone IR were used.*

*Study 1001:* Three subjects experienced elevated LFTs. Two of these subjects experienced LFT’s >3xULN but causality to study drug alone could not be determined

due to confounders as subjects were on other medications that may have been contributory. The case which showed the highest elevated ALT (7xULN) and AST (5xULN) is summarized as follows: Subject 0001-0007, a 56-year-old male, had normal LFTs on 8/11/11 (Visit 9) and on 2/13/12 (Visit 15) had abnormal LFTs with ALT 286 (7xULN), AST 180 (5xULN) and total bilirubin 0.28 (normal). No labs were reported after Visit 15. The investigator coded this AE of elevated LFTs as mild, non-serious. A full narrative for this subject was not included in the CSR and the lab values were located in the individual laboratory line listings. The ISS (Integrated Summary of Safety) contained a brief summary which included additional information not included in the CSR. Concomitant medications were acetylsalicylic acid (aspirin), topical clobetasol (corticosteroid), co-diovan (valsartan/hydrochlorothiazide), and warfarin. *Reviewer's comment: Causality of the elevated LFTs to study drug cannot be ruled out, although the role of concomitant medications, including over-the-counter, in an open-label study must also be taken into consideration.*

### 7.4.3 Vital Signs

Notable changes in vital signs (heart rate, blood pressure, and respiratory rate) in the Phase 3 studies revealed no trends that could be determined to be solely related to ALO-02.

In the Maintenance Phases of Studies 1001 and 1002 and the Long-Term Maintenance Phase of Study 1001, for ALO-02 treated subjects, the most frequently occurring vital sign change was due to hypertension which occurred in <1% of subjects in Study 1001, 1% in Study 1002, and < 1% pooled. In the long-term Maintenance Phase in Study 1001, 2% of subjects experienced hypertension.

As shown in Table 48 below, in the Pooled studies, it is noted that incidences of increased blood pressure were greater in the placebo group than ALO-02 group. Heart rate values >120 (ranging from 122-128) occurred in four subjects (three subjects in the ALO-02 group and one in the pooled placebo group). No subjects reported a respiratory rate <10 breaths/min and one experienced respiratory rate >24.

**Table 47. Incidence of Vital Signs Results of Potential Clinical Significance Phase 3 Studies**

	ALO-02 Titration Phase N=797 n (%)	ALO-02 Maintenance Phase N=428 n (%)	Pooled Placebo N=134 n (%)
<b>Heart Rate (beats/min)</b>			
<40	0 (0.0%)	0 (0.0%)	0 (0.0%)
>120	2 (0.3%)	1 (0.2%)	1 (0.7%)
<b>Blood Pressure Value (mm Hg)</b>			
Systolic <90 and change ≤-30	0 (0.0%)	1 (0.2%)	2 (1.5%)
Systolic BP change ≥30	28 (3.5%)	21(4.9%)	11 (8.2%)
Diastolic BP <50 and change ≤-20	1 (0.1%)	1 (0.2%)	0 (0.0%)
Diastolic BP change ≥20	31 (3.9%)	21 (4.9%)	10 (7.5%)
<b>Respiration rate &lt;10 or &gt;24/min</b>	0 (0.0%)	1 (0.2%)	0 (0.0%)

Abbreviations: ALO-02=oxycodone HCl and naltrexone HCl ER capsules, min=minute; N=number of subjects evaluated against criteria; n=number of subjects that met criteria; BP=blood pressure.

Change from baseline, where baseline is defined as the last observation prior to dosing.

Titration Phase is programmed as first 6 weeks for Study B4531001 and defined by Study B4531002 (planned as 4-6 weeks). Maintenance Phase is programmed as weeks 7-18 for Study B4531001 and defined in Study B4531002 as Double Blind + Taper Phase.

(Applicant's table, ISS, p. 156)

#### 7.4.4 Electrocardiograms (ECGs)

In the Phase 3 studies, there were no clinically important findings in the mean change from baseline on ECGs overall.

#### 7.4.5 Special Safety Studies/Clinical Trials

The pharmacodynamics effects of oxycodone alone or in combination with naltrexone were assessed in five studies in 167 subjects including two studies (ALO-02-07-201 and ALO-02-09-2001) for determining the optimum ratio of naltrexone to oxycodone to mitigate abuse potential and three studies (B4531008 [oral] and B4531009 [intranasal] which used the final to-be-marketed formulation and study B4981002 [IV] abuse potential which used simulated crushed ALO-02 in non-dependent recreational drug users. The results from the Dose Ratio Studies supported the Applicant's selection of 12% naltrexone HCl ratio relative to oxycodone HCl dose in the ALO-02 formulation, (b) (4) These studies are discussed in further detail below and summarized in Table 49.

***1) Dose Ratio Studies:*** The key safety findings for the two dose ratio studies are summarized below. There were no unexpected safety findings, which were generally consistent with opioid-related AEs.

