CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207621Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	207621
Applicant Name	Pfizer, Inc.
Date of Submission	December 19, 2014
PDUFA Goal Date	January 19, 2016
Proprietary Name / Established (USAN) Name	Troxyca ER (Oxycodone Hydrochloride and Naltrexone Hydrochloride) Capsules
Dosage Forms / Strength	Capsules; 10/1.2, 20/2.4, 30/3.6, 40/4.8, 60/7.2, and 80/9.6 mg/mg
Proposed Indication(s)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Elizabeth Kilgore, MD, Joshua Lloyd, MD
Statistical Review	Feng Li, PhD, Freeda Cooner, PhD Ling Chen, PhD, Qianyu Dang, PhD
Pharmacology Toxicology Review	Elizabeth Bolan, PhD, R. Daniel Mellon, PhD
OPQ Review	Benjamin Stevens, PhD, Venkateswara Pavuluri, PhD, Yong Hu, PhD, Yong Hu, PhD, Sunita Lyer, Ciby Abraham, PhD, Steven Kinsley, PhD, Tien Mien Chen, PhD
Clinical Pharmacology Review	Suresh Naraharisetti, PhD, Yun Xu, PhD
Controlled Substances Staff	James Tolliver, PhD, Silvia Calderon
OSE/DMEPA	James Schlick, MBA, RPh, Vicky Borders-Hemphill, PharmD
OPDP/DCDP	Koung Lee, Jessica Fox
OMP/DMPP	LaShawn Griffiths, MSHS-PH, BSN, RN, Barbara Fuller, RN, MSN, CWOCN, Morgan Walker, PharmD, MBA
OSI	John Lee MD, Janice Pohlman, MD, MPH, Susan Thompson, MD, Kassa Ayalew, MD, MPH
OSE/DRISK	Danny S Gonzalez, Pharm D, MS, Joan Blair, RN, MPH, Kim Lehrfeld, Pharm D

OND=Office of New Drugs
DMEPA=Division of Medication Errors Prevention
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy Initiatives
OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations
DCDP=Division of Consumer Drug Promotion
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

Pfizer Inc. has submitted a 505(b)(2) application for Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride) capsules, an extended-release formulation of oxycodone with properties intended to deter abuse by the oral, intranasal and intravenous routes of administration. The Applicant intends to rely on the Agency's prior findings of efficacy and safety for Roxicodone (NDA 021011) and Revia (NDA 018932), and has cross-referenced another of their products (b) (4) Embeda (NDA 022321, morphine sulfate with sequestered naltrexone hydrochloride).

Troxyca ER capsules contain small pellets that are coated with oxycodone and excipients that result in an extended-release profile for the oxycodone. The abuse-deterrent properties are based on the presence of naltrexone, which is sequestered within the pellets. With oral administration of intact capsules or with sprinkling the pellets on food, there is little to no exposure of the naltrexone in the blood. However, any crushing of the capsule, or crushing and dissolution of the pellets results in release of the naltrexone, which is intended to antagonize the effects of the oxycodone and blocks the extent of euphoria experienced by an abuser, whether by oral, intranasal, or intravenous routes of administration. (b) (4)

Troxyca ER was developed under IND 107037, and was referred to as ALO-02 during development. The Applicant has provided the product-specific chemistry, manufacturing, and controls (CMC) information required for review of the NDA. Nonclinical support for oxycodone hydrochloride is based on reliance on the Agency's previous findings for the referenced drug, Roxicodone, and for naltrexone hydrochloride, on the Agency's previous findings for the referenced drug, Revia. The Applicant has provided support for the formulation, including novel excipients and excipients that exceed the amount present in the Inactive Ingredients Guide in the Nonclinical Pharmacology and Toxicology section of the application. Support for the clinical efficacy and safety of the oxycodone in Troxyca ER is based in part on reliance on the Agency's previous findings for the referenced drug, Roxicodone using relative bioavailability as the scientific bridge for doing so, and in part on a clinical efficacy study conducted by the Applicant. One adequate and well-controlled efficacy study was required for several reasons. First, bioequivalence cannot be established for an extended-release oxycodone product for twice a day dosing and an immediate-release product for dosing every 4 to 6 hours. Next, the indications for Roxicodone and Troxyca ER are different and the clinical study was conducted in the intended population to support the proposed indication. In addition, because there are measurable naltrexone levels in some patients following oral administration of Troxyca ER, it was necessary to ensure that the naltrexone exposure is not sufficient to block efficacy. The safety and efficacy of naltrexone is based on reliance of the Agency's prior findings for the referenced drug Revia and published literature. The Applicant conducted in vitro and in vivo studies to evaluate the abuse-deterrent properties of the formulation. The in vivo studies were required because, (b) (4) the finding of abuse-deterrent properties for

Embeda could not be inferred for Troxyca given the different active opioid agonists. This review will focus on the clinical efficacy and safety data from clinical studies conducted by the Applicant, data from pharmacokinetic studies of Troxyca ER, and the results of the studies evaluating the abuse-deterrent properties of the formulation.

2. Background

As described in the Guidance for Industry, Abuse-Deterrent Opioids – Evaluation and Labeling[1], the development of abuse-deterrent formulations of opioid analgesics is recognized by FDA as an important approach to reducing abuse of prescription opioids. Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

In general, the primary route of abuse of opioid analgesics is oral, followed by different frequencies of intranasal and intravenous abuse depending on the specific product. This is true for both immediate-release and extended-release products. Extended-release products are often manipulated to defeat the extended-release characteristics for all routes of abuse, including oral, resulting in an earlier and larger peak drug level. Because extended-release opioid analgesics often contain more of the opioid analgesic than immediate-release products, the risk for overdose is greater, particularly if the extended-release characteristics are defeated. It is important to remember that even when a product has abuse-deterrent properties that may reduce abuse by one or several routes, it does not mean that there is no risk of abuse or addiction. It means, rather, that the risk of abuse by certain routes is lower than it would be without the abuse-deterrent properties. Abuse-deterrent is not synonymous with abuse-proof. Troxyca ER remains under schedule II of the Controlled Substances Act.

Upon approval, Troxyca ER will be the third extended-release, analgesic combination drug product containing an opioid agonist and an opioid antagonist on the US market. Troxyca ER is the first extended-release combination analgesic drug product containing oxycodone hydrochloride and naltrexone hydrochloride. Embeda, NDA 022321, approved August 13, 2009, is an extended-release combination analgesic drug product containing morphine sulfate and naltrexone hydrochloride. Embeda and Troxyca ER are (b) (4) capsules filled with pellets, and were designed to have abuse-deterrent properties based on the presence of sequestered naltrexone. The pellets have (b) (4) naltrexone, a barrier layer, then the opioid agonist, morphine and oxycodone for Embeda and Troxyca ER, respectively, followed by a rate-limiting layer that provides the extended-release pharmacokinetic profile. If the capsule is swallowed whole, or the pellets swallowed without chewing or crushing, little to no naltrexone is released. However, if the pellets are crushed, chewed, or dissolved naltrexone is released. Targiniq, NDA 205077, approved July 23, 2014, is an extended-release combination analgesic drug product containing oxycodone hydrochloride and naloxone hydrochloride. The naloxone in this formulation is not sequestered. When taken orally, naloxone undergoes

[1] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

extensive first pass hepatic metabolism resulting in very low blood levels. However, if abused by being crushed and snorted the naloxone is absorbed across the nasal mucosa bypassing the initial circulation through the liver that follows gastrointestinal absorption and is available to block the opioid agonist effects of oxycodone. Similarly, if abused by being crushed and injected, the full amount of naloxone is available in the blood along with the oxycodone. Targiniq has not yet been marketed in the US.

Although sequestered, some naltrexone can be detected in the blood of subjects who take Troxyca ER and Embeda orally as whole capsules, without crushing. There are no established pharmacokinetic and pharmacodynamic relationships that describe whether a given level of naltrexone following oral administration of intact Troxyca ER and Embeda would impede the analgesic effect or cause adverse events. As a result, an adequate and well-controlled efficacy trial was required to demonstrate acceptable efficacy for the proposed indication for each of these applications, as well as to contribute information about whether the naltrexone caused unacceptable adverse events in patients being treated for pain.

(b) (4)

it is not known if the amount of naltrexone present in Embeda would be appropriate to create the same deterrent effects in Troxyca ER, or impact efficacy or safety in the same way, given the different opioid drug substances, morphine in Embeda and oxycodone in Troxyca ER. For this reason, the efficacy, safety, and abuse-deterrent data from Embeda were not adequate to substitute for studies conducted with Troxyca ER.

There are no established pharmacokinetic and pharmacodynamic relationships that demonstrate whether the levels of the respective opioid antagonists present following oral administration of intact Troxyca ER and Targiniq would impede the analgesic effect from oxycodone. As a result, for each of these applications, an adequate and well-controlled efficacy trial was required to demonstrate acceptable efficacy for the proposed indication. Similarly, the adverse events that may result from exposure to naloxone in Targiniq cannot be substituted for clinical trials that evaluate possible adverse events from exposure to naltrexone from Troxyca ER. Because Troxyca ER and Targiniq contain different opioid antagonists, and the naloxone in Targiniq is not sequestered while the naltrexone in Troxyca ER is sequestered, the human abuse potential studies conducted for Targiniq cannot be used to provide information about the abuse-deterrent characteristics of Troxyca ER. Therefore, based on the different antagonists in the two products and the formulation differences described, studies conducted with Targiniq cannot be relied upon to provide data about the effect of naltrexone on the efficacy of oxycodone, the effect of naltrexone on the safety of Troxyca ER, or the abuse-deterrent properties of Troxyca ER.

There are two single-entity extended-release oxycodone products formulated to deter abuse. OxyContin (NDA 022272, approved April 5, 2010) and Xtampza ER (NDA 208090, approved April 26, 2016) are formulated as a tablet and capsule, respectively, that contain excipients intended to create physicochemical properties responsible for the abuse-deterrent properties of the formulation. Neither product contains naltrexone, and as a result, studies conducted with OxyContin or Xtampza ER could not be relied upon to support a finding for the abuse-deterrent properties of Troxyca ER.[2]

[2] Targiniq, OxyContin, and Xtampza ER are discussed for background purposes and were not relied on for approval

Therefore, the applicant was required to conduct an adequate and well-controlled clinical trial to support a finding of efficacy or Troxyca ER for the proposed indication, and to conduct studies with Troxyca ER to provide safety data, and to conduct clinical studies to evaluate the abuse-deterrent properties of Troxyca ER.

