FDA ADVISORY COMMITTEE MEETING

BRIEFING DOCUMENT

**ALO-02: Extended-Release Oxycodone
Hydrochloride and Naltrexone Hydrochloride
Capsules**

Meeting Date: 08 June 2016

Pfizer Inc.

Available for Public Disclosure

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AADPAC	Anesthetic and Analgesic Drug Products Advisory Committee
AC	Advisory Committee
ADO	Abuse-deterrent opioid
AE	Adverse event
ALO-02	Extended-release oxycodone hydrochloride and naltrexone hydrochloride
ASI-MV	Addiction Severity Index-Multimedia Version
AUC	Area under the concentration versus time curve
AUC_{inf}	Area under the concentration versus time curve from time 0 to infinity
AUE	Area under the effect curve
BA	Bioavailability
BID	Twice daily
BMI	Body mass index
BPI-sf	Brief Pain Inventory-Short Form
CI	Confidence interval
C_{5min}	Concentrations of oxycodone observed 5 minutes after the start of infusion
C_{max}	Maximum plasma concentration
COMM	Current Opioid Misuse Measure
COWS	Clinical Opiate Withdrawal Scale
DEA	Drug Enforcement Agency
DSaRM	Drug Safety and Risk Management Advisory Committee
eDiary	Electronic Diary
EERW	Enriched enrollment, randomized withdrawal
ER	Extended-release
E_{max}	Maximum effect
FDA	Food and Drug Administration
HAP	Human abuse potential
HCl	Hydrochloride
IR	Immediate-release
ITT	Intent-to-treat
IV	Intravenous
LA	Long-acting
LOQ	Limit of quantitation
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
N	number of subjects evaluable
NDA	New drug application

Abbreviation	Definition
NRS	Numerical Rating Scale
PBO	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetic
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SOCF	Screening observation carried forward
$t_{1/2}$	Drug half-life
T_{max}	Time of occurrence for maximum (peak) drug concentration
US	United States
USPI	United States Product Insert
VAS	Visual Analogue Scale

1. EXECUTIVE SUMMARY

ALO-02 is in registration as an agonist/antagonist abuse-deterrent opioid (ADO) containing extended-release (ER) oxycodone hydrochloride (HCl) and 12% sequestered naltrexone HCl. This briefing document has been prepared to support the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), which is scheduled for 08 June 2016. The joint advisory committee meeting is hereafter referred to as the AC meeting. The AC meeting aims to answer the question whether the data submitted for ALO-02 in New Drug Application (NDA) 207621 are sufficient to support labeling of the product with the properties expected to deter abuse.

As noted in the Food and Drug Administration's (FDA) Guidance,[1] opioids, especially those without abuse-deterrent properties, are often manipulated for purposes of abuse by routes of administration other than intended, or to defeat the ER properties of the product. The objective of an ADO analgesic is to render drug manipulation more difficult and less rewarding, thereby reducing unintended misuse by patients and making manipulated product less attractive to abusers. The FDA Guidance defines abuse-deterrent properties as "those properties shown to meaningfully deter abuse, even if they do not fully prevent abuse".

Pfizer, the Sponsor of ALO-02, currently markets EMBEDA® (morphine sulfate and naltrexone HCl), an ER morphine that was approved and labeled with abuse-deterrent properties in October 2014.[2] ALO-02 is an ER oxycodone and employs the same proprietary sequestered naltrexone abuse-deterrent formulation technology used in EMBEDA. When ALO-02 is taken by the patient as directed, oxycodone is released in an extended manner to provide sustained pain relief and the naltrexone remains sequestered, thus imparting no clinical effect. However, if the product is manipulated (eg, by crushing), naltrexone is released and acts as a competitive opioid antagonist at the mu opioid receptor, resulting in reduced abuse potential.

Currently available ER ADOs containing oxycodone utilize a physical/chemical barrier technology to deter abuse. The agonist/antagonist abuse-deterrent technology of ALO-02 will provide an additional pain treatment option for prescribers and patients, addressing the public health epidemic related to prescription opioids.

The ALO-02 development program has incorporated ongoing feedback from FDA and is consistent with the FDA Guidance for ADOs.[1]

1.1. Proposed Indication, Dosing Route and Regimen

ALO-02 is intended to be used as an ER opioid analgesic for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Because of the risks of addiction, abuse and misuse with opioids even at recommended doses, and because of the greater risks of overdose and death with ER opioids, it is intended that ALO-02 should be reserved for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release [IR] opioids) are ineffective, not tolerated, or would be otherwise inadequate to

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provide sufficient pain relief. ALO-02 is not intended to be indicated as an as-needed (prn) analgesic.

The ALO-02 formulation has been developed to deter abuse and misuse associated with common methods of product manipulation and unintended routes of administration. Naltrexone HCl remains sequestered if ALO-02 is taken as directed, but is released if ALO-02 is crushed, antagonizing the pharmacodynamic (PD) effects of oxycodone, including Drug-Liking and High.

ALO-02 will be a Schedule II drug under the Controlled Substances Act and subject to the class labeling of an ER/long-acting (LA) opioid analgesic and will require a Medication Guide for patients. ALO-02 will also be subject to the ER/LA Opioid Analgesic Risk Evaluation and Mitigation Strategy (opioid analgesic class REMS). Further information is provided in Section 4.3.

If approved, ALO-02 is to be administered every 12 hours, twice daily (BID), by the oral route, with or without food.

1.2. Regulatory History

A 505(b)(2) NDA 207621 for ALO-02 was developed using Revia® (naltrexone HCl) and Roxicodone® (oxycodone HCl) as the reference products. The NDA has provided full reports of abuse deterrent, clinical pharmacology, and efficacy and safety studies conducted with ALO-02, as well as the evidence to bridge ALO-02 to Revia and Roxicodone. The NDA was submitted 19 December 2014, accepted for filing on 23 February 2015 as a standard review with a Prescription Drug User Fee Act (PDUFA) date of 19 October 2015. The PDUFA date was subsequently extended to 19 January 2016 due to the submission of a major amendment of nonclinical data supporting the safety of an excipient. The FDA has deemed the review complete and has reached agreement with the Sponsor on most aspects of the ALO-02 label. On 4 February 2016, the FDA announced an action plan on opioids to comprehensively review their portfolio of activities and reassess current strategies to respond to the growing epidemic of opioid abuse, addiction and overdose related to the widespread use of opioid pain medications. On 25 February 2016, the FDA confirmed that all opioids including ADOs in registration, including ALO-02, would be taken to an Advisory Committee.

During the ALO-02 development, the FDA provided input through meetings and advice letters on the studies necessary to evaluate abuse deterrence. The advice was implemented, and the studies conducted with ALO-02 are consistent with FDA final guidance for the evaluation and labeling of ADOs (CDER 2015).[1]

1.3. Background on Condition to be Treated

There is a considerable burden of chronic pain in the United States (US) adult population and a variety of analgesics, including opioids, are available to manage it. Opioids are an effective treatment option when used appropriately; however, increased misuse, abuse and diversion associated with opioids is a well-recognized problem in the US. Further information is provided in Section 2.1.

1.4. Abuse-Deterrent Properties

Per FDA guidance, data from Categories 1, 2 and 3 studies demonstrated the abuse-deterrent properties of ALO-02 in support of the proposed prescribing information (Section 9.2 of the United States Product Insert [USPI]). The in-vitro and pharmacokinetic (PK) data demonstrated that crushing ALO-02 pellets resulted in the simultaneous release and absorption of oxycodone HCl and naltrexone HCl, providing the abuse deterrent properties of ALO-02. These data in combination with results from the human abuse potential (HAP) studies indicate that ALO-02 has properties that are expected to reduce abuse via oral and non-oral routes. Further information is provided in Section 3.2.1.

1.5. Clinical Pharmacology and Biopharmaceutics

The ALO-02 formulation provides ER of oxycodone with Bioavailability (BA) equivalent to Roxicodone, time of occurrence for maximum (peak) drug concentration (T_{max}) of 12 hours and drug half-life ($t_{1/2}$) of approximately 7 hours. Upon BID administration of ALO-02 capsules, oxycodone steady-state was reached within 48 hours. ALO-02 capsules may be taken with or without food. The capsules may also be opened and the pellets sprinkled on applesauce and swallowed without crushing. Data obtained following the administration of single doses of ALO-02 20 mg/2.4 mg capsules with 20% or 40% ethanol solutions did not suggest an over-exposure to oxycodone. When ALO-02 capsules are crushed and administered orally, the sequestered 12% naltrexone HCl is released with BA equivalent to that of the same dose of naltrexone HCl in solution. Further information is provided in Section 3.2.2.

1.6. Clinical Efficacy and Safety

The analgesic efficacy and safety of ALO-02 were demonstrated in 2 Phase 3 clinical studies, B4531002 and B4531001. Study B4531002, with an enriched enrollment, randomized withdrawal study design, enrolled a total of 410 subjects with moderate-to-severe chronic lower back pain. The primary efficacy endpoint was met in this pivotal study. A 12-month open-label safety study B4531001, with a total of 395 enrolled subjects, demonstrated ALO-02 significantly reduced pain, in subjects with chronic non-cancer pain, for the duration of the study. Further information is provided in Section 3.2.3. In these studies, the safety and tolerability profile of ALO-02 was consistent with other opioids. The evaluation of safety events of special interest produced few signals of drug abuse, dependence, aberrant behavior, or withdrawal. Most of the events of drug withdrawal occurred during study medication dosage adjustment. Further information is provided in Section 3.2.4.

1.7. Benefit/Risk Balance

ALO-02 has demonstrated a favorable benefit/risk balance, as summarized below.

- The analgesic benefits of ALO-02 have been demonstrated in a double-blind, placebo-controlled study in subjects with moderate-to-severe chronic lower back pain and supported by the demonstration of effectiveness in a long-term open-label safety study in subjects with chronic non-cancer pain (Section 3.2.3).

- The safety profile of ALO-02 was consistent with that of other opioids in this patient population (Section 3.2.4).

- There were no measurable naltrexone exposures with oral administration of ALO-02 across all Phase 1 studies. In the 2 Phase 3 studies, low levels of naltrexone exposure were observed in ~18-23% of samples collected; however, they were not related to ALO-02 dose, nor did they impact clinical efficacy/safety (Section 3.2.2).

- The in-vitro (Category 1 studies) and PK (Category 2 studies) data demonstrate that crushing ALO-02 pellets results in simultaneous release and absorption of oxycodone and naltrexone (Sections 3.2.1.1 and 3.2.2).

- The HAP (Category 3) studies in recreational opioid abusers demonstrated reduced abuse potential of ALO-02 following manipulation via the oral, intranasal and intravenous (IV) routes (Section 3.2.1.2.2).

- These data indicate that ALO-02 is expected to meaningfully deter abuse following manipulation by oral and non-oral routes, and consistent with the Agency's final guidance, ALO-02 is not expected to completely prevent abuse.

In summary, the clinical program for ALO-02 has established a favorable benefit/risk profile for ALO-02 in the treatment of chronic low back pain and chronic non-cancer pain and provided robust evidence to support labeling for abuse-deterrent properties. Further information is provided in Section 4.

2. INTRODUCTION

There is a considerable burden of chronic pain in the US adult population. Opioids can be an effective treatment option for chronic pain when used appropriately; however, opioid use has been associated with increased opioid abuse, addiction and overdose.[3]

2.1. Non-Medical Use of Opioids in the US

Increasing use of opioids over time has resulted in a significant degree of illicit use including abuse and diversion. In 2014, the US-based National Survey on Drug Use and Health estimated that approximately 10.3 million persons aged ≥12 years used pain relievers non-medically in the past year.[4] The number of admissions to substance abuse treatment centers due to opioid abuse increased from approximately 327,000 in 2003 to 472,000 in 2013.[5] Likewise, there has been a similar increase in emergency department visits related to non-medical use of opioid pain medications from approximately 145,000 in 2004 to 366,000 in 2011.[6] Finally, there has been a corresponding increase in deaths associated with overdose of prescription opioids from approximately 4,030 in 2000 to almost 19,000 in 2014.[3,7] Diversion of legitimately prescribed opioids from patients to other individuals appears to be a significant source of opioid medications for non-medical use. While approximately 25% of non-medical users reported obtaining their prescriptions from one or more doctors, approximately 66% of non-medical users obtained their opioid for free or bought or stole it from relatives or friends.[4]

Most individuals in the US who acknowledge non-medical use (ie, misuse/abuse) of prescription opioids ingest the medication intact, and even among individuals in treatment for substance abuse, the oral route predominates. However, data collected from opioid abusers entering substance abuse treatment centers using the Inflexxion Addiction Severity Index-Multimedia Version (ASI-MV) system suggest that the predominant route of abuse varies from product to product. For instance, while patients admitted to substance abuse treatment centers report that oral ingestion of intact pills is the most common route of abuse for IR combination products containing oxycodone or hydrocodone (82-89%), oral ingestion following chewing and non-oral routes of abuse is common for ER opioids.[8] Moreover, in a recent survey of 251 participants from the US National Health and Wellness survey who reported prescription opioid abuse, over half reported tampering with their opioid to get high and approximately 40% of the respondents reported chewing, snorting or injecting the opioid.[9]

Poison center data show that opioid exposures involving an unintended route were 63% more likely to be associated with death or major medical outcomes than oral ingestion. Death or major medical outcomes occurred in 12.5% of inhalation and in 13.4% of injection cases compared to 7.2% of cases with oral ingestion.[10] This suggests that abuse by non-oral routes of administration is associated with more serious negative health consequences.

The development of ADOs addresses the continuing medical need for relief of moderate to severe chronic pain using prescription opioids while offering approaches to reduce their misuse/abuse. The FDA has highlighted the development of ADOs as "one potentially important step towards the goal of creating safer opioid analgesics". The FDA's recent guidance[1] on ADOs outlined for sponsors the in-vitro and in-vivo studies that would be required to evaluate the abuse-deterrent performance of novel formulations and labeling that might be expected based on the results of these studies; these include in-vitro laboratory experiments (Category 1 studies), clinical pharmacology studies (Category 2 studies) and HAP studies (Category 3 studies) in which the performance of the ADO is compared to products that do not have abuse-deterrent features. The guidance identified 7 major possible categories of abuse-deterrent technologies which include physical/chemical barrier, agonist/antagonist, aversion, delivery systems, prodrugs, combinations of the above and novel, not yet identified approaches. To date, only 2 of these platforms have reached the market, and the only ADO containing ER oxycodone on the market is OxyContin® (a physical/chemical barrier approach). While Targiniq ER, an agonist/antagonist formulation containing ER oxycodone and naloxone was approved, it has not been made available by its sponsor. A second ADO containing ER oxycodone has been approved (Xtampza ER) and utilizes a physical/chemical barrier approach.

2.2. OxyContin®

OxyContin, an ER version of oxycodone, was first approved in 1995.[11] In 2010, OxyContin was reformulated (OxyContin OP®) and replaced the original formulation (OxyContin OC®) on the market. OxyContin OP was shown to have reduced Drug-Liking and High with intranasal administration compared to the original formulation in a study in recreational opioid users.[12] Data from this Category 3 study as well as the Category 1 studies were

determined by the FDA in 2013 to support claims that OxyContin is expected to reduce abuse by the intranasal and IV routes but not by the oral route.[13]

Prior to reformulation of OxyContin, non-oral abuse of OxyContin OC was common. For instance, in a study of a limited number of patients admitted to an abuse treatment center in Kentucky for abuse of the original formulation of OxyContin, the majority (83%) of patients reported first using OxyContin by the oral route; however, by the time they were admitted to the treatment center, the routes of abuse had shifted to predominately non-oral routes (88%).[14] Similarly, in a separate study, non-oral abuse of OxyContin was commonly reported by subjects entering abuse treatment centers. For example, in one analysis, 54.5% of subjects reported oral abuse (which included chewing in addition to swallowing intact), 52.7% of the subjects reported snorting, and 35.7% reported injecting OxyContin.[8,14]

With the introduction of the ADO OxyContin OP, the pattern of routes of abuse shifted to oral routes, such that the majority of subjects reported abuse by the oral route (76.1%) with a smaller percentage of abusers reporting snorting (25.4%) or injection (15.9%).[8] In addition to a shift in the pattern of routes of abuse, the introduction of OxyContin OP resulted in a decrease in its overall abuse as measured by a reduction in the prevalence of "past 30-day abuse" of OxyContin reported by patients admitted into substance abuse treatment centers.[8] Qualitatively similar results were also reported in a separate study of 2566 subjects entering abuse treatment centers for prescription opioid abuse.[15] These studies reported reductions in overall abuse and shift in routes of abuse of OxyContin; however, abuse has not been completely eliminated.

3. PRODUCT OVERVIEW

3.1. Abuse-Deterrent Technology

To address the continued problem of ER oxycodone abuse, including abuse via the oral route when crushed, the Sponsor has developed an abuse-deterrent ER oxycodone that uses a technology different from that of OxyContin. Instead of a physical/chemical barrier approach used with OxyContin, ALO-02 utilizes an agonist/antagonist technology that combines ER oxycodone with a sequestered opioid antagonist, naltrexone. As with EMBEDA® which uses this proprietary abuse-deterrent formulation technology,[2] ALO-02 was designed to reduce abuse by the intranasal and IV routes when crushed. Furthermore, in contrast to OxyContin, ALO-02 is also expected to reduce abuse by the oral route when crushed and then swallowed. ALO-02 capsules are hard gelatin capsule shells filled with pellets from a single common formulation to achieve the dosage strengths of 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg oxycodone HCl/naltrexone HCl dosage strengths, respectively. As illustrated in Figure 1, the ALO-02 pellets consist of inert seed cores coated with multiple drug and polymer layers in which ER oxycodone HCl surrounds sequestered naltrexone HCl.

Figure 1. Diagram of the Cross-Section of an ALO-02 (Agonist/Antagonist) Pellet

Rate-controlling membrane
Oxycodone HCl
Sequestering membrane/barrier coat
Sequestered naltrexone HCl core
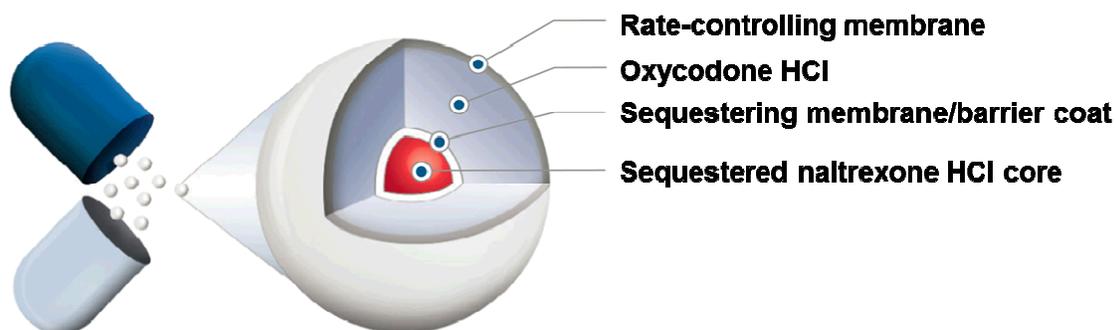
3.2. ALO-02 Development Program

Prior to the initiation of pivotal studies within the development program, 2 dose ratio studies were conducted to characterize the dose response for the antagonist effect of naltrexone on oxycodone agonist across the range of naltrexone/oxycodone dose ratios of 4-24%. Based on the results of these studies, an optimum dose ratio of 12% naltrexone HCl/oxycodone HCl was selected for the ALO-02 formulation.

The ALO-02 development program consisted of 4 clinical pharmacology studies conducted in healthy volunteers, a battery of in-vitro laboratory extraction studies, 3 abuse potential studies in non-dependent recreational opioid users and 2 Phase 3 studies in chronic pain subjects (one of which was a long-term safety study). The key elements of design and treatment for these studies are provided in Table 1.

Table 1. Overview of Pivotal Studies Conducted in the ALO-02 Development Program

Study	Design and Treatments
Clinical Pharmacology Studies in Healthy Volunteers	
Food Effect (B4531003)	Open-label, single-dose, randomized, three-way cross-over ALO-02 40 mg/4.8 mg capsules fasted, ALO-02 40 mg/4.8 mg capsules fed, ALO-02 40 mg/4.8 mg as pellets sprinkled on applesauce
Ethanol Interaction (B4531004)	Open-label, single-dose, randomized, cross-over ALO-02 20 mg/2.4 mg with ethanol 20% and 40% and water
Single- and Multiple-Dose Pharmacokinetics (B4531006)	Open-label, single- and multiple-dose randomized cross-over study for steady state pharmacokinetics, safety, and tolerability of ALO-02 80 mg/9.6 mg once-daily; ALO-02 40 mg/4.8 mg BID, OxyContin 40 mg BID, as single and multiple dose
Pivotal Relative Bioavailability (B4531007)	Open-label, single-dose, randomized, two-way cross-over ALO-02 40 mg/4.8 mg capsules vs IR Roxicodone 20 mg tablets
Abuse-Deterrent Studies	

Table 1. Overview of Pivotal Studies Conducted in the ALO-02 Development Program

Study	Design and Treatments
In-vitro Laboratory Abuse-Deterrent Studies	Examine extraction of naltrexone and oxycodone from crushed and intact pellets in different solvents, different conditions over time in large and small volumes.
Oral ALO-02 vs Oxycodone IR (B4531008)	Randomized, Double-blind, Placebo (PBO) and Active Controlled, cross-over ALO-02 (intact 60 mg/7.2 mg, crushed, 60 mg/7.2 mg, and 40 mg/4.8 mg); oxycodone IR (crushed 60 and 40 mg), PBO
Intranasal ALO-02 vs Oxycodone IR (B4531009)	Randomized, Double-blind, PBO and Active Controlled, cross-over ALO-02 (30 mg/3.6 mg, crushed; oxycodone IR 30 mg, crushed) weight-matched PBO for each
Intravenous (IV) Simulated Crushed ALO-02 vs Oxycodone IR (B4981002)	Randomized, Double-blind, PBO and Active Controlled, cross-over IV oxycodone 20 mg, IV oxycodone 20 mg + naltrexone 2.4 mg, IV PBO
Efficacy and Safety Studies in Subjects With Chronic Pain	
Long-Term Safety (B4531001)	Open-label 12 month, single-arm ALO-02 extended-release (20 mg to 160 mg/day); Chronic non-cancer pain
Safety and Efficacy (B4531002)	Double-Blind; Enriched Enrollment, Randomized Withdrawal x 12 weeks, ALO-02 (20 mg to 160 mg/day) vs PBO; Chronic lower back pain

Abbreviations: BID=twice-daily, IR=immediate release, IV=intravenous, PBO=placebo, vs=versus.