**Table 48. Major Safety Findings Dose Ratio Studies**

Study	Major Safety Findings
ALO-02-07-201	<p><u>Title/Design:</u> Randomized, Double-Blind, Cross-Over, Placebo-Controlled Trial Evaluating the Effect of Dose Ranging of Naltrexone on the Oxycodone-Induced Euphoria in Non-Dependent, Opiate-Experienced Subjects Under Fasting Conditions.</p> <p><u>Safety Results:</u> The treatment included five treatment periods with a single oral dose in each treatment period of oxycodone 60 mg + naltrexone in one of the following strengths: naltrexone 2.4 mg (4%), 4.8 mg (8%), 7.2 mg (12%), 12 mg (20%) or naltrexone placebo. The washout period between treatments was six to 14 days. Thirty healthy subjects (24 males and 6 females) aged 18-55 years with previous experience with opiates (defined as non-therapeutic use at least 10 times in the last 12 months at least once in the 12 weeks prior to screening) were enrolled. There were no deaths, non-fatal SAEs, or severe AEs. No subjects withdrew for safety reasons. The most common AEs following treatment of oxycodone with or without active doses of naltrexone were pruritus, somnolence, euphoric mood, vomiting, and nausea.</p>
ALO-02-09-2001	<p><u>Title/Design:</u> Randomized, Double-Blind, Double-Dummy, Six-Way, Crossover, Placebo-Controlled Trial Evaluating the Effect of a Dose Range of Naltrexone on Oxycodone-Induced Euphoria in Non-Dependent, Opioid-Experienced Subjects Under Fasting Conditions.</p> <p><u>Safety Results:</u> The Treatment Phase consisted of six 3-day inpatient treatment sessions in which subjects received one of the following: oxycodone 60 mg + naltrexone placebo; oxycodone placebo + naltrexone placebo; oxycodone 60 mg + naltrexone 7.2 mg (12%), 9.6 mg (16%), 12 mg (20%) or 14.4 mg (24%) in a randomized, double-blind, double-dummy manner. The safety population included 31 subjects (26 males and 5 females). No deaths or other SAEs occurred during the study. The most common AEs observed following treatment with oxycodone, with or without active doses of naltrexone, included pruritus, euphoric mood, somnolence, nausea, feeling hot, and dizziness. Overall, the incidence of these AEs declined with increasing doses of naltrexone, except for somnolence. Two subjects discontinued due to AE which included AEs terms of prostatitis in the oxycodon/naltrexone 12% group and high blood pressure in the oxycodone/naltrexone 16%. Both of these events were not likely due to study drug.</p>

(Table, reviewer)

**II) Human Abuse Potential Studies**

See Dr. Jim Tolliver’s CSS review for full discussion of the HAP studies.

The human abuse potential studies were single-dose, double-blind, cross-over, placebo and active-controlled studies in healthy, non-dependent, recreational opioid users. The primary objectives were to determine the relative abuse potential, safety, and tolerability of ALO-02 compared to IR oxycodone and placebo. The Applicant discussed the designs of the abuse potential studies with the Agency prior to initiation and incorporated the Agency’s Draft Guidance dated January 2013 into the designs with regard to endpoints, population, and statistical analysis.

The key safety findings for the HAP studies are summarized below in Table 50. There were no unexpected findings which were generally consistent with opioid-related AEs.

**Table 49. HAP (Human Abuse Potential) Studies Key Safety Findings**

<b>Study</b>	<b>Major Safety Findings</b>
B4531008 Oral Abuse Potential Study	There were no deaths or SAEs. Of the 32 subjects treated, fewer experienced AEs after administration of intact ALO-02 compared to crushed. The most common AEs with crushed product were euphoric mood, pruritus, somnolence, dizziness, nausea, feeling hot and fatigue. The most common TEAEs after dosing with intact ALO-02 60 mg/7.2 mg were pruritus, euphoric mood, somnolence, dizziness, headache, nausea, fatigue, and vomiting. One subject discontinued due to second degree AV block seen on Holter monitoring in the intact ALO-02 40 mg/4.8 mg group. He was otherwise asymptomatic for cardiac symptoms and was referred to the emergency department and advised to follow up with his physician. There is insufficient information in the narrative to rule out other causes for the AV block as the subject had an extensive history of recreational opioids and stimulant use.
B4531009 Intranasal Abuse Study	Of the 28 subjects treated, there were no deaths, other SAEs or discontinuation AEs during the Treatment Phase of this study. In the Treatment Phase, all of the AEs were mild in severity. The most common TEAEs after dosing with ALO-02 30 mg/3.6 mg were euphoric mood, dysgeusia, fatigue, somnolence, headache, feeling hot, hyperhidrosis, and nausea.
B4981002 IV Abuse Potential Study)	Of the 29 subjects treated, there were no deaths, SAEs, dose reductions or temporary discontinuation due to AEs in the study for subjects who received ALOA-02. One case of Exposure in Utero (EIU) was reported in one subject during the Drug Discrimination Phase. The majority of AEs in the Treatment Phase were mild or moderate in severity. The most common

	TEAE occurring after dosing with simulated ALO-02 20 mg/2.4 mg IV was headache. One subject each experienced irritability, dizziness and hot flush.
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(Table, reviewer)

#### **7.4.6 Immunogenicity**

Not applicable.

### **7.5 Other Safety Explorations**

#### **7.5.1 Dose Dependency for Adverse Events**

Dose dependency of TEAEs was analyzed for the long-term safety study 1001 with exposures of 10 mg to  $\geq 120$  mg/day. Most subjects (72%) received an average daily dose  $\leq 80$  mg/day and 11% of subjects received an average daily dose  $> 120$  mg/day.

The most frequent ( $\geq 5\%$ ) TEAEs were nausea, constipation, vomiting, somnolence, headache, and dizziness, as shown in Table x below, which did not appear to be dose-dependent. The most likely reason why opioid-related AEs were not dose-related is due to the design of the studies in which ALO-02 was titrated to effect. Similarly, discontinuations due to AEs were more common in the 10-40 mg dose group and least common in the  $> 120$  dose group. This is most likely due to the fact that if patients were having difficulty tolerating up-titration to get to a dose  $> 120$  mg, they were likely to discontinue so discontinuations were lower at the higher dose.

Table 51 summarizes the incidence of TEAEs  $\geq 5\%$ .