3. CMC/Device

Troxyca ER is an extended-release oxycodone and naltrexone drug product formulated as a capsule for oral administration. Troxyca ER capsules are manufactured in six strengths: 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 of oxycodone HCl/naltrexone HCl.

The capsule contains pellets containing naltrexone and oxycodone. As shown in Figure 1, the pellet has a (b) (4) naltrexone, a barrier layer, oxycodone, and then the rate controlling layer that provides the extended-release characteristics. All strengths are (b) (4) encapsulated in hard gelatin capsule shells.

The naltrexone is sequestered from the oxycodone by a membrane (b) (4) This membrane acts as a barrier for naltrexone release in aqueous solutions, but, as described in more detail below, can be disrupted by certain organic solvents or physical manipulations including crushing and chewing.

Figure 1. ALO 02 (Troxyca ER) Pellet Schematic Diagram

(b) (4)

of this product. Although there are a few articles in some underlying reviews for this application that mention OxyContin, it was not necessary to rely on them for approval.

The Applicant referenced DMFs for naltrexone and oxycodone drug substances. The naltrexone HCl drug substance is manufactured (b) (4) and is referenced in DMF# (b) (4) (adequate, last reviewed May 26, 2015). The oxycodone HCl drug substance, is manufactured (b) (4) and is referenced in DMF# (b) (4) (adequate, last reviewed 4/20/2015). There are adequate controls on drug substance impurities and degradants. The Applicant has added oxycodone particle size specifications, and a limit for the related substance, (b) (4) to the naltrexone drug substance release specifications with an acceptance criterion of NMT (b) (4) ppm as requested. The Applicant has agreed to submit any proposed changes in drug substance supplier as a prior approval supplement.

The process review team had a number of requests for additional information, and comments requesting modification to the manufacturing process that were satisfactorily addressed.

The proposed exclusion of microbial limits in the drug product specifications was found acceptable based on the following elements (reproduced from the OPQ review):

(b) (4)

The biopharmaceutics reviewer found the dissolution method development report submitted in support of the proposed method and acceptance criteria to be acceptable. An In Vitro Stability/Compatibility study was conducted and found acceptable to support labeling for opening the capsule and sprinkling the contents onto food (e.g., applesauce).

A request for a biowaiver (b) (4) was granted based on the following:

(b) (4)

An in vitro alcohol dose-dumping study showed release of oxycodone in 40% alcohol, but not lower concentrations. An oral bioavailability study was conducted to evaluate the co-administration of Troxyca ER with 40% and 20% ethanol. There was no increase in release of oxycodone with 20% ethanol, but, with 40% ethanol, the Tmax was shortened to 8 hours compared to 12 hours with water and there was an approximately 13% increase in AUC0-∞, and a 37% increase in Cmax. The biopharmaceutics review mentions discussion about requesting a simulation study with the highest strength Troxyca ER, but (b) (4) it was determined that no further studies were needed to support the biowaiver request.

I concur with the conclusions reached by the chemistry review team regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections

were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The following has been excerpted verbatim from the review by Dr. Bolan:

> Since NTX is not approved to be used intravenously, two toxicology studies were conducted to support the safety of a human abuse potential study with intravenous administration of OC and NTX. The studies were considered acceptable to support the safety of the clinical study. No other pharmacology or toxicology studies were required with either OC or NTX.
>
> Genetic toxicology studies were conducted with two NTX drug substance and NTX-derived drug product degradants, (b) (4) that exceeded ICH Q3A(R2) and ICH Q3B(R2) thresholds for qualification. Both compounds tested negative in the Ames assay and the in vivo mouse micronucleus assay. In contrast, both impurities tested positive for clastogenic activity in the in vitro chromosome aberration assay. As per ICH S2(R1), an additional in vivo clastogenicity study will be required for both compounds to fully evaluate their clastogenic potential. Since these two compounds are both NTX drug substance impurities and NTX-derived drug product degradants and are in currently approved products, it is acceptable to conduct these studies as post-marketing requirements.
>
> The Troxyca ER formulation contains excipients that are intended to confer abuse-deterrent properties. When the Troxyca ER product is consumed at the maximum theoretical daily dose (MTDD) of OC ((b) (4) g), several excipients exceeded levels used in products previously approved for chronic use. Written safety justification was provided by the Applicant. A literature-based justification of dibutyl sebacate (DBS) did not contain adequate information to support the safety of the levels in the product. It was communicated to the Applicant that as per the FDA excipient guidance, general toxicology studies in two species, a full reproductive toxicology battery as well as carcinogenicity studies in two species (unless adequate justification for a waiver of the carcinogenicity studies is provided as per the FDA excipient guidance) will be required to qualify DBS as a novel excipient. The Applicant subsequently submitted two 26-week general toxicology studies which tested DBS up to the limit dose in rat and dog. No adverse effects were observed at any dose in either species and the NOAELs in rat and dog yielded exposure margins 35-fold and 117-fold, respectively, the amount of DBS in the Troxyca ER drug product if the MTDD of OC is consumed. These studies adequately qualify DBS for chronic dosing from a general toxicology perspective. Additionally, three reproductive toxicology studies were submitted. Dibutyl sebacate can be considered qualified for male and female fertility (M & F rat: 35-fold) and embryofetal development (rat: 35-fold; rabbit: 21-fold) with acceptable safety margins. However, the fourth study in the reproductive toxicology battery, a pre- and post-natal study in rat, was not conducted. Given that DBS is currently in approved products, albeit at lower levels,

and low toxicity was observed in the studies conducted, it is considered acceptable to conduct the pre-and post-natal study post-approval.

Carcinogenicity studies in two species will not be required with DBS based on the previous human experience, the lack of histopathological changes in modern chronic toxicology studies in two species, the negative genetic toxicology studies, and the summary review of the literature cited in the Applicant's written justification which included discussion of an older 2-year rat study. This approach is consistent with recent input received from the OND Associate Director of Pharmacology and Toxicology and the FDA guidance document titled: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, which notes that "The Centers recognize that existing human data for some excipients can substitute for certain nonclinical safety data, and an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation in the full battery of toxicology studies outlined in this guidance."

Dr. Bolan notes the following, taken verbatim from her review:

The Applicant did not conduct a pre- and post-natal development study with DBS. This study is required for full characterization of the developmental effects of DBS. The 1953 Smith paper described a multi-generation study in rats with very limited endpoints using one relatively high dose of DBS. Minor reductions in body weight preweaning and more substantial reductions post-weaning were seen in offspring of treated dams. No gross pathological changes were observed. Because of the decreases in body weights, no NOAEL can be calculated for this study. However, the dose that was used was fairly high (6.25%; 3125 mg/kg) with an exposure of 109-fold higher than amount of DBS in this product when calculated for the MTDD of OC based on body surface area comparisons. Because of the previous human experience, the high exposure margins seen in the studies conducted in the existing reproductive and developmental studies in rat and rabbit and the 6-month rat and dog general toxicology study, and because the MTDD of OC is not expected to be used in the pregnant population, the pre- and post-natal study may be conducted post-approval.

With a post-marketing requirement for the pre- and post-natal study with DBS, the levels of excipients in this formulation when the product is used at the MTDD of OC can be considered acceptable.

Additionally, Dr. Bolan notes the following for two drug substance and drug product impurities/degradants taken verbatim from her review:

(b) (4) are both NTX drug substance impurities and ALO-02 drug product degradants. The drug product degradant specifications are (b) (4) for this product. (b) (4) These compounds are also likely to have been in many other NTX-containing products as impurities and degradants at specifications that meet ICH Q3A&B but not the Agency's NMT 1.5 mcg/day

threshold for potentially genotoxic compounds. Given the long history of clinical use of NTX and the lack of a safety signal, conducting the qualification studies as post-marketing requirements is considered acceptable from the pharmacology/toxicology perspective.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology studies were conducted to describe the pharmacokinetic profile of Troxyca ER, the effects of food and alcohol on oxycodone and naltrexone levels, and to provide a scientific bridge for reliance on the Agency's prior findings of safety and effectiveness for Roxicodone.

Study B4531006 evaluated the single- and multiple-dose pharmacokinetics of Troxyca ER. Single doses of Troxyca ER 40 mg and 80 mg provided dose proportional pharmacokinetics based on AUC_{24} and Cmax. Oxycodone steady-state levels were reached within 48 hours for 40 mg dosed twice daily and 80 mg dosed daily. Average oxycodone concentrations over the dosing interval were similar for 80 mg daily and 40 mg twice daily. On Day 5, the oxycodone geometric mean AUC_{24} and Cmax values over the entire 24 hours interval were 6% and 15% higher, respectively for Troxyca ER 80 mg daily compared to 40 mg twice daily, and the accumulation ratios for oxycodone (Day 5/ Day 1) based on AUCτ was approximately 3-fold and Cmax was 2-fold for Troxyca ER 40 mg twice daily compared to nearly no accumulation for Troxyca ER 80 mg once daily.

Study B4531003 evaluated the effect of food on the absorption of oxycodone from Troxyca ER. Administration of 40 mg Troxyca ER under fed conditions resulted in no change in AUC and the ratio of adjusted geometric means (90% CIs) for Cmax was 107% (98-116%). The median oxycodone Tmax was delayed from 1two hours (range 12-16 hours) fasted to 14 hours (range 12-24 hours) under fed conditions.

Study B4531004 was an open-label, single-dose, randomized, 3-period crossover study that evaluated the effect of 20% and 40% alcohol on the release of oxycodone from a 20 mg Troxyca ER capsule in naltrexone-blocked subjects. There was no change in mean AUC or Cmax from administration of 20% alcohol. With 40% alcohol there was a 12% increase in AUCinf and a 38% increase in Cmax. One subject demonstrated much greater effects of alcohol than others and contributed to the observed differences in the presence of alcohol. This subject had an apparent 6.4-fold increase in Cmax with 40% alcohol and a 2.7-fold increase with 20% alcohol. The corresponding increase in AUC was 2.2-fold and 4.8-fold with 20% and 40% alcohol, respectively. Further examination demonstrated that this subject's Cmax and AUC values with 20% or 40% alcohol were within the range of exposures seen in other subjects, whereas the exposures following Troxyca ER with water were the lowest, driving the ratios to the observed, highest values. There was no shift to earlier Tmax values in alcohol for this subject among the treatments (6 hours with water, 8 hours with both 20% alcohol and 40%

alcohol), which would have indicated the occurrence of dose dumping in the presence of alcohol. The exact reason for the lower exposure in this subject is not known.