3.2.1. Abuse-Deterrent Evaluation

As described in Section 2.1, there are 3 categories of studies advised by the FDA to support potential claims for reduction in abuse; these include Category 1 (in-vitro), Category 2 (clinical pharmacology) and Category 3 (HAP) studies. The following sections discuss studies in the ALO-02 development program that demonstrate the abuse-deterrent features of the product and support proposed labeling.

3.2.1.1. Category 1 Studies With ALO-02

As described above, the ALO-02 formulation consists of capsules containing pellets of ER oxycodone HCl that surround sequestered naltrexone HCl. When ALO-02 is taken intact, the oxycodone is released in an extended manner to provide pain relief and the naltrexone remains sequestered. However, if the product is manipulated (e.g., by crushing), naltrexone is released and acts as a competitive opioid antagonist at the mu opioid receptor, resulting in reduced abuse potential (see Section 3.2.1.2). The goal of laboratory-based Category 1 studies described below was to evaluate the ease with which the abuse-deterrent properties of the ALO-02 formulation can be potentially defeated or compromised.

In Category 1 studies with ADOs that use a physical/chemical barrier technology (such as OxyContin), the objective is to identify conditions in which one can grind or crush the tablet into small particles to either snort, or dissolve in small or large volumes of solvent for IV or oral administration, respectively. In addition, these physical/chemical barrier technologies

typically contain excipients which when combined with liquids form a viscous gel and syringability and injectability studies are done to evaluate the ease with which these viscous gels can be withdrawn or ejected from syringes with different gauge needles. In contrast, as an agonist-antagonist platform, ALO-02 by design is not resistant to mechanical manipulation (e.g., crushing) and in fact crushing releases naltrexone when manipulated for abuse. Likewise, ALO-02 does not contain excipients that increase the viscosity when added to liquids. Consequently, and based on the FDA guidance for agonist/antagonist platforms and discussions with FDA, the objective of the Category 1 studies for ALO-02 was to explore if any simple or sophisticated conditions could be identified in which oxycodone could be preferentially extracted relative to naltrexone (exposing a potential vulnerability of the formulation). Thus, the abuse deterrent properties of ALO-02 have been evaluated in a comprehensive and diverse battery of in vitro studies (Category 1)[1] with ALO-02 pellets in both the manipulated (crushed) and the non-manipulated (intact) state and simulate procedures that may be used by drug abusers that require different amounts of time and effort.

All Category 1 studies were performed by an external laboratory (AAIPharma, Durham, NC). These studies were extensive, including nine discrete conditions, more than 30 different solvents/media with 3 to 6 replicates, and resulted in over 5000 individual data points.

The studies were performed under controlled laboratory conditions using a specific instrumental method of analysis to provide an accurate assay of both oxycodone HCl and naltrexone HCl. In comparing this level of experimental rigor to the real world situation, the expectation is that abusers would employ less controlled approaches and experience much greater variation in manipulation of ALO-02.

3.2.1.1.1. Overview and Selection Rationale for Studies

Manipulating ER formulations by crushing or chewing is a common method by which abusers attempt to defeat the extended release properties of ADO formulations. For reasons described above, studies to specifically evaluate mechanical manipulation for the purpose of abuse of ALO-02 were not performed. However, particle size reduction techniques were assessed for the purpose for achieving consistent particle size for subsequent extraction studies with crushed pellets. Similarly, because ALO-02 utilizes an agonist/antagonist formulation technology not designed to specifically overcome syringability and injectability, these studies were not conducted.

The rationale for selection, design and prosecution of the in vitro studies was based on:

- The physical and chemical properties of the ALO-02 formulation as an agonist/antagonist platform

- Scientifically rigorous exploration of the potential vulnerabilities of the ALO-02 formulation to the goal of defeating its abuse deterrent properties

- The principles outlined in the FDA Guidance[1]

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- FDA feedback received prior to submission and during review of the ALO-02 NDA

- The expected route of abuse, manipulation and mode of administration and use of an appropriate comparator where relevant

Table 2 summarizes the routes of abuse, manipulation methods, mode of administration of prescription opioids, and the relevant in vitro studies that Pfizer has completed for ALO-02.

Table 2.   Routes of Abuse and Manipulation and Related In Vitro Studies for ALO-02

Route of Abuse	Manipulation Method	Mode of Administration	In Vitro Studies	Study Condition/ Codes
Oral	None (Intact)	Swallow	Not applicable. Formulation not designed to reduce overconsumption	Not applicable
		Dissolve in solvent & swallow	Large volume solvent extraction studies	A, B, D, E, F
	Chew or Crush	Swallow	Not applicable	See Cat. 2/3 studies
	Crush	Dissolve in solvent & swallow	Large volume solvent extraction studies	C
Intranasal	Crush	Snort crushed powder	Not applicable	See Cat. 2/3 studies
IV	None (Intact)	Dissolve in small volumes heat & inject	Small volume solvent extraction studies	G
	Crush	Dissolve in small volumes & inject	Not performed	Refer to C[a]
Smoking	None (Intact)	Heat & vaporize, then inhale	Volatilization studies	H
	Crush	Heat & vaporize, then inhale	Volatilization studies	I

a. Refer to study condition C :large volume solvent extraction studies with crushed pellets

The extensive battery of tests employed multiple assaults on the formulation in an intact and crushed state with exposure to a diversity of physiochemical conditions. Figure 2 summarizes the different attributes of the media (solvents/ matrices) and parameters (conditions) that were explored in the development of the testing strategy for ALO-02.

Figure 2.   Overview of In Vitro Testing Strategy for ALO-02
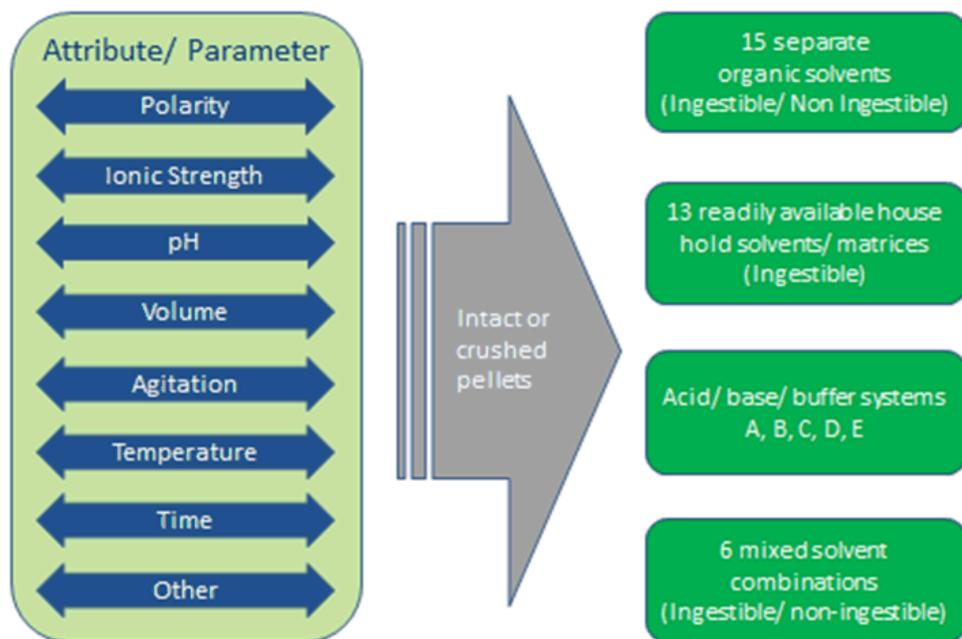
3.2.1.1.2. Summary of Results

For each time point in each solvent/condition studied, an assessment was made of the potential vulnerability of the formulation to abuse. This was based on conservative criteria developed such that the formulation was determined to be abuse deterrent if oxycodone extraction was <30% or if the ratio of %naltrexone to %oxycodone extraction was ≥0.5. The formulation was considered to have a potential vulnerability if oxycodone extraction was ≥30% and the ratio of %naltrexone to %oxycodone extraction was <0.5. The criteria of a 0.5 ratio of naltrexone to oxycodone was selected, as an analysis of dose response data from studies in recreational drug abusers with oxycodone and different ratios of naltrexone indicates a 50% reduction in naltrexone/oxycodone ratio from 12% to 6% would still be associated with at least 60% of the maximum achievable reduction in drug liking.

Large Volume Extraction Studies: Crushed Pellets (Condition C):

Figure 3 (top panel) shows extraction of oxycodone and naltrexone from crushed ALO-02 pellets under condition C at time point 1 for all solvents tested and presented in order of increasing oxycodone extraction. At time point 1, there was similar and nearly complete release of oxycodone and naltrexone in 30 of 31 solvents studied. In one solvent (M27) there was somewhat selective extraction of oxycodone from crushed pellets.

Figure 3 (bottom panel) applied the criteria described above and shows that with the exception of that one solvent (M27), the formulation maintained its abuse deterrent properties. The solvent in which potential vulnerabilities were identified is a non-ingestible hazardous solvent that would require additional steps to separate the oxycodone for oral abuse.

Figure 3. Extraction of Naltrexone and Oxycodone (Mean ± SEM[a]) from Crushed Pellets under Condition C at Time Point 1 (Top Panel) and Abuse Deterrence Profiles Across all Solvents and all Time Points (Bottom Panel)

☐ = time point 1

🟩 % Oxycodone extraction <30% or %Naltrexone extraction/ %Oxycodone extraction ≥0.5

🟧 Oxycodone extraction ≥30%, and %Naltrexone extraction/ %Oxycodone extraction <0.5

a   SEM : Standard error of the mean

Large Volume Extraction Studies: Intact Pellets (Condition B and A)

For condition B, Figure 4 (top panel) shows extraction of oxycodone and naltrexone from intact pellets at time point 1 in the same 31 solvents examined with crushed pellets. These studies demonstrated that at time point 1 there was negligible release of oxycodone and naltrexone from intact pellets for the majority of the solvents. This is consistent with the intended design of ALO-02 to provide extended release of oxycodone and sequestration of naltrexone when taken intact. In a subset of the solvents tested, there was significant extraction of oxycodone (>30%), but extraction of naltrexone also occurred.

Figure 4 (bottom panel) shows the assessment of the abuse deterrence across the 31 solvents over time. The figure demonstrates that for most solvents and time points there was minimal extraction of oxycodone, and that significant extraction(>30%) occurs only at later time points, well beyond one hour, again consistent with its intended design to provide extended release of oxycodone. In some solvents (e.g., M28), there was a brief window of time where oxycodone was extracted with lower amounts of naltrexone (i.e. naltrexone/oxycodone extraction ratio <0.5) but in all solvents this was short lived, as more naltrexone was extracted over time.

For condition A, Figure 5 (top panel) shows for most solvent combinations that oxycodone and naltrexone were rapidly extracted from intact ALO-02 pellets into one of the solvents. In one combination (M10/M11) the oxycodone extraction was slow reaching ~25% over 24 hours from intact ALO-02 pellets in both solvents with no extraction of naltrexone occurring, consistent with its intended design to provide extended release of oxycodone.

Figure 5 (bottom panel) shows the assessment of greatest potential vulnerability for the particular combination over time. The figure demonstrates that for most time points there was either minimal extraction of oxycodone or co-extraction of both oxycodone and naltrexone. For few of the solvent combinations, there was a short window of time where oxycodone was extracted at or above 30% with lower amounts of naltrexone extracted (i.e. naltrexone/oxycodone extraction ratio <0.5). However, at later time points more naltrexone was extracted and abuse deterrence restored. Under one set of conditions (which used M33) preferential separation of oxycodone occurred though this required an extended period of exposure while still co-extracting some naltrexone. Additional time, effort and expertise would be required to further separate the oxycodone from the solvents to enable abuse.

Figure 4. Extraction of Naltrexone and Oxycodone (Mean ± SEM[a]) From Intact Pellets Under Condition B at Time Point 1 (Top Panel) and Abuse Deterrence Profiles Across all Solvents and all Time Points (Bottom Panel)

[ ] = time point 1

%Oxycodone extraction <30%

%Naltrexone extraction/ %Oxycodone extraction ≥0.5

Oxycodone extraction ≥30%, and %Naltrexone extraction/ %Oxycodone extraction <0.5

a   SEM : Standard error of the mean

Figure 5. Extraction of Naltrexone and Oxycodone (Mean ± SEM[a]) From Intact Pellets Under Condition A at Time Point 1(Top Panel) and Potential Abuse Deterrence Across all Solvents and all Time Points (Bottom Panel)

= time point 1

%Oxycodone extraction <30%

%Naltrexone extraction/ %Oxycodone extraction ≥0.5

Oxycodone extraction ≥30%, and %Naltrexone extraction/ %Oxycodone extraction <0.5

a   SEM : Standard error of the mean
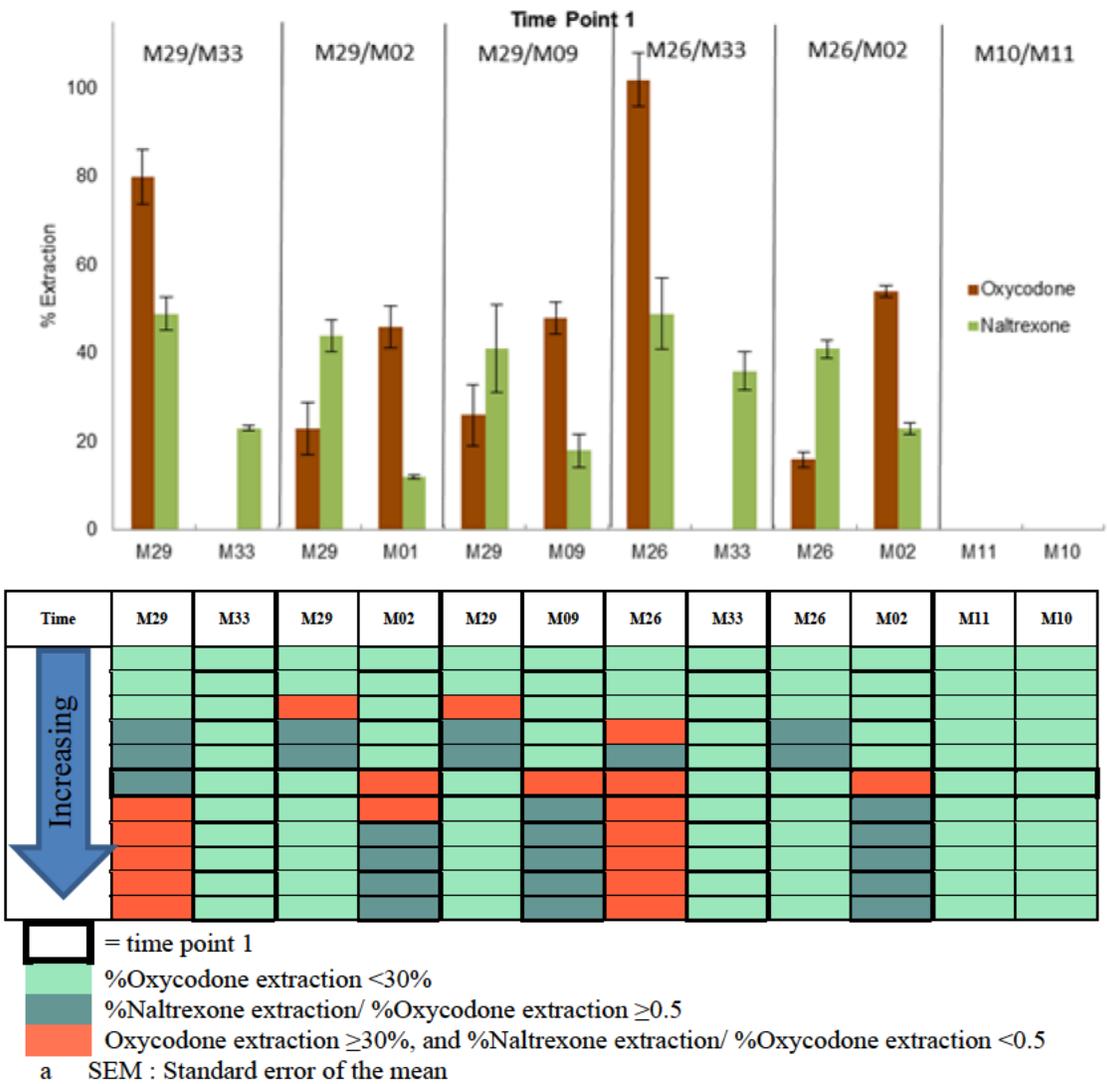
Large Volume Extraction Studies: Intact Pellets (Condition D, E and F)

A select group of solvents were tested in additional large volume studies with intact pellets under condition D. Under these conditions, the rate of release of both oxycodone and naltrexone from intact pellets was enhanced. In some solvents a potential vulnerability was observed at time point 1 (Figure 6 (top panel), (e.g., solvent M05), whereas in other solvents (e.g., solvent M27) a potential vulnerability of the formulation in that solvent was eliminated compared to condition B due to increased co-extraction of naltrexone. Figure 6 (bottom panel) indicates that when potential vulnerabilities of intact ALO-02 pellets occurred with specific solvents when exposed to condition D, there was only a short window of opportunity where appreciable oxycodone was extracted in the relative absence of naltrexone. Moreover, the onset of this potential vulnerability was different from solvent to solvent.

A selection of media was tested under conditions E and F. It was observed that selective extraction (>75%) of oxycodone from intact ALO-02 pellets occurred in the relative absence of naltrexone (<10%). The combination of these media and conditions represents potential methods by which an abuser could defeat the abuse deterrent properties of ALO-02 and selectively extract oxycodone into large volumes of media for oral abuse.

Figure 6. Extraction of Naltrexone and Oxycodone (Mean ± SEM[a]) From Intact Pellets Under Condition D at Time Point 1(Top Panel) and Potential Abuse Deterrence Across all Solvents and all Time Points (Bottom Panel)

☐ = time point 1

%Oxycodone extraction <30%

%Naltrexone extraction/ %Oxycodone extraction ≥0.5

Oxycodone extraction ≥30%, and %Naltrexone extraction/ %Oxycodone extraction <0.5

a   SEM : Standard error of the mean
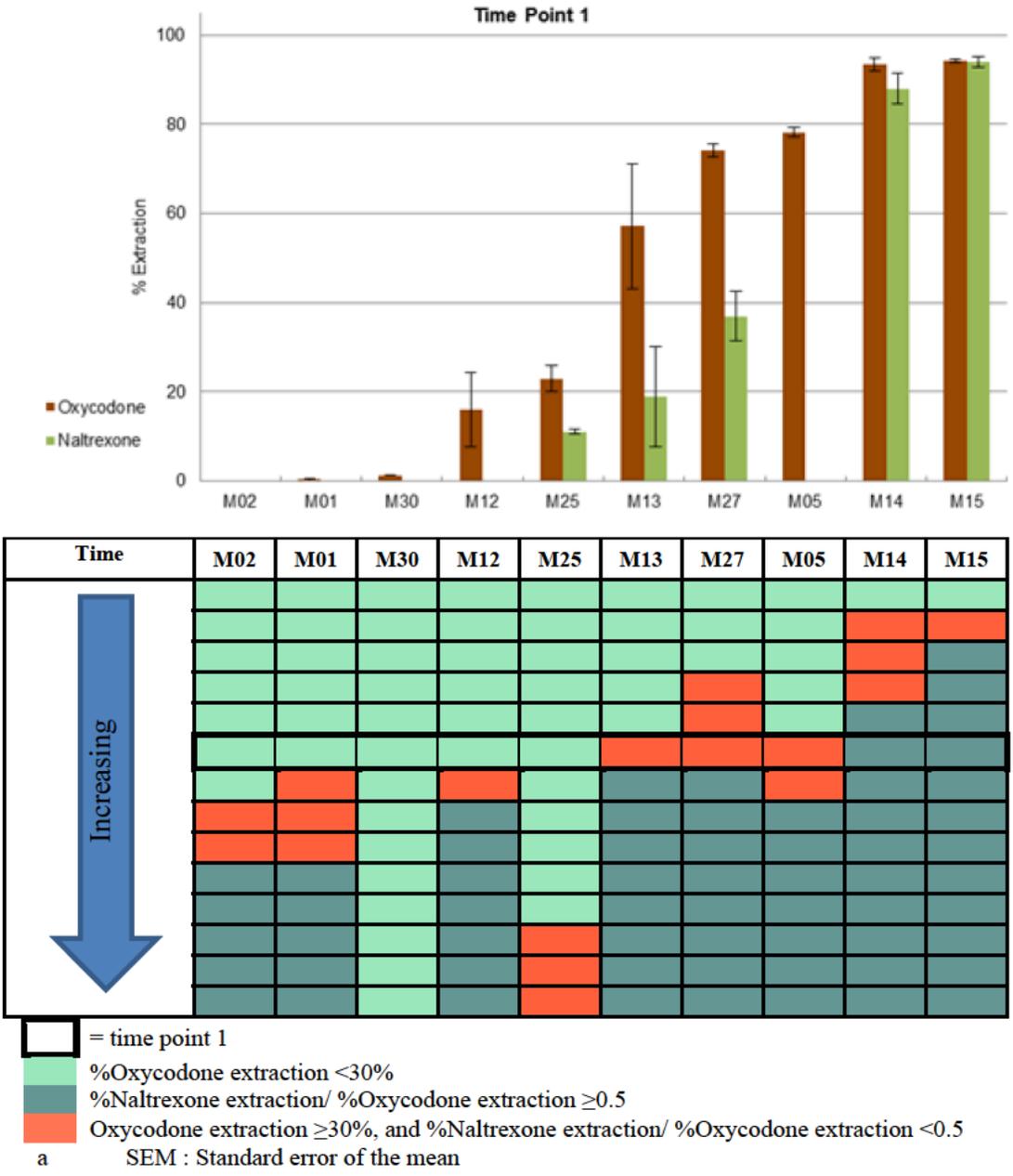
Small Volume Extraction Studies: Intact Pellets (Condition G)

Extraction studies were conducted using condition G to determine the potential to selectively extract oxycodone from intact ALO-02 pellets into small volumes of select solvents to simulate conditions an abuser might use to prepare solutions for IV abuse. As described in Figure 7 less than 25% of oxycodone could be extracted into small volumes of solvent M01 tested over the duration of the test. Oxycodone extraction was dependent upon both time and volume. When looking at other solvents, 20% of oxycodone could be extracted into a small volume of solvent M31. Oxycodone extraction was less than 15% in the other solvents studied.