**Table 50. Incidence of TEAE ≥5% of Subjects in Any Average Daily Dose Group Safety Population Study B4531001**

System Organ Class Preferred Term	Average Daily Dose				Total (N=395) n (%)
	10-40 mg (N=129) n (%)	>40-80 mg (N=155) n (%)	>80-120 mg (N=58) n (%)	>120 mg (N=43) n (%)	
<b>Any Adverse Events</b>	<b>110 (85.3)</b>	<b>140 (90.3)</b>	<b>49 (84.5)</b>	<b>38 (88.4)</b>	<b>343 (86.8)</b>
Related to study drug	78 (60.5)	82 (52.9)	20 (34.5)	22 (51.2)	207 (52.4)
Not related to study drug	32 (24.8)	58 (37.4)	29 (50.0)	16 (37.2)	136 (34.4)
<b>Gastrointestinal disorders</b>	<b>58 (45.0)</b>	<b>53 (34.2)</b>	<b>10 (17.2)</b>	<b>8 (18.6)</b>	<b>133 (33.7)</b>
Constipation	23 (17.8)	38 (24.5)	5 (8.6)	3 (7.0)	71 (18.0)
Nausea	31 (24.0)	18 (11.6)	4 (6.9)	5 (11.6)	59 (14.9)
Vomiting	10 (7.8)	7 (4.5)	1 (1.7)	1 (2.3)	20 (5.1)
Diarrhea	3 (2.3)	1 (0.6)	1 (1.7)	3 (7.0)	8 (2.0)
<b>Nervous system disorders</b>	<b>29 (22.5)</b>	<b>30 (19.4)</b>	<b>9 (15.5)</b>	<b>8 (18.6)</b>	<b>78 (19.7)</b>
Somnolence	12 (9.3)	15 (9.7)	4 (6.9)	1 (2.3)	33 (8.4)
Dizziness	9 (7.0)	9 (5.8)	2 (3.4)	1 (2.3)	22 (5.6)
Headache	7 (5.4)	5 (3.2)	1 (1.7)	1 (2.3)	14 (3.5)
<b>General disorders and administration site conditions</b>	<b>12 (9.3)</b>	<b>16 (10.3)</b>	<b>5 (8.6)</b>	<b>8 (18.6)</b>	<b>42 (10.6)</b>
Fatigue	9 (7.0)	12 (7.7)	2 (3.4)	4 (9.3)	27 (6.8)
<b>Skin and subcutaneous tissue disorders</b>	<b>13 (10.1)</b>	<b>13 (8.4)</b>	<b>6 (10.3)</b>	<b>2 (4.7)</b>	<b>34 (8.6)</b>
Pruritus	8 (6.2)	5 (3.2)	3 (5.2)	0 (0.0)	16 (4.1)
Hyperhidrosis	5 (3.9)	3 (1.9)	3 (5.2)	2 (4.7)	13 (3.3)
<b>Vascular disorders</b>	<b>3 (2.3)</b>	<b>3 (1.9)</b>	<b>0 (0.0)</b>	<b>3 (7.0)</b>	<b>9 (2.3)</b>
Hot flush	2 (1.6)	1 (0.6)	0 (0.0)	3 (7.0)	6 (1.5)

Abbreviations: N=number of subjects; n=a subset of subjects with the event.

Note: 10 subjects were not included in an average daily dose column (2 subjects had an average daily dose <10 mg and 8 subjects had missing study drug accountability data).

Subjects were counted only once per column in each row. If a subject experienced an adverse event more than once with differing values for relationship to study drug, only the adverse event related to study drug was counted.

MedDRA (v13.1) coding dictionary was applied.

(SCS, p. 53)

## 7.5.2 Time Dependency for Adverse Events

The most common adverse events occurred in a larger proportion of subjects in the open-label period of the controlled study than in the double-blind period, indicating that most adverse events occur early on in therapy. This is consistent with what has been observed in other development programs and with other opioids.

Time dependency of TEAEs were analyzed from the long-term safety Study B4531001 for a duration of up to 12 months. The incidence and prevalence of TEAEs was highest during the 30 days after the first dose of study drug. Incidence decreased or stabilized thereafter relative to the first 30 days.

## 7.5.3 Drug-Demographic Interactions

Subgroup analyses were performed for the Phase 3 Studies B4531001 and B4531002 by age, gender, race and previous opioid status discussed below.

*Age:* In the pooled Phase 3 studies, as shown below in Table x, the overall incidence of the most common TEAEs during the Titration Phase across the age groups was similar, with GI-related AEs being the most frequently occurring. Other AEs terms which occurred with an incidence  $\geq 5\%$  in the Titration Phase included hyperhidrosis and hypertension, but these occurred only in the  $\geq 75$  year group. In the Maintenance Phase, GI AEs were again the most frequently occurring across all ages. Other AE terms which occurred in the Maintenance Phase with a frequency  $>5\%$  included fall, contusion, excoriation, tooth fracture, hyperhidrosis, musculoskeletal pain, arthralgia, and cough but these AEs terms occurred only in the  $\geq 75$  years age. The small number of subjects  $\geq 75$  years in the Titration and Maintenance Phases in these clinical trials makes it problematic to generalize safety findings to the larger population for this age group. As would be expected, the incidence of AEs was greater in the ALO-02 treatment group than placebo. There was only one subject in the placebo group  $\geq 75$  years in the Maintenance Phase so this subject was not included in the table below. In general, the safety profile for the common AEs by age are similar across age groups, excluding  $\geq 75$  years. There was a slightly higher incidence of constipation in the  $\geq 65$  years compared to  $\leq 65$  years, but the subjects in the  $\geq 65$  year age group are often on polypharmacy which may affect the results. Findings are summarized in Table 52.