The clinical pharmacology study conducted to create the scientific bridge to support reliance on the Agency's prior findings of safety and effectiveness for Roxicodone, was a relative bioavailability study comparing a 40 mg dose of Troxyca ER and a 20 mg dose of Roxicodone (as one 15 mg and one 5 mg tablet) in Study B4531007, a single-dose, 2-way crossover study. The dose normalized ratio (90% CIs) of adjusted geometric means for AUCinf was 107% (97%, 119%) for Troxyca ER compared to Roxicodone. The Cmax was 67% lower compared to Roxicodone. The Tmax ranged from 8 to 16 hours (median, 12 hours) for Troxyca ER.

No relative BA study was conducted to create a scientific bridge to support reliance on the Agency's prior findings of safety and effectiveness for Revia because of safety concerns associated with possible study designs. The usual study design used to create the aforementioned scientific bridge is a crossover design, in which subjects are dosed with the study drugs in different treatment periods.[3] When evaluating an opioid analgesic, subjects are usually premedicated with naltrexone to avoid opioid agonist toxicity. In this setting, that would interfere with the evaluation of the amount of naltrexone absorbed from Troxyca ER. Opioid-tolerant subjects who would be at substantially less risk for serious opioid toxicity such as respiratory depression from the oxycodone could be enrolled, but they would not be able to tolerate a dose of Revia without developing an acute opioid withdrawal syndrome. The only study design possible would be a parallel arm study, but this design does not address the inter-individual variability that is addressed by a crossover study. In deciding whether to require a parallel arm study, the amount of naltrexone in Troxyca ER and Revia, and the exposures were considered. The amount of naltrexone HCl in the highest strength of Troxyca ER is 9.6 mg, slightly more than 5-fold lower than the amount of naltrexone in the lowest strength of Revia, 50 mg, and it is sequestered. In Study B4531007, naltrexone concentrations from intact Troxyca ER were below the limit of quantitation (BLQ) (<4 pg/mL) and 6-β-naltrexol levels were observed in only 3 out of 13 subjects. In the clinical efficacy study, B4531002, naltrexone and 6-B-naltrexol levels were low or undetectable. It was decided that, as only a parallel arm study design was possible, and the dose and extent of exposure to naltrexone from Troxyca ER was substantially lower than from Revia, a pharmacokinetic study would not be necessary to create the scientific bridge in this setting, and an adequate scientific bridge can be established by relying on the information in the package insert and the published literature for Revia.

Based on cross-study comparison of Phase 1 single- and multiple-dose studies, there were dose-linear increases in oxycodone AUC and Cmax across the 20, 40, 60 and 80 mg strengths. This was also supported by pharmacokinetic data from the Phase 3 study, B4531001.

Based on experience with Embeda, it was anticipated that there would be some exposure to naltrexone in patients dosed with intact Troxyca ER. In the Phase 1 pharmacokinetic studies in subjects without naltrexone blockade, there were no quantifiable naltrexone plasma concentrations and very low levels of 6-β-naltrexol observed in 19 out of 37 subjects at time

[3] Draft Guidance for Industry, Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations, http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf

points ranging from 1 hour to 120 hours post dose with a maximum concentration of 45 pg/mL. Naltrexone and 6-β-naltrexol levels were measured in the Phase 3 studies (B4531002 and B4531001), and evaluated for the presence of any relationship between the release of naltrexone and capsule strength or total daily dose, and for any relationship between naltrexone concentrations and opioid withdrawal events. Dosing during the Phase 3 studies ranged from 10 mg/1.2 mg to 80 mg/9.6 mg twice daily, and naltrexone levels were observed in 249 subjects (34%) of the 725 subjects with a median of 11.65 pg/mL and a range of 4.05 to 1090 pg/mL, and 6-β- naltrexol levels were observed in 536 subjects (73%) with a median of 42.75 pg/mL and a range of 4.05 to 7320 pg/mL. Plasma naltrexone or 6-β-naltrexol concentrations did not accumulate at any time during either study. As noted by Dr. Naraharisetti, in comparison, the mean naltrexone Cmax following a 50 mg dose of Revia was 8550 pg/mL.[4]

The highest naltrexone and 6-β-naltrexol concentrations observed were 1090 pg/mL in Subject 10271011 and 7320 pg/mL in Subject 10221015 during Study B4531002. Neither subject experienced symptoms of opioid withdrawal with COWS scores consistently less than 2. For reference, in the studies in which Troxyca ER was administered orally after the pellets were crushed to assess the abuse-deterrent properties, maximum naltrexone levels ranged from 1074 pg/mL after a 40/4.8 mg dose to 1810 pg/mL after a 60/7.2 mg dose.

Of the 15 out of 725 subjects who had opioid withdrawal events, the highest naltrexone concentration was 139 pg/mL. There was no correlation between opioid withdrawal symptoms and naltrexone levels.

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

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The nature of the dose-response relationship for the effects of exposure to low levels of naltrexone and analgesic efficacy in patients receiving oxycodone for pain has not been defined. As a result, the Applicant was advised that at least one adequate and well-controlled efficacy trial would be required if there were measurable levels of naltrexone in patients taking Troxyca ER. As noted above, naltrexone and 6-β-naltrexol levels were found after oral ingestion of intact Troxyca ER in some patients.

Study B4531002 was a multicenter, 12-week, double-blind, placebo-controlled, randomized withdrawal design study to evaluate the efficacy and safety of Troxyca ER in patients with moderate to severe chronic low back pain. Details of the study can be found in the reviews by

[4] Meyer et al, J Clin Psychiatry. 1984 Sep; 45 (9 Pt 2):15- 9

Dr. Kilgore and Dr. Li. Patients intended for the study were adults with a diagnosis of moderate to severe low back pain for at least three months, with or without radiation into the posterior thigh, meeting Classification 1 or 2 according to the Quebec Task Force on Spinal Disorders. Patients were to have a need for continuous around-the-clock opioid analgesic (at an oxycodone equivalent dose of no more than 160 mg per day) for an extended period of time. Patients' daily average pain intensity by a 0 to 10 numerical rating scale was to have been at least 5 and no worse than 9 for at least four of the last seven days of the Screening Period, including patients previously managed with a non-opioid analgesic, an opioid on an as needed basis, or already managed with daily opioid therapy.

The following has been excerpted verbatim from Dr. Li's review:

> The study consisted of four study periods: screening period (up to 2 weeks), open-label conversion and titration period (4 to 6 weeks), double-blind treatment period (12 weeks), and post-treatment period (2 weeks).
>
> During the open-label conversion and titration period, all subjects were initiated on, or converted to ALO-02 and titrated to response.

The following has been excerpted verbatim from Dr. Kilgore's review:

> 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 ≤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 ≤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.

The following has been excerpted verbatim from Dr. Li's review:

Only subjects who tolerated and achieved satisfactory efficacy with ALO-02 according to the protocol-defined treatment response criteria were randomized to continue ALO-02 or to switch to placebo for a comparison of the efficacy and adverse events (AEs) during the 12-week double-blind treatment period. In order to avoid opioid withdrawal signs and symptoms during the first two weeks of this period, a subject randomized to receive placebo underwent a two-week double-blind gradual tapering from the ALO-02 dose identified from the open-label conversion and titration period to placebo treatment. A subject demonstrating all of the following criteria was considered a treatment responder:

- the subject had a reduction score (to ≤ 4) in the daily average pain scores based on Numeric Rating Scale (NRS) for low back pain for at least four of the last seven days of open-label treatment prior to randomization;
- the treatment with ALO-02 was considered tolerated by the subject and corroborated as such by the investigator;
- the subject had remained on the same fixed dose of ALO-02 without a change in the dose for at least seven consecutive days prior to randomization.

> Eligible subjects were randomized in a 1:1 ratio to receive either ALO-02 or the matching placebo based on their ALO-02 dose strength at the end of the open-label titration period. Subjects were permitted to administer acetaminophen up to 3000 mg per day throughout the study as the rescue medication.
>
> The primary efficacy assessment was the daily average low back pain. Daily average low back pain was assessed with an 11-point Numerical Rating Scale (NRS). Subjects rated their average low back pain intensity during the past 24 hours by choosing the appropriate number from 0 (no pain) to 10 (worst pain). The secondary efficacy assessments included Patient's Global Assessment (PGA), Brief Pain Inventory-Short Form (BPI-SF) and rescue medication use. The applicant did not propose any multiplicity adjustment to control overall Type I error rate.
>
> The primary efficacy variable was the difference between ALO-02 and placebo in the mean changes from randomization baseline to the average of the scores from the final two weeks (Weeks 11 and 12) of the double-blind treatment period in the daily average NRS-pain scores for low back pain. The primary efficacy population included all subjects who were randomized and received at least one dose of double-blind study drug. The primary analysis was based on an analysis of covariance (ANCOVA) model with terms of treatment, prior pain analgesic (opioid or non-opioid), randomization baseline pain score and final total daily dose of the titration period.

Further details of the statistical methods and imputation strategy can be found in Dr. Li's review.

There were numerous secondary efficacy endpoints with analyses of the Roland Morris Disability Questionnaire, the Patient's Global Assessment of Low Back Pain. Safety data were collected and patients were monitored with the Clinician Opioid Withdrawal Scale and Subjective Opioid Withdrawal Scale.

The Applicant also proposed to use the 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 evaluated.

The following has been excerpted verbatim from Dr. Kilgore's review:

> 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%).
>
> 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[a]	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)

Dr. Kilgore reviewed the protocol violations and noted that they were comparable between the two groups. Details can be found in her review. Unexpectedly for a clinical trial, 14 subjects discontinued from the study due to a protocol violation of positive urine drug screen. Drug-seeking behavior for an opioid analgesic is known to occur in clinical trials, and part of the reason for including it. It is uncommon for there to be this many positive urine drug screens as subjects know they will be providing these samples.

The demographic and baseline characteristics were similar between the two treatment groups. Subjects were on average, approximately 50 years of age, a little more than half were female, 73% were white and 25% were black, 58% had been on a nonopioid analgesic prior to enrollment, mean screening pain intensity was 7 and at randomization mean pain intensity was 3.