Figure 7.   Small Volume Experiments Measuring % Extraction of Oxycodone (Mean ± SEM[a]) From Intact Pellets (Condition G)
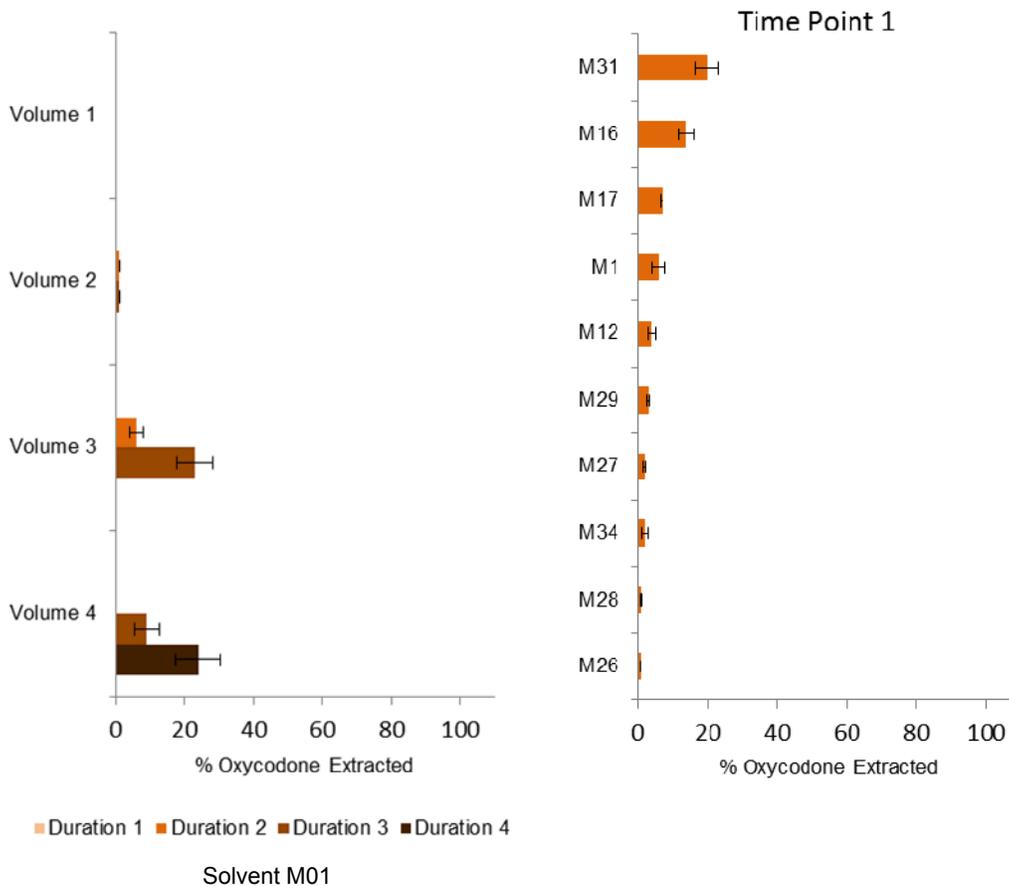
a. SEM: Standard error of the mean.

Volatilization Studies with Intact and Crushed Pellets (Condition H, I)

Experiments were conducted with intact and crushed ALO-02 pellets in test conditions to examine the ability to abuse ALO-02 by smoking. Figure 8 shows minimal extraction of oxycodone (< 2%) from intact or crushed ALO-02 pellets under conditions to simulate smoking. Greater amounts of volatized oxycodone were produced when the pure product (oxycodone HCl reference standard) were tested under the same conditions.

Figure 8. Volatilization Studies Measuring %Oxycodone From ALO-02 Pellets (Mean ± SEM[a]) (Condition H, I)
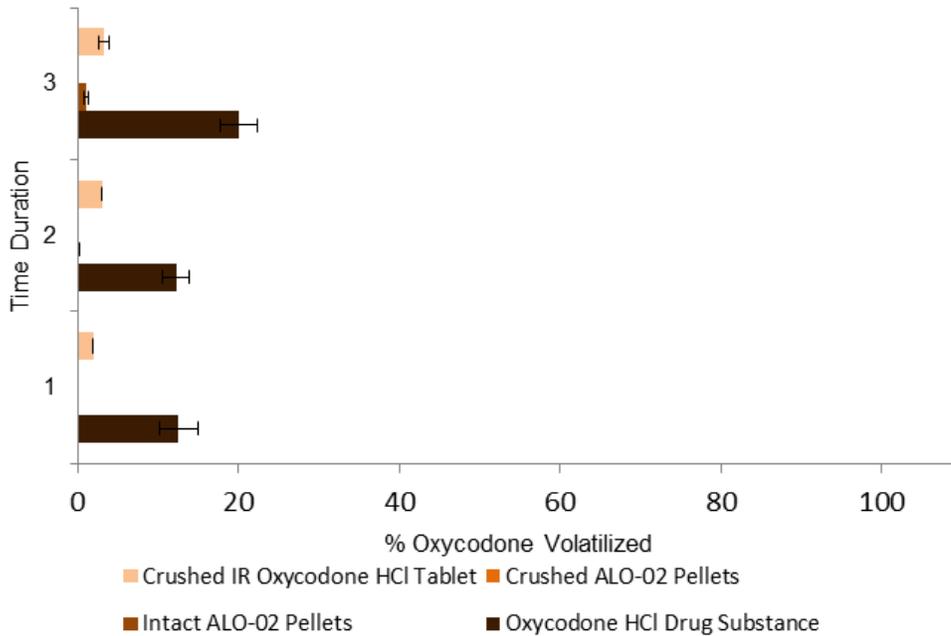
a. SEM: Standard error of the mean

3.2.1.1.3. Discussion/ Conclusion

These Category 1 in vitro studies explored the possibility of selective extraction of oxycodone preferentially to naltrexone from ALO-02 pellets across a wide range of solvents, times, volumes and conditions. Consistent with the intended abuse deterrent properties of ALO-02, there was similar extraction of oxycodone and naltrexone from crushed pellets in a wide array of solvents. Only one solvent showed somewhat selective extraction of oxycodone over naltrexone from crushed pellets, but additional steps would be required to isolate oxycodone from this hazardous organic solvent. This indicates that ALO-02 would be resistant to oral abuse by crushing and swallowing or by crushing, mixing with solvents, and then swallowing.

In addition, extraction studies were done with intact pellets and small volumes using conditions abusers typically use to prepare opioids for intravenous administration. These studies demonstrate that extraction of oxycodone from intact ALO-02 pellets was limited (<25%) across all time points, volumes and solvents. The low yields of oxycodone in these

small volume extraction studies are likely to deter most individuals from attempting preparations for injection of ALO-02. Similarly, in conditions that simulated smoking, there was negligible extraction (<2%) of oxycodone from intact or crushed pellets. Consequently, these data indicate that attempts at smoking ALO-02 is not effective and would not likely be used by most individuals attempting to abuse the product.

In many solvents and conditions, there was slow extraction of oxycodone with no naltrexone extraction in large volume studies with intact pellets. This is consistent with the intended extended release of oxycodone and sequestration of naltrexone when ALO-02 is taken intact. In these studies with intact pellets, there were some potential vulnerabilities identified, using the applied criteria, that could form the basis for potential methods to prepare ALO-02 for oral abuse. These potential vulnerabilities depended on the solvent, the condition, and the time. The brief windows of opportunity differed from solvent to solvent and from condition to condition, with respect to the timing of onset of potential vulnerability. There were some solvents, and conditions in which there was potential vulnerability of the formulation at earlier time points but this was short lived as additional naltrexone was extracted at a slightly later time thus restoring ALO-02's abuse deterrence.

Thus, these in-vitro data indicate that under most conditions ALO-02 retains its abuse deterrent properties thereby limiting the attractiveness of ALO-02 for abusers who manipulate opioid formulations to facilitate more immediate drug release. As with all abuse deterrent opioids, there are limitations or potential vulnerabilities in the formulation, hence ALO-02 is not abuse proof and there are some conditions under which oxycodone could be preferentially and more rapidly extracted from intact ALO-02 pellets. However, it would be considered difficult for an abuser to take advantage of these windows of vulnerability, particularly where there are no visual cues to indicate whether selective extraction has occurred. The only way to test the recipe requires a trial and error approach, subject to variability in which an abuser would have to experiment with different solvents, different times, and different conditions and then self-administer to identify the perfect conditions for abuse. In such an approach, experiences of limited high (either when oxycodone extraction is low, or when naltrexone is also extracted) or experiences of withdrawal in the dependent abuser (when naltrexone is extracted) would deter further experimentation. This may be why some abusers express negative sentiments with EMBEDA® on internet chat rooms where abusers often go to share information on opioids. EMBEDA is an ER morphine sulfate ADO that uses a similar sequestered naltrexone technology in ALO-02. Posts on these sites include communications to avoid EMBEDA because of potential withdrawal associated with naltrexone.

In summary, after most physical and chemical challenges of ALO-02, the formulation retained its abuse-deterrent features. Only transient vulnerabilities were seen in most extraction studies. The difficulties involved in discovery of these vulnerabilities suggest that ALO-02 will exhibit substantial abuse deterrence when the product is manipulated for purposes of misuse and abuse.

3.2.1.2. Category 2 and Category 3 Studies With ALO-02

The Sponsor conducted 3 HAP studies to support Category 2 and Category 3 claims. The HAP studies evaluated the PK and the abuse potential of manipulated ALO-02 by the oral

(B4531008) and intranasal (B4531009) routes and simulated ALO-02 (B4981002) by the IV route. An IV solution of oxycodone HCl and an IV solution of naltrexone HCl was combined in a 12% ratio of naltrexone HCl to oxycodone HCl to simulate IV administration of crushed ALO-02 as it may not be safe to administer crushed ALO-02 by the IV route in healthy volunteers. These studies were developed with guidance from the Agency and are aligned to the FDA Draft Guidance (January 2013) in regards to the basics of design, endpoints, population, and statistical analysis.

3.2.1.2.1. Methodology for HAP Studies

Table 3 below summarizes the design and treatments of each of the 3 HAP studies conducted. All 3 HAP studies were randomized, double-blind, placebo-controlled, single-dose, crossover studies. The objectives of these studies were to determine the relative abuse potential, safety, and tolerability of ALO-02 compared to IR oxycodone and placebo. A total of 106 subjects in the 3 abuse potential studies received at least one dose of study drug.

Table 3.   Human Abuse Potential Studies: Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Crossover Studies

Study Number	Treatments	Number of Subjects*
Oral/B4531008	1. Placebo 2. ALO-02 60 mg/7.2 mg intact 3. ALO-02 40 mg/4.8 mg crushed 4. Oxycodone IR 40 mg crushed (2 x 20 mg) 5. ALO-02 60 mg/7.2 mg crushed 6. Oxycodone IR 60 mg crushed (3 x 20 mg) Crushed treatments administered in solution.	31
Intranasal/B4531009	1. Placebo (sugar spheres) 2. ALO-02 30 mg/3.6 mg crushed 3. Placebo (lactose) 4. Oxycodone IR 30 mg crushed	27
IV/B4981002	1. Placebo (0.9% NaCl) 2. Oxycodone 20 mg IV + Naltrexone 2.4 mg IV (simulated crushed ALO-02) 3. Oxycodone 20 mg IV All treatments administered over 4 minutes.	29

Abbreviations: IR=immediate-release (oxycodone HCl), NaCl=sodium chloride, IV=intravenous
* Number of subjects who completed the study and were included in the final analysis.

Study subjects were healthy males or females 18-55 years of age and a body mass index (BMI) of 17.5-32.0 kg/m^2; and a total body weight >50.0 kg. Study subjects were non-dependent, recreational opioid users defined as a user of opioids for non-therapeutic purposes (ie, for psychoactive effects) on at least 10 occasions within the last year and at least once in the 8 weeks before the Screening Visit. For the intranasal study (B4531009), subjects must have had experience with intranasal opioid administration, defined as intranasal use on at least 3 occasions within the last year before Screening. For the IV study (B4981002),

subjects must have had intranasal use on at least 3 occasions in the past year or IV use on at least 1 occasion within the past year prior to Screening.

The primary PD measures for all 3 studies were the Visual Analogue Scale (VAS) scores for Drug-Liking and High and the primary endpoints were E_{max} (maximum effect), calculated as maximum change from pre-dose response if pre-dose assessment was performed (High), and as maximum post-dose response if no pre-dose assessment was performed (Drug-Liking), and the effects occurring within 2 hours after dosing, as assessed by the AUE_{0-2h} (area under the effect curve, 0-2 h post-dose). The studies used these standardized instruments for measuring the subjective effects and are consistent with the Guidance.[1] Drug-Liking was measured using a bipolar VAS (as defined below) in response to the statement "At this moment, my liking for this drug is:" High was measured using a unipolar VAS (as defined below) in response to the statement "I am feeling high". Other PD measures using the VAS instrument in all 3 studies included: Take Drug Again, Overall Drug-Liking, Any Drug Effects, Good Drug Effects, Bad Drug Effects, Feel Sick, Nausea, Sleepy, and Dizzy. Pupil size was also measured in all studies. Take Drug Again was measured using a bipolar VAS (as defined below) in response to the statement "I would take this drug again". The measure of Overall Drug-Liking also used a bipolar scale and all other PD measures used a unipolar scale.

1. *The bipolar VAS for Drug-Liking was defined as: 0=strong disliking, 50=neither like nor dislike, 100=strong liking*

2. *The unipolar VAS for High was defined as: 0=not at all, 100=extremely*

3. *The bipolar VAS for Take Drug Again was defined as: 0=definitely not, 50=neutral, 100=definitely so*

All 3 studies included a naloxone challenge phase to ensure subjects were not physically dependent on opioids and a drug discrimination phase (i.e., pre-qualification phase) to ensure subjects could discriminate between the active control (i.e., IR oxycodone) and placebo for the measures of Drug-Liking, Take Drug Again, and High when administered by the route designated for each study. Subjects were allowed to enroll into the randomized, double-blind treatment phase of each study after demonstrating that they were not physically dependent and could distinguish between the active control and placebo.

3.2.1.2.2. Results From HAP Studies

Three (3) HAP studies assessed the PK for oxycodone and naltrexone and abuse potential of the to-be-marketed ALO-02 pellet formulation by the oral (B4531008) and intranasal (B4531009) routes, and with IV administration of simulated crushed ALO-02 (B4981002). These studies demonstrated that the 12% naltrexone HCl/oxycodone HCl ratio in ALO-02 resulted in a significant reduction in abuse potential across the 3 routes, and demonstrated that oxycodone and naltrexone were released and simultaneously absorbed by the oral and intranasal route in the to-be-marketed formulation. Validity of each study was demonstrated through statistical comparison of E_{max} for the primary endpoints (Drug-Liking and High) between the active comparator (oxycodone HCl) and placebo.

a). Oral HAP Study (B4531008)

A total of 41 subjects were randomized into the double-blind, 6-way crossover treatment phase and constituted both the safety and PK population. A total of 31 subjects completed all 6 treatments and were included in the final PD analysis.

As shown in Figure 9, following manipulation (by crushing) and upon oral administration of ALO-02, oxycodone and naltrexone were absorbed rapidly with similar PK profiles. Oxycodone PK profiles were similar following administration of crushed ALO-02 compared with crushed IR oxycodone, at both 40 mg and 60 mg dose levels; the maximum plasma concentration (C_{max}) and AUC_{inf} (area under the concentration vs time curve from time 0 to infinity) values appeared to increase in a dose proportional manner for both formulations. The median T_{max} and mean drug half-life ($t_{1/2}$) values ranged from 0.58-1.04 hours and 4.22-4.42 hours, respectively, and appeared to be unrelated to the dose level or formulation. However, when intact ALO-02 was administered orally, there was no detectable exposure of naltrexone as assessed by all plasma samples showing naltrexone concentrations levels below the limit of quantitation (LOQ) (<4 pg/mL). In addition, median oxycodone T_{max} was prolonged to 12 hours and mean C_{max} was reduced by at least 3-fold compared with IR oxycodone, when intact ALO-02 was taken orally.

Figure 9. Oxycodone and Naltrexone Plasma Concentration-Time Profiles Following Oral Administration of Crushed or Intact ALO-02 or Crushed IR Oxycodone
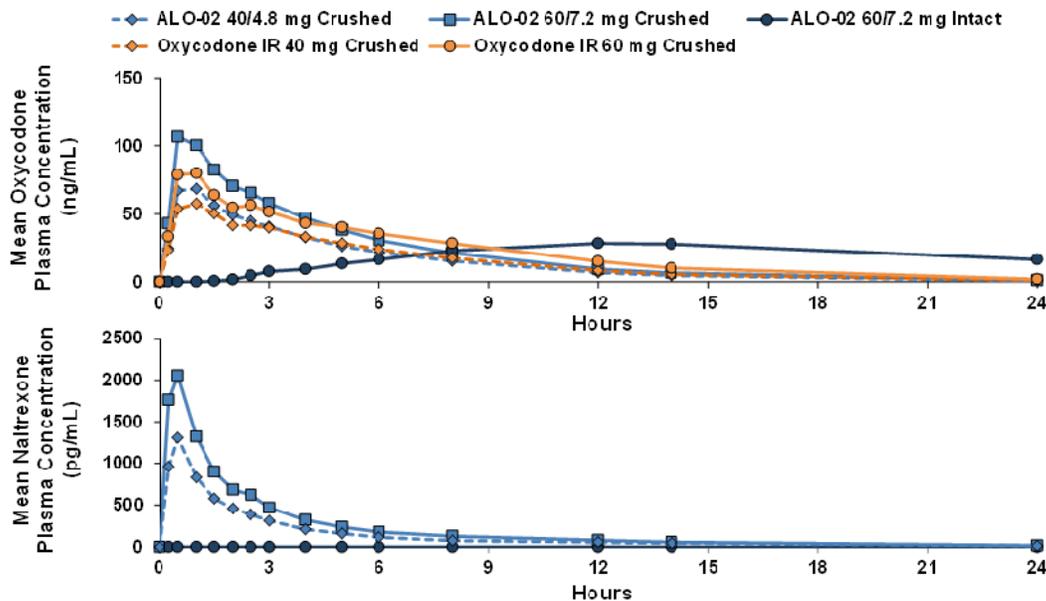
Abbreviation: IR=immediate-release.

Figure 10 and Figure 11 illustrate the least squares (LS) mean Drug-Liking and High E_{max} scores for the oral HAP study; the primary endpoints. The results of the oral abuse potential study (B4531008) indicated that the mean E_{max} for Drug-Liking VAS scores for crushed ALO-02 (at both 40 mg/4.8 mg and 60 mg/7.2 mg) were significantly lower than equivalent

IR oxycodone doses (p=0.0007 and p=0.0002, respectively). Placebo showed significantly lower mean Drug-Liking E_{max} responses compared to all active treatments. The mean High E_{max} scores for crushed ALO-02 (both doses) were also significantly lower than equivalent IR oxycodone doses (p<0.0001 for each). Placebo showed significantly lower mean High E_{max} responses compared to all active treatments, except ALO-02 60 mg/7.2 mg intact.