**Table 51. Most Frequent ( $\geq 5\%$ ) TEAEs Occurring in ALO-02 Treated Subjects by Age in Titration and Maintenance Phases of Phase 3 Studies Pooled**

Age (Years)	Titration Phase			Maintenance Phase				
	<65 N=684	$\geq 65$ N=121	$\geq 75$ N=28	<65 N=119	$\geq 65$ N=15	<65 N=368	$\geq 65$ N=68	$\geq 75$ N=17
<b>Preferred Term</b>				Placebo	Placebo	Drug	Drug	Drug
	<b>% Subjects Experiencing AE</b>							
Nausea	18	24	21	4	0	10	9	12
Constipation	14	17	14	2	0	3	10	12
Vomiting	9	7	4	3	0	4	7	6
Headache	8	7	7	5	7	<1	3	12
Somnolence	8	9	4	<1	0	2	4	6
Dizziness	6	7	7	<1	0	3	4	6
Fatigue	4	6	11	<1	0	2	6	6
Pruritus	5	8	7	--	--	--	--	--
Decreased appetite	1	5	4	--	--	--	--	--

(Table, reviewer, modified from Applicant's tables); -- denotes that these AE terms did not occur with incidence  $\geq 5\%$  for that age group; Drug=ALO-02.

*Proposed Troxyca ER Label:*

- *Use in Specific Populations:*

(b) (4)

- *Section 8.5 Geriatric Use:* The pharmacokinetics of TROXYCA ER have not been investigated in elderly patients ( $\geq 65$  years) although such patients were included in clinical studies. Clinical studies with TROXYCA ER did not include sufficient numbers of subjects aged 65 and older to determine if they respond differently than younger subjects. Elderly patients (aged 65 years or older) may have increased sensitivity to [REDACTED] (b) (4). Use caution when selecting a dose for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease, and use of other drug therapy.

**II) Sex:** In the pooled Phase 3 studies, the most frequent AEs in both Titration and Maintenance phases and in both sexes were GI disorders. Otherwise, no clinically relevant trends in the TEAEs profiles were observed with ALO-02 and no patterns emerged.

*Proposed Troxyca ER Label: 8.8 Gender Differences* - There are no clinically significant differences in oxycodone pharmacokinetics following oral administration of TROXYCA ER to males or females; therefore, no specific dosage adjustment is recommended for the initiation or maintenance of TROXYCA ER doses based on the gender of the patient [see *Clinical Pharmacology (12.3)*].

**III) Race:** Pooled data for race was analyzed into categories of White or Non-White. In both the Titration and Maintenance Phases, the most frequent TEAEs were GI-related across all races. No clinically relevant trends by race in the TEAE profiles were observed but interpretation of these findings is limited due to the small number of Non-White subjects. There were 164 Non-White compared to 641 White in the Titration Phase and 74 Non-White compared to 362 White in the Maintenance Phase with 103 White placebo compared to 31 Non-White placebo.

**IV) Previous Opioid Status:** Of the 805 subjects exposed to ALO-02 in the Phase 3 program, 60% were opioid-experienced in the Titration Phase and 65% were opioid-experienced in the Maintenance Phase. The most common preferred term in both Phases was nausea which occurred more frequently in opioid naïve in both the Titration and Maintenance Phases. It was also notable that somnolence occurred in opioid-naïve (11%) more frequently in the Titration Phase compared to opioid experienced (7%). As would be expected, there were more AEs in ALO-02 treated than placebo. There were, otherwise, no major safety differences between the opioid naïve and opioid experienced subjects treated with ALO-02. Incidence of AEs by opioid status is shown in Table 53 below.

**Table 52. Most Frequent (≥5%) TEAEs Occurring in ALO-02 Treated Subjects by Prior Opioid Status in Titration and Maintenance Phases of Phase 3 Studies Pooled**

Preferred Term	Titration Phase		Maintenance Phase			
	Opioid Naïve N=323	Opioid Experienced N=482	Opioid Naïve		Opioid Experienced	
			Drug N=154	Placebo N=74	Drug N=282	Placebo N=60
	% Subjects Experiencing AE					
Nausea	26	14	14	5	8	2
Constipation	19	12	5	4	4	0
Vomiting	11	7	6	4	4	2
Somnolence	11	7	--	--	--	--
Dizziness	9	4	--	--	--	--
Headache	7	9	--	--	--	--
Pruritus	8	4	--	--	--	--
Fatigue	5	4	--	--	--	--

(Table, reviewer, modified from Applicant's tables); -- denotes that these AE terms did not occur with incidence ≥5% for that age group; Drug=ALO-02.

#### 7.5.4 Drug-Disease Interactions

Specific testing for drug-disease interactions was not conducted. However, no new drug-disease interactions were observed in the safety data. The proposed Troxyca ER label will include those diseases in current opioid labels to be consistent class-wide.

#### 7.5.5 Drug-Drug Interactions

There were no AE reports of suspected drug-interaction in either Phase 3 study. While no specific drug interaction studies have been performed with ALO-02, an interaction with inhibitors and inducers of the cytochrome P450 (CYP)3A4 enzyme is expected based on the metabolism of oxycodone predominantly by CYP3A4, and the results of drug-drug interaction studies conducted with immediate release oxycodone. Proposed Troxyca ER labeling will be consistent with class-wide opioids.

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

There were no reports of tumor development. One subject was diagnosed with anal cancer on Day 270 of open-label, long-term Study 1001, and subsequently died due to

metastatic squamous cell anal cancer with disease progression. There was no clear evidence in the narrative to determine that the onset of the anal cancer was due to treatment with ALO-02.

### **7.6.2 Human Reproduction and Pregnancy Data**

A Pediatric and Maternal Health Consult was obtained. See Dr. Miriam Dinatale's review for further discussion. The proposed Troxyca ER label will be consistent with class-wide labeling for other ER opioids.

Two subjects who received ALO-02 (Troxyca ER) experienced pregnancies. One was a presumed fetal death in utero and the other delivered a healthy baby.