The Applicant's analysis of the primary efficacy outcome, mean change in pain intensity from randomization baseline to the final two weeks of the 12-week study was demonstrated a statistically significantly greater increase for placebo patients compared to study drug. The Applicant conducted a number of sensitivity analysis that were supportive of the primary analysis. The results of the efficacy analyses were confirmed by Dr. Li and are shown in the following table and figures from his review.

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
Randomization Baseline	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
Final 2 Weeks[a]	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
Change from Randomization Baseline to Final 2 Weeks[a]	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
Model-Adjusted Change from Randomization Baseline to Final 2 Weeks[b]		
LS Mean (SE)	1.23 (0.179)	0.60 (0.168)
95% CI	0.87, 1.58	0.27, 0.93
Model-Adjusted Change from Randomization Baseline to Final 2 Weeks ALO-02 versus Placebo (multiple imputations)[b,c]		
Difference of LS Means (SE)		-0.62 (0.246)
95% CI		-1.11, -0.14
p-value		0.0114

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

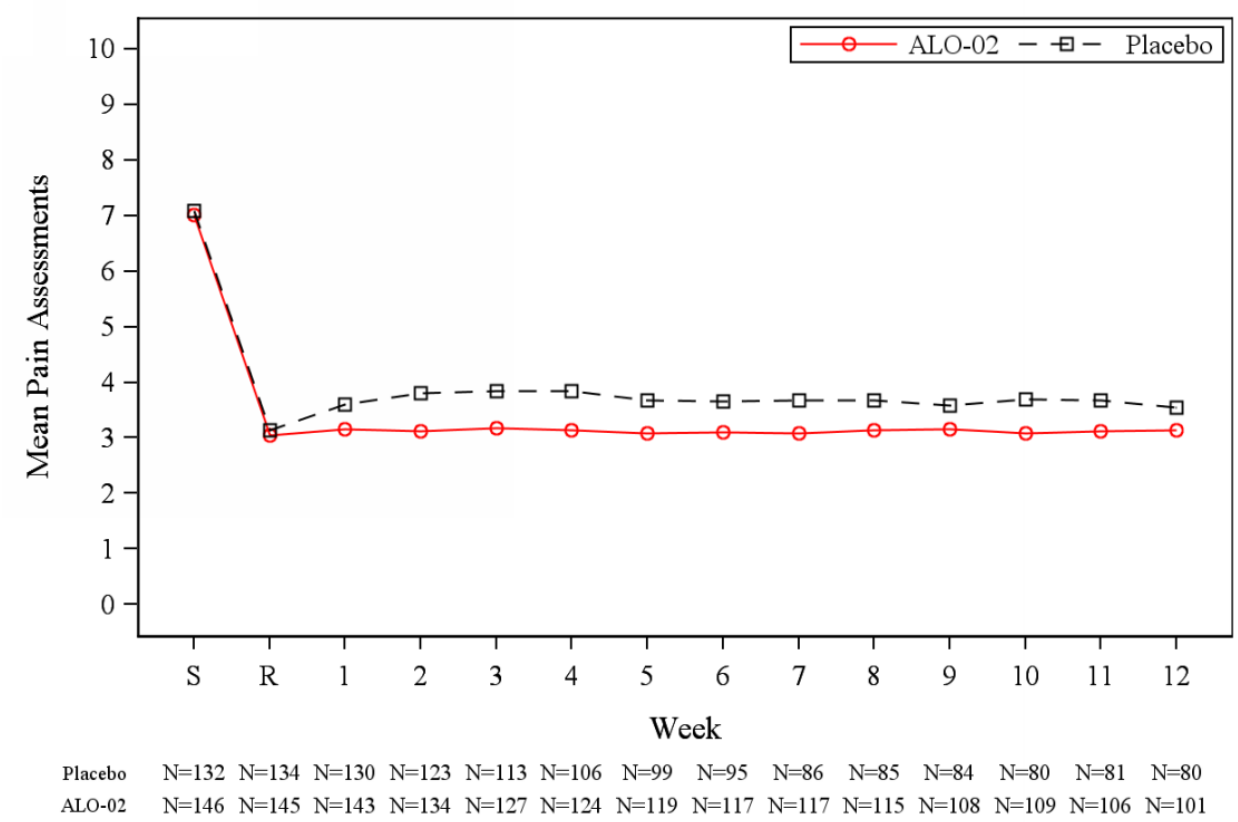
a. The averaged value for each subject from the 100 imputed datasets was used for this summary.

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.

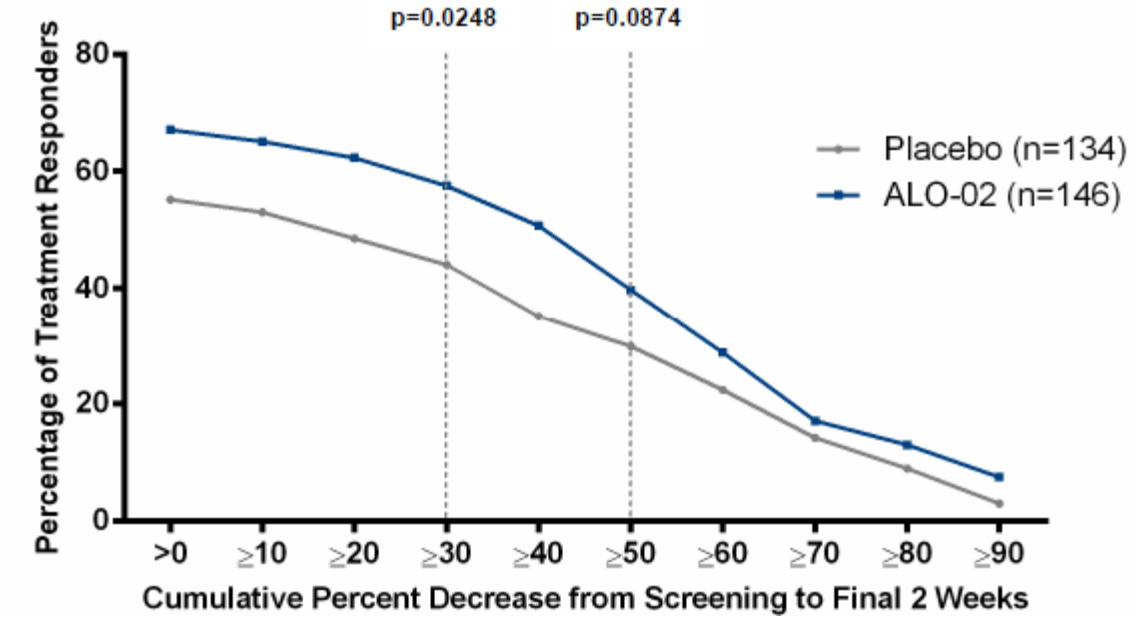
(Applicant's table, CSR, p. 92)

Figure 2 Mean Pain Intensity over Time, Study B4531002



There is a separation between the continuous responder curves of the two treatments (Figure 3). The results for a 30% percent reduction in weekly average pain scores from screening to the final two weeks of the double blind period was 44% for the placebo group and 57% for Troxyca ER group, and for a 50% reduction in pain intensity, 30% and 40% for the placebo group and Troxyca ER group, respectively. In the following figure from Dr. Li's review, the percentage of subjects is plotted against the percent reduction in pain intensity, showing that the percentage of subjects in the Troxyca ER group with a reduction in pain intensity was greater than the placebo group for all percent reductions from 0 through to 70%. Subjects who discontinued study drug were considered as non-responders in the calculations.

Figure 3 Continuous Responder Curve, Study B4531002



The study was not powered for statistical analysis of subgroups. Subgroup analyses by sex, age, and race were notable for a larger effect size in patients over 65 years of age and no numerical difference between treatment groups in non-white subjects. Of the 387 subjects in Study B4531001 with pain score at baseline, 338 (87%) were White and 49 (13%) were Non-white subjects. The average pain score decreased from 6.6 to 4.3 for Non-white subjects and 5.8 to 4.0 for White subjects from baseline to Month 12 of treatment. The Applicant was unable to explain the difference in response in White and Non-white subjects in B4531002, and noted comparable pain scores at baseline. The Applicant performed a literature search from 1966 to September 2014 that was based on Ovid Medline, Embase, Embase Daily Alerts, Biosis Previews, CAB Abstracts and Derwent Drug File, but did not find any articles that could shed light on this finding.

Forty-two percent of the subjects enrolled in Study B4531002 had been on opioid analgesics prior to the study. The effect size was similar for patients previously on opioids and those previously on non-opioids. This is an important finding because it demonstrates that patients on opioid analgesics for longer than the study period based on prior use, continued to respond to opioids at the end of the 12-week double-blind period

There were numerous secondary analyses, but there were no prespecified statistical adjustment for multiplicity so the p-values reported by the applicant were not adjusted. Rescue use was slightly higher in the placebo group.

Table 1: Amount of Rescue Acetaminophen Administered During the Double-Blind Period

		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.

There was no difference across treatment groups in the change for the Roland-Morris Disability Questionnaire from Randomization baseline to Week 12/Early Termination, although there was improvement described for the overall group from Screening to the time of Randomization. A similar pattern was noted for the Patient Global Assessment.

Overall, Study B4531002 demonstrates efficacy for Troxyca ER in a patient population with chronic pain. The lack of an apparent treatment effect in the small subpopulation of non-white subjects may be due to differences in perception of pain, and response to oxycodone. However, the small number of subjects makes it difficult to draw any conclusions about this subgroup.

8. Safety

A total of 1,033 subjects received at least one dose of Troxyca ER or simulated Troxyca ER (oxycodone HCl/naltrexone HCl with naltrexone in a 12% ratio to oxycodone): 805 subjects in the two Phase 3 studies, 160 subjects in the naltrexone dose ratio/abuse potential studies, and 68 subjects in the clinical pharmacology studies. The to-be-marketed formulation was used in the two Phase 3 studies, the intranasal and oral abuse liability studies, and four clinical pharmacology studies.