Figure 10. Drug-Liking E_{max} in Oral HAP Study B4531008
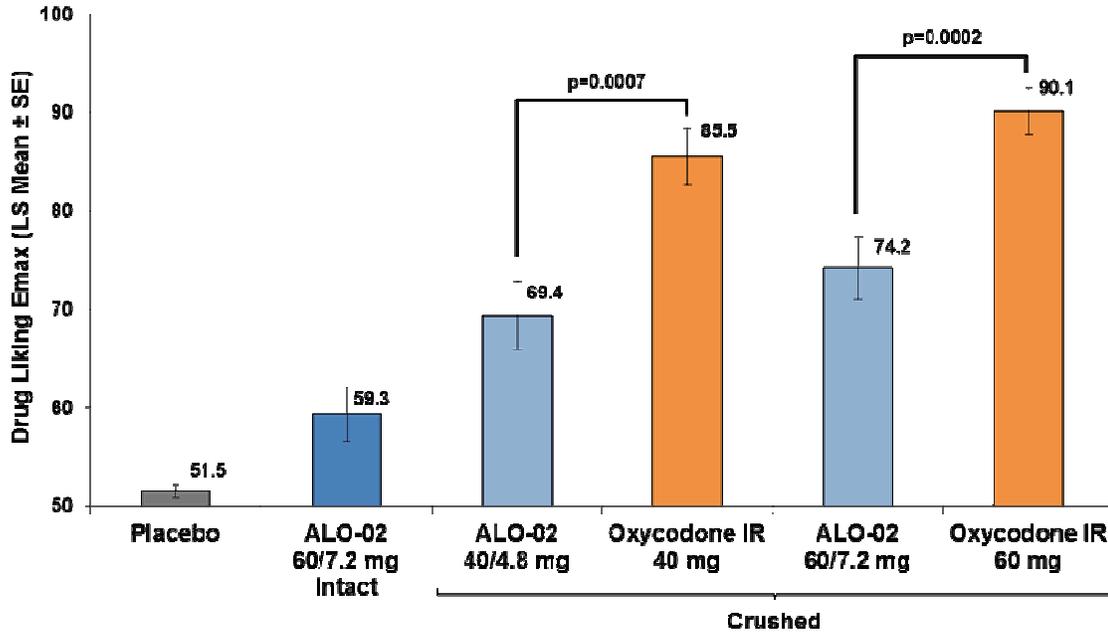
Abbreviations: E_{max}=maximum effect, HAP=human abuse potential, IR=immediate-release, LS=least squares, SE=standard error, VAS= Visual Analogue Scale.
The bipolar VAS for Drug-Liking was defined as: 0=strong disliking, 50=neither like nor dislike, 100=strong liking

Figure 11. High E_{max} in Oral HAP Study B4531008
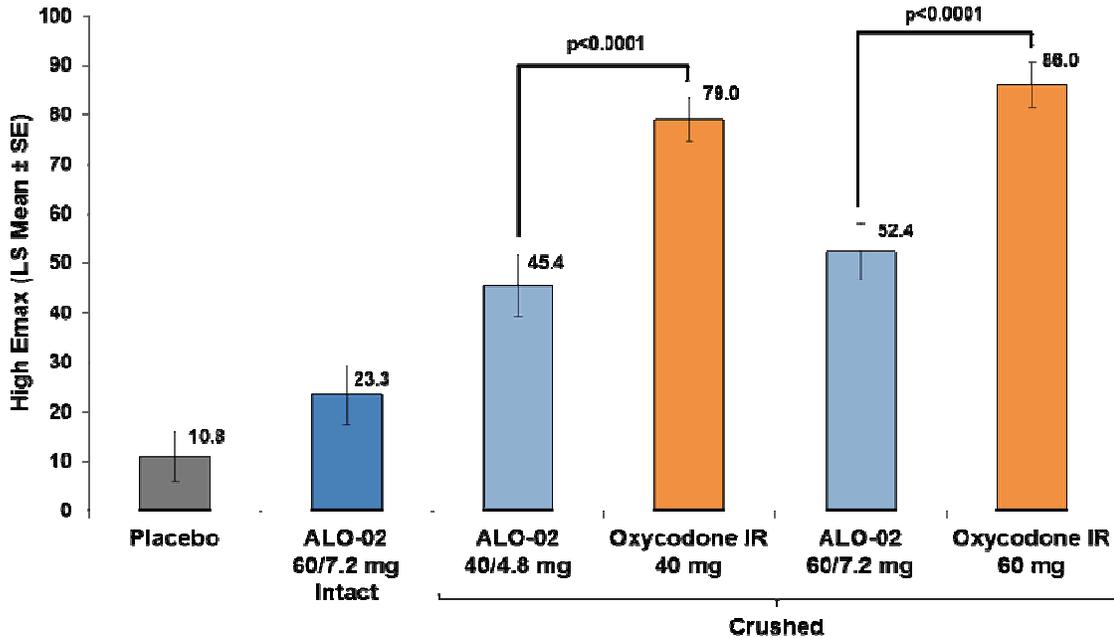
Abbreviations: E_{max}=maximum effect, HAP=human abuse potential, LS=least square, SE=standard error, VAS= Visual Analogue Scale.
The unipolar VAS for High was defined as: 0=not at all, 100=extremely.

Figure 12 illustrates the LS mean Take Drug Again E_{max} score (an important secondary endpoint) for each treatment. The Take Drug Again E_{max} score was significantly lower for crushed ALO-02 40 mg/4.8 mg than IR oxycodone 40 mg (p=0.0001). The mean Take Drug Again E_{max} score for crushed ALO-02 60 mg/7.2 mg was numerically lower than IR oxycodone 60 mg (p=0.0768). Placebo showed significantly lower mean Take Drug Again E_{max} responses compared to IR oxycodone 40 mg crushed, ALO-02 60 mg/7.2 mg crushed, and IR oxycodone 60 mg crushed. The mean placebo Take Drug Again E_{max} was numerically lower than ALO-02 40 mg/4.8 mg crushed (p=0.1030) and ALO-02 60 mg/7.2 mg intact (p=0.6660). The mean Take Drug Again E_{max} score for ALO-02 60 mg/7.2 mg intact was numerically lower than ALO-02 40 mg/4.8 mg crushed and statistically significantly lower than IR oxycodone 40 mg crushed, ALO-02 60 mg/7.2 mg crushed, and IR oxycodone 60 mg crushed.

Figure 12. Take Drug Again E_{max} in Oral HAP Study B4531008
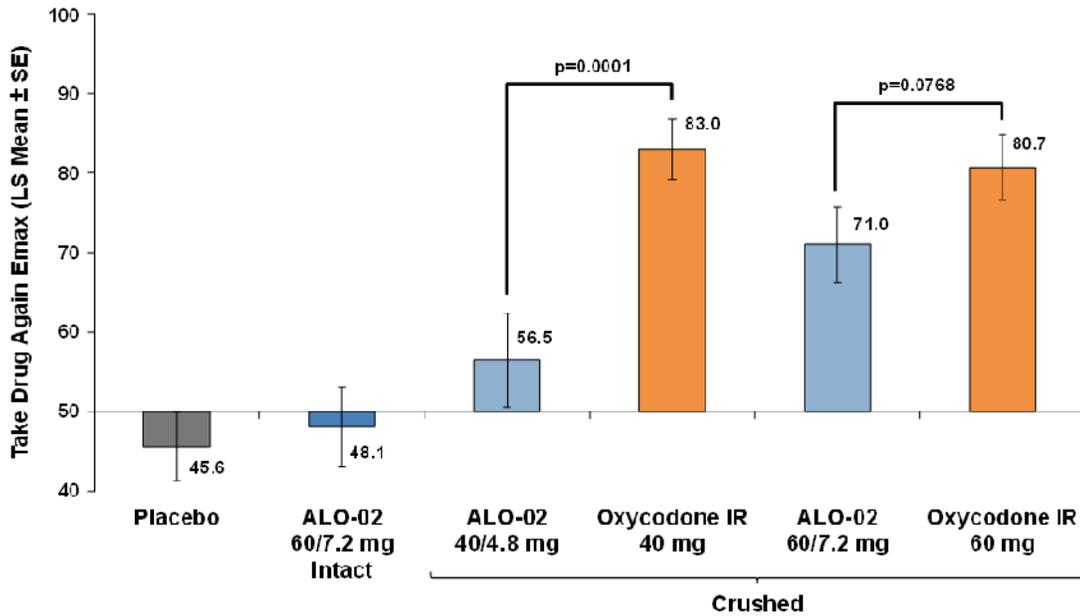
Abbreviations: E_{max}=maximum effect, HAP=human abuse potential, LS=least squares, SE=standard error, VAS=Visual Analogue Scale.
The bipolar VAS for Take Drug Again was defined as: 0=definitely not, 50=neutral, 100=definitely so

Figure 13 is a responder analysis that illustrates the percentage reduction in maximum Drug-Liking VAS for intact and crushed ALO-02 compared to crushed IR oxycodone when given by the oral route. For intact ALO-02 60 mg/7.2 mg, 90% and 87% of subjects had at least a 30% and 50% reduction in maximum Drug-Liking, respectively. For crushed ALO-02 40 mg/4.8 mg, 65% and 55% of subjects had at least a 30% and 50% reduction in maximum Drug-Liking, respectively. For crushed ALO-02 60 mg/7.2 mg, 61% and 45% of subjects had at least a 30% and 50% reduction in Drug-Liking, respectively.

Figure 13. Percent Reduction for E_{max} of Drug-Liking VAS for Oral Administration of Intact and Crushed ALO-02 vs Crushed IR Oxycodone (Completer Population in HAP Study B4531008)
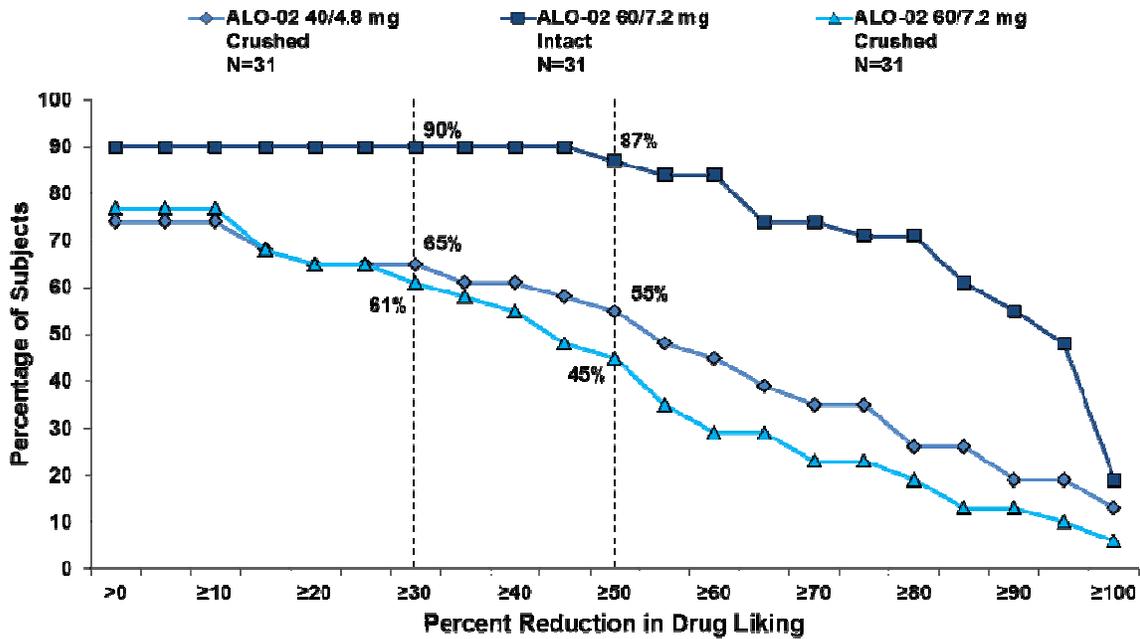
Abbreviations: E_{max}=maximum effect, VAS= Visual Analogue Scale, HAP=human abuse potential, IR=immediate-release, N=total number of subjects who have non-missing E_{max} values for both ALO-02 and the same dose of Oxycodone IR.

b). Intranasal HAP Study (B4531009)

A total of 32 subjects were randomized into the double-blind, 4-way crossover treatment phase and constituted both the safety and PK population. A total of 27 subjects completed all 4 treatments and were included in the final PD analysis.

As shown in Figure 14, the intranasal absorption of oxycodone was somewhat slower following the administration of crushed ALO-02 compared with crushed IR oxycodone, whereas naltrexone from ALO-02 was rapidly absorbed intranasally. Oxycodone AUC_{inf} was approximately 20% lower for crushed ALO-02 compared to crushed IR oxycodone tablets, likely related to the formulation differences between ALO-02, an ER product, and IR oxycodone. The median T_{max} for ALO-02 30 mg/3.6 mg (1.59 hours) was longer compared to IR oxycodone 30 mg (0.475 hours). The mean $t_{1/2}$ for oxycodone was similar with crushed ALO-02 (4.17 hours) and IR oxycodone (4.13 hours) given intranasally.

Figure 14. Oxycodone and Naltrexone Plasma Concentration-Time Profiles Following Intranasal Administration of Crushed ALO-02 or Immediate Release Oxycodone
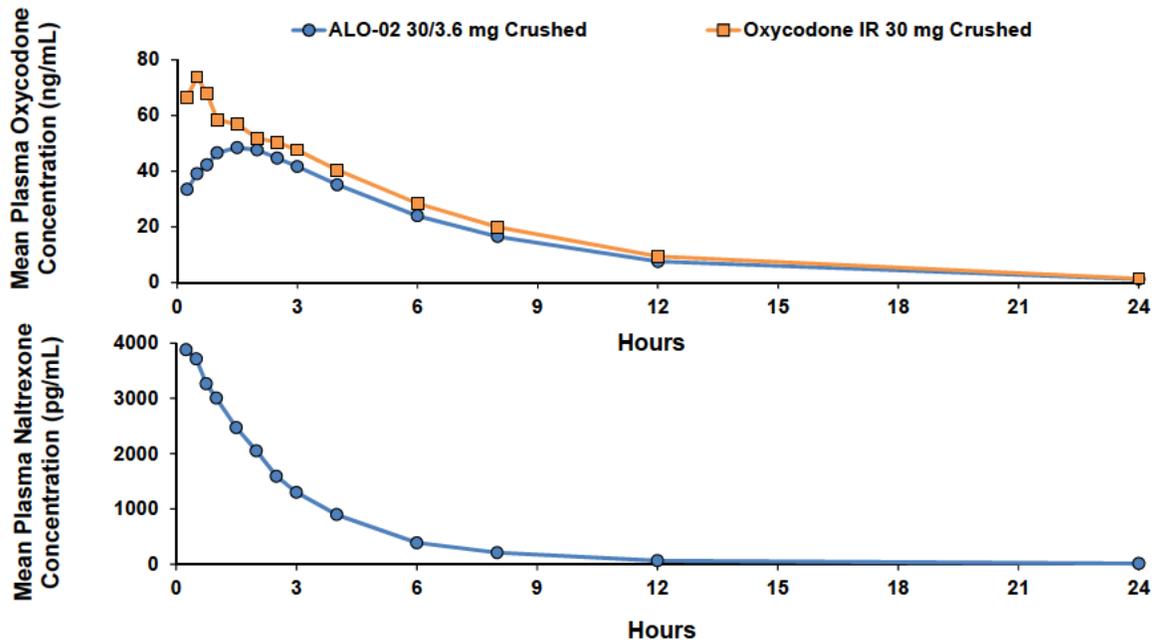
Abbreviation: IR=immediate-release.

Figure 15, Figure 16 and Figure 17 illustrate the LS mean Drug-Liking, High and Take Drug Again E_{max} scores for the intranasal HAP study. The results of the intranasal abuse potential study (B4531009) indicated that crushed ALO-02 (30 mg/3.6 mg crushed) showed statistically significantly lower mean E_{max} responses for Drug-Liking ($p < 0.0001$), High ($p < 0.0001$) and Take Drug Again ($p = 0.0002$) than crushed IR oxycodone 30 mg. Weight-matched placebo responses for Drug-Liking E_{max} were significantly lower compared to both ALO-02 ($p = 0.0006$) and IR oxycodone ($p < 0.0001$). Weight-matched placebo responses for Take Drug Again E_{max} were numerically lower compared to ALO-02 ($p = 0.1054$) but were significantly lower compared to IR oxycodone ($p < 0.0001$).

Figure 15. Drug-Liking E$_{max}$ in Intranasal HAP Study B4531009
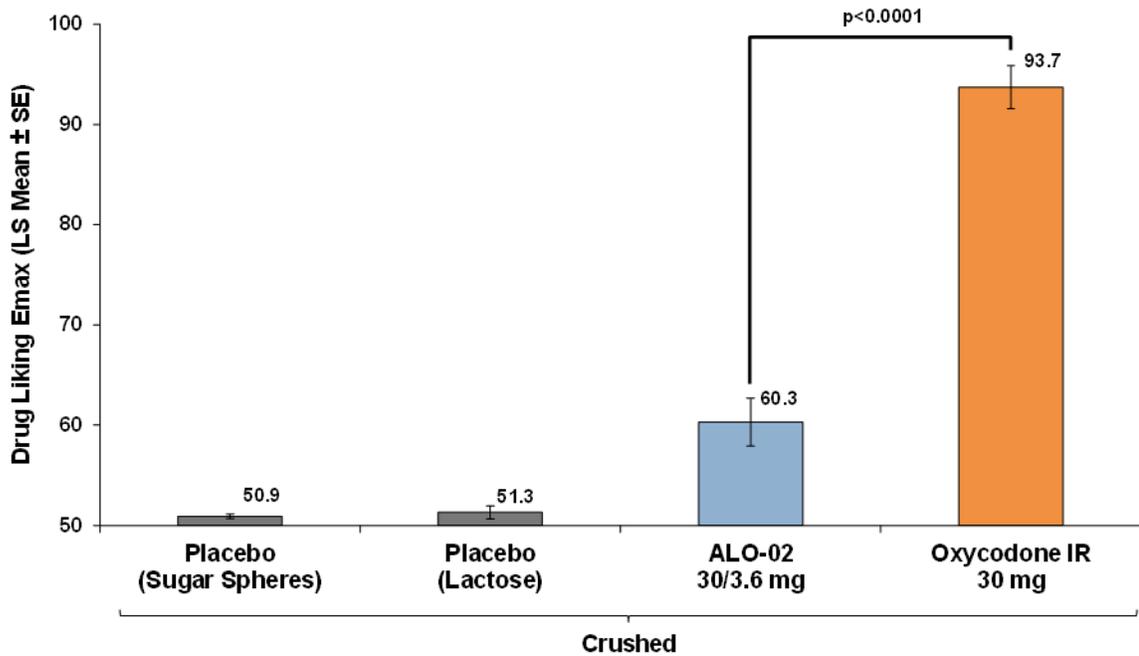
Abbreviations: E$_{max}$=maximum effect, IR=immediate-release, HAP=human abuse potential, LS=least squares, SE=standard error, VAS= Visual Analogue Scale.
The bipolar VAS for Drug-Liking was defined as: 0=strong disliking, 50=neither like nor dislike, 100=strong liking.

Figure 16. High E$_{max}$ in Intranasal HAP Study B4531009
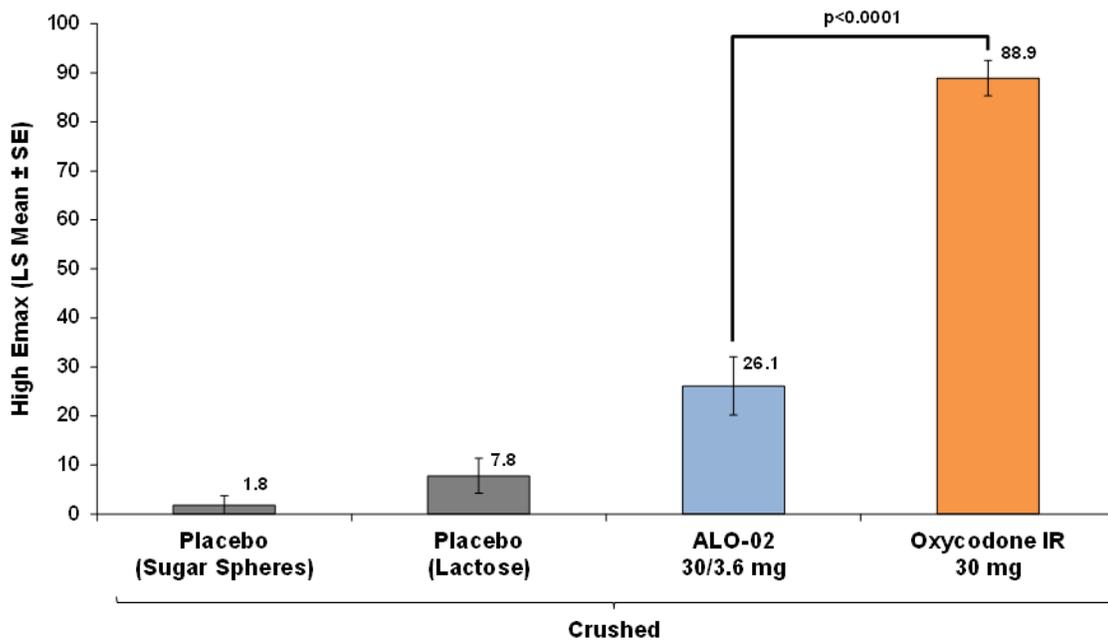
Abbreviations: E$_{max}$=maximum effect, HAP=human abuse potential, IR=immediate-release, LS=least squares, SE=standard error, VAS= Visual Analogue Scale.
The unipolar VAS for High was defined as: 0=not at all, 100=extremely.

Figure 17. Take Drug Again E_{max} in Intranasal HAP Study B4531009
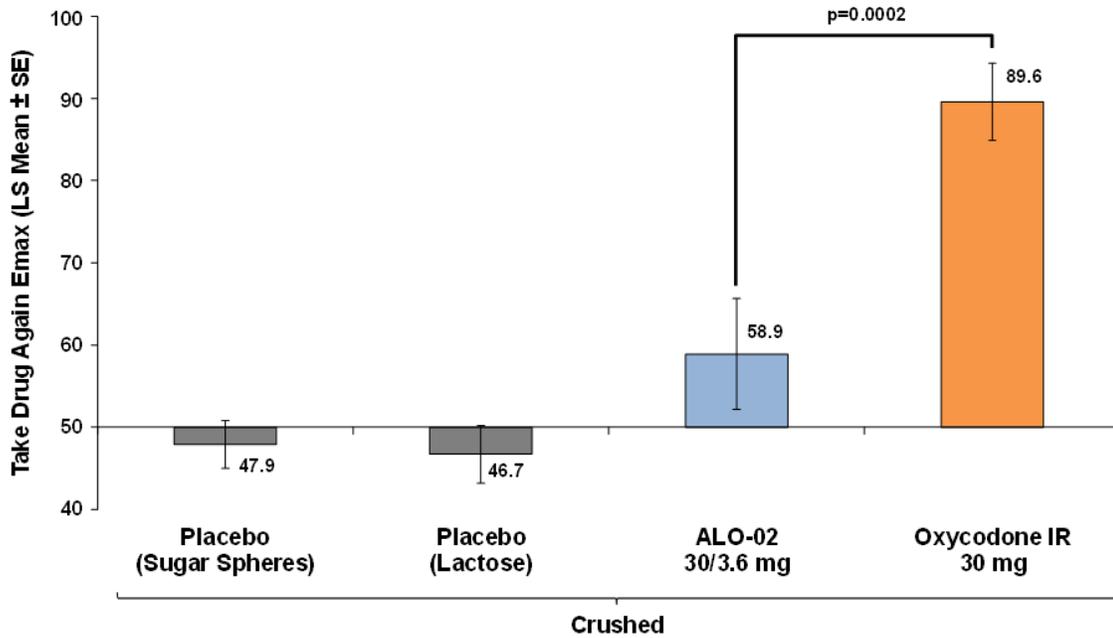
Abbreviations: E_{max}=maximum effect, IR=immediate-release, HAP=human abuse potential, LS=least squares, SE=standard error, VAS=Visual Analogue Scale.
The bipolar VAS for Take Drug Again was defined as: 0=definitely not, 50=neutral, 100=definitely so.

Figure 18 is a responder analysis that illustrates the percentage reduction in maximum Drug-Liking VAS for crushed ALO-02 30 mg/3.6 mg compared to crushed IR oxycodone 30 mg following intranasal administration in subjects who received both treatments. For crushed ALO-02 30 mg/3.6 mg administered intranasally, 93% and 85% of subjects had at least a 30% and 50% reduction in Drug-Liking compared to crushed IR oxycodone, respectively.