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

Troxyca ER (study drug ALO-02) was not studied in the pediatric population.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

The opioid withdrawal cases have been discussed in Section 7.3.5. Across all studies, there was one case each of overdose, drug abuse, intentional drug misuse, drug dependence, and mood altered state discussed below:

Overdose: Subject 10181007 in Study 1002 was suspected of overdose by the Principal Investigator. The subject arrived at the study center for Visit 9/DB Week 1. Compliance was calculated by the site as 214%. The subject reportedly stated that she misunderstood the instructions for the taper card and had taken a double dose during the first week of the taper. Instead of taking one capsule of 60 mg/7.2 mg BID (120 mg TDD), the subject took two capsules of 60 mg BID (240 mg TDD). The subject was asymptomatic at the visit but left the clinic before the visit was over. She then returned 11 days later and withdrew consent. No AEs were reported. It is not clear from the information provided in the submission why this subject would be classified as an overdose. It appears to be more consistent with noncompliance or misuse of study drug.

Drug Abuse: Subject 10361001 in Study 1002 was a suspected case of drug abuse. The narrative for this subject was reviewed and revealed that the subject did not return the correct amount of IP (investigational product) over three weeks. ALO-02 capsules were permanently discontinued in response to this event. This subject was withdrawn from the study. No additional information was provided. No AEs were reported.

Intentional drug misuse: Subject 10321008 Study 1002 was recorded as intentional drug misuse. The subject was discontinued from the study during the OL period by the

Investigator and did not enter the double-blind period. The Investigator considered this event to be a case of intentional drug misuse after it was found that the subject tampered with the investigational product and returned capsules drained of their ingredients. No AEs were reported for this subject.

Drug dependence and mood altered: One case each was reported in Study B4531001, (Subject 0016-0007 and Subject 0013-0011, respectively). No action was required.

The proposed Troxyca ER label addresses Overdose, Drug Abuse, and Withdrawal Effects consistent with class-wide ER opioids.

## 7.7 Additional Submissions / Safety Issues

The 120-day Clinical Safety Update was submitted March 27, 2015 to provide any new safety information captured from the Applicant's safety database since the June 12, 2014 data lock point for incidences of deaths and SAEs. No new deaths or SAEs were reported. No new safety information was reported which would result in changes to the overall safety findings in the initial submission.

The Safety Update also addressed the Agency's Drug Safety Communication of January 9, 2015 regarding risks of pain medications during pregnancy, which included a review of two retrospective case-control studies that reported on opioid exposure in early pregnancy and risk of neural tube defects.<sup>1,2</sup> The studies used interviews to gather information from over 28,000 women on maternal opioid use during pregnancy. Both studies found that mothers of infants with neural tube defects were more likely than mothers of infants without neural tube defects to report opioid use in early pregnancy. The Agency determined that because of limitations of the studies, further investigation of this issue would be needed before it can be determined if the weight of evidence supports the presence of an increased risk of neural tube defects related to opioid exposure in early pregnancy and that the Agency recommendations on how pain medicines are used during pregnancy would remain unchanged pending additional information.

## 8 Postmarket Experience

ALO-02 has not been marketed in any country. No post-marketing data are available for review.

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<sup>1</sup> Yazdy MM, Mitchell AA, Tinker SC, et al. Periconceptional use of opioids and the risk of neural tube defects. *Obstet Gynecol* 2013;122:838-44.

<sup>2</sup> Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol*. 2011;204:314.e1-11.

## 9 Appendices

### Appendix A: Opioid Conversion Table Study 1002

#### Conversion Factors Table During OL Titration Period

CONVERSION FACTORS FOR CONVERTING THE DAILY DOSE OF PRIOR ORAL OPIOIDS TO THE ESTIMATED EQUIANALGESIC OXYCODONE TOTAL DAILY DOSE FOR ALO-02 EXTENDED-RELEASE CAPSULES ADMINISTRATION

(mg/day prior opioid × factor = mg/day ALO-02 extended-release capsules)

Prior Oral Opioid	Multiply Dose By Factor of:
Codeine (including combination drugs)	0.1
Hydrocodone (including combination drugs)	0.67
Hydromorphone	2.67
Levorphanol	5
Meperidine	Not recommended
Methadone	2
Morphine	0.67
Oxycodone (including combination drugs)	1
Oxymorphone	2
Pentazocine	0.4
Tapentadol	0.2
Tramadol	See below
Transdermal buprenorphine	See below
Transdermal fentanyl	See below

Adapted from Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, Sixth Edition 2008 and Gordon DB, Stevenson KK, Griffie J, Muchka S, Rapp C, Ford-Roberts K. Opioid equianalgesic calculations. J Palliat Med. 1999 Summer;2(2):209-18.

(Final CSR Protocol 1002 , p. 102)

Supporting Text for ConversionTable above:

- The conversion factors in this table are only to be used for the conversion from current oral opioid therapy to ALO-02 extended-release capsules.
- Sum the total daily dose for the current opioid and multiply by the conversion factor to calculate the oxycodone total daily dose.
- For subjects on a regimen of mixed opioids, calculate the approximate oral oxycodone dose for each opioid and sum the totals to estimate the oxycodone total daily dose. After conversion, if the total daily opioid requirement is  $\leq 20$  mg per day of oral oxycodone, initiate the therapy with ALO-02 10 mg twice a day (i.e., 20 mg per day).

- For subjects on around-the-clock opioid who are not on oxycodone, reduce the estimated equianalgesic oxycodone total daily dose by half (50%) to take into account the consideration of the possibility of incomplete cross-tolerance between opioids. After conversion, if the total daily opioid requirement is  $\leq 20$  mg per day of oral oxycodone, initiate the therapy with ALO-02 10 mg twice a day (i.e., 20 mg per day).
- Round down to an available daily dose level for this study.
- Divide the total daily oxycodone dose in half to obtain the twice daily dose of ALO-02 extended-release capsules.