In addition to Study B45321002 described above, safety data were obtained from chronic pain patients in Study B45321001, an open-label, single-arm safety study of Troxyca ER in subjects with moderate to severe chronic noncancer pain. The study entry criteria and dosing regimen were comparable to Study B45321002, except patients could have chronic noncancer pain from a variety of etiologies, not just low back pain, and Troxyca ER could be dosed once or twice daily at the discretion of the investigators. The plan was to enroll at least 350 male and female adult subjects with moderate-to-severe chronic noncancer pain who required a continuous around-the-clock opioid analgesic for an extended period of time. Subjects could have been receiving an opioid or non-opioid for the management of their pain at the time of study entry. 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 oxycodone in a 24-hour time interval, administered twice daily. The dosing for this study was nearly the same as those for Study 1002. However, investigators were permitted

to use an alternative opioid conversion schedule at their discretion, and were permitted to opt for once daily dosing of study drug. Opioid-naive subjects were started on Troxyca ER 10 mg/1.2 mg twice daily. The starting dose for opioid-experienced subjects was calculated based on the subject's prior total daily dose of opioids converted to an equivalent dose of oxycodone using established conversion factors where applicable and then halved to obtain the twice daily dose and rounded down to an available dose strength of Troxyca ER. For subjects taking fentanyl prior to starting the study, it was recommended that approximately 10 mg twice daily of Troxyca ER be substituted for each 25 mcg/hour fentanyl transdermal patch.

The rescue was acetaminophen 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 Troxyca ER. At the end of the study, subjects were tapered from Troxyca ER and transitioned to an investigator-determined standard of care.

In the Phase 3 studies, subjects were dosed twice daily in Study B45321002 and once or twice daily in Study B45321001. The total daily dose and duration of exposure to the dose in the Phase 3 studies are shown in the following table from Dr. Kilgore's review. For the first 90 days of exposure, most patients were maintained on doses between 40 and 60 mg of oxycodone, followed by 20 to 40 mg and then 80 to 100 mg. Five patients titrated and remained on doses between 100 to 120 mg for as long as a year, and 10 patients were on doses of 140 to 160 mg per day for the last six months of the year-long open-label safety study. Three patients titrated to more than an average of160 mg per day of oxycodone, maximum 164 mg/day, but only one remained on this dose for as long as a year. One patient reached an average of 189 mg/day of oxycodone and another 173 mg per day, but neither were maintained on these doses long having failed to respond with a reduction in pain.

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

Dose Duration (Days)	Average Daily Dose of Oxycodone HCl (mg)									
	≤20	>20-40	>40-60	>60-80	>80-100	>100-120	>120-140	>140-160	>160	Total
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.

There were two deaths during the Phase 3 clinical trials, both during the open-label safety study. Neither appears to be related to exposure to Troxyca ER. One death was due to a myocardial infarction in a 66 year old man with a history of prior myocardial infarction, hypertension, dyslipidemia, and peripheral vascular disease, two months after starting Troxyca ER. The second death was a 48 year old man who was diagnosed with metastatic squamous cell cancer on Day 270 of treatment with study drug, who subsequently died of disease progression.

There was a total of 10 subjects out of 410 (2%) who experienced 18 serious adverse events during Study B45321002. Of the 10 subjects, eight were treated with Troxyca ER at the time of

the serious adverse event and two were on placebo. The events were atrial flutter, myocardial infarction, cholecystitis, cholelithiasis, cholesterosis, chronic obstructive pulmonary disease, bronchitis, arthritis, costochondritis, drug administration error (maladministration of birth control) with unintended pregnancy and spontaneous abortion, urinary tract infection, suicide attempt with depression, and peripheral vascular disease. It is possible that the cholecystitis may have been associated with use of an opioid and a traffic accident by a 48 year old man may have been related to being on an opioid with sedation.

In Study B45321001, there was a total of 26 subjects out of 395 who experienced 36 serious adverse events, including two that were fatal. The Applicant attributed two of the serious adverse events to possibly being associated with study drug, one subject with cholelithiasis and one with abdominal pain. The following table from the study report by way of Dr. Kilgore's review shows all of the serious adverse events from this study.

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
0004-0010	F/45	162 mg	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
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
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
0029-0002	M/66	83.18 mg	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

Adverse events leading to study discontinuation were most often related to the gastrointestinal symptoms such as nausea, vomiting, constipation, along with somnolence, dizziness and headache.

Common treatment emergent adverse events were generally consistent with the known adverse events associated with oxycodone. The most frequent (greater than or equal to 5%) treatment emergent adverse events in the Phase 3 studies for were nausea, constipation, vomiting, somnolence, headache, and dizziness, with abdominal pain, constipation, diarrhea, and vomiting the most common after Week 19. The following tables are from Dr. Kilgore's review.

Table 45. SOC and Preferred Term Treatment Emergent Adverse Events Occurring in greater than or equal to 2% of Subjects During any Treatment Period (Study 1002)

MedDRA SOC Preferred Term	Open-Label Titration Period (Titration Period Safety Population)	Double-Blind Treatment Period (Double-Blind Safety Population)	
	ALO-02 N=410 n (%)	Placebo N=134 n (%)	ALO-02 N=146 n (%)
Subjects with at least one TEAE	**258 (62.9)**	**75 (56.0)**	**83 (56.8)**
Gastrointestinal disorders	**156 (38.0)**	**23 (17.2)**	**34 (23.3)**
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)
General disorders and administration site conditions	**36 (8.8)**	**6 (4.5)**	**17 (11.6)**
Edema peripheral	3 (0.7)	1 (0.7)	3 (2.1)
Fatigue	13 (3.2)	1 (0.7)	5 (3.4)
Infections and infestations	**54 (13.2)**	**27 (20.1)**	**26 (17.8)**
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)
Injury, poisoning, and procedural complications	**11 (2.7)**	**12 (9.0)**	**6 (4.1)**
Investigations	**4 (1.0)**	**7 (5.2)**	**6 (4.1)**
Metabolism and nutrition disorders	**10 (2.4)**	**1 (0.7)**	**4 (2.7)**
Musculoskeletal and connective tissue disorders	**24 (5.9)**	**13 (9.7)**	**14 (9.6)**
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)
Nervous system disorders	**90 (22.0)**	**10 (7.5)**	**15 (10.3)**
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)
Psychiatric disorders	**25 (6.1)**	**11 (8.2)**	**8 (5.5)**
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)
Respiratory, thoracic and mediastinal disorders	**18 (4.4)**	**3 (2.2)**	**11 (7.5)**
Oropharyngeal pain	1 (0.2)	1 (0.7)	4 (2.7)
Skin and subcutaneous tissue disorders	**41 (10.0)**	**2 (1.5)**	**12 (8.2)**
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.

Dr. Kilgore conducted an assessment of opioid withdrawal adverse events including review of the COWS and SOWS scores. The following has been excerpted verbatim from Dr. Kilgore's 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 (±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 greater than or equal to 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 (±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 in15/129 (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.

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.

The results for the SOWS were similar to the COWS and details can be found in Dr. Kilgore's review.

Of the 11 events in Study B4531002 that were consistent with opioid withdrawal (either investigator-identified or with COWS scores of 13 or greater), five occurred during the open-label titration phase and six during the maintenance phase, four of the five were subjects treated with Troxyca ER. Only one of these subjects had a naltrexone level over 100 pg/mL, and only one event occurred during a period of stable dosing. Five subjects had opioid withdrawal (either investigator-identified or with a COWS score of 13 or greater) in Study B4531001, all associated with dose conversion, taper, or interruption of dosing.

In addition, Dr. Kilgore reviewed cases of possible overdose, misuse, abuse, and dependence. The following is from her review:

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.

Overall, the safety profile of Troxyca ER is consistent with an opioid analgesic. There were no cases of withdrawal thought to be associated with exposure to naltrexone. There were no actual overdoses or cases consistent with inadvertent dose dumping. Troxyca ER, as an extended-release opioid analgesic, will be added to the ERLA Opioid Analgesic REMS and will have the same postmarketing requirements as the other ERLA opioid analgesic products. It will remain under schedule II of the Controlled Substances Act.

9. Advisory Committee Meeting

No novel concerns arose for this application. Troxyca has an abuse-deterrent formulation (b) (4) which was discussed at two advisory committee meetings (November 14, 2008 and October 22, 2010). A joint meeting of the Anesthetic and Analgesic Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held on June 8, 2016, because of the amount of general interest about what abuse-deterrence means in the context of opioid analgesics, and the concern about the abuse of prescription opioids. After presentations by the Applicant and by the Agency, and after an open public hearing, the committee members were asked the following questions.

1. **DISCUSSION:** Please discuss whether there are sufficient data to support a finding that Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules) has properties that can be expected to deter abuse, commenting on support for abuse-deterrent effects for each of the three possible routes of abuse:

    a. Oral
    b. Nasal
    c. Intravenous

Committee Discussion: The committee agreed there was sufficient data to support a finding that Troxyca ER fulfilled the criteria for abuse-deterrent characteristics for the oral, nasal and intravenous routes of administration.

Comment: Most commonly, opioid analgesics are abused by the oral route, and with extended-release formulations, by crushing the product to defeat the extended-release profile to accelerate release and absorption of the opioid. These products are also crushed for snorting and to assist the extraction of opioid for injection. When crushed, there was a clear effect from the sequestered naltrexone in Troxyca in reducing drug liking and willingness to take the drug again by the oral and nasal routes of abuse. However, a number of committee members focused on the extraction studies with regard to oral abuse, and were concerned about the oxycodone being extracted for the purpose of oral abuse which is reflected in the vote on oral abuse below. However, the committee members did not find the extraction properties problematic with regard to preparing the product for intravenous abuse. It is unclear why the committee took this perspective as there were no new data or comments presented to suggest a change in the behavior underlying abuse by the oral route.

2. **VOTE:** Should Troxyca ER be approved for the proposed indication, management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate?

   Vote Result: Yes: 9 No: 6 Abstain: 0

   Committee Discussion: The members who voted in favor of approval noted that Troxyca met the current standards for approval of an extended-release product with regard to clinical efficacy and safety data. Those members who voted "No" stated that the new Centers for Disease Control guidelines[5] recommend against the use of opioids for chronic pain and thought the criteria for approving an extended-release opioid should be modified in accordance with the guidelines.