Figure 18. **Percent Reduction for E_{max} of Drug-Liking VAS for Intranasal Administration of Crushed ALO-02 vs Crushed IR Oxycodone (Completer Population in HAP Study B4531009)**
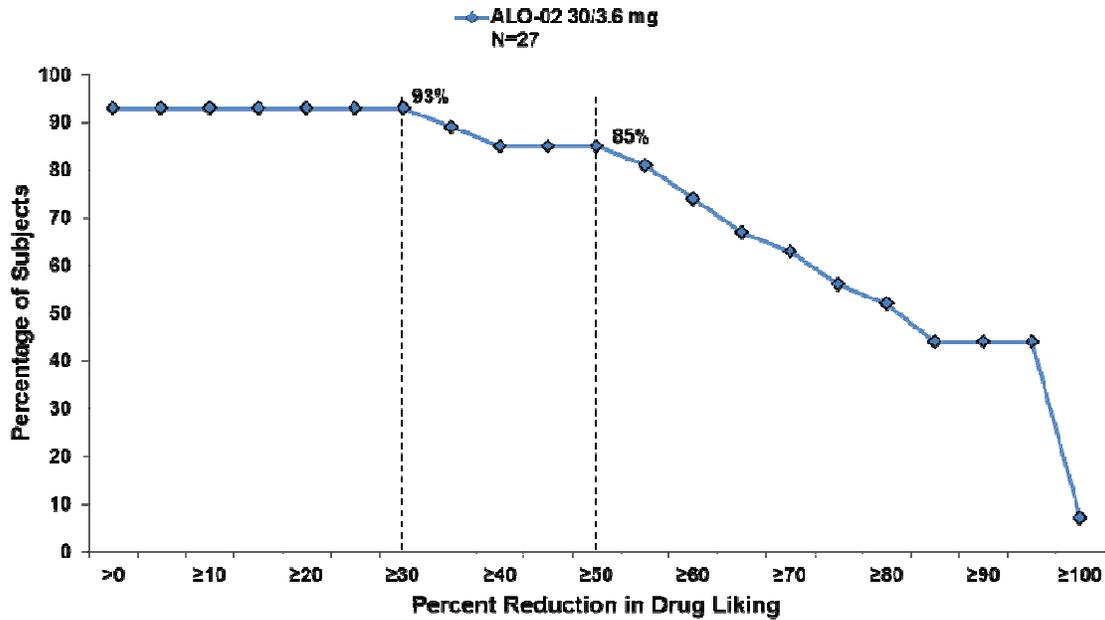
Abbreviations: E_{max}=maximum effect, IR=immediate-release, VAS=Visual Analogue Scale, HAP=human abuse potential, N=Total number of subjects who have non-missing E_{max} values for both ALO-02 and the same dose of Oxycodone IR.

c). <u>IV Study (B4981002)</u>

A total of 33 subjects were randomized into the double-blind, 3-way crossover treatment phase and constituted both the safety and PK population. A total of 29 subjects completed all 3 treatments and were included in the final PD analysis.

As shown in Figure 19, IV co-administration of 20 mg oxycodone HCl and 2.4 mg naltrexone HCl (simulated crushed ALO-02 20 mg/2.4 mg) in solution, results in systemic exposures of both moieties with a similar time course. Furthermore, oxycodone PK was similar when oxycodone HCl 20 mg was given alone compared with oxycodone HCl 20 mg given with 2.4 mg naltrexone. The mean concentrations of oxycodone observed 5 minutes after the start of infusion (C_{5min}) and area under the concentration versus time curve (AUC) values were 134.6-140.6 ng/mL and 393.7-420.3 ng*hr/mL, respectively; the mean $t_{1/2}$ was 3.66 hours for both treatments. For naltrexone, the mean C_{5min} and AUC_{inf} values were 12780 pg/mL and 17170 pg*hr/mL, respectively; the mean $t_{1/2}$ was 2.8 hours.

Figure 19. Oxycodone and Naltrexone Plasma Concentration-Time Profiles Following IV Administration of Oxycodone with Naltrexone (Simulated Crushed ALO-02 in Solution) or Oxycodone Alone
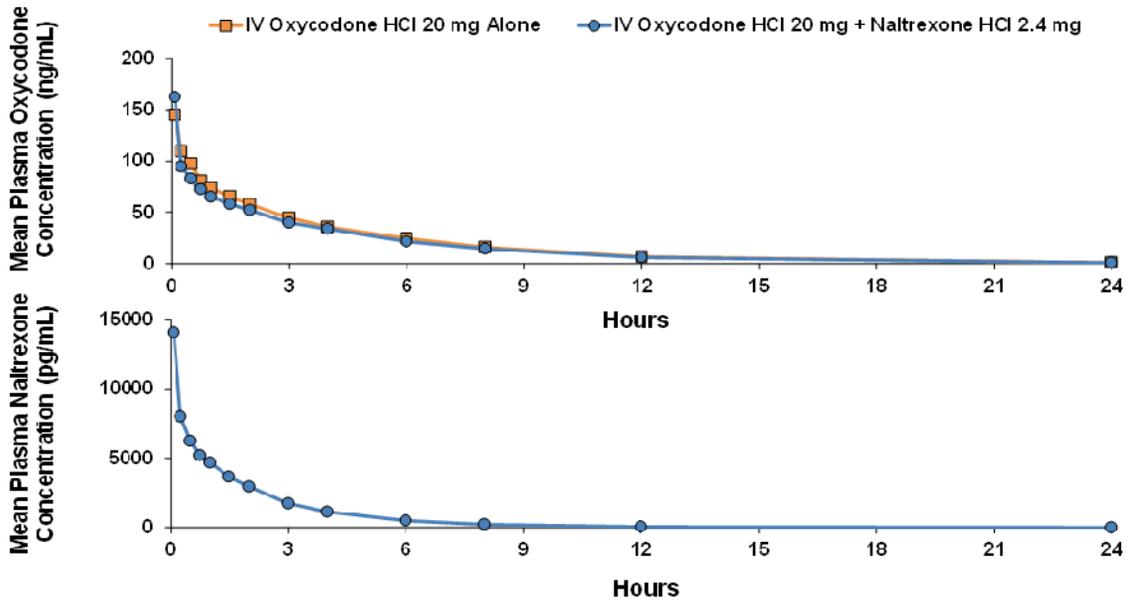
Abbreviation: IV=intravenous, HCl= hydrochloride.

Figure 20, Figure 21 and Figure 22 illustrate the LS mean E_{max} for Drug-Liking, High and Take Drug Again. The results of the IV abuse potential study (B4981002) indicated that IV administration of simulated crushed ALO-02 20 mg/2.4 mg showed significantly (p<0.0001) lower mean E_{max} responses for Drug-Liking, High and Take Drug Again compared to IV oxycodone 20 mg. Placebo responses for Drug-Liking and High were significantly lower compared to both IV administration of simulated crushed ALO-02 and oxycodone. Placebo response for Take Drug Again was numerically lower than simulated crushed ALO-02 (p=0.3965) but was significantly lower than oxycodone (p<0.0001).

Figure 20. Drug-Liking E_{max} in IV HAP Study B4981002
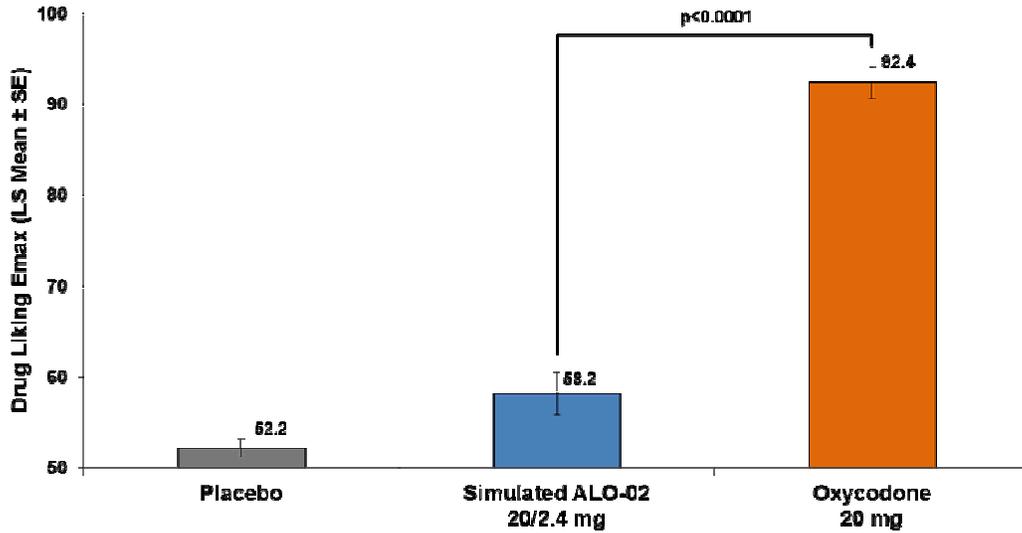
Abbreviations: E_{max}=maximum effect, IV=intravenous, HAP=human abuse potential, LS=least squares, SE=standard error, VAS=Visual Analogue Scale.
The bipolar VAS for Drug-Liking was defined as: 0=strong disliking, 50=neither like nor dislike, 100=strong liking.

Figure 21. High E_{max} in IV HAP Study B4981002
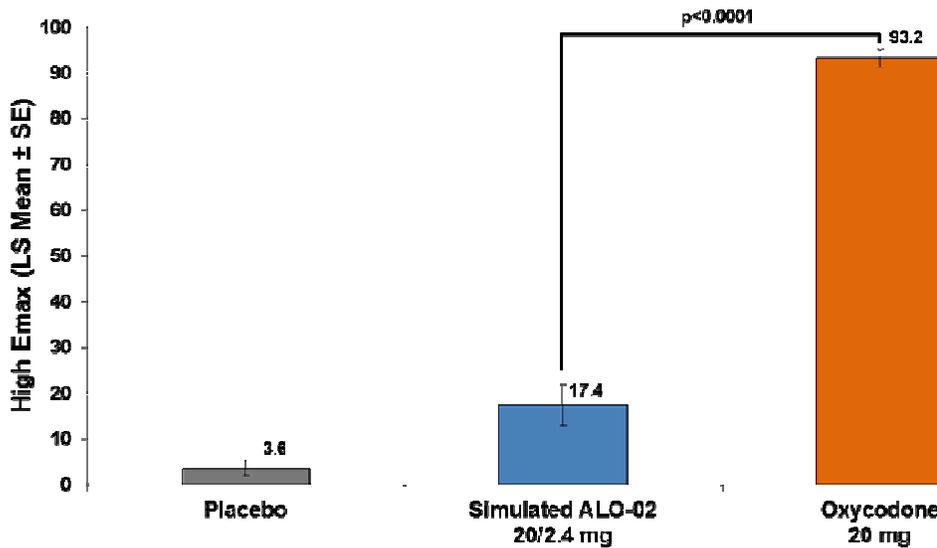
Abbreviations: E_{max}=maximum effect, IV=intravenous, HAP=human abuse potential, LS=least squares, SE=standard error, VAS=Visual Analogue Scale.
The unipolar VAS for High was defined as: 0=not at all, 100=extremely.

Figure 22. Take Drug Again E_{max} in IV HAP Study B4981002
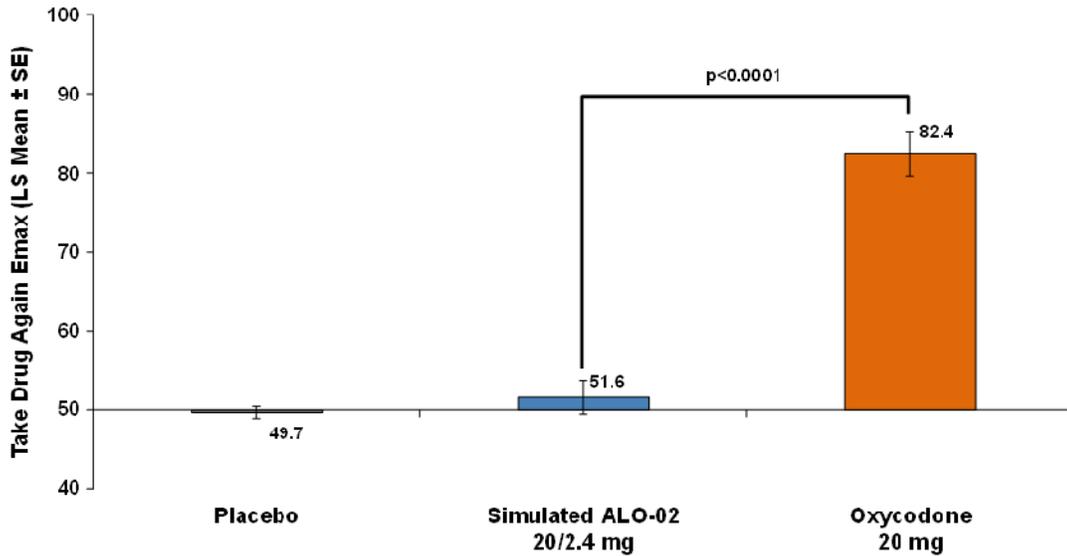
Abbreviations: E_{max}=maximum effect, HAP=human abuse potential, IV=intravenous, LS=least squares, SE=standard error, VAS=Visual Analogue Scale.
The bipolar VAS for Take Drug Again was defined as: 0=definitely not, 50=neutral, 100=definitely so.

Figure 23 is a responder analysis that illustrates the percentage reduction in maximum Drug-Liking VAS for IV administration of simulated crushed ALO-02 20 mg/2.4 mg compared to 20 mg of IV oxycodone in subjects who received both treatments. For IV simulated crushed ALO-02, 90% and 83% of subjects had a reduction of at least 30% and 50% in Drug-Liking compared to IV oxycodone, respectively.

Figure 23. Percent Reduction for E_{max} of Drug-Liking VAS for IV Administration of Simulated Crushed ALO-02 vs Oxycodone (Completer Population in HAP Study B4981002)
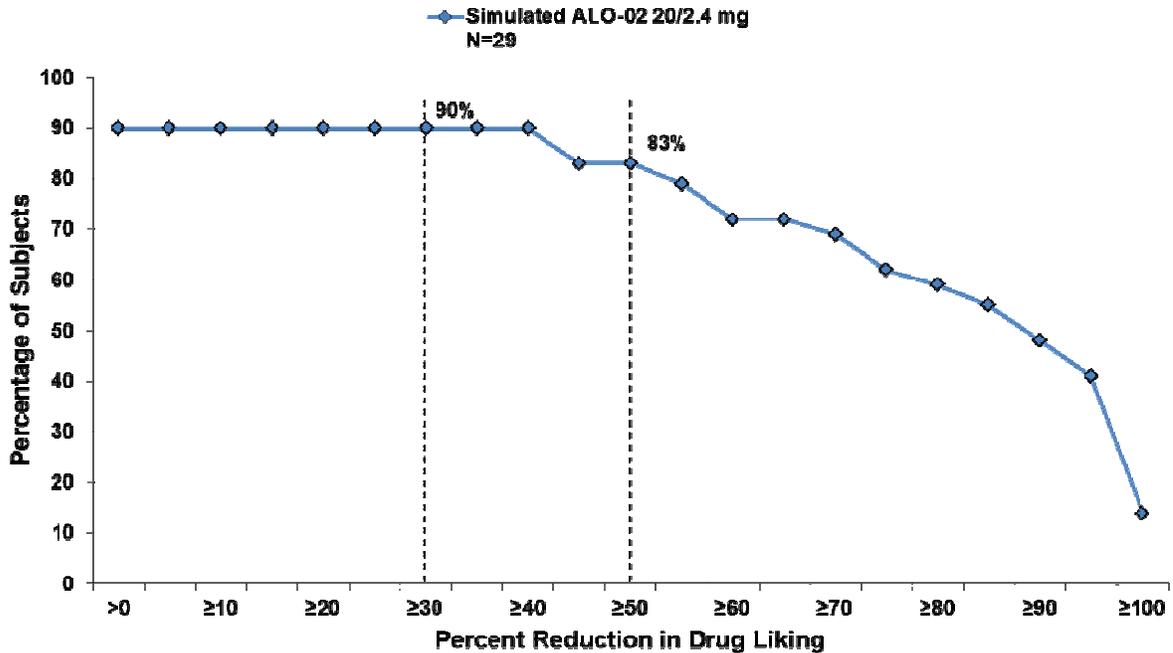
Abbreviations: E_{max}=maximum effect, VAS=Visual Analogue Scale, IV=intravenous, HAP=human abuse potential, N=total number of subjects who have non-missing E_{max} values for both ALO-02 and the same dose of Oxycodone IR.

3.2.1.3. Abuse-Deterrent Evaluation Conclusions

The in-vitro and PK data demonstrate that crushing ALO-02 pellets results in the simultaneous release and absorption of oxycodone HCl and naltrexone HCl. These data in combination with the results from the HAP studies demonstrate that ALO-02 has abuse deterrent properties following manipulation and administration via the oral and non-oral routes.

3.2.2. Clinical Pharmacology and Biopharmaceutic Evaluation

The results of key Phase 1 clinical pharmacology studies evaluating single-dose PK, effects of food, ethanol, and relative BA of the to-be-marketed ALO-02 formulation compared to the reference products Roxicodone and Revia, and a multiple-dose PK study are described in this section. In addition, the highlights of the oxycodone and naltrexone BA results from the oral, intranasal and IV HAP study are also summarized.

3.2.2.1. Bridge of ALO-02 to Reference Product Roxicodone®

In a single-dose crossover study B4531007, the extent of oxycodone BA following ALO-02 40 mg/4.8 mg capsules was demonstrated to be equivalent to that following IR oxycodone 20 mg (Roxicodone) tablets, with the 90% confidence interval (CI) for dose-normalized

AUC ratios contained entirely within the 80-125% acceptance range. Consistent with the ER properties of ALO-02 formulation (Figure 24), the ALO-02 vs Roxicodone dose-normalized C_{max} ratio was markedly lower (approximately 33%), median T_{max} was delayed (12 hours vs 1 hour), and apparent terminal elimination half-life ($t_{1/2}$) was prolonged (7.2 hours vs 4.6 hours).

Figure 24. Mean Dose-Normalized Oxycodone Plasma Concentration-Time Profiles Following Single Oral Doses of ALO-02 40 mg/4.8 mg vs Roxicodone 20 mg
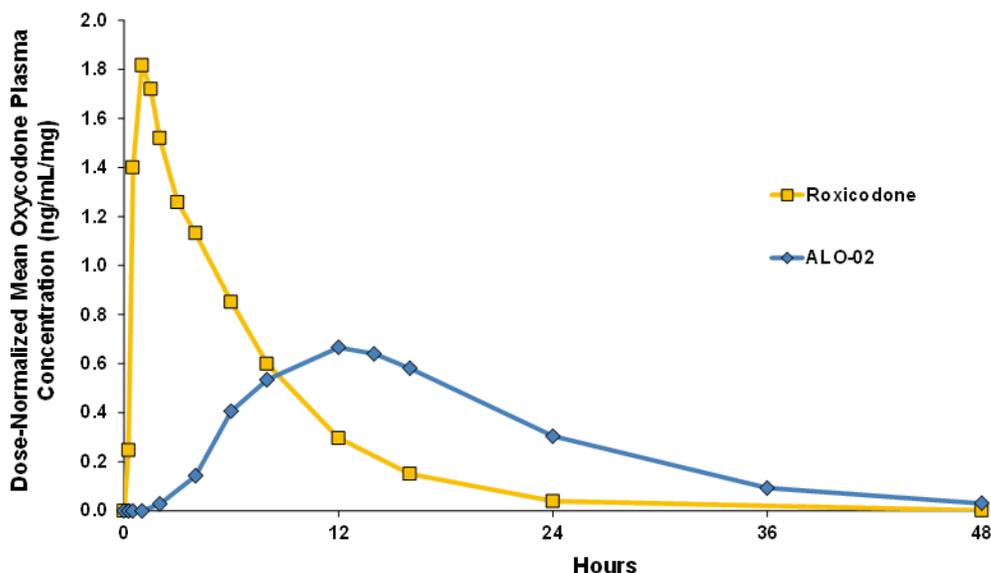
These PK results confirm the ER properties of the ALO-02 formulation and support the BID administration of ALO-02 for the treatment of pain. Furthermore, the marked reduction in oxycodone C_{max} and delay of T_{max} predict a reduction in abuse potential of ALO-02 capsules when used as intended (intact) compared with IR oxycodone. These oxycodone PK results of equivalent extent of BA establish a scientific bridge to rely on the Agency's findings of safety and efficacy for Roxicodone.

3.2.2.2. Bridge of ALO-02 to Reference Product Revia®

Based on dose, the systemic exposure following complete release of naltrexone from the highest strength of crushed ALO-02 (80 mg/9.6 mg) would be expected to be 1/5th of the plasma exposure achieved with the approved 50 mg dose of Revia. This comparison of the 1/5th lower naltrexone dose and systemic exposures from ALO-02 80 mg/9.6 mg compared with Revia 50 mg tablets establish a scientific bridge to the Agency's findings of safety for Revia.

3.2.2.3. Effect of Manipulation of ALO-02 on PK of Oxycodone and Naltrexone

When ALO-02 60 mg/7.2 mg was crushed and administered orally, the sequestered naltrexone HCl was completely released with BA equivalent to that of naltrexone HCl

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7.2 mg in solution, as indicated by AUC and C_{max} ratios of 100% and 103%, respectively, and the 90% CI was contained entirely within 80-125% for AUC (Figure 25).