Conversion from tramadol to ALO-02 extended-release capsules or transdermal buprenorphine to ALO-02 extended-release capsules

- For subjects who prestudy are managing CLBP with tramadol or transdermal buprenorphine (i.e., Butrans) will be initiated with ALO-02 at 10 mg/1.2 mg twice daily at the beginning of the Open-Label Conversion and Titration Period. If a patient is taking another opioid and tramadol, the tramadol component should be ignored in the conversion calculation.

Conversion from transdermal fentanyl to ALO-02 extended-release capsules

- Treatment with ALO-02 extended-release capsules can be initiated 18 hours following removal of the fentanyl transdermal patch. Although there has been no systematic assessment of conversion to extended-release oxycodone, approximately 10 mg twice daily of ALO-02 should be initially substituted for each 25 mcg/hour fentanyl transdermal patch. The subject should be followed closely for early titration, as there is very limited clinical experience with this conversion.

## Appendix B: Double-Blind Taper Regimen Study 1002

**Table 53. Dosing Information for the Double-Blind Gradual Taper Over Two Weeks**

ALO-02 Total Daily Dose Prior to Taper (mg/day)	ALO-02 Total Daily Dose Per Day (mg/day) During the Double-Blind Gradual Taper Over Two Weeks													
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
$\geq 20$ to 40	20	20	20	20	20	20	20	10	10	10	10	10	10	10
$>40$ to $\leq 60$	40	40	40	40	40	40	20	20	20	20	20	20	10	10
$>60$ to $\leq 80$	60	60	60	40	40	40	40	20	20	20	20	20	10	10
$>80$ to $\leq 120$	80	80	80	60	60	60	40	40	40	20	20	20	10	10
$>120$ to $\leq 160$	120	120	120	80	80	80	60	60	40	40	20	20	10	10

(Protocol Amendment 3, p. 104)

## Appendix C: Opioid Conversion Table Study 1001

Prior oral opioid	Multiply dose by factor of: <sup>a</sup>
Codeine (including combination drugs)	0.1
Hydrocodone (including combination drugs)	0.67
Hydromorphone	2.67
Levophanol	5
Meperidine	Not recommended
Methadone	2
Morphine	0.67
Oxycodone (including combination drugs)	1
Oxymorphone	2
Pentazocine	0.4
Tramadol	See below
Transdermal fentanyl	See below

<sup>a</sup> Subjects who are currently taking oral opioid medication will be started on an oxycodone dose equivalent to the current daily opioid dose. The average total daily opioid dose over the last week should be ascertained.

Adapted from Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, Sixth Edition 2008 and Gordon DB, Stevenson KK, Griffie J, Muchka S, Rapp C, Ford-Roberts K. Opioid equianalgesic calculations. J Palliat Med. 1999 Summer;2(2):209-18.

### Conversion from tramadol to oxycodone HCl and naltrexone HCl extended-release capsules

Tramadol is an analgesic with a dual mechanism of action involving both the opioid and norepinephrine/serotonin pathways. Because it is not a “pure” opioid, there has been no systematic assessment of conversion from tramadol to other opioids. Therefore, subjects taking tramadol should be considered opioid-naïve. If a patient is taking another opioid and tramadol, the tramadol component should be ignored in the conversion calculation.

## Appendix D: Clinical Investigator Financial Disclosure Review

Clinical Investigator Financial Disclosure  
Review

Clinical Review  
 Elizabeth Kilgore, MD  
 NDA 207-621  
 Troxyca ER (oxycodone/naltrexone)

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Application Number: NDA 207-621

Submission Date(s): December 19, 2014

Applicant: Pfizer

Product: Oxycodone/Naltrexone

Reviewer: Elizabeth Kilgore, MD

Date of Review: September 13, 2015

Covered Clinical Study (Name and/or Number): B4531002

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 195		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>2</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>193</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

For the 193 investigators with no financial interests to disclose, the Applicant submitted Form 3454 Financial Certification and Disclosure in accordance with 21CFR 54. According to the form, Pfizer certified that as the sponsor of the submitted studies, they acknowledged that they did not enter into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54, no investigator had a proprietary interest in the product or significant equity in the sponsor, and no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

*Please mark the applicable check box.*

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

For the two investigators with financial interests to disclose, the Applicant submitted Form 3455 Financial Certification and Disclosure in accordance with 21CFR 54. The compensations <sup>(b) (6)</sup> were for consulting and honorariums for speaking. Compensations <sup>(b) (6)</sup> were for symposia speaker and honorariums for speaking as shown below:

Clinical Review  
Elizabeth Kilgore, MD  
NDA 207-621  
Troxyca ER (oxycodone/naltrexone)

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The following information concerning [REDACTED] <sup>(b) (6)</sup> who participated as a clinical investigator in the submitted study B453:B4531002, is submitted in accordance with 21 CFR part 54. The named individual has participated in one or more of the following financial arrangements or hold financial interests that are required to be disclosed as follows:

*Please mark the applicable check box.*

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

The following information concerning [REDACTED] <sup>(b) (6)</sup> who participated as a clinical investigator in the submitted study B453:B4531002, is submitted in accordance with 21 CFR part 54. The named individual has participated in one or more of the following financial arrangements or hold financial interests that are required to be disclosed as follows:

*Please mark the applicable check box.*

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

The disclosed financial information revealed no issues which would affect approvability of the application.