Comment: While not a topic for this advisory committee meeting, the CDC guidelines do not recommend against the use of opioid for chronic pain. Rather the CDC guidelines found that nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain, and that clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. As noted in the CDC guideline, "the clinical evidence review found insufficient evidence to determine whether pain relief is sustained and whether function or quality of life improves with long-term opioid therapy." The CDC guidelines say that there is clear risk with chronic use of opioids. In addition, while the CDC guidelines say, "Experts agreed that opioids should not be considered first-line or route therapy for chronic pain…" but "This does not mean that patients should be required to sequentially "fail" nonpharmacologic and nonopioid pharmacologic therapy before proceeding to opioid therapy.. Rather the clinical context should be weighed against risks before initiating therapy." In the clinical trial for Troxyca, patients were enrolled only if they had a need for continuous around-the-clock opioid analgesic (at an oxycodone equivalent dose of no more than 160 mg per day) based on a daily average pain intensity by a 0 to 10 numerical rating scale was to have been

[5] https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1 htm

at least 5 and no worse than 9 for at least four of the last seven days of the Screening Period. These were patients previously managed with a non-opioid analgesic, an opioid on an as needed basis, or already managed with daily opioid therapy. So these were not newly presenting patients with chronic pain, rather, patients who had failed nonopioid therapy or were already treated with opioid analgesics by their physicians. So the study entry criteria were somewhat consistent with the CDC guidelines.

3. **VOTE:** If approved, should Troxyca ER be labeled as an abuse-deterrent product by the oral route of abuse?

   Vote Result: Yes: 6 No: 9 Abstain: 0

   Committee Discussion: The majority of the committee voted "No," stating that Troxyca ER should not be labeled as an abuse-deterrent product for the oral route of abuse. Those members who voted "No" were concerned with the extraction of oxycodone and separation from naltrexone in particular solvents as described above. Those members who voted "Yes" stated that the benefits of having another product on the market outweighed the risks.

4. **VOTE:** If approved, should Troxyca ER be labeled as an abuse-deterrent product by the nasal route of abuse?

   Vote Result: Yes: 11 No: 4 Abstain: 0

   Committee Discussion: The majority of the committee voted "Yes," stating that Troxyca ER should be labeled as an abuse-deterrent product for the nasal route of abuse. Those members who voted "Yes" agreed that there was sufficient data provided to show that the product would not separate when crushed. Those members who voted "No" were concerned with the potential of abuse and stated that the determination of an abuser should not be underestimated. Some members of the committee recommended the Agency set different standards for abuse-deterrence.

5. **VOTE:** If approved, should Troxyca ER be labeled as an abuse-deterrent product by the intravenous route of abuse?

   Vote Result: Yes: 9 No: 6 Abstain: 0

   Committee Discussion: The majority of the committee voted "Yes," stating that Troxyca ER should be labeled as an abuse-deterrent product for the intravenous route of abuse. Those members who voted "Yes" agreed that the data was compelling and the drug would provide another option for patients. Those members who voted "No" suggested that the Agency clarify the meaning of abuse-deterrence.

10. Pediatrics

No pediatric studies had been submitted with this application. The new drug combination does trigger the requirements for pediatric studies under the Pediatric Research Equity Act. Opioids can be expected to have similar efficacy for managing pain in pediatric patients over the age of two as in adults. However, the use of an extended-release formulation is of limited value in pediatric pain management below the age of seven because the number of pediatric patients with chronic pain in this age group is extremely small. As a result, the pediatric study requirement for ages birth to less than seven years is waived because necessary studies are impossible or highly impracticable.

Therefore, the Application will be required to conduct a pharmacokinetic and safety study of an age-appropriate formulation of Troxyca ER (oxycodone and naltrexone) in patients seven to less than 17 years of age with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This study is deferred because this product is ready for approval for use in adults, the pediatric study has not been completed, and pediatric studies needed to be delayed until safety and effectiveness was established in adults due to the potential for systemic exposure to naltrexone.

11. Other Relevant Regulatory Issues

Abuse Deterrence

The in vitro assessment of the abuse-deterrent characteristics of Troxyca ER was reviewed by OPQ. Extraction studies were conducted on the equivalent of 40 mg/4.8 mg, intact and crushed Troxyca ER pellets. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The following are important limitations to the studies excerpted from the OPQ review:

The basis for the selection of the time points at which these comparisons are made is unclear and skew the data interpretation. (b) (4)

(b) (4) Overall, this study and the resulting data are of limited value.

Additional data were requested and the Applicant conducted additional extraction studies. (b) (4) The details of these and the original studies are discussed in the OPQ review.

Three human abuse liability studies were conducted to evaluate the abuse-deterrent effects of Troxyca ER. The study phases for all three human abuse potential studies were:

- Screening Visit
- Naloxone Challenge Phase
- Drug Discrimination Phase
- Randomization and entry into the 6 period Treatment Phase
- End-of-Study Visit

Study B4531008 was a randomized, double-blind, double-dummy, placebo-controlled, six-way crossover oral study. The treatment groups were:

- Intact Troxyca ER 60 mg/7.2 mg
- Crushed Troxyca ER 60 mg/7.2 mg
- Crushed Troxyca ER 40 mg/4.8 mg
- Crushed oxycodone HCl immediate-release (IR) 60 mg
- Crushed oxycodone HCl IR 40 mg
- Placebo

Subjects were adult recreational opioid users, defined as a user of opioids for non-therapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 8 weeks before the Screening Visit (Visit 1).

In order to be eligible for the randomized phase, during the discrimination phase subjects had to be able to distinguish oxycodone IR 40 mg from placebo on select subjective drug measures i.e., a greater than or equal to 15 point peak increase for Drug Liking and Take Drug Again, and a greater than or equal to 30 point peak increase for High within two hours following dosing with oxycodone IR relative to placebo. A peak score of greater than or equal to 65 was required on the bipolar measures of Drug Liking within two hours post dose and Take Drug Again at five hours post dose in response to oxycodone IR were required. Subjects were also required to have an acceptable placebo response, defined as a VAS response between 0 to 10 inclusive for High or 40 to 60 inclusive for Drug Liking and Take Drug Again. Subjects had to be able to tolerate study treatments (e.g., no episodes of vomiting within the first four hours post dose).

Of the 81 subjects screened, 75 eligible subjects participated in the Naloxone Challenge Phase, of which 72 subjects completed and three subjects were discontinued; two subjects due to adverse events not related to study drug and one subject discontinued because the entrance criteria were not met. Seventy-two subjects entered the Drug Discrimination Phase; 31 subjects discontinued and 41 subjects successfully completed. Forty one subjects were randomized to the Treatment Phase. A total of 32 subjects completed the Treatment Phase and constituted the Completer Population used for the primary pharmacodynamic analysis.

Although the study was planned with Drug liking and High as the primary endpoints, when it comes to abuse deterrence, it is difficult to know whether small changes are clinically relevant. Therefore, another critical endpoint is whether there is any difference in the subject's willingness to take the drug again.

Oral administration of crushed 40 mg/4.8 mg Troxyca ER was associated with statistically significantly lower means and medians for Drug Liking and Take Drug Again E_{max} compared with crushed 40 mg IR oxycodone HCl. Oral administration of crushed 60 mg/7.2 mg Troxyca ER was associated with statistically significantly lower means and medians for Drug Liking E_{max} compared to crushed 60 mg IR oxycodone HCl. There were numerically lower mean and median Take Drug Again E_{max} for crushed 60 mg/7.2 mg Troxyca ER compared with crushed 60 mg IR oxycodone HCl. These outcomes are shown in the following table.

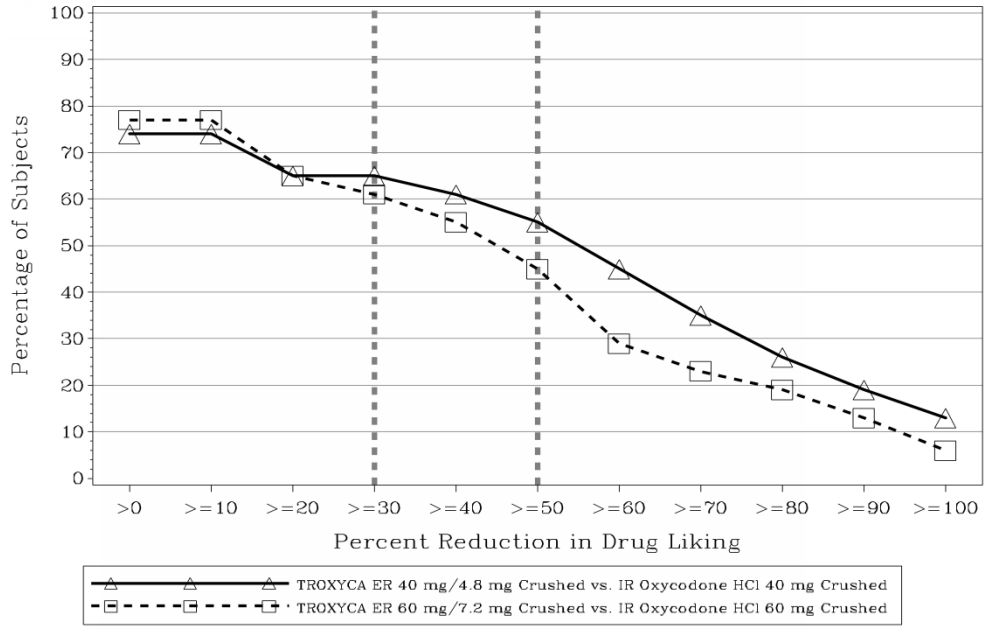
Table 6. Summary Statistics of Abuse Potential Measures of Drug Liking and Take Drug Again with Oral Administration of Crushed Troxyca ER Compared to Crushed IR Oxycodone HCl

Bipolar VAS Scale (100 point)		Placebo N=31	Troxyca ER 40 mg/4.8 mg Crushed N=31	IR Oxycodone 40 mg Crushed N=31	Troxyca ER 60 mg/7.2 mg Crushed N=31	IR Oxycodone 60 mg Crushed N=31
Drug Liking (E_{max})*	Mean (SE)	51.6 (0.68)	69.5 (3.45)	85.6 (2.94)	74.3 (3.30)	90.0 (2.46)
	Median (range)	51.0 (50,68)	64.0 (50,100)	94.0 (50,100)	73.0 (50,100)	100.0 (57,100)
Take Drug Again (E_{max})*	Mean (SE)	45.5 (3.47)	56.7 (6.00)	82.9 (3.66)	71.1 (5.08)	80.6 (4.56)
	Median (range)	50.0 (0,92)	58.0 (0,100)	90.0 (30,100)	77.0 (0,100)	90.0 (0,100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).
E_{max} = maximal response for Drug Liking and Take Drug Again; ER = extended-release; IR = immediate-release; SE = standard error

The following figure describes a comparison of Drug Liking E_{max} for crushed Troxyca ER compared to crushed IR oxycodone HCl when given by the oral route in subjects who received both Troxyca ER and IR oxycodone treatments. The Y-axis represents the percent of subjects attaining a percent reduction in Drug Liking E_{max} with crushed Troxyca ER vs. IR oxycodone greater than or equal to the value on the X-axis. Among the 31 subjects, 74% (23) and 77% (24) experienced some reduction in Drug Liking E_{max} with crushed 40 mg/4.8 mg Troxyca ER and crushed 60 mg/7.2 mg Troxyca ER, respectively, compared to crushed IR oxycodone, while 26% (8) and 23% (7) of subjects had no reduction in Drug Liking E_{max} for crushed 40 mg/4.8 mg Troxyca ER and crushed 60 mg/7.2 mg Troxyca ER, respectively. With crushed 40 mg/4.8 mg Troxyca ER, 65% of subjects had at least a 30% reduction and 55% of subjects had at least a 50% reduction in Drug Liking E_{max} compared to crushed 40 mg IR oxycodone. With crushed 60 mg/7.2 mg Troxyca ER, 61% of subjects had at least a 30% reduction and 45% of subjects had at least a 50% reduction in Drug Liking E_{max} compared to crushed 60 mg IR oxycodone.