Figure 25. Mean Naltrexone Plasma Concentration-Time Profiles Following Single Oral Doses of Crushed ALO-02 60 mg/7.2 mg in Study B4531008 vs Naltrexone 7.2 mg in Solution in Study 1 and Study 2
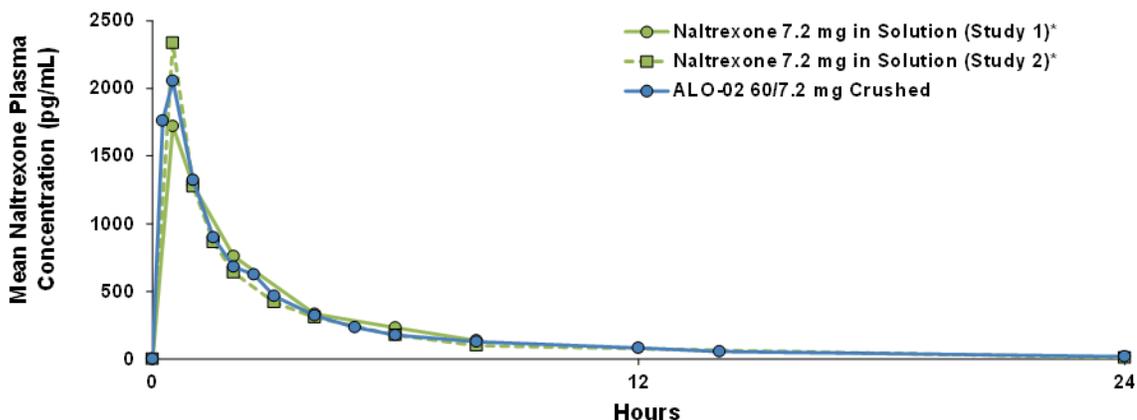
* **Study 1**: ALO-02-07-201, **Study 2**: ALO-02-09-2001 (B4531008).

In the oral abuse potential Study B4531008, upon oral administration of crushed ALO-02, 100% of the sequestered naltrexone is released, with BA equivalent to IR naltrexone in solution at the same dose. Across the 1.5-fold dose increment of naltrexone HCl in ALO-02 (from 4.8 mg to 7.2 mg), the naltrexone C_{max} and AUC_{inf} values appeared to increase in a dose proportional manner by 1.69- and 1.63-fold, respectively. The median T_{max} and mean $t_{1/2}$ values were 0.55 hours and 5.44-5.57 hours, respectively, and appeared to be unrelated to the dose level.

The mean absolute oral BA of naltrexone appeared to be independent of the dose level; it was estimated to be about 9.1% at the 4.8-mg dose level and about 8.4% at the 7.2 mg dose level. The absolute intranasal BA of naltrexone was considerably higher compared with oral BA, and was estimated to be about 41.6% at the 3.6 mg dose level.

The absolute oral BA of oxycodone appeared to be independent of dose level; compared with the mean AUC across the 2 oxycodone treatments in IV Study B4981002, the absolute oral BA of oxycodone was estimated to be about 42.3-43.1% for crushed IR oxycodone, 41.2-42.8% for crushed ALO-02 and 51.5% for intact ALO-02. The absolute intranasal BA of oxycodone was higher compared with oral BA, and was estimated to be about 56.8% for crushed ALO-02 and 70.9% for IR oxycodone at the 30 mg dose level.

3.2.2.4. Assessment of Naltrexone Sequestration in Intact ALO-02 Formulation

Following single-dose administration of intact ALO-02 in Phase 1 studies, naltrexone was undetected (LOQ, 4 pg/mL). 6-β-naltrexol (LOQ, 4 pg/mL), a metabolite of naltrexone, was observed in 20 of 37 subjects with a median (range) of 7.8 (4.1-45.4) pg/mL.

Naltrexone plasma concentrations were undetected in the majority (78%) of the samples (n=2407) collected from subjects in the Phase 3 studies B4531001 and B4531002. In the samples with measurable naltrexone concentrations, the median (range) was 11.2 (4.1-1090) pg/mL. At least one measureable naltrexone level was observed in 249 (34%) of 725 subjects. Additionally, 6-β-naltrexol plasma concentrations were undetected in 40% of the samples (n=2544) collected from subjects. In the samples with measurable 6-β-naltrexol concentrations, the median (range) was 42.5 (4.1-7320) pg/mL. At least one measureable 6-β-naltrexol level was observed in 536 (73%) of 735 subjects.

In summary, upon administration of single oral doses of intact ALO-02 40 mg/4.8 mg or 60 mg/7.2 mg capsules in healthy volunteers, the systemic exposures of naltrexone were <LOQ (ie, less than 4.00 pg/mL) in all samples. The BA of naltrexone from intact ALO-02 capsules is low compared with naltrexone tablets; the mean naltrexone C_{max} following naltrexone 50 mg tablets (8550 pg/mL) [16] is over 750-fold higher compared with the median concentration in samples with measurable naltrexone concentrations (11.2 pg/mL) and over 7-fold higher than the highest individual concentration (1090 pg/mL) observed following ALO-02 capsules. In the subject with the highest observed concentration, there were no reports of withdrawal and the Clinical Opiate Withdrawal Scale (COWS) scores were low.

The potential clinical impact of the observed measurable naltrexone and 6-β-naltrexol concentrations in the Phase 3 studies was assessed by analyzing for correlation with time-matched Brief Pain Inventory-Short Form (BPI-sf) average pain (efficacy) and COWS (safety) scores (see Section 3.2.3.3.5 and Section 3.2.4).

3.2.2.5. Effect of Food and Sprinkling of ALO-02 Pellets on Applesauce

There was no effect of administration of single doses of ALO-02 40 mg/4.8 mg with a high-fat meal or of administration of pellets from ALO-02 40 mg/4.8 mg capsules sprinkled on applesauce on the PK of oxycodone relative to administration of ALO-02 40 mg/4.8 mg capsules under fasted conditions in study (B4531003) (Figure 26). All of the 90% CIs for oxycodone AUC and C_{max} ratios were entirely contained within 80-125%. The mean $t_{1/2}$ (6.7-7.9 hours) and median T_{max} (12-14 hours) values for oxycodone were similar regardless of treatment.

Figure 26. Mean Oxycodone Plasma Concentration-Time Profiles Following Administration of ALO-02 40 mg/4.8 mg Capsules in Fed vs Fasted States; ALO-02 Pellets Sprinkled on Applesauce in Fasted State
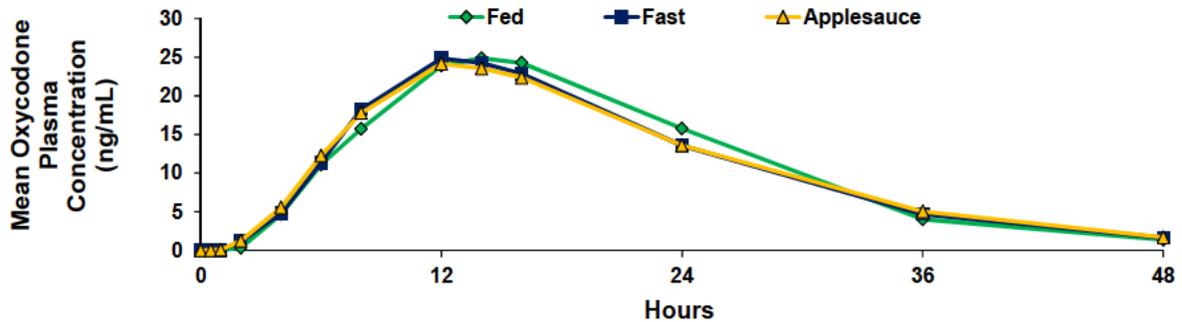
Naltrexone plasma concentrations for all treatments were undetectable suggesting that when ALO-02 capsules are administered with food or when pellets are sprinkled on applesauce and swallowed without chewing, naltrexone remains sequestered.

3.2.2.6. Effect of Administration of ALO-02 With Ethanol

Plasma oxycodone concentration-time data (Figure 27) following single doses of ALO-02 20 mg/2.4 mg capsules administered with 20% or 40% ethanol relative to water under fasted conditions in healthy volunteers did not suggest an over-exposure to oxycodone in the presence of ethanol (Study B4531004).

Figure 27. **Mean Oxycodone Plasma Concentration-Time Profiles Following Administration of ALO-02 20 mg/2.4 mg Capsules with 20% Ethanol, 40% Ethanol, or Water in Fasted State**
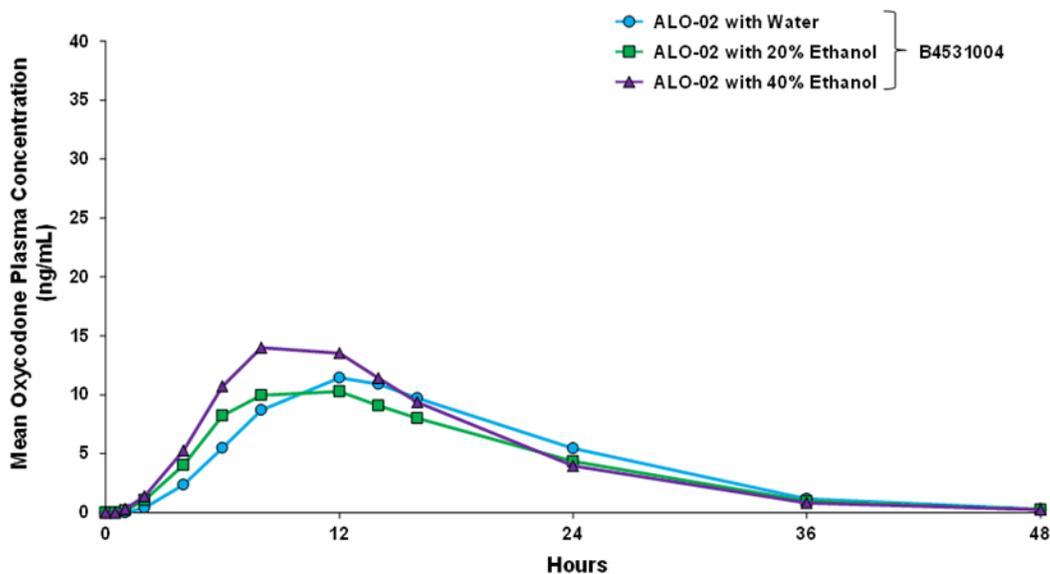
Oxycodone AUC_{inf} and C_{max} values were similar between ALO-02 administered with water or with 20% ethanol. However, following administration of ALO-02 with 40% ethanol, oxycodone AUC_{inf} and C_{max} values increased by approximately 13% and 37%, respectively, compared to administration of ALO-02 with water. The median T_{max} value was 12 hours for ALO-02 given with water or with 20% ethanol and 8 hours for the ALO-02 given with 40% ethanol treatment. The mean $t_{1/2}$ values were similar (approximately 6 hours) for all 3 treatments.

One subject in this study showed a 5.4-fold higher C_{max} and a 3.8-fold increase in AUC_{inf} when ALO-02 was administered with 40% alcohol compared with water, and a 1.7-fold higher C_{max} and a 1.2-fold increase in AUC_{inf} when ALO-02 was administered with 20% alcohol compared with water. The apparent increase in oxycodone exposures for this subject is likely attributable to the low exposures for ALO-02 20 mg/2.4 mg with water, the reference treatment. While the C_{max} and AUC_{inf} values following ALO-02 administered with 20% or 40% ethanol were all well within the range of exposures seen in other subjects, the exposures following ALO-02 with water were the lowest observed of all subjects.   This is demonstrated in Figure 28, as highlighted by red diamonds for each treatment for both AUC_{inf} and C_{max}.

Figure 28. Individual and Geometric Mean Values for Oxycodone AUC_{inf} and C_{max} in Study B4531004
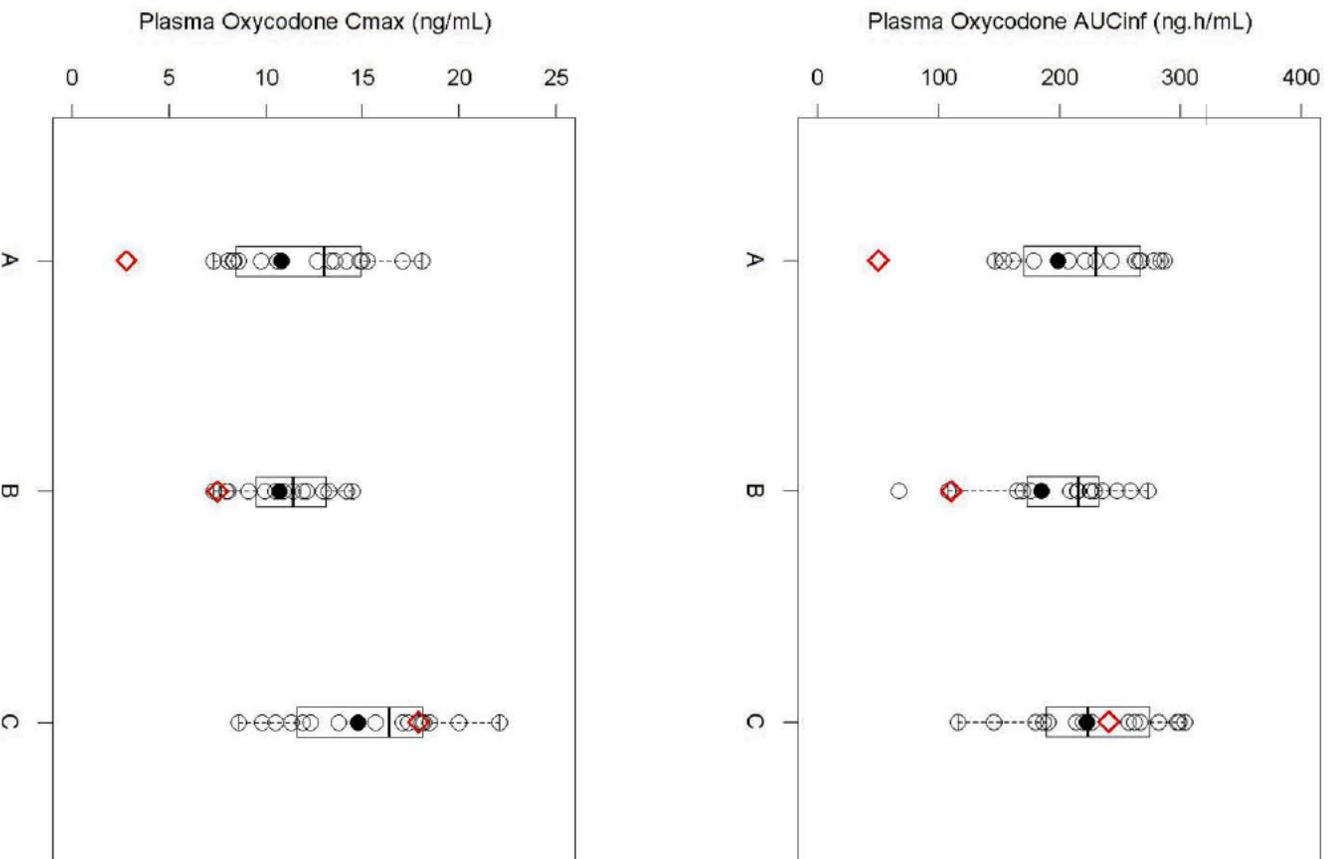
Abbreviations: AUC_{inf}=Area under the concentration versus time curve from time 0 to infinity, C_{max} =Maximum plasma concentration.
A: ALO-02 20 mg/2.4 mg administered with water
B: ALO-02 20 mg/2.4 mg administered with 20% ethanol
C: ALO-02 20 mg/2.4 mg administered with 40% ethanol
Geometric mean is calculated for each treatment group.
Circle identifies individual subject value.

Dot identifies geometric mean.
Red diamonds identify the single individual subject that had an apparent high relative increase in oxycodone exposures when ALO-02 was administered with 20% or 40% ethanol (Test) due to low exposures when ALO-02 was given with water (Reference).

The mean increased values upon administration of ALO-02 capsules with 40% ethanol remain markedly lower than those seen with IR oxycodone. In conclusion, these data did not suggest an over-exposure to oxycodone in this subject when ALO-02 was administered with 20% or 40% ethanol.

3.2.2.7. Steady-State PK of ALO-02

In a multiple-dose study B4531006, upon BID administration of ALO-02 capsules every 12 hours, oxycodone steady state was reached within 48 hours (Figure 29). Compared to Day 1, there was an approximately 86% increase in oxycodone C_{max} and approximately 168% increase in oxycodone AUC_{0-24} on Day 5.

Figure 29. Mean Trough Plasma Oxycodone Concentrations Following Twice-Daily Administration of ALO-02 40 mg/4.8 mg
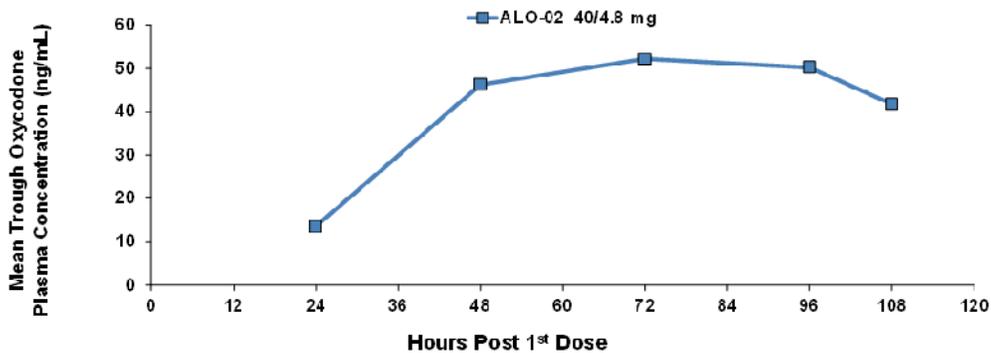
3.2.2.8. Covariate Analysis for ALO-02 PK

A meta-analysis of PK population was conducted to assess covariate effects across 5 Phase 1 studies comprised of healthy volunteers. These studies included single- and multiple- dose regimens of ALO-02, as well as crossover designs evaluating the effects of dose regimen, formulation, alcohol, and food on the PK of oxycodone. Oxycodone AUC and C_{max} following single- and multiple dose of ALO-02 in the 5 Phase 1 studies were analyzed with the following conclusions:

- ALO-02 exposure exhibits approximately dose proportional increases in oxycodone AUC and C_{max} in healthy volunteers over ALO-02 dose ranges of 20 mg/2.4 mg to 80 mg/9.6 mg.

- Differences in typical population values of AUC across the age range studied, as well as for gender and race were less than 20%.

3.2.2.9. Effect of Intrinsic Factors on ALO-02 PK

Although no specific studies have been conducted to evaluate the effects of intrinsic factors on ALO-02, the information below is available to estimate the effects of hepatic or renal impairment on systemic exposures of oxycodone and naltrexone. In assessing the clinical relevance of the corresponding effects of intrinsic factors on oxycodone and naltrexone PK, it is important to consider that naltrexone is sequestered following the intended oral use of intact ALO-02 capsules. Although hepatic impairment affects the systemic exposures of naltrexone to a greater degree compared with oxycodone, this disproportionate effect is considered to be of potential clinical relevance only if the sequestered naltrexone was to be released upon manipulation of ALO-02 capsules.

When ALO-02 capsules are used as intended, systemic exposure of naltrexone is not expected because it is sequestered in the pellets. However, in situations of misuse or unintended systemic exposure, since naltrexone and its primary metabolite are excreted primarily in urine, caution is recommended in administering ALO-02 to patients with renal impairment.

3.2.3. Clinical Efficacy Evaluation

Two (2) Phase 3 studies, B4531002 and B4531001, were conducted to evaluate the clinical efficacy of ALO-02. These studies demonstrate that ALO-02 provides effective and persistent analgesia in patients for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

- In the pivotal Phase 3 Study B4531002, a 12-week double-blind placebo-controlled randomized withdrawal study in opioid-naïve and opioid-experienced subjects with moderate-to-severe chronic lower back pain, the primary efficacy endpoint was met.

- The results of Study B4531002 demonstrated the efficacy of ALO-02 in reducing pain based on the primary endpoint and secondary efficacy endpoints of pain intensity. The LS mean change in the weekly average Numerical Rating Scale (NRS)-Pain score from Randomization Baseline to the end of the study was statistically different between the ALO-02 group and the placebo group, indicating that subjects in the placebo group experienced a significantly greater mean change (increase or worsening) in pain than subjects treated with ALO-02 during the Double-Blind Treatment Period (LS mean treatment difference=-0.62, p=0.0114).

  o A 12-month, open-label safety study (B4531001) demonstrated that ALO-02 provided statistically significant decreases in pain in opioid-naïve and opioid-experienced subjects with chronic non-cancer pain for the duration of the study. These results provided supportive evidence for the long-term maintenance of efficacy for up to 12 months. A subject was considered opioid-experienced if the

subject received opioids at any time within 30 days prior to beginning ALO-02 treatment.

- The mean average daily dose of rescue acetaminophen in mg/day was numerically lower for ALO-02 treated subjects compared to placebo in Study B4531002, while the median daily rescue acetaminophen dose decreased from baseline through Month-3 and remained generally stable thereafter in Study B4531001.

Study Design for B4531002

Study B4531002 was a 12-week, double-blind, placebo-controlled, randomized withdrawal study conducted in the US with the primary objective to determine the analgesic efficacy of ALO-02 compared to placebo in opioid-naïve and opioid-experienced subjects with moderate–to-severe chronic lower back pain (Figure 30).

Figure 30. Schematic Presentation of Study Design for the Double-Blind Study B4531002
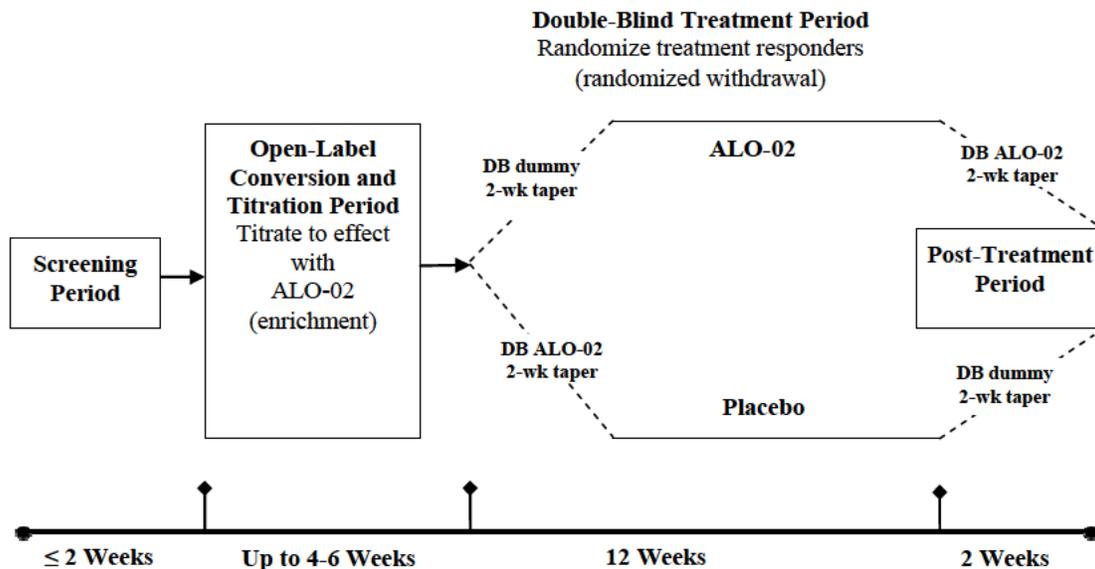
Abbreviations: DB=double-blind, HCl=hydrochloride, wk=week.