Clinical Investigator Financial Disclosure  
Review

Clinical Review  
 Elizabeth Kilgore, MD  
 NDA 207-621  
 Troxyca ER (oxycodone/naltrexone)

---

Application Number: NDA 207-621

Submission Date(s): December 19, 2014

Applicant: Pfizer

Product: Oxycodone/Naltrexone

Reviewer: Elizabeth Kilgore, MD

Date of Review: September 13, 2015

Covered Clinical Study (Name and/or Number): B4981002

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 8		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>1</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>7</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

For the 7 investigators with no financial interests to disclose, the Applicant submitted Form 3454 Financial Certification and Disclosure in accordance with 21CFR 54. According to the form, Pfizer certified that as the sponsor of the submitted studies, they acknowledged that they did not enter into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54, no investigator had a proprietary interest in the product or significant equity in the sponsor, and no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

*Please mark the applicable check box.*

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

For the one investigator with financial interests to disclose, the Applicant submitted Form 3455 Financial Certification and Disclosure in accordance with 21CFR 54. The compensations [REDACTED] for covered Study B4981002 were for research and development grants as shown below:

The following information concerning [REDACTED] <sup>(b)(6)</sup> who participated as a clinical investigator in the submitted study B453:AL002103001, B498:B4981002, is submitted in accordance with 21 CFR part 54. The named individual has participated in one or more of the following financial arrangements or hold financial interests that are required to be disclosed as follows:

*Please mark the applicable check box.*

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

The disclosed financial information revealed no issues which would affect approvability of the application.

Clinical Review  
 Elizabeth Kilgore, MD  
 NDA 207-621  
 Troxyca ER (oxycodone/naltrexone)

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Clinical Investigator Financial Disclosure  
 Review

Application Number: NDA 207-621

Submission Date(s): December 19, 2014

Applicant: Pfizer

Product: Oxycodone/Naltrexone

Reviewer: Elizabeth Kilgore, MD

Date of Review: September 13, 2015

Covered Clinical Study (Name and/or Number): B4531009

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 14		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>14</u>		

Clinical Review  
Elizabeth Kilgore, MD  
NDA 207-621  
Troxyca ER (oxycodone/naltrexone)

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Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)
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The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

For the 14 investigators with no financial interests to disclose, the Applicant submitted Form 3454 Financial Certification and Disclosure in accordance with 21CFR 54. According to the form, Pfizer certified that as the sponsor of the submitted studies, they acknowledged that they did not enter into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54, no investigator had a proprietary interest in the product or significant equity in the sponsor, and no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

*Please mark the applicable check box.*

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The disclosed financial information revealed no issues which would affect approvability of the application.

### Clinical Investigator Financial Disclosure Review

Application Number: NDA 207-621

Submission Date(s): December 19, 2014

Applicant: Pfizer

Product: Oxycodone/Naltrexone

Reviewer: Elizabeth Kilgore, MD

Date of Review: September 13, 2015

Covered Clinical Study (Name and/or Number): ALO-02-07-201 (Alias numbers AP-104, ALO-02-101, B4531012)

Clinical Review  
 Elizabeth Kilgore, MD  
 NDA 207-621  
 Troxyca ER (oxycodone/naltrexone)

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 13		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>13</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

For the 13 investigators with no financial interests to disclose, the Applicant submitted Form 3454 Financial Certification and Disclosure in accordance with 21CFR 54. According to the form, Pfizer certified that as the sponsor of the submitted studies, they acknowledged that they did not enter into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54, no investigator had a proprietary interest in the product or significant equity in the sponsor, and no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The disclosed financial information revealed no issues which would affect approvability of the application.

## 9.1 Literature Review/References

The efficacy and safety of reference products Roxicodone and Revia are well established. The Applicant referenced numerous literature reports in support of the efficacy and safety.

The Applicant's submission referenced approximately 97 articles in support of efficacy, safety, biopharmaceutics or other aspects of their drug development. Specifically for efficacy support, the Applicant conducted a literature search for the period January, 1995 through March, 2014 and found a total of 24 publications which evaluated the efficacy and/or safety of extended-release (ER) oxycodone or a combination of ER oxycodone and naloxone that met the established criteria for inclusion and determined that this literature was supportive of efficacy of ER oxycodone or combined ER oxycodone/naloxone for the treatment of chronic pain associated with various chronic pain conditions.

*Reviewer's Comments:* Although the literature articles referenced by the Applicant are generally supportive, my approval recommendation does not rely in any part on these articles. Rather, my recommendation rests upon the Applicant's demonstrated efficacy in one adequate and well controlled trial in addition to establishing a scientific bridge to the Agency's previous finding for efficacy of Roxicodone with Study B4531007.

In addition to the articles cited supporting efficacy and safety, the Applicant also cited literature to support proposed labeling in section 12.2 for Effects on the Endocrine System and Immune System, discussed below:

I) Effects on the Endocrine System: The Applicant's proposed labeling for this section is summarized below:

### **Effects on the Endocrine System**

Opioids inhibit the secretion of adrenocorticotrophic hormone (ACTH), cortisol, testosterone, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to hormonal changes that may manifest as symptoms of hypogonadism.

The Applicant referenced an article by Daniell 3 to support the proposed label language, summarized below:

*Study Overview:* Male opioid users in an outpatient setting were referred by their treating physicians to participate in the study for hormone analysis. Eligibility criteria included daily consumption of at least 20 mg of hydrocodone for two or more weeks or the analgesic equivalent of another opioid, the absence of hospitalization within the preceding two months, and absence of a prior diagnosis of hormone deficiency, prior pelvic or testicular therapeutic radiation, chronic liver or kidney disease, a history of malignancy requiring system therapy, and prior ovarian or testicular surgery. Free testosterone (FT), total testosterone (TT), estradiol (E2), dihydrotestosterone (DHT), luteinizing hormone (LH), and follicle stimulating hormone (FSH) were measured in 54 outpatient men consuming oral sustained-action dosage forms of opioids several times daily for control of nonmalignant pain compared to 27 control subjects who were not using opioids.