Figure 1. Percent Reduction Profiles for E_{max} of Drug Liking VAS for Oral Administration of Crushed Troxyca ER vs. Crushed IR Oxycodone HCl



The study results show that oral crushed Troxyca ER 40 mg/4.8 mg resulted in statistically significant reductions in maximum drug liking and willingness to take the drug again compared to immediate-release oxycodone 40 mg so it can be expected to deter oral abuse. There were statistically significant reductions in the scores for Troxyca ER 60 mg/7.2 mg for drug liking and high compared to immediate-release oxycodone 60 mg, but only a numerical reduction in willingness to take the drug again. These data are supportive that there may be a deterrent effect for the 60 mg dose, but are not as strong as for the 40 mg dose.

Study B4531009 was a single center, intranasal, randomized, double-blind, placebo- and active-controlled, four-way crossover study in healthy, non-dependent, recreational opioid users. For this study, a recreational opioid user was defined as a user of opioids for non-therapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the eight weeks before the Screening Visit (Visit 1). Subjects were required to have had experience with intranasal (IN) opioid administration, defined as IN use on at least three occasions within the last year before Screening. The treatments in this study were:

- Crushed Troxyca ER 30 mg/3.6 mg
- Crushed oxycodone HCl IR 30 mg
- Crushed placebo (sugar spheres) weight match to Troxyca ER 30 mg/3.6 mg
- Crushed placebo (lactose tablets) weight matched to oxycodone HCl IR 30 mg.

In order to advance to the Treatment Phase, during the Discrimination Phase, subjects were required to be able to distinguish oxycodone from placebo on select subjective drug measures, i.e., greater than or equal to 15 points peak increase for Drug Liking and Take Drug Again, and greater than or equal to 30 points peak increase for High within two hours following dosing with oxycodone relative to placebo) when administered IV. A peak score of greater than or equal to

65 on bipolar measures of Drug Liking within two hours post-dose and Take Drug Again at five hours post-dose in response to oxycodone were required. Subjects must have also displayed an acceptable placebo response (defined as a VAS response between 0 to 10 inclusive for High or 40 to 60 inclusive for Drug Liking and Take Drug Again) and tolerate study treatments safely (i.e., SpO2 >90%, no episodes of vomiting within the first two hours post-dose).

The weights and crushed (b) (4) volumes of the Troxyca ER 30 mg/3.6 mg capsule and the oxycodone IR three 10 mg tablets differed ((b) (4) mg versus (b) (4) mg, respectively). In order to reduce the risk of unblinding of the subjects during intranasal administration, this study utilized two placebo controls. Placebo lactose tablets were crushed and weight matched to the oxycodone IR three 10 mg tablets, and placebo sugar spheres were crushed and matched to the Troxyca ER to fill weight.

Forty-five subjects entered the Drug Discrimination Phase and a total of 32 subjects successfully completed the Drug Discrimination Phase. Three subjects were discontinued after treatment with oxycodone HCl IR due to an adverse event and one subject was discontinued after treatment with placebo lactose due to a protocol violation. Nine subjects completed drug discrimination procedures, but were discontinued because they did not meet the entrance criteria. The 32 subjects were randomized in the Treatment Phase.

Intranasal administration of crushed Troxyca ER was associated with statistically significantly lower means and medians for Drug Liking and Take Drug Again E_{max} compared with crushed IR oxycodone HCl (Table 7).

Table 7. Summary Statistics of Abuse Potential Measures for Drug Liking and Take Drug Again with Intranasal Administration of Crushed Troxyca ER Compared to Crushed IR Oxycodone HCl

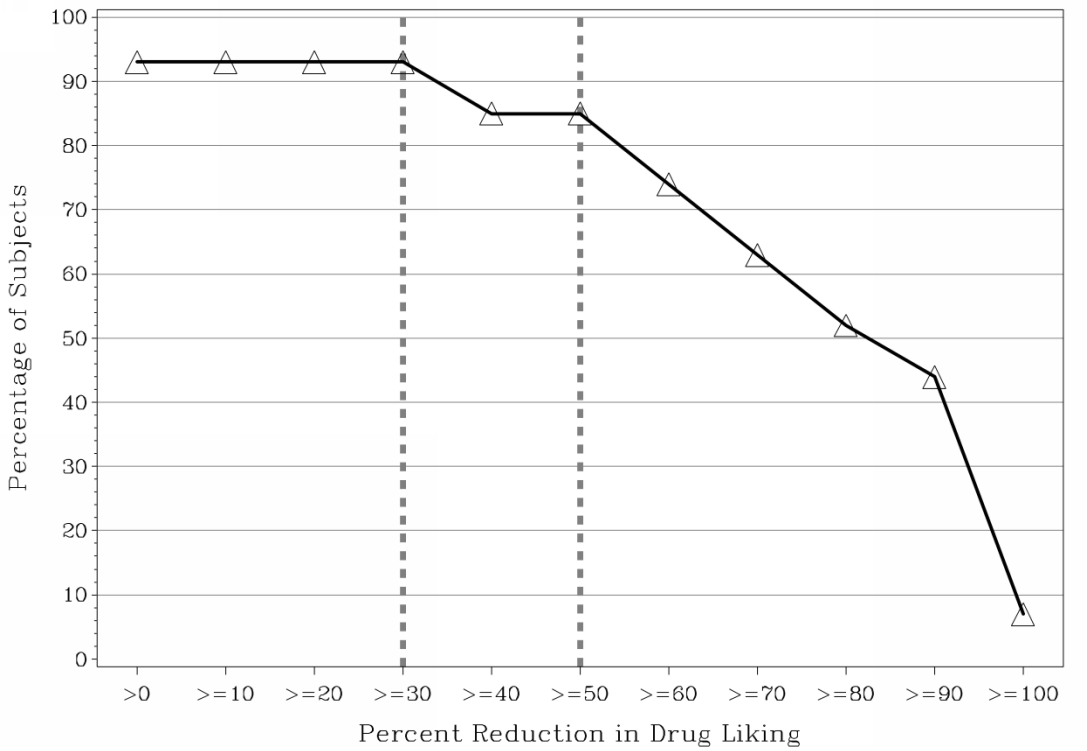
VAS Scale (100 point)		Placebo for Troxyca ER N=27	Troxyca ER 30 mg/3.6 mg Crushed N=27	Placebo for IR Oxycodone N=27	IR Oxycodone 30 mg Crushed N=27
Drug Liking (E_{max})*	Mean (SE)	51.0 (0.23)	60.3 (2.36)	51.3 (0.65)	93.7 (2.11)
	Median (range)	51.0 (50,56)	55.0 (50,100)	51.0 (50,68)	100.0 (50,100)
Take Drug Again (E_{max})*	Mean (SE)	47.9 (2.92)	58.1 (6.27)	46.5 (3.67)	88.5 (5.18)
	Median (range)	50.0 (0,83)	51.0 (0,100)	50.0 (0,98)	100.0 (0,100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).
E_{max} = maximal response for Drug Liking and Take Drug Again; ER = extended-release; IR = immediate-release; SE = standard error

The following figure describes a comparison of drug liking E_{max} for crushed 30 mg/3.6 mg Troxyca ER compared to crushed 30 mg IR oxycodone HCl in subjects who received both treatments in terms of percent reduction. Among 27 subjects, 93% (25) experienced some

reduction in Drug Liking E_{max} with crushed Troxyca ER compared to crushed IR oxycodone, while 7% (2) of subjects had no reduction in Drug Liking E_{max} for crushed Troxyca ER compared to crushed IR oxycodone HCl. With crushed Troxyca ER 93% of subjects had at least a 30% reduction in Drug Liking E_{max} and 85% of subjects had at least a 50% reduction in Drug Liking E_{max} compared to crushed IR oxycodone HCl.

Figure 2. Percent Reduction Profile for E_{max} of Drug Liking VAS for Intranasal Administration of Crushed 30 mg/3.6 mg Troxyca ER vs. Crushed 30 mg IR Oxycodone HCl in the Intranasal Study



These data support a finding that Troxyca ER has abuse-deterrent properties that can be expected to reduce abuse by the intranasal route of administration.

Study B4981002 was a randomized, single-dose, placebo-controlled, double-blind, three-way crossover study. Treatments in this study were simulated Troxyca ER 20 mg/2.4 mg IV, oxycodone HCl 20 mg IV, and placebo. Treatments were administered intravenously over four minutes (±15 seconds).

During the Drug Discrimination Phase, subjects randomly received one of the two treatments, one treatment per day, over two consecutive days (Days 1 and 2), to fasted subjects in a double-blind fashion:

- Oxycodone HCl 20 mg IV push
- Placebo (0.9% sodium chloride)

Of the 60 subjects screened, all passed the Naloxone Challenge Test and entered the Drug Discrimination Phase. Twenty-seven subjects did not complete the Drug Discrimination Phase. Five subjects were discontinued after treatment with oxycodone HCl 20 mg IV due to treatment-related adverse events. Seventeen subjects completed drug discrimination procedures, but were discontinued because they did not meet randomization criteria for the Treatment Phase. One subject was discontinued after treatment with placebo due to unwillingness to participate in the study. Four subjects were discontinued due to other reasons unrelated to the study drug. In the Treatment Phase, 33 subjects were randomized and constituted both the Safety and pharmacokinetic populations. Three subjects were discontinued in the Treatment Phase due to testing positive in urine drug screens.