Rescue therapy: acetaminophen was permitted as a rescue medication throughout the study.

Study Design for B4531001

Study B4531001 was a long-term, single-arm, open-label safety study with the primary objective to evaluate the safety of ALO-02 administered for up to 12 months in opioid-naïve and opioid-experienced subjects with moderate–to-severe chronic non-cancer pain. Assessments of analgesic effectiveness were secondary endpoints and are supportive of the efficacy data from Study B4531002.

Rescue therapy: acetaminophen was permitted as a rescue medication during the treatment period of the study.

3.2.3.1. Statistical Considerations

For the pivotal efficacy study B4531002, the primary analgesic efficacy endpoint was the change from Randomization Baseline to the final 2 weeks of the 12-week Double-Blind Treatment Period in the daily average NRS-Pain scores for chronic lower back pain, performed on the intent-to-treat (ITT) population. The NRS-Pain assessment was recorded daily in an Electronic Diary (eDiary) by the subjects.

For supportive Study B4531001, efficacy results were secondary and included summaries and tests of change and percent change from baseline in BPI-sf pain scores at study visits over time.

3.2.3.2. Study Population Demographics

Baseline characteristics were similar across the placebo and ALO-02 treatment groups in the double-blind treatment period of Study B4531002 (Table 4).

Table 4.   Key Baseline Characteristics: Double-Blind, Placebo-Controlled 12-Week Efficacy Study B4531002 in Subjects with Chronic Lower Back Pain

Demographic	Placebo (N=134)	ALO-02 (N=147)
Females, n (%)	75 (56.0)	81 (55.5)
Age, mean (range), years	49.3 (19 – 76)	50.6 (23 – 89)
Prior opioid use, n (%)	58 (43.3)	61 (41.8)
Duration since diagnosis of CLBP (years), mean (range)[a]	12.5 (0.6 – 50.7)	12.3 (0.3 – 42.5)
Pain score at screening, mean (SD)	7.1 (1.2)	7.0 (1.1)
Pain score at randomization, mean (SD)	3.1 (1.0)	3.0 (1.3)

Abbreviations: CLBP=chronic lower back pain, SD=standard deviation, n=number of subjects in group, N=number of subjects evaluable for safety.
a. CLBP duration calculated as time from diagnosis until Screening.

A total of 410 subjects were enrolled into the open-label titration period of the study. Of these, 281 (134 placebo, 147 ALO-02) subjects completed the open-label titration period as responders and were randomized to the double-blind treatment period.

In Study B4531001, a total of 395 subjects were enrolled. Baseline characteristics of the study participants in Study B4531001 are provided in Table 5 below.

Table 5.   Key Baseline Characteristics: Open-Label, Single-Arm, 12-Month Safety Study B4531001 in Subjects with Chronic Non-Cancer Pain

Demographic	ALO-02 (N=395)
Females, n (%)	203 (51.4)
Age, mean (range)	53.8 (25 – 88)
Prior opioid use, n (%)	303 (77)
Duration since diagnosis of CNCP, mean (years)	11.2
Cause of primary pain, n (%)	
- Chronic Lower Back Pain	242 (61.3)
- Osteoarthritis (knee, hip, hand, or neck)	71 (18.0)
- Neuropathic Pain	12 (3.0)
- Other	79 (20.0)
Pain score in the last 24 hours, mean (SD)	5.9 (1.7)

Abbreviations: CNCP=chronic non-cancer pain, SD=standard deviation, n=number of subjects in group, N=number of subjects evaluable for safety.

3.2.3.3. Key Efficacy Results

3.2.3.3.1. Primary Efficacy Assessment in Study B4531002

In the primary endpoint analysis, the LS mean (±standard error, SE) change in eDiary NRS-Pain score from Randomization Baseline to the final 2 weeks was statistically different (p=0.0114) between the ALO-02 group (0.6 [1.81]) and the placebo group (1.2 [1.93]), indicating that subjects in the placebo group, who were tapered off ALO-02 at randomization, experienced a significantly greater mean change (increase or worsening) in weekly average eDiary NRS-Pain score from Randomization Baseline to the final 2 weeks compared to subjects treated with ALO-02 during the Double-Blind Treatment Period. The LS mean treatment difference was -0.62, (p=0.0114).

Five (5) sensitivity analyses were evaluated for various missing data assumptions: completer cases, pattern mixture model, single imputation, mixed model repeated measures (MMRM), and screening observation carried forward (SOCF). All 5 sensitivity analyses were directionally consistent with the primary analysis, ie, favoring ALO-02; 3 of 5 were statistically significant.

The standardized effect size (-0.33) in Study B4531002 was within the range of effect sizes in other similarly designed trials with opioids in chronic lower back pain subjects.[17,18,19,20,21,22]

3.2.3.3.2. Secondary Efficacy Endpoints in Study B4531002

a). Numerical-Rating Scale for Pain Score

Figure 31 presents the mean weekly average eDiary NRS-Pain scores (with corresponding standard errors) at Screening, Randomization Baseline, and the end of each double-blind week for observed cases in the ITT population. At Screening, weekly average eDiary NRS-Pain scores were 7.1 and 7.0 for the placebo and ALO-02 groups, respectively. The weekly average eDiary NRS-Pain scores decreased at each week during the Open-Label Titration

Period from Screening through Week 6 of open-label treatment. During the Double-Blind Treatment Period, weekly average eDiary NRS-Pain scores for subjects in the placebo group increased at each week from Randomization Baseline (3.1) to Week 4 (3.8) and Week 8 (3.7) while scores for those in the ALO-02 group indicated less change (3.0 at Randomization Baseline to 3.1 at Week 4 and remained the same 3.1 at Week 8).

Figure 31. Weekly Average eDiary NRS-Pain Scores During the Double-Blind Treatment Period – Observed Cases, ITT Population in the Placebo-Controlled 12-Week Efficacy Study B4531002
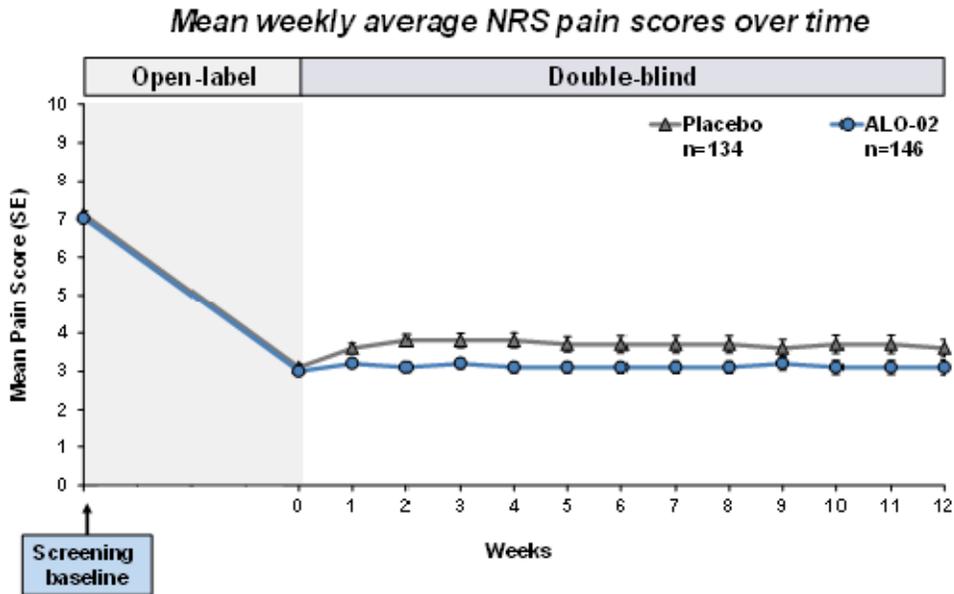
Abbreviations: NRS-Pain=Numeric Rating Scale for Pain, n=number of subjects in the group, ITT=intent-to-treat.
Data points represent mean ± standard error (SE).

b). Responder Analysis

For subjects treated with ALO-02, 84 (57.5%) subjects had at least a 30% decrease (improvement) in weekly average NRS-pain score from screening to the final 2 weeks of the double-blind period, compared to 59 (44.0%) subjects in the placebo group (p=0.0248) (Figure 32). Similarly, 58 (39.7%) subjects treated with ALO-02 had at least a 50% decrease in weekly average NRS-Pain score compared to 40 (29.9%) subjects in the placebo group (p=0.0874).

Figure 32. Percent Reduction in Weekly Average Diary NRS-Pain Scores from Screening to Final 2 Weeks – Observed Cases, ITT Population in Study B4531002
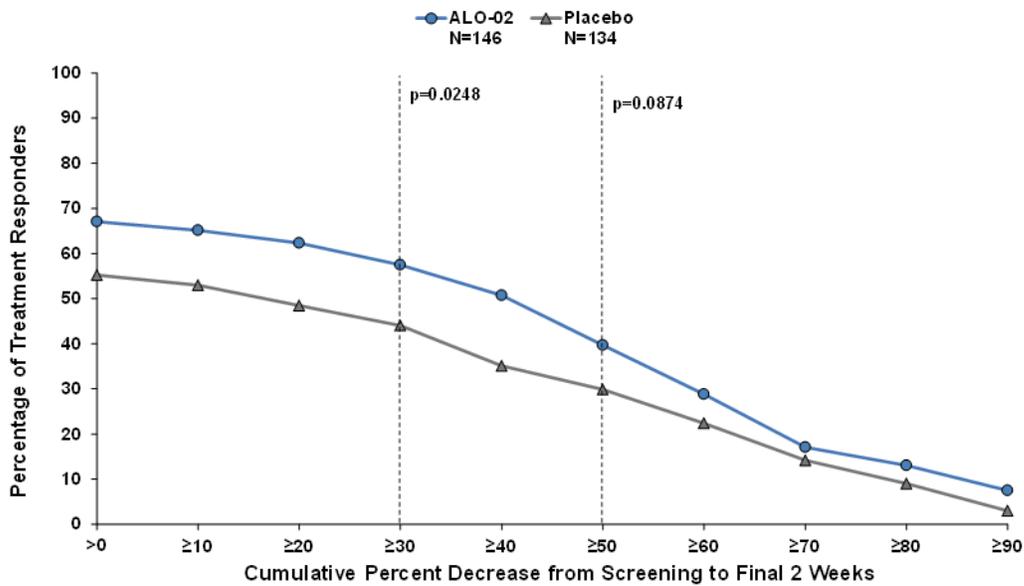
Abbreviations: ITT=intent-to-treat, NRS=Numerical Rating Scale, N=number of subjects evaluable.

c). Rescue Medication

The mean average daily dose of rescue acetaminophen was numerically higher (252.1 mg/day) for the placebo group than for the ALO-02 group (167.7 mg/day). More subjects in the placebo group required rescue medication 58/134 (43.3%) compared to 51/146 (34.9%) subjects in the ALO-02 group.

d). Time-to-Discontinuation (related to lack of efficacy)

Subjects in the ALO-02 group had a significantly longer time to discontinuation from the study for Investigator-reported lack of efficacy than the subjects in placebo group (p=0.006).

3.2.3.3.3. Effectiveness Assessment in Study B4531001

a). Pain Intensity

Overall, the mean pain intensity scores improved from baseline at each visit. The mean percent decrease from baseline for BPI-sf average pain was statistically significantly different from 0 at all visits (p≤0.0003).

b). Rescue Medication Use

The median daily dose of acetaminophen rescue medication decreased from baseline through Month 3 and remained stable thereafter, the monthly average for all subjects ranged from 48 to 178 mg.

3.2.3.3.4. Intrinsic Factors

In Study B4531002, the primary analgesic endpoints and in Study B4531001, the secondary analgesic endpoints were also evaluated in subgroups of subjects defined by the baseline demographic variables of age (<65, ≥65), race (White, Non-White) and gender. Subgroup analyses were consistent with the primary efficacy analyses.

Pre-Study Opioid Status

Of the 280 subjects in the ITT population in Study B4531002, 60 (45%) in the placebo group and 62 (42.5%) in the ALO-02 group were opioid-experienced and 74 (55.2%) in the placebo group and 84 (57.5%) in the ALO-02 group were opioid-naïve. Consistent with the overall population in the ALO-02 group, a similar pattern in the primary analgesic efficacy endpoint by treatment was noted for both groups of subjects treated with ALO-02 regardless of prior opioid status, although the magnitude of the treatment difference was greater in the opioid-experienced group.

Of the 387 subjects in the ALO-02 ITT population of Study B4531001, 297 (76.7%) were opioid-experienced and 90 (23.3%) subjects were opioid-naïve prior to study entry. Similar to the overall population, average pain intensity scores decreased over time across treatment groups of subjects treated with ALO-02 regardless of prior opioid status, although the magnitude of the treatment difference was greater for the opioid-naïve subjects compared to the opioid-experienced subjects from baseline to Month 12 of treatment. The average pain intensity scores decreased over time with ALO-02 treatment.

Subjects managing their chronic lower back pain or chronic non-cancer pain (pre-study) exclusively with a non-opioid analgesic were considered as opioid-naïve and ALO-02 treatment was initiated at 10 mg/1.2 mg BID approximately 12 hours apart at the beginning of the Open-Label Conversion/Titration Period (Study B4531002) or the Treatment Period (Study B4531001).

3.2.3.3.5. BPI-sf Average Pain Score by Treatment and Naltrexone Concentration

To evaluate the clinical effects of naltrexone exposures on pain scores, the observed naltrexone concentration in plasma samples from Studies B4531002 and B4531001 were assessed for correlation with time-matched BPI-sf average pain scores (Figure 33 and Figure 34, respectively).

There was no apparent relationship between naltrexone exposure and time-matched BPI-sf average pain scores with ALO-02 treatment in either of the pivotal Phase 3 studies.

Figure 33. Change from Randomization Baseline to Week 12/Early Termination in Time-Matched Pain Score by Treatment and Naltrexone Concentration Group - ITT Population in Study B4531002

Abbreviations: ITT=intent-to-treat, LLOQ=lower limit of quantitation =4 pg/mL, LOQ=Limit of Quantitation, n=number of subjects in each group, BPI= Brief Pain Inventory.
Below LOQ includes all ALO-02 subjects with all naltrexone values below LLOQ.
Equal to or Above LOQ includes all ALO-02 subjects with at least one naltrexone value ≥LLOQ.
BPI Average Pain Score is reported as Average Pain in Last 24 Hours, 0=No Pain, 10=Worst Pain.
Box and whisker plots display minimum. Q1 (Lower Quartiles), median, Q3 (Upper Quartiles), maximum values and (+) represents mean value.

Figure 34. Change From Baseline to End of Study/Early Termination in Time-Matched Pain Score by Naltrexone Concentration Group - ITT Population in Study B4531001
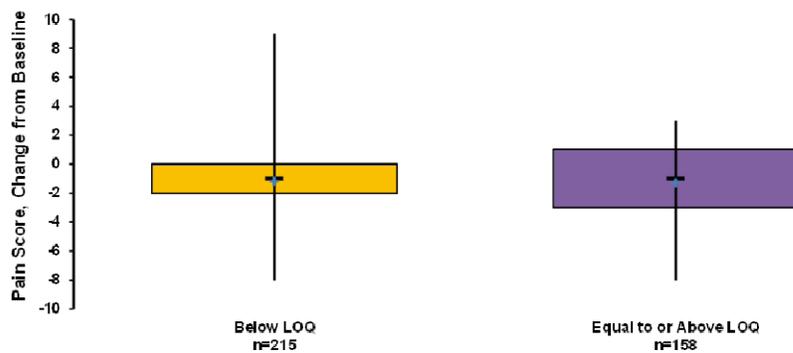
Abbreviations: ITT=Intent-to-Treat; LLOQ=lower limit of quantitation=4 pg/mL, LOQ=Limit of Quantitation, n=number of subjects in each group, BPI= Brief Pain Inventory.
Below LOQ includes all ALO-02 subjects with all naltrexone values below LLOQ.
Equal to or Above LOQ includes all ALO-02 subjects with at least one naltrexone value ≥LLOQ.
BPI Average Pain Score is reported as Average Pain in Last 24 Hours, 0=No Pain, 10=Worst Pain.
Box and whisker plots display minimum. Q1 (Lower Quartiles), median, Q3 (Upper Quartiles), maximum values and (+) represents mean value.

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3.2.4. Clinical Safety Evaluation

The results from the 2 Phase 3 studies (B4531001 and B4531002) in a safety population of adult subjects (>18 years) with moderate-to-severe chronic lower back pain and chronic non-cancer pain requiring a continuous, around-the-clock opioid analgesic for an extended period of time demonstrated the following:

- ALO-02 administered in doses ranging from 10 mg/1.2 mg up to 80 mg/9.6 mg BID for up to 12 months has a safety and tolerability profile consistent with other opioids.

- The evaluation of safety topics of special interest demonstrated few signals of drug abuse, dependence, or aberrant behavior.

- In the Phase 3 program, events of withdrawal were infrequent (14/805 subjects); one subject had 2 events of withdrawal. Most events (13/15) of drug withdrawal occurred during study medication dosage adjustment.

- In plasma samples with measureable naltrexone concentration, there was no apparent relationship between naltrexone exposure and time-matched COWS scores.

For the pivotal placebo-controlled efficacy Study (B4531002), 410 subjects were enrolled in the open-label titration period and received at least 1 dose of study drug, 68.5% (281/410) of subjects completed the open-label titration period and were randomized to the double-blind treatment period. The most common reasons subjects did not enter the double-blind treatment period were adverse events (AEs) (13.9%) and did not meet entrance criteria (10.0%). No subjects discontinued the study during the open-label titration period due to insufficient clinical response.

For the open-label 12-month Study (B4531001), 395 subjects were enrolled, 158 (40.0%) completed the study, and 237 (60.0%) discontinued early. The most common reason for premature discontinuation from the study was due to an adverse event (75 [19.0%] subjects). Other common reasons for study discontinuation, reported by ≥5% of subjects, were subject withdrew consent (51 [12.9%] subjects), lack of efficacy (37 [9.4%] subjects), and noncompliance (25 [6.3%] subjects). The percentage of subjects who discontinued was highest in the 10-40 mg dose group (68.2%) and lowest in the >40-80 mg dose group (52.9%).

Of the 805 subjects in the 2 Phase 3 studies, the majority (482; 59.9%) were opioid-experienced. More opioid-naïve (200/323; 61.9%) subjects compared to opioid-experienced (257/482; 53.3%) had a total duration of exposure of ≤90 days. The majority of opioid-naïve subjects was exposed to an average daily dose of oxycodone ≤40 mg/day (187/323; 57.9%), whereas the majority of opioid-experienced subjects was exposed to an average daily dose of oxycodone ≤60 mg/day (256/482; 53.1%). Only 21/323 (6.5%) of opioid-naïve subjects were exposed to an average total daily dose of oxycodone ≥80 mg/day, whereas 133/482 (27.6%) opioid-experienced subjects were exposed to an average total daily dose of oxycodone ≥80 mg/day.

In the 2 Phase 3 studies, the most common adverse reactions were nausea, constipation, vomiting, headache, and somnolence. The most common adverse reactions leading to discontinuation (≥1% in any of the treatment phases) were nausea, constipation, vomiting, somnolence, headache, fatigue, and dizziness.

Adverse reactions reported in ≥2% of subjects receiving ALO-02 in either the titration phase or maintenance phase of the placebo-controlled study are presented in Table 6.

Table 6.   Adverse Drug Reactions Reported in ≥2% of Subjects Receiving ALO-02 in the Placebo-Controlled Study

System Organ Class Adverse Drug Reaction (ADR)	Open-Label Titration Phase ALO-02 (N=410) n (%)	Double-Blind Maintenance Phase ALO-02 (N=146) n (%)	Double-Blind Maintenance Phase Placebo (N=134) n (%)
Gastrointestinal disorders			
Abdominal pain[a]	12 (2.9)	2 (1.4)	8 (6.0)
Constipation	61 (14.9)	5 (3.4)	3 (2.2)
Diarrhea	9 (2.2)	8 (5.5)	6 (4.5)
Dry mouth	13 (3.2)	0	0
Nausea	84 (20.5)	21 (14.4)	5 (3.7)
Vomiting	37 (9.0)	9 (6.2)	4 (3.0)
General disorders and administration site conditions			
Drug withdrawal syndrome[b]	4 (1.0)	4 (2.7)	2 (1.5)
Fatigue	13 (3.2)	5 (3.4)	1 (0.7)
Edema peripheral	3 (0.7)	3 (2.1)	1 (0.7)
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (0.7)	3 (2.1)	1 (0.7)
Back pain	5 (1.2)	3 (2.1)	8 (6.0)
Muscle spasms	1 (0.2)	4 (2.7)	1 (0.7)
Nervous system disorders			
Dizziness	24 (5.9)	6 (4.1)	1 (0.7)
Headache	30 (7.3)	2 (1.4)	7 (5.2)
Hypoesthesia	0	3 (2.1)	0
Somnolence[c]	37 (9.0)	1 (0.7)	1 (0.7)
Psychiatric disorders			
Insomnia	8 (2.0)	1 (0.7)	1 (0.7)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	1 (0.2)	4 (2.7)	1 (0.7)
Skin and subcutaneous tissue disorders			
Hyperhidrosis[d]	10 (2.4)	4 (2.7)	1 (0.7)
Pruritus[e]	27 (6.6)	3 (2.1)	0
Vascular disorders			
Hot flush[f]	10 (2.4)	2 (1.4)	3 (2.2)

Table 6. Adverse Drug Reactions Reported in ≥2% of Subjects Receiving ALO-02 in the Placebo-Controlled Study

System Organ Class Adverse Drug Reaction (ADR)	Open-Label Titration Phase ALO-02 (N=410) n (%)	Double-Blind Maintenance Phase ALO-02 (N=146) n (%)	Double-Blind Maintenance Phase Placebo (N=134) n (%)

Abbreviations: ADR=adverse drug reaction, N=number of subjects evaluable.

a. Abdominal pain also includes Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, and Gastrointestinal pain.
b. Drug withdrawal syndrome ADR includes the following MedDRA Preferred Terms: Drug withdrawal syndrome and Withdrawal syndrome or a score of greater than or equal to 13 on the Clinical Opiate Withdrawal Scale.
c. Somnolence also includes Sedation.
d. Hyperhidrosis also includes Cold sweat.
e. Pruritus also includes Pruritus generalized.
f. Hot flush also includes Flushing.