*Results:*

- Hormone levels averaged much lower in opioid users than in control subjects in a dose-related pattern ( $P < .0001$  for all comparisons). FT, TT, and E2 levels were subnormal in 56%, 74%, and 74%, respectively, of opioid consumers. Forty-eight men (89%) exhibited subnormal levels of either FT or E2. Either TT or E2 level was subnormal in all 28 men consuming the equivalent of 100 mg of methadone daily and in 19 of 26 (73%) consuming smaller opioid doses.
- Eighty-seven percent (39 of 45) of opioid users who reported normal erectile function before opioid use reported severe erectile dysfunction or diminished libido after beginning their opioid therapy.

*Study Conclusions:* There is a high frequency of apparently symptomatic hypogonadotropic hypogonadism in outpatient men consuming multiple daily doses of commonly prescribed opioids. Of the opioid users, 24 were using methadone, 18 extended-release oxycodone, and 12 extended release morphine sulfate with some subjects also using short-acting opioids in addition.

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3 Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. The Journal of Pain. 2002, 3:377-384.

*Reviewer's comments: This language is currently in other opioid labeling so will most likely be acceptable for inclusion, although final labeling discussions are ongoing at the time of this review. This study alone, however, does not support the proposed labeling due to the limitations listed below:*

- *The study was not placebo controlled.*
- *Of the opioid-users in the study, 43% were taking antidepressants, 10% anticonvulsants, and 28% were smokers. The impact of any of these concomitant medications and nicotine use on the results of the study limit interpretation.*
- *The study does not specifically evaluate thyroid stimulating hormone.*
- *The proposed labeling that chronic use of opioids influences the hypothalamic-pituitary-gonadal axis leading to hormonal changes that may manifest of symptoms of hypogonadism cannot be drawn based on this one study.*

#### *II) Effects on the Immune System:*

Proposed label: Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

*Reviewer's comments: The Applicant's supporting article for the proposed label was an article by Eisenstein<sup>4</sup> which was a review of the literature discussing the effects of opioids and immune function including the effect of opioid withdrawal on immune function, on mechanisms of immune modulation, and on sensitization to infection for in vitro studies. There is no determination for how these in vitro findings relate to humans. As such, this article alone does not support the proposed label. However, the proposed wording is consistent with class-wide labeling for opioids.*

Of note, neither of the referenced articles above included Tradenames of products.

## **9.2 Labeling Recommendations**

The labeling reviews are ongoing at the time of this review. Based upon the safety findings, the labeling will generally be consistent with class-wide ER opioids.

The following labeling changes have been recommended based upon my review:

- Section 6.1 Clinical Trial Experience: Applicant must include a column in the Adverse Reactions Table which shows the placebo comparator.

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<sup>4</sup> Eisenstein TK, Rahim RT, Feng P, et al. Effects of opioid tolerance and withdrawal on the immune system. *J Neuroimmune Pharmacol.* 2006;1, (3): 237-249.

- Section 14: Inclusion of the use of rescue medication.
- Section 14 Clinical Studies: Inclusion of a responder analysis curve.

### **9.3 Advisory Committee Meeting**

An Advisory Committee Meeting was not held for this NDA.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELIZABETH M KILGORE  
09/14/2015

JOSHUA M LLOYD  
09/14/2015

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number:** 207621

**Applicant:** Pfizer, Inc.

**Stamp Date:** 12/19/14 (electronic)

**Drug Name:** ALO-02 (oxycodone + sequestered naltrexone)

**NDA/BLA Type:** Initial NDA;  
Standard Review

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

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				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			
<b>LABELING</b>					
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			
<b>SUMMARIES</b>					
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			
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).	X			505(b)(2)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?				Roxicodone (oxycodone; NDA 21-011) and Revia (naltrexone; NDA 18-932)
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	X			
15.	Describe the scientific bridge (e.g., BA/BE studies): <ul style="list-style-type: none"> <li>• Roxicodone bridge: 1 PK BA bridging study (B4531007) of study drug 40 mg/4.8 mg compared with Oxycodone IR 20 mg in healthy volunteers</li> <li>• Revia bridge: Per prior Agency advice, the Sponsor was given the option to conduct a BA study or provide a scientific argument to justify relying on the Agency's prior findings of safety and efficacy for Revia.</li> </ul>				1.Sponsor conducted a BA study to bridge to listed drug, Roxicodone and support BID administration. 2. Sponsor provided scientific justification

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					sites.
<b>SAFETY</b>					
21.	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			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			Although the Applicant did not provide exposures based on ICH guidelines for chronically administered drugs and was not required to do as the Applicant is referencing the Agency's previous findings as part of a 505(b)(2) application, the submitted exposures appear acceptable.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
27.	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			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			The applicant also submitted narratives for cases of opioid withdrawal as agreed.
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?  5 pharmacodynamics studies in non-dependent recreational	X			Because this is an abuse-deterrent (AD) formulation, additional studies were required to support the AD

<sup>1</sup> 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.

<sup>2</sup> 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).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	opioid users (2 studies to determine naltrexone to oxycodone dose ratio and 3 studies evaluated abuse potential of the formulation)				features.
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Partial waiver <7 years; Deferral 7 to <17 years; Applicant has an agreed iPSP (letter dated 11/13/2014)
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? There were four studies conducted in Canada. All other studies were conducted in the US. Of the studies conducted in Canada, 2 were Human Abuse Potential (HAP) studies, which enrolled a healthy population of recreational opioid users. The other 2 studies conducted in Canada were Dose Ratio studies in non-dependent opiate-experienced healthy subjects.		X		We do not expect any significant differences between these study populations and comparable populations in the U.S. to adversely impact the applicability of data generated from these studies to the U.S. population.
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_Yes\_\_**

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

No clinical issues to communicate in the 74-day letter.

Elizabeth Kilgore

February 17, 2015

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Reviewing Medical Officer

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Date

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Clinical Team Leader

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Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELIZABETH M KILGORE  
02/17/2015

JOSHUA M LLOYD  
02/17/2015