A total of 29 subjects completed the Treatment Phase and constituted the Completer Population used for the primary pharmacodynamic analysis. Twenty-nine subjects completed all treatment sessions. The study results show that compared to oxycodone HCl 20 mg IV, simulated Troxyca ER 20 mg/2.4 mg IV had statistically significant reductions of 65% and 70% mean maximum liking and high, respectively. The majority of the subjects had at least 65% reduction in both maximum liking and high. While this study is supportive of a deterrent effect for the intravenous abuse of Troxyca ER, because of unknowns regarding the actually amount of oxycodone and naltrexone administered following preparation for intravenous abuse, the results are not sufficient to support a labeling statement for abuse-deterrent properties by the intravenous route of administration.

Inspections

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. (b) (4) Site 1001 in Canada was selected to represent a Canadian site.

No problems were found at the two clinical efficacy and one human abuse potential study site inspected.

Financial Disclosures

Dr. Kilgore reviewed the financial disclosure documentation. The following is from her review:

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 …

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. There were no investigators for whom financial disclosure demonstrated a reason for why the study data from their sites could not be included in the analyses.

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling reviews were obtained from the Office of Surveillance and Epidemiology and the Office of Prescription Drug Promotion. Suggested changes were incorporated into the product labeling and carton and container labeling. The proprietary name was reviewed and found acceptable.

The REMS material for adding Troxyca ER to the Extended-Release and Long-Acting Opioid Analgesic REMS was reviewed by the Office of Surveillance and Epidemiology and the final version found acceptable.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval
- Risk Benefit Assessment

The Applicant has provided an adequate assessment of the pharmacokinetic properties of Troxyca ER, in comparison to Roxicodone, to create the scientific bridge needed to rely on the Agency's prior finding of clinical safety and effectiveness for Roxicodone and has provided an adequate justification in lieu of a clinical pharmacology study to support a scientific bridge to the Agency's prior finding of clinical safety and effectiveness for Revia. There is an effect of co-administration with alcohol on the pharmacokinetic profile of oxycodone, but it is not large enough to be of clinical concern. There are adequate data describing the chemistry, manufacturing and controls to support marketing Troxyca ER with a 36-month expiry. There are adequate data from studies and literature to support the nonclinical assessment of the formulation and excipients to support approval, however, a post-marketing requirement is necessary for pre- and post-natal study to complete the safety qualification for one of the excipients, DBS, when the product is used at the maximum theoretical daily dose.

There are adequate data from the clinical efficacy trial to confirm that the systemic exposure to naltrexone does not block the efficacy of the oxycodone from Troxyca ER, and there are adequate clinical data to support the safety of the formulation and support the proposed dosing instructions. As discussed, the patient population enrolled in the study was not new to treatment for chronic pain. The population may not have met all of the criteria regarding nonpharmacologic treatment prior to and during pharmacologic treatment for chronic pain as described in the CDC guidelines, but the 42% of the patients who had a history of opioid use were able to contribute to the demonstration of efficacy. The adverse events were consistent with an opioid analgesic and there were no unexpected findings. There has been much written and said over the past few years about concern that there are no data to support the efficacy of opioid analgesics beyond three months, because the available adequate and well-controlled efficacy studies are of 12 weeks duration. Forty-two percent of the subjects enrolled in Study B4531002 had been on opioid analgesics prior to the study, and there was no difference in the treatment effect in these patients indicating they were able to respond to opioid analgesics beyond the 12-week study period.

The human abuse potential studies support that Troxyca ER has properties that can be expected to deter abuse by the oral and nasal routes of administration. (b) (4) There are adequate data to support the Applicant's request to include the results of the assessment of the abuse-deterrent properties of Troxyca ER and to conclude that Troxyca ER is likely to deter abuse by the oral and intranasal routes of administration, although abuse by these routes, and the intravenous route of administration, is still possible. As noted, the advisory committee members decided that possible extraction of oxycodone made the deterrent characteristics less impressive for oral abuse, but not intravenous abuse, although, oral abuse is generally occurs by crushing extended-release opioid analgesics to defeat the extended-release pharmacokinetic profile and intravenous abuse is generally more often a result of some type of extraction. The committee was concerned that motivated abusers would find a way to defeat the abuse-deterrent properties. That is not just a real concern, but, because abuse-deterrent opioid analgesic must be able to deliver the opioid to the pain patient, it is expected.

Abuse-deterrent does not mean abuse-proof. Abuse-deterrent means that that there are properties of a formulation that are likely to make abuse by one or more routes more difficult than non-abuse-deterrent products. As newer formulations are developed, there may be evidence of incremental improvement with regard to abuse-deterrent properties, but as long as the product can deliver the opioid, abuse will remain possible. Also, as long as the product can deliver the opioid, addiction will remain a risk. That is why it is critically important that prescribers understand the risks of opioid analgesics, screen patients for risk factors for substance abuse, educate their patients about the importance of following directions, not using more than prescribed, and how to identify symptoms that may indicate the beginning of a problem. Prescribers must know how to look for signs of a substance abuse problem and how to identify and monitor their patients closely for signs they may be having a problem early, and then what to do if they find a problem developing. Ideally, patients with chronic pain would be managed using a carefully coordinated, multidisciplinary team using nonpharmacologic and pharmacologic therapies. However, such programs are not widely available in the US and generally not well reimbursed by insurance carriers.[6] Many insurance carriers also place limits on the amount of nonpharmacologic treatments that patients can undertake. That leaves physicians few options when managing patients with chronic pain besides pharmacologic therapy. Until these problems of access are addressed, physicians will undoubtedly continue to rely on managing chronic pain with pharmacologic therapies including opioids. Troxyca offers prescribers a treatment option that may be less desirable for abuse than opioid analgesics that lack abuse-deterrent properties. In addition, Troxyca has met the requirements for demonstrating efficacy and safety, and for these reasons, should be approved, with labeling describing the abuse-deterrent properties for the oral and nasal routes of abuse based on the in vivo studies, and with mention of the likely abuse-deterrent properties for the intravenous route based on the simulated intravenous abuse study.

- Recommendation for Postmarketing Risk Management Activities

Troxyca ER will be part of the Extended-Release and Long-Acting Opioid Analgesic (ERLA) Opioid REMS and will be subject to the same postmarketing requirements as the other products in this group.

- Recommendation for other Postmarketing Study Commitments

Pediatric postmarketing study requirement:

2965-1. Conduct a pharmacokinetic and safety study of an age-appropriate formulation of Troxyca ER (oxycodone and naltrexone) in patients seven to less than 17 years of age with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

ERLA opioid class postmarketing study requirements:

[6] Jeffery MM, Butler M, Stark A, Kane RL. Multidisciplinary pain programs for chronic noncancer pain. Rockville, MD: Agency for Healthcare Research and Quality; 2011

3033-1 A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.

This study must address at a minimum the following specific objectives:

a. Estimate the incidence of misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, and addiction.

b. Evaluate and quantify other risk factors for misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	11/2015
Interim Report (Cumulative Enrollment of 470 patients)	05/2017
Interim Report (Cumulative Enrollment of 1,042 patients)	09/2017
Interim Report (Cumulative Enrollment of 1,609 patients)	01/2018
Interim Report (Cumulative Enrollment of 2,300 patients)	06/2018
Study Completion:	10/2019
Final Report Submission:	03/2020

3033-2 An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records.

This study must address at a minimum the following specific objectives:

a. Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain. Stratify overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of abuse/addiction, overdose, and death.

b. Evaluate and quantify other risk factors for abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify overdose by intentionality wherever possible.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission: 11/2014
Study Completion: 04/2019
Final Report Submission: 09/2019

3033-3 A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission: 04/2015
Study Completion: 10/2015
Final Report Submission: 01/2016

3033-4 An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission: 04/2015
Study Completion: 10/2016
Final Report Submission: 02/2017

3033-5 An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioid analgesics for chronic pain.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission: 04/2015
Study Completion: 12/2016
Final Report Submission: 05/2017

3033-6 An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	11/2014
Study Completion:	09/2016
Final Report Submission:	12/2016

3033-7 An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	11/2014
Study Completion:	10/2016
Final Report Submission:	01/2017

3033-8 An observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	03/2015
Study Completion:	10/2017
Final Report Submission:	01/2018

3033-9 An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	03/2015
Study Completion:	09/2018
Final Report Submission:	12/2018

3033-10 An observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	03/2015
Study Completion:	03/2017
Final Report Submission:	06/2017

3033-11 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy.

In addition, all of the abuse-deterrent opioid analgesics with premarketing studies supportive of abuse-deterrent properties are required to conduct the following postmarketing studies to evaluate the abuse-deterrent effects after approval.

2965- 2. In order to provide the baseline data to support the hypothesis-testing studies required under PMR 2965-3, conduct a descriptive study that analyzes data on the following:

(1) utilization of TROXYCA ER (oxycodone and naltrexone) and selected comparators. Reports should include nationally-projected quarterly retail dispensing, overall and by age group and census region; AND

(2) abuse of TROXYCA ER (oxycodone and naltrexone) and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for TROXYCA ER (oxycodone and naltrexone) as well as mutually agreed-upon, selected comparators to provide context.

- Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.

- Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.

- Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g. 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

2965-3 Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of TROXYCA ER (oxycodone and naltrexone) actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of TROXYCA ER (oxycodone and naltrexone) and should incorporate recommendations contained in *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry* (April 2015). Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's *Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.*

The following nonclinical postmarketing study requirements are necessary to conclude the evaluation of two impurity/degradants and excipients in the formulation:

2965-4. Conduct an in vivo comet assay for (b) (4) an excipient in Troxyca ER (oxycodone and naltrexone).

2965-5. Conduct an in vivo comet assay for (b) (4) an excipient in Troxyca ER (oxycodone and naltrexone).

2965-6. Conduct a pre- and post-natal development study in the rat model to assess the potential impact of dibutyl sebacate, an excipient in Troxyca ER (oxycodone and naltrexone), on growth and development.

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/s/

SHARON H HERTZ
08/19/2016