An additional 395 subjects received at least one dose of ALO-02 in the open-label, 12-month safety study of subjects with moderate-to-severe chronic non-cancer pain. In this study, 193 subjects received ALO-02 for at least 6 months and 105 subjects received ALO-02 for approximately 12 months.

Adverse reactions reported in ≥2% of subjects of the 12-month open-label safety study are presented in Table 7.

Table 7.   Adverse Drug Reactions Reported in ≥2% of Subjects in the 12-Month Open-Label Safety Study

System Organ Class	ALO-02 (N=395)
Adverse Drug Reaction (ADR)	**n (%)**
Gastrointestinal disorders	
Abdominal pain[a]	33 (8.4)
Constipation	84 (21.3)
Diarrhea	36 (9.1)
Dry mouth	9 (2.3)
Nausea	100 (25.3)
Vomiting	55 (13.9)
General disorders and administration site conditions	
Fatigue	36 (9.1)
Edema peripheral	15 (3.8)
Musculoskeletal and connective tissue disorders	
Arthralgia	13 (3.3)
Back pain	25 (6.3)
Muscle spasms	9 (2.3)
Nervous system disorders	
Dizziness	34 (8.6)
Headache	46 (11.6)
Somnolence[b]	38 (9.6)
Tremor	8 (2.0)
Psychiatric disorders	
Depression	13 (3.3)
Insomnia	20 (5.1)
Restlessness	9 (2.3)
Respiratory, thoracic and mediastinal disorders	
Cough	10 (2.5)
Oropharyngeal pain	9 (2.3)
Skin and subcutaneous tissue disorders	
Hyperhidrosis[c]	27 (6.8)
Pruritus[d]	22 (5.6)
Vascular disorders	
Hot flush[e]	17 (4.3)

Abbreviations: ADR=adverse drug reaction, n=number of subjects in the group.
a.   Abdominal pain also includes: Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, and Gastrointestinal pain.
b.   Somnolence also includes Sedation.
c.   Hyperhidrosis also includes Cold sweat.
d.   Pruritus also includes Pruritus generalized.
e.   Hot flush also includes Flushing.

There were 2 deaths that were evaluated as unrelated to study medication. One death occurred after approximately 2 months of ALO-02 treatment following an acute myocardial infarction, in a patient with history of prior myocardial infarction and cardiovascular risk factors.

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A second death was reported approximately 1 year after the last dose of study medication. This subject was diagnosed with a serious adverse event (SAE) of metastatic squamous cell cancer, anal, and died approximately 1 year after the last dose of ALO-02. Cause of death was provided as disease progression, which was not considered to be related to study medication.

A total of 36 subjects experienced 54 SAEs in the Phase 3 studies (N=805); 26 subjects in Study B4531001 (N=395) experienced 36 SAEs and 10 subjects in Study B4531002 (N=410) experienced 18 SAEs (2 subjects that had received placebo experienced 3 SAEs). In Study B4531001, for those subjects who received ALO-02, 2 SAEs (cholelithiasis and abdominal pain) were considered related to study medication, all others were considered unrelated to study medication. None of the SAEs in Study B4531002 were considered to be related to study medication.

There were few reports of drug abuse, dependence, aberrant behavior or withdrawal. The majority of withdrawal events or elevated COWS scores (13/15) occurred during study medication dosage adjustment and 2 occurred while the subject was on study medication without any evidence of study medication dosage adjustment.

To evaluate the clinical effects of naltrexone exposures on withdrawal, the COWS scores from plasma samples with naltrexone concentration were compared to COWS scores from samples without detectable naltrexone concentration in Studies B4531002 and B4531001. COWS scores of both population of samples were comparable leading to the conclusion that there was no apparent relationship of naltrexone concentration on withdrawal in either of the pivotal Phase 3 studies (see Figure 35 and Figure 36).

Figure 35. Relationship of Naltrexone and COWS Scores: Change From Randomization Baseline to Week 12/Early Termination by ALO-02 and Naltrexone Concentration in the Placebo-Controlled Study B4531002
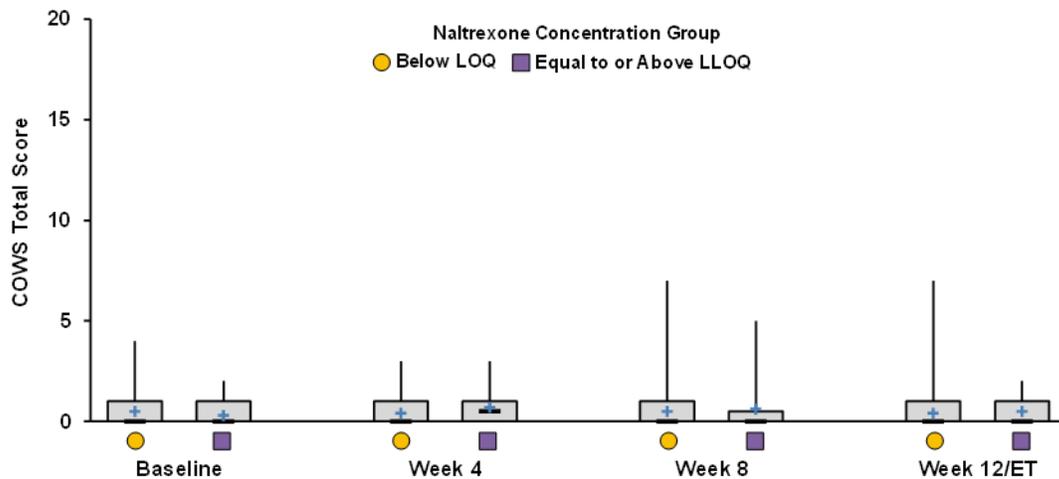
Abbreviations: COWS=Clinical Opiate Withdrawal Scale, LOQ=limit of Quantitation, LLOQ=Lower Limit of Quantitation=4 pg/mL.
Below LOQ includes all ALO-02 subjects with all naltrexone values below LLOQ.
Equal to or Above LOQ includes all ALO-02 subjects with at least one naltrexone value ≥LLOQ.

COWS Score ranges from 0 to 48: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal.
Box and whisker plots display minimum, Q1 (Lower Quartiles), median, Q3 (Upper Quartiles), maximum values and (+) represents mean value.

Figure 36. Relationship of Naltrexone and COWS Scores: Change From Randomization Baseline to Week 12/Early Termination by ALO-02 and Naltrexone Concentration in the 12-Month Open-Label Safety Study B4531001
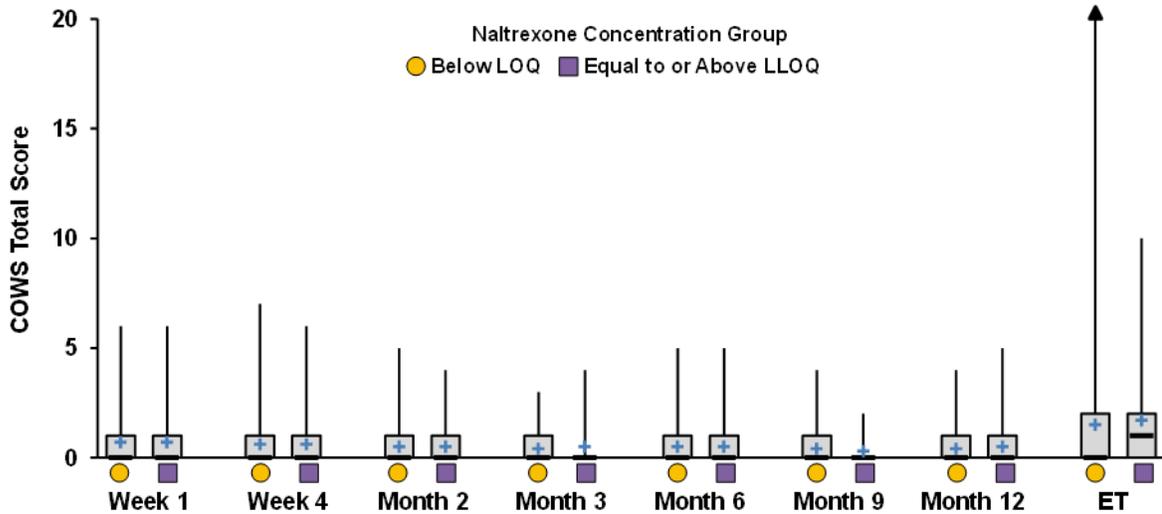
Abbreviations: COWS=Clinical Opiate Withdrawal Scale, LOQ=limit of Quantitation, LLOQ=Lower Limit of Quantitation=4 pg/mL.
Below LOQ includes all ALO-02 subjects with all naltrexone values below LLOQ.
Equal to or Above LOQ includes all ALO-02 subjects with at least one naltrexone value ≥LLOQ.
COWS Score ranges from 0 to 48: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal.
Box and whisker plots display minimum, Q1 (Lower Quartiles), median, Q3 (Upper Quartiles), maximum values and (+) represents mean value.

Only 1 (0.1%) treatment-emergent adverse event of drug abuse was reported in the Phase 3 program (Study B4531002, one subject who was on 20 mg/2.4 mg ALO-02 BID when the AE started). The terms, Euphoria and somnolence, both known to be associated with opioids, were the most common potential abuse-related Medical Dictionary for Regulatory Activities (MedDRA) terms identified in the ALO-02 development program. All of the euphoria-related events (euphoria/euphoric mood, feeling of relaxation) were reported in the naltrexone dose ratio/abuse potential studies, primarily during the qualification or discrimination phase. Compared to ALO-02, nearly twice as many subjects that received IR oxycodone alone reported euphoric mood.

There were few signals of aberrant behavior related to positive urine drug test (UDT) for illicit drugs and opioids not permitted per protocol which was supported by few reports of concomitant use of non-study drug opioid medication. In Study B4531001, the percentage of subjects with Current Opioid Misuse Measure (COMM) scores ≥9 decreased with the duration of the study indicating fewer subjects with aberrant medication related behavior as

the study continued. There was no apparent relationship between COMM scores and reasons for discontinuations. Finally, of the 79 investigational sites that participated in the Phase 3 studies, missing investigational medication was noted at 3 sites (3.8%), 1 site in Study B4531001 and 2 sites in Study B4531002. The Drug Enforcement Agency (DEA) was notified in all 3 cases.

In summary, the evaluation of safety topics of special interest demonstrate few signals of drug abuse, dependence, or aberrant behavior and indicate that reported events of withdrawal were not associated with naltrexone exposure. The majority of withdrawal events were related to adjustments of dose strengths during the initial conversion to ALO-02, tapering off ALO-02, or stopping, interrupting, or non-compliance with study medication.

3.2.4.1. Safety Conclusions

In the 2 Phase 3 studies, the safety population consisted of adult patients (>18 years) with moderate-to-severe chronic lower back pain and chronic non-cancer pain requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Overall, these studies demonstrate that ALO-02 administered in doses ranging from 10 mg/1.2 mg up to 80 mg/9.6 mg BID for up to 12 months has a safety and tolerability profile consistent with other opioids.

In the ALO-02 development program, the evaluation of MedDRA terms from the drug abuse, dependence, and withdrawal , evaluation of COWS scores in the Phase 3 studies, and evaluation of COMM scores indicated that there were few reports of drug abuse, dependence, aberrant behavior or withdrawal. The majority of withdrawal events and elevated COWS scores (13/15) occurred during study medication dosage adjustment and 2 occurred while the subject was on study medication without any evidence of study medication dosage adjustment. In addition, there was no association between naltrexone concentration and COWS scores. These data suggest that events of withdrawal were not associated with naltrexone exposure.

The results from the Phase 3 studies (B4531001 and B4531002) are consistent with the findings of an expert panel of the American Pain Society and American Academy of Pain Medicine that reported the most frequent opioid-related AEs were constipation, nausea and vomiting, sedation or clouded mentation, pruritis, and myoclonus and that AEs of nausea, vomiting, and sedation tend to wane over time.[23]

4. BENEFIT/RISK BALANCE

ALO-02 is an ER opioid analgesic intended for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. ALO-02 capsules contain polymer-coated pellets of ER oxycodone surrounding sequestered naltrexone HCl. The 2 active ingredients of ALO-02 are currently marketed separately in the US. When ALO-02 is taken intact as directed by a physician as part of a comprehensive pain management program, it provides continuous pain relief. However, if ALO-02 pellets are manipulated by crushing, naltrexone is released and rapidly absorbed and reduces the positive subjective effects (eg, euphoria or Drug-Liking) of oxycodone.

4.1. Benefits of Extended-Release Oxycodone with Sequestered Naltrexone

The analgesic efficacy of oxycodone in the treatment of chronic pain is well established in the literature, and the analgesic efficacy of ALO-02 was confirmed in the pivotal 12-week EERW design study in patients with moderate-to-severe chronic lower back pain. In this study, ALO-02 demonstrated superior efficacy to placebo. The mean change in the weekly average pain scores from randomization baseline to the final 2 weeks was greater (ie, an increase or worsening in pain) for placebo-treated subjects than subjects treated with ALO-02 during the double-blind treatment phase. Efficacy of ALO-02 is supported by the results from a long-term open-label study in subjects with chronic non-cancer pain with up to 12 months treatment with ALO-02. This study demonstrated a significant decrease in average pain scores at each weekly visit. Single dose PK studies in healthy volunteers demonstrated no observable plasma naltrexone levels, confirming sequestration of naltrexone. Measurable levels of naltrexone were observed in a minority of plasma samples collected in the pivotal efficacy study (18%) and long-term safety study (23%). The observed naltrexone exposures were low and did not appear to be clinically relevant as there was no apparent relationship between naltrexone exposure and change in pain scores.

Abuse and misuse of prescription opioids are a major public health concern. Non-abuse-deterrent ER formulations opioids can be easily and rapidly manipulated to "defeat" the ER technology, convert it into an IR form for oral abuse, and enable intranasal and IV abuse.[24] While abuse of intact opioids by the oral route is the most common route of abuse of prescription opioids, tampering with the formulation to enable abuse by other non-oral routes is common.[9] Furthermore, evidence suggests that tampering and abuse by non-oral routes of administration, is associated with more severe negative health consequences when overdosed[9] and with greater healthcare utilization.[24]

The sequestered naltrexone in ALO-02 is intended to reduce the abuse potential of oxycodone by reducing the euphoria produced by oxycodone when the pellets are physically manipulated by crushing and administered by the oral, intranasal or IV routes of administration. In-vitro studies performed with ALO-02 demonstrated that when ALO-02 is crushed and mixed in a variety of solvents, oxycodone HCl and naltrexone HCl are simultaneously extracted. PK data with crushed ALO-02 demonstrated that naltrexone was absorbed as rapidly as oxycodone by the oral and intranasal routes and would be expected to reduce the effects of oxycodone. This reduction was confirmed in the 3 abuse potential studies in recreational non-dependent opioid abusers in which crushed ALO-02 (or simulated crushed ALO-02 in the case of the IV study) was associated with significant reductions in Drug-Liking and other measures of abuse potential compared to oxycodone when administered by the oral, intranasal or IV routes. Thus, the preclinical and clinical data indicate that when manipulated, the naltrexone in ALO-02 would be expected to reduce abuse when administered by the oral, intranasal and IV routes.

4.2. Risks of Oxycodone With Sequestered Naltrexone

The risks of ALO-02 can be characterized as the known risks of ER oxycodone and the risks associated with the possible release of sequestered naltrexone. The adverse reaction profile, dose response, and dose toxicity of ALO-02 were consistent with those seen with other IR and ER opioids. The commonly reported adverse reactions in the ALO-02 clinical program,

such as nausea, constipation, vomiting, headache, and somnolence were consistent with the well described adverse reactions of oxycodone and other opioids. Other known risks associated with opioids include respiratory depression, severe hypotension, spasm of the sphincter of Oddi, and impaired mental and/or physical abilities needed to perform potentially hazardous activities. Clinical management of oxycodone-related risks includes individualized treatment of patients using a progressive plan of pain management. Health care professionals should follow appropriate principles of pain management including careful assessment and ongoing monitoring. It is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience.

Chronic use of oxycodone may be associated with the development of tolerance, physical dependence and addiction. Tolerance is defined as the diminution in the effect of the drug on repeated administration. Physical dependence is defined as an altered physiological state brought about by repeated administration of a drug, which necessitates continued use of the drug to prevent the appearance of characteristic signs and symptoms (ie, withdrawal). Addiction refers to craving and compulsive use of the drug.[25] The abrupt withdrawal of opioid treatment or the administration of opioid antagonists such as naltrexone to opioid-dependent subjects is known to precipitate withdrawal. The opioid withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, and mydriasis.

Other symptoms may also develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. Following chronic exposure to ALO-02, detectable levels of naltrexone were observed in a minority of plasma samples obtained from subjects during the Phase 3 program (see Section 3.2.4). However, there was no apparent relationship between naltrexone plasma concentration and COWS scores. In addition, the majority of withdrawal related AEs were associated with dosage adjustment of ALO-02 or subject noncompliance.

In summary, the adverse drug reactions reported in the ALO-02 clinical program support a risk profile for ALO-02 that is comparable to other opioids, including oxycodone.

4.3. Risks and Mitigation Strategy

ALO-02 will be a Schedule II drug under the Controlled Substances Act, and will have appropriate class labeling of an ER/LA opioid analgesic, as well as a Medication Guide for patients. ALO-02 will also be subject to the ER/LA Opioid Analgesic REMS. The Sponsor is also committed to conducting pharmacovigilance and surveillance activities to monitor for safety issues during post-authorization use, including abuse, misuse, addiction, and overdose.

The goal of the ER/LA Opioid Analgesic REMS[26] is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics, while maintaining patient access to important pain medication. Adverse outcomes of concern include addiction, unintentional overdose, and death. The Sponsors of all ER/LA opioid analgesic medications have collaborated together with the FDA to develop and implement the REMS, which is focused on educating healthcare professionals through accredited Continuing Medical Education/Continuing Education (CE) to reduce serious

adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics. The content of REMS-compliant CE activities are based on the FDA Blueprint, which covers topics related to assessment and counseling of patients, initiation, dose modification, ongoing management and discontinuation of therapy, as well as general information about the class of ER/LA opioid analgesics and specific characteristics of medications within the class. The REMS also includes annual distribution of Dear Healthcare Provider letters to new DEA-registered prescribers (Schedule II or III prescribers), a Patient Counseling Document, a website, and a call center. The REMS includes the preparation of annual assessment reports in order to monitor progress of the REMS and inform on any changes necessary to improve the program.

In addition to surveillance of spontaneous reports of adverse events, the Sponsor will also employ a strategy of active surveillance for abuse, overdose, tampering and diversion of ALO-02 and other ER oxycodone by regular, periodic monitoring of data collected from multiple sources: patients entering a national network of methadone treatment and private substance abuse treatment centers; poison centers covering over 92% of the US population; multi-annual online surveys of nationally representative samples of college-age students; monitoring of electronic posts to social media such as web sites, online blogs, web forums and other internet sites; and a national network of drug diversion investigators representing municipal police departments, multi-jurisdictional drug task forces, county sheriffs' departments and other pharmaceutical boards and departments of health.

In summary, the Sponsor is committed to a program of risk mitigation, communication and monitoring activities via the ER/LA opioid analgesics REMS and post-marketing pharmacovigilance and surveillance activities to monitor for safety issues during post-authorization use, including abuse, misuse, addiction, and overdose. In combining the abuse-deterrent properties of ALO-02 with these programs, the Sponsor aims to positively impact this public health epidemic of abuse and misuse of prescription opioids.

4.4. Benefit/Risk Balance

ALO-02 has demonstrated a favorable benefit/risk balance, as summarized below.

- The analgesic benefits of ALO-02 have been demonstrated in a double-blind, placebo-controlled study in subjects with moderate-to-severe chronic lower back pain and supported by the demonstration of effectiveness in a long-term open-label safety study in subjects with chronic non-cancer pain.

- The safety profile of ALO-02 was consistent with that of other opioids in this patient population.

- Sequestration of naltrexone was demonstrated in the clinical pharmacology program; there is no measurable naltrexone exposure with oral administration of ALO-02 in a controlled setting across all Phase 1 studies.

- Low levels of naltrexone exposure were observed in ~18-23% of samples collected in the 2 Phase 3 studies with ALO-02. These data suggest that the observed naltrexone exposures tend to occur randomly without evidence of accumulation at any point in

time over the course of the studies. The observed naltrexone exposures were not related to the ALO-02 doses, nor did they impact clinical efficacy/safety.

- The in-vitro (Category 1 studies) and PK (Category 2 studies) data demonstrate that crushing ALO-02 pellets results in simultaneous release and absorption of oxycodone and naltrexone.

- The HAP (Category 3) studies demonstrated reduced abuse potential of ALO-02 following manipulation via the oral, intranasal and IV routes in recreational opioid abusers.

5. CONCLUSION

In conclusion, ALO-02 has a favorable benefit/risk profile in the management of chronic lower back pain and chronic non-cancer pain when alternative treatment options are inadequate. ALO-02 has robust evidence to support labeling for abuse-deterrent properties.

6. REFERENCES